p-ISSN 2301-4369
e-ISSN 2685-7898

Medica Hospitalia

Journal of Clinical Medicine

Med Hosp 2023 Vol 10 (3) November 2023 www.medicahospitalia.rskariadi.co.id

Original Articles

Case Report

Published by
Medica Hospitalia – Dr. Kariadi Hospital

Medica Hospitalia

Journal of Clinical Medicine

Med Hosp 2023; Vol 10 (3)

November 2023

p-ISSN 2301-4369 e-ISSN 2685-7898

Alamat Redaksi & Sirkulasi

Tim Kerja Penelitian Gedung Pendidikan dan Pelatihan (DIKLAT)

Jl. Dr. Sutomo No. 16, Semarang, Jawa Tengah

Website E-Journal: http://medicahospitalia.rskariadi.co.id/medicahospitalia/index.php/mh/index

Email: medicahospitalia@rskariadi.co.id atau medica.hospitalia@yahoo.com

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; Vol 10 (3)
November 2023

Original Articles

295 Effect of Kinesio Taping on Muscle Spasticity in Post-Stroke Patients Receiving Infrared Therapy and Stretching Exercise : A Quasi-Experimental Study

Andirezeki Riswanti[1], Robby Tjandra Kartadinata[1], Hari Peni Julianti[1], Hindun Zuhdiana[2], Lilik Sigit Wibisono[3]
[1]Physical Medicine and Rehabilitation Faculty of Medicine Diponegoro University / Kariadi Hospital Semarang, Indonesia
[2]Physical Medicine and Rehabilitation Faculty of Medicine Diponegoro University / KRMT Wongsonegoro Hospital Semarang, Indonesia
[3]Physiotherapist / KRMT Wongsonegoro Hospital Semarang, Indonesia

Kinesio Taping has been demonstrated to significantly reduce plantar flexor muscle spasticity in stroke survivors.

302 Relationship between Stress Level and Risk of Eating Disorder in Undergraduate Students during the COVID-19 Pandemic

Jessica Clara[1], Titis Hadiati[2], Innawati Jusup[2], Widodo Sarjana A.S.[2]
[1]Faculty of Medicine, Diponegoro University, Indonesia
[2]Department of Psychiatry, Faculty of Medicine, Diponegoro University, Indonesia

There is a significant correlation (p=0.005) between the stress level and risk of eating disorder with very weak positive relationship direction (r=0.097).

312 Comparison between Immunohistochemistry and Modified Giemsa Staining for Identification of *Helicobacter spp* in Stomach Biopsy

Fenny Halim[1], Devia Eka Listiana[2], Vega Karlowee[1], Hermawan Istiadi[1], Awal Prasetyo[1], Meira Dewi Kusuma Astuti[2]
[1]Anatomical Pathology Department, Faculty of Medicine, Diponegoro University, Semarang, Central Java, Indonesia
[2]Department of Anatomical Pathology, dr Kariadi Central General Hospital Semarang, Central Java, Indonesia

Modified Giemsa is still reliable for identifying *Helicobacter spp*, especially in classical form, compared to immunohistochemistry. Due to the administration of PPI, there are a lot of cases with atypical form of *Helicobacter spp* which can be differentiated into coccoid form and intraepithelial located. Immunohistochemistry staining is useful in identify these cases.

319 The Relationship between Obesity and Allergies with Olfactory Disorders in Covid-19 Patients

Yudistira Pratama, Anna Mailasari Kusuma Dewi, Muyassaroh, Riece Hariyati, Willy Yusmawan
Department of Otorhinolaryngology Head Neck Surgery, Faculty of Medicine, Diponegoro University, Semarang, Indonesia

Obesity and allergies are corelated with impaired smell in COVID-19 patients.

324 Factors Affecting Gastric Perforation Patient Outcome with History of Arthritis and Long Term Use of NSAIDs in Dr. Kariadi Semarang Period 2020–2022

Leonardo Cahyo Nugroho[1], Ardi Fauzi[2], Agus Priambodo[3]
[1]General Surgery, Faculty of Medicine, Duta Wacana Christian University Yogyakarta, Indonesia
[2]General Surgery, Faculty of Medicine, Diponegoro University Semarang, Indonesia
[3]Orthopedic Surgery, Faculty of Medicine Diponegoro University Semarang, Indonesia

NSAIDs pose a risk of gastric perforation in long-term use. tNSAIDs carry a higher risk inducing gastric perforation than selective NSAIDs.

334 Assessing the Inter-observer Agreement of Electrocardiography Interpretation in the Elderly Surgical Patients: A Cross-Sectional Study

Yudo Murti Mupangati[1,2,3], Henry Setyawan[4], Czeresna Heriawan Soejono[5], Muhammad Hussein Gasem[6], Ignatius Riwanto[3,7]
[1]Doctoral Study Program of Medical and Health Science, Faculty of Medicine, Diponegoro University Semarang, Indonesia
[2]Geriatric Division, Internal Medicine Department Dr. Kariadi Hospital Semarang, Indonesia
[3]Faculty of Medicine, Diponegoro University Semarang, Indonesia
[4]Epidemiology Master Study Program/School of Public Health Diponegoro University Semarang, Indonesia
[5]Geriatric Division, Internal Medicine Department, Faculty of Medicine Indonesia University, Jakarta, Indonesia
[6]Center for Tropical and Infectious Diseases, Dr. Kariadi Hospital and Diponegoro University Semarang, Indonesia
[7]Indonesian Digestive Surgeon Association, Indonesia

The value of agreement between junior internists in ECG interpretation among elderly surgical patients is good (kappa value >0.8). Even though the observers are junior internist, the result of the interpretation with a high kappa is considered to have reliable validity.

Case Report

370 Case Series Report: Subarachnoid Hemorrhage and ICU Management

Retnaningsih[1], Dodik Tugasworo[1], Yovita Andhitara[1], Rahmi Ardhini[1], Aditya Kurnianto[1], Daynuri[2], Erlangga Pradipta Harianto[3]
[1]Neurology Department, Dr. Kariadi General Center Hospital Semarang, Indonesia
[2]Neurology Program Study, Faculty of Medicine, Diponegoro University Semarang, Indonesia
[3]Faculty of Medicine, Diponegoro University Semarang, Indonesia

Rapid diagnosis and attentive management of patients with SAH are essential, as early deterioration is possible within the first few hours after the onset of SAH. The risk for early neurologic damage and high rates of severe long-term complications necessitated aggressive early management. Prevention and Management of Complications. The most common complications were pneumonia, aspiration, respiratory failure/distress, sepsis and imbalance electrolyte (hyponatremia). Approximately 50% of deaths after SAH are due to medical complications.

377 Rare Case of Inguinal Endometriosis Lump : Case Report and Literature Review

Indra Adi Susianto[1,2], Edward Hartono[1,2], Barkah Fajar Riyadi[1], Siti Amarwati[3], Alberta Widya Kristanti[2], Aprilia Karen Mandagie[2], Mohammad Haekal[4]
[1]Department of Obstetrics and Gynecology Anugerah Women and Children Hospital Semarang, Indonesia
[2]Medical Faculty of Soegijapranata Catholic University Semarang, Indonesia
[3]Department of Patology Kariadi Hospital Semarang, Indonesia
[4]Harapan Kita National Women and Children Health Center Jakarta, Indonesia

The low incidence of inguinal endometriosis is one of the considerations in the different diagnosis of painful inguinal hernias in the inguinal area in women with childbearing age. The diagnosis of endometriosis can be demonstrated clearly on High-Definition Ultrasound by trained personnel. Surgery is the optional treatment and is curative in this case.

382 Lucio's Phenomenon in Lepromatous Leprosy Patient: A Rare Case Report

Irma Amalia[1], Agnes Sri Widayati[2], Holy Ametati[1], Yosep Ferdinand Rahmat Sugianto[1], Sri Windayati[2]
[1]Department of Dermatovenereology, Medical Faculty of Diponegoro University /Central General Hospital of Kariadi Semarang, Indonesia
[2]Department of Dermatovenereology, Medical Faculty of Diponegoro University /Tugurejo General Hospital Semarang, Indonesia

Early detection is crucial in order to deliver therapy earlier and prevent disease worsening.

387 Concomitant Colon Adenocarcinoma and Tuberculous Lymphadenitis

Albertus Magnus Arya Abisatya[1], Ajeng Andini Prameswari[1], Agung Rahmat Fauzi[1], Aji Pratama Febrianto[1], Alexander Steven Nugroho[1], Hendrata Erry Andisari[2], Pandu Harijono[2], Redemptus Yudadi[2]
[1]Medical Faculty of Hang Tuah Surabaya, Indonesia
[2]Navy Central Hospital of Dr. Ramelan Surabaya, Indonesia

The etiological and pathophysiological relationship between tuberculous lymphadenitis and colon cancer is still under debate, but surgeons need to be aware of this occurrence, to choose treatment and avoid post-operative worsening.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; Vol 10 (3)
November 2023

Editorial

Thank God Almighty for the Covid-19 pandemic has passed. Indonesia and other countries in the world have started to relax rules regarding social distancing. It could be that the virus causing the pandemic has really disappeared from the earth. However, this condition still remains an interesting research object and produces good articles.

In this edition, there are also articles about Covid-19 reviewed from several aspects. This proves that it still allows researchers to collaborate, strengthen research, and create new breakthroughs that can bring positive change in society. Whatever field of research is carried out, from there communication is established between interested researchers, which leads to collaboration, inspiring each other and obtaining valuable data and feedback.

A good scientific journal must go through a strict peer review process, which requires independent experts to evaluate the authenticity, methodology and quality of the articles submitted. This helps ensure that published research is high quality and reliable work.

The Medica Hospitalia journal also continually improves internal processes to produce research that is relevant, innovative and can reach a wider readership. In the near future, improvements to the Open Journal System will be launched, which has become the standard for publishing scientific writing, including efforts to increase accreditation ranking. Therefore, it is important for us, especially academics, to continue supporting and promoting publication of high quality scientific journals so that they can continue to be a source of inspiration and knowledge for the scientific community, especially in Indonesia.

Happy researching,

Editor.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 264–269

OPEN ACCESS

Original Article

Body Composition and Its Related to Hypertension in Elderly: A Cross-Sectional Study from Surakarta

Wahyu Tri Sudaryanto[1], Wahyuni Wahyuni[1], Isnaini Herawati[1], Ika Yuli Ayuningrum[2], Bhisma Murti[2], Rizki Setiawan[1], Nuristiqomah Dwi Putri[1]

[1]Physiotherapy Department, Faculty of Health Sciences, Universitas Muhammadiyah Surakarta, Indonesia
[2]Masters Program in Public Health, Universitas Sebelas Maret, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.873

Accepted: December 23th, 2022
Approved: August 15th, 2023

Author Affiliation:
Physiotherapy Department,
Faculty of Health Sciences,
Universitas Muhammadiyah Surakarta,
Surakarta, Indonesia

Author Correspondence:
Wahyu Tri Sudaryanto
Ahmad Yani Street, Mendungan,
Pabelan, Kartasura, Sukoharjo,
Central Java 57169,
Indonesia

E-mail:
wts831@ums.ac.id

Abstract

Background : Several studies reported that obesity was linked to abnormal blood pressure. Obesity increases cardiovascular disease risk in adults and elderly. Body composition has been commonly measured using basic anthropometry, i.e body mass index (BMI). However, waist circumference (WC) is assumed to be more capable of capturing long-term visceral fat accumulation than BMI. Studies comparing BMI and WC to the risk of hypertension in the elderly are needed. The aim of this study was to compare the risk of body composition using body mass index and waist circumference as risk factors for hypertension in the elderly.
Methods : A cross-sectional study was carried out in Surakarta, Central Java. A sample of 91 elderly was selected by convenience sampling. The dependent variable was hypertension. The independent variables included age, gender, body mass index (BMI), and central obesity (assessed by waist circumference). BMI and central obesity were used to measure body composition. Blood pressure was measured by a sphygmomanometer, body weight was measured by digital scale (kg), and body height was measured by stature meter (cm). Central obesity was categorized by waist circumference (WC in centimeter) measurement. The other variables were obtained from questionnaire. Comparison of body composition on hypertension were examined using simple logistic regression run on Stata 13.
Results : Elderly with central obesity (waist circumference ≥94 cm for males or ≥80 cm for females) had higher risk hypertension and it was statistically significant (OR= 3.07; 95% CI= 1.10 to 8.53; p= 0.032).
Conclusion : Central obesity is significantly increase the risk hypertension in elderly.

Keywords : body composition, body mass index, elderly, hypertension, waist circumference

INTRODUCTION

Body mass index (BMI) is the most common anthropometric measurement for assessing obesity.[1] However, there have been many studies that recommend not only using BMI as an indicator of cardiovascular health risk. It is because measuring BMI alone can result in misclassification and understate the possibility of populations at risk. For example, individuals with normal weight sometimes have central obesity.[2]

Ideally, direct measurement of abdominal fat uses imaging techniques such as computed tomography scanning and magnetic resonance imaging.[3] However, this gold standard technique is expensive, time-consuming, and impractical when carried out in resource-limited environments and during large-scale epidemiological surveys.[4]

Previous studies suggested the assessment of central obesity to assess cardio-metabolic risk, including hypertension.[5,6] Recent studies have shown the ability to measure proxies for anthropometric indicators such as waist circumference (WC), waist-hip ratio (WHR), and waist-to-height ratio (WHTR) to examine the distribution of central obesity.[7] However, previous studies have focused on adolescents and adults populations and studies in the elderly group are relatively sparse.

The purpose of this study was to compare the risk of body composition using body mass index and waist circumference on hypertension in elderly.

METHODS

Study design

This was an analytic observational study with a cross sectional design. The study was carried out at the elderly integrated health posts (posyandu) in Surakarta, Central Java, Indonesia, from August to September 2022.

Population and sample

The study population was elderly aged ≥60 years. We employed a convenience sampling method to select participants. They were recruited from four local elderly integrated health posts (posyandu) in Surakarta. 91 elderly who visit the elderly "posyandu" was selected for this study. Older people who are not physically capable to undergo standing height measures or weight measures were then excluded to execute a sensitivity analysis.

Study variables

The dependent variable was hypertension. The independent variables were age, gender, body mass index (BMI), and central obesity.

Blood pressure was measured using sphygmomanometers. Hypertension was defined according to World Health Organization, using the following criteria: (1) Normal: SBP less than 120 and DBP less than 80mmHg; (2) elevated hypertension: SBP 120 to 129 and DBP less than 80mmHg; (3) Stage 1 hypertension: SBP 130 to 139 or DBP 80 to 89mmHg; and (3) Stage 2 hypertension: SBP ≥140 mmHg or DBP ≥90 mmHg.[8]

Body weight was measured using digital weight scale and body height was measured using stature meter. BMI and central obesity were used to measure body composition. Body mass index (BMI) is calculated as body weight (kg)/height (m^2). BMI is categorized according to WHO classification as underweight (BMI <18.5), normal (BMI 18.5–24.9), overweight (BMI 25.0–29.9), and obese (BMI >30.0).[9]

Central obesity was assessed by waist circumference. Waist circumference (WC) was measured at the level of the narrowest point between the lower costal margin and the iliac crest at the end of a normal expiration with the arms relaxed at the sides. Central obesity is defined according to WHO criteria (WC >94 cm for men and >80 cm for women).[1]

Data collection

The data were collected during routine medical check-up in the elderly health post in Surakarta. Anthropometric measurements, including body weight, height, and waist circumference were performed to all participants

Data analysis

Descriptive analyses were expressed as means, standard deviation (SD), absolute frequency, and percentage. T-test and Chi-square were used to determine the differences between gender in the variables. Simple logistic regression analyses were used to determine the association between the anthropometric indicators (i.e., BMI and WC) and hypertension. In all statistical evaluations, the significance level was set at $p < 0.05$. The data analysis run on Stata 13.

Research ethics

This study was approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Muhammadiyah Surakarta, Central Java, Indonesia (number: 4333/B.2/KEPK.FKUMS/VI/2022). All participants signed a written informed consent.

RESULTS

Table 1 showed that the study participant's age ranged from 60 to 91 years, with a mean (SD) of 64.53 (8.16) years. Mean of systolic blood pressure was 141 mmHg (SD= 23.79) and diastolic blood pressure was 85.8 mmHg (SD= 13.19). Mean of body mass index was 25.6 kgBW/m^2. Mean of waist circumference was 95.7 cm (SD= 19.40).

Table 2 showed the overall percentage of pre-hypertension, hypertension stage 1, and hypertension stage-2 were 28.57%, 32.97%, and 15.38%, respectively. Majority (71.43%) of the elderly was female; (83.52%) did

TABLE 1
Sample characteristics of continous data

Study Variables	n	Mean	SD	Min.	Max.
Age (year)	91	64.5	8.16	60	91
SBP (mmHg)	91	141.0	23.79	94	225
DBP (mmHg)	91	85.8	13.19	61	128
Body weight (kg)	91	59.4	11.17	36	85
Body height (cm)	91	152.3	7.31	136	175
BMI (kgBW/m^2)	91	25.6	4.42	16.41	37.44
WC (cm)	91	95.7	19.40	70	195

* SBP= systolic blood pressure; DBP= diastolic blood pressure; BMI= body mass index; WC= waist circumference

TABLE 2
Sample characteristics of dichotomous data

Study Variables		n	%
Gender	Female	65	71.43
	Male	26	28.57
Smoking	No	76	83.52
	Yes	15	16.48
Body mass index	Thin	3	3.30
	Underweight	1	1.10
	Normal	35	38.46
	Overweight	21	23.08
	Obesity	31	34.07
Central obesity*	No	26	28.57
	Yes	65	71.43
Hypertension	Normal	21	23.08
	Pre-hypertension	26	28.57
	Hypertension stage 1	30	32.97
	Hypertension stage 2	14	15.38

*Central obesity: WC ≥94 cm for male and WC ≥80 cm for female

not smoke; and (71.43%) had high waist circumference (central obesity). A third of the participant had hypertension stage-1 (32.97%).

Table 3 showed the differences in the characteristics of study variables based on gender. Table 3 showed that the mean of systolic blood pressure (mmHg) in women (Mean= 139.8; SD= 22.39) was lower than male (Mean= 144.3; SD= 27.18). Mean of diastolic blood pressure (mmHg) in women (Mean= 84.2; SD= 13.39) was lower than male (Mean= 89.7; SD= 12.03). There was no difference of body mass index between male (Mean= 25.5; SD= 4.40) and female (Mean= 25.9; SD= 4.56), p= 0.69. There was no difference of waist circumference between male (Mean= 94.9; SD= 17.89) and female (Mean= 97.5; SD= 23.05), p= 0.57.

This study found that normal weight (OR= 4.36; 95% CI= 0.36 to 53.39; p= 0.25), overweight (Or= 12; 95% CI= 0.81 to 177.44; p= 0.071), and obesity (OR= 10.4; 95%

TABLE 3
Difference between gender in study variables

Study Variables	Female (n= 65)		Male (n= 26)		p
	Mean	SD	Mean	SD	
SBP (mmHg)	139.8	22.39	144.3	27.18	0.42
DBP (mmHg)	84.2	13.39	89.7	12.03	0.08
BMI (kgBW/m^2)	25.5	4.40	25.9	4.56	0.69
Central obesity (WC, cm)	94.9	17.89	97.5	23.05	0.57

TABLE 4
Simple logistic regression between body mass index and hypertension in elderly (n= 91)

Body mass index	OR	95% CI		p
		Lower limit	Upper limit	
Underweight	Ref.			
Normal	4.36	0.36	53.39	0.25
Overweight	12.0	0.81	177.44	0.071
Obesity	10.4	0.78	137.83	0.076

TABLE 5
Simple logistic regression between central obesity and hypertension in elderly (n= 91)

Central obesity	OR	95% CI		p
		Lower limit	Upper limit	
No	Ref.			
Yes	3.07	1.10	8.53	0.032

*Central obesity= WC ≥94 cm in male and ≥80 cm in female

CI= 0.78 to 137.83; p= 0.076) were not significantly associated with hypertension in elderly (Table 4).

Table 5 reported that elderly with central obesity (waist circumference ≥94 cm in male and ≥80 cm in female) had higher risk of hypertension than those without central obesity (Or= 3.07; 95% CI= 1.10 to 8.53; p= 0.032).

DISCUSSION

Current study was designed to evaluate the effect of body mass index and central obesity on hypertension. Using a simple logistic regression on a conceptual model, the authors found that central obesity (waist circumference measurement) was associated with hypertension in elderly.

Hypertension is a common problem among the elderly, with increasing prevalence, and is associated with the risks of several non-communicable diseases.[10] Excess weight gain is long recognized as a significant cause of hypertension, contributing to about 78% of the risk for primary hypertension in men and 65% in women.[11,12] The prevalence of obesity is rising in elderly individuals.[13] Obesity is one of the modifiable risk factors associated with cardiovascular disease.[14] As an individual grow older, body composition changes with respect to fat distribution and height estimation.[15] Intra-abdominal fat has been shown to increase with age across both cross-sectional and longitudinal studies.[16,17] High intra-abdominal fat are commonly hypothesized had correlation with insulin resistance, which leads to type 2 diabetes and cardiovascular disease.[17]

Nowadays, BMI has been widely used for defining total obesity and has been observed to have a relationship with cardiovascular disease-specific mortality and all-cause mortality.[18,19] However, many studies reported BMI inability to reflect body fat distribution has limited its application in evaluating obesity-related cardiovascular risk because of the heterogeneous nature of obesity. While fat mass increases and redistributes, lean mass simultaneously tends to decrease with age, mostly as a consequence of sarcopenia.[17,20] The cut-off values of the obesity indices have not been defined for the elderly population because sarcopenia causes loss of muscle mass and fatty tissues increase with ageing.[21,22] Ageing and sarcopenia cause muscle loss and increase fat deposition, making BMI an inaccurate reference.[23]

Recent studies reported that visceral fat has a closer association with metabolic abnormalities compared with subcutaneous fat.[24–26] As the central component of the metabolic syndrome, abdominal obesity tends to aggregate with hypertension and other cardiometabolic risk factors.[27] Central adiposity has been seen to be more appropriated as a predictor of metabolic risk than BMI and its simple measurement can be done through WC.[28] A study in Brazil found that the risk of hypertension was higher with increasing waist circumference and age.[29] A cohort study by Cai *et al*.[30] found that abdominal obesity measured by WC or WHR had higher discriminative ability than BMI or body weight alone in predicting diabetes mellitus, high fasting plasma glucose, or other metabolic syndrome among elderly Spanish.

This study resulted that high body composition, categorized as overweight or obese (total obesity or central obesity), had higher risk to hypertension in elderly. Current finding supports that body mass index or waist circumference measurement should be implemented by the health professionals as hypertension disease preventive program in elderly. Further research needed to compare which is the best index as a predictor of hypertension, body mass index or waist circumference.

CONCLUSION

This study concluded that central obesity increase the risk for hypertension in elderly.

Financial Support

This paper is based on the Education, Research and Community Service (Tri Dharma) integration grant sponsored by Universitas Muhammdiyah Surakarta, Central Java, Indonesia, with grant number 950.1/A.3-III/FIK/IV/2022.

Conflict of interest

All authors have nothing to disclose.

REFERENCES

1. WHO. *Waist circumference and waist-hip ratio: report of a WHO expert consultation*. [Internet]. 2011 [cited 2022 Dec 12]. Available from: https://www.who.int/publications/i/item/9789241501491.
2. Ashwell M, Gibson S. A proposal for a primary screening tool: "Keep your waist circumference to less than half your height.". *BMC Med*. 2014;12(1):1–6. https://doi.org/10.1186/s12916-014-0207-1.
3. Onuoha FM, Ebirim CC, Ajonuma BC, Alabi NT, Eseigbe P, Okezue OS. Correlation between central obesity and blood pressure in an adult Nigerian population. *J Insul Resist*. 2016;1(1):5. http://dx.doi.org/10.4102/jir.v1i1.16.
4. Goon D, Libalela M, Amusa L, Muluvhu T. Screening for total and abdominal obesity among University of Venda students. *African J Phys Act Heal Sci*. 2013;19(4):1014–24. Available from: https://www.ajol.info/index.php/ajpherd/article/view/98416
5. Ashwell M, Gibson S. Waist-to-height ratio as an indicator of "early health risk": simpler and more predictive than using a "matrix" based on BMI and waist circumference. *BMJ Open*. 2016;6(3). https://doi.org/10.1136/bmjopen-2015-010159.
6. Thaikruea L, Thammasarot J. Prevalence of normal weight central obesity among Thai healthcare providers and their association with CVD risk: a cross-sectional study. *Sci Rep*. 2016 Nov 16;6. Available from: https://pubmed.ncbi.nlm.nih.gov/27848990/.
7. Owolabi EO, Ter Goon D, Adeniyi OV. Central obesity and normal-weight central obesity among adults attending healthcare facilities in Buffalo City Metropolitan Municipality, South Africa: a cross-sectional study. *J Health Popul Nutr*. 2017;36(1). https://doi.org/10.1186%2Fs41043-017-0133-x.
8. American College of Cardiology. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71(19):e127248. Available from: https://www.acc.org/latest-in-cardiology/articles/2017/11/08/11/47/mon-5pm-bp-guideline-aha-2017.
9. Center for Disease Control and Prevention. *Body Mass Index (BMI)*. 2022. Available from: https://www.cdc.gov/healthyweight/assessing/bmi/index.html
10. Lin YA, Chen YJ, Tsao YC, Yeh WC, Li WC, Tzeng IS, *et al*. Relationship between obesity indices and hypertension among middle-aged and elderly populations in Taiwan: a community-based, cross-sectional study. *BMJ Open*. 2019;9(10). http://dx.doi.org/10.1136/bmjopen-2019-031660.
11. Sun JY, Hua Y, Zou HYY, Qu Q, Yuan Y, Sun GZ, *et al*. Association Between Waist Circumference and the Prevalence of (Pre) Hypertension Among 27,894 US Adults. *Front Cardiovasc Med*. 2021;8:717257. https://doi.org/10.3389%2Ffcvm.2021.717257.
12. Putri MS, Supratman S. Gambaran Kualitas Hidup Pada Aspek Hubungan Sosial Penderita Hipertensi Di Wilayah Puskesmas Pajang Surakarta. *Jurnal Berita Ilmu Keperawatan*. 2021;14(2):

65–72. https://doi.org/10.23917/bik.v14i2.10441.
13. Kvamme JM, Holmen J, Wilsgaard T, Florholmen J, Midthjell K, Jacobsen BK. Body mass index and mortality in elderly men and women: the Tromsø and HUNT studies. *J Epidemiol Community Health*. 2012; 66:611e617. http://dx.doi.org/10.1136/jech.2010.123232.
14. Ortega FB, Lavie CJ, Blair SN. Obesity and Cardiovascular Disease. *Circ Res*. 2016;118(11):175–270. https://doi.org/10.1161/circresaha.115.306883.
15. St-Onge M-P, Gallagher D. Body composition changes with aging: the cause or result of alterations in metabolic rate and macronutrient oxidation? *Nutrition*. 2010;26(2):152–155.
16. Noppa H, Andersson M, Bengtsson C, Bruce A, Isaksson B. Longitudinal studies of anthropometric data and body composition: the population study of women in Göteborg. *Sweden Am J Clin Nutr*. 2019; 33(1):1–6.
17. Javed AA, Aljied R, Allison DJ, Anderson LN, Ma J, Raina P (2020). Body mass index and all-cause mortality in older adults: A scoping review of observational studies. *Obesity Reviews*. 2020;1–12.
18. Di Angelantonio E, Bhupathiraju SN, Wormser D, Gao P, Kaptoge S, de Gonzalez AB, *et al*. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet (London, England)*. 2016;388(10046):776–86. https://doi.org/10.1016/s0140-6736(16)30175-1.
19. Bhaskaran K, dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK. *Lancet Diabetes Endocrinol*. 2018;6(12):944–53. https://doi.org/10.1016/s2213-8587(18)30288-2.
20. Beaufrère B, Morio B. Fat and protein redistribution with aging: metabolic considerations. *Eur J Clin Nutr*. 2000;54 (July 2000):S48–S53. https://doi.org/10.1038/sj.ejcn.1601025.
21. Mathus-Vliegen EMH. Obesity and the elderly. *J Clin Gastroenterol*. 2012;46(7):53344. https://doi.org/10.1097/mcg.0b013e31825692ce.
22. Cetin DC, Nasr G. Obesity in the elderly: More complicated than you think. *Cleve Clin J Med*. 2014;81(1):51–61. https://doi.org/10.3949/ccjm.81a.12165.
23. Setters B, Holmes HM. Hypertension in the Older Adult. *Prim Care*. 2017;44(3):529. https://doi.org/10.1016/j.pop.2017.05.002.
24. Chau YY, Bandiera R, Serrels A, Martínez-Estrada OM, Qing W, Lee M, *et al*. Visceral and subcutaneous fat have different origins and evidence supports a mesothelial source Europe PMC Funders Group. *Nat Cell Biol*. 2014;16(4):367–75. https://doi.org/10.1038%2Fncb2922.
25. Neeland IJ, Poirier P, Després JP. The Cardiovascular and Metabolic Heterogeneity of Obesity: Clinical Challenges and Implications for Management. *Circulation*. 2018;137(13):1391. https://doi.org/10.1161/circulationaha.117.029617.
26. Wahyuni Y, Kholifah U, Jus'at I (2019). Macronutrient intake, vitamin c, purine intake, body mass index and uric acid levels in man (aged 26–45 years old) in rw 05 Sub-District Bukit Duri Jakarta. *Jurnal Kesehatan*. 12(2): 73–80. https://doi.org/10.23917/jk.v12i2.9763.
27. Fezeu L, Balkau B, Kengne AP, Sobngwi E, Mbanya JC. Metabolic syndrome in a sub-Saharan African setting: central obesity may be the key determinant. *Atherosclerosis*. 2007;193(1):70. https://doi.org/10.1016/j.atherosclerosis.2006.08.037.
28. De Lorenzo A, Bianchi A, Maroni P, Iannarelli A, Di Daniele N, Iacopino L, *et al*. Adiposity rather than BMI determines metabolic risk. *Int J Cardiol*. 2013;166(1):111–7. https://doi.org/10.1016/j.ijcard.2011.10.006.
29. Olinto M, Nacul L, Gigante D, Costa J, Menezes A, Macedo S. Waist circumference as a determinant of hypertension and diabetes in Brazilian women: a population-based study. *Public Health Nutr*. 2004;7(5):629–35. https://doi.org/10.1079/phn2003582.
30. Cai L, Liu A, Zhang Y, Wang P. Waist-to-height ratio and cardiovascular risk factors among Chinese adults in Beijing. *PLoS One*. 2013; 8: e69298.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 270–276

OPEN ACCESS

Original Article

Breast Cancer Metastases Based on Molecular Subtypes at RSUD Dr. H. Abdul Moeloek Lampung

Nurmayeni[1], Nurul Islamy[2], Agustyas Tjiptaningrum[3], Bintang Abadi Siregar[4], Aditya Kusumaningtyas[4], Indri Windarti[5]

[1]Medical Education, Faculty of Medicine, University of Lampung, Bandar Lampung, Indonesia
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, University of Lampung, Bandar Lampung, Indonesia
[3]Clinical Pathology Department, Faculty of Medicine, University of Lampung, Bandar Lampung, Indonesia
[4]Department of Surgery, Faculty of Medicine, University of Lampung/ RSUD Dr. H. Abdul Moeloek Bandar Lampung, Indonesia
[5]Department of Anatomical Pathology, Faculty of Medicine, University of Lampung, Bandar Lampung, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.904

Accepted: January 06th, 2023
Approved: August 08th, 2023

Author Affiliation:
Medical Education Study Program,
Faculty of Medicine, University of Lampung,
Bandar Lampung,
Indonesia

Author Correspondence:
Indri Windarti
Prof. Dr. Ir. Soemantri Brojonegoro Street No. 1,
Gedong Meneng, Bandar Lampung,
Lampung 35141, Indonesia

E-mail:
indriwindarti08@gmail.com

Abstract

Background : Breast cancer is the most common cancer in Indonesia and is a leading cause of cancer-related deaths in the country. Metastases are responsible for most deaths among breast cancer patients. Breast cancer is typically classified into four subtypes based on immunohistochemistry: luminal A, luminal B, HER2+, and TNBC. The objectives of this study was to determine the association between the metastatic pattern of breast cancer and their molecular subtypes at RSUD Dr. H. Abdul Moeloek Lampung.
Methods : This study was an observational analytic study with a cross-sectional design. The sample comprised 81 individuals who had suffered from breast cancer and were recorded in the medical records section of RSUD Dr. H. Abdul Moeloek Lampung between 2013–2021 and met the inclusion and exclusion criteria. The association between breast cancer subtypes and the incidence and metastase sites were tested using the Chi-Square test.
Results : This study found a significant association between breast cancer subtypes and the incidence of metastases ($p < 0.05$). The TNBC subtype had a more frequent rate of metastases (34.5%) than the other subtypes (31% luminal B, 20.7% luminal A, and HER2+ 13.8%). The study also revealed a relationship between ER status and the incidence of metastases ($p < 0.05$). The luminal A subtype tends to metastasize to the liver, luminal B tends to metastasize to the bone, HER2+ tends to metastasize to the lung and liver, and TNBC tends to metastasize to the lung. However, no significant association was found between breast cancer subtypes and metastatic sites.
Conclusion : There was a significant association between breast cancer subtypes and the incidence of metastases, but not with the metastatic sites.

Keywords : breast cancer; molecular subtypes; metastases

INTRODUCTION

According to the World Health Organization (WHO) data in 2019, cancer was ranked as the top cause of death before age 70 in 112 countries, and 23 other countries ranked third or fourth. Based on data from GLOBOCAN in 2020, breast cancer is the most common cancer in women worldwide. In addition, breast cancer is also the major cause of cancer deaths worldwide, with a total of 685.000 deaths or 29% of total breast cancer cases.[1]

In Indonesia, breast cancer is ranked first with the most cancer cases and has become the leading cause of cancer death. Aligned with the data, data from the Dharmais Cancer Hospital in 2018 also mentions that breast cancer is cancer with the highest incidence rate among other types of cancer.[2] The number of new cases of breast cancer is estimated at 68.585 cases (16.6%) of the total 396.914 new cases of cancer in Indonesia. The number of deaths due to breast cancer is estimated to reach more than 22 thousand people or 32% of total breast cancer cases.[3]

Death in breast cancer patients is mainly caused by metastasis. Patients diagnosed with breast cancer have a 30% metastasis rate of all cancer patients.[4] Patients with metastatic breast cancer have a survival rate of 27%, much lower than patients with localized breast cancer.[5] The process of metastasis in breast cancer patients is related to the high heterogeneity of breast cancer.

Breast cancer is grouped into four subtypes based on the immunohistochemistry test (IHC) of the hormone receptors, namely estrogen receptor (ER) and progesterone receptor (PR), as well as the protein, namely human epidermal growth factor receptor-2 (HER2).[6] The four subtypes are Luminal A (ER positive, PR positive, HER2 negative and Ki-67<20%), Luminal B (ER positive and PR positive, HER2 positive or negative, and Ki-67 >20%), HER2+ (ER negative, PR negative, and HER2 positive), and Triple Negative Breast Cancer (TNBC) (ER negative, PR negative, and HER2 negative).[7]

Hormone receptor (HR) status is closely related to breast cancer treatment and prognosis. Patients with positive HR are known to be more responsive to hormone therapy and have a better prognosis than patients with negative HR. However, breast cancer is a disease with high heterogeneity at the molecular level from its various subtypes. This heterogeneity can certainly influence the response to therapy given and the prognosis. Heterogeneity in breast cancer includes differences in metastatic sites, number of metastases, and differences in prognosis between patients with primary breast cancer and metastases from different subtypes.[8]

Several previous studies have explored the relationship between molecular subtypes of breast cancer and metastatic patterns in breast cancer patients but with varied results. A study conducted in Indonesia found that the breast cancer subtype was closely related to the incidence of metastasis but not to the location of the metastasis.[9] Several studies conducted in other countries found the opposite result, the subtype of breast cancer had a close relationship with the location of the metastasis.[10–12] Other studies even found a close relationship between breast cancer subtypes and patient survival.[13] The differences in results in these various studies encourage the need to continue to explore the relationship between breast cancer subtypes and metastasis patterns, especially in local populations in Indonesia, considering its importance in the treatment plan and prognosis of breast cancer. Unfortunately, until now, there is no research data regarding the relationship between breast cancer subtypes and metastasis patterns in Lampung. Therefore, it is necessary to conduct research on the pattern of breast cancer metastasis based on molecular subtypes at RSUD Dr. H. Abdul Moeloek Lampung.

RESEARCH METHODS

This research is an observational analytical study with a cross-sectional design. The research was carried out in the medical records section of RSUD Dr. H. Abdul Moeloek Lampung Province during October–December 2022. The target population in this study is all breast cancer cases that have been recorded and have been diagnosed clinically, pathologically, and with other supporting examinations from January 1st, 2013 – December 31th 2021 and have complete medical record data, have been followed up and allowing the data to be used for this research. The sample used is the entire population that meets the inclusion and exclusion criteria. The inclusion criteria used are patients diagnosed with breast cancer who have conducted immunohistochemistry tests (IHC) for breast cancer (ER, PR, HER2, and Ki-67) and those experiencing metastases and non-metastases. The exclusion criteria are patients with incomplete IHC test results and HER2 results showing 2+ or borderline results. Sampling methods used a consecutive sampling technique, where the entire population that met the inclusion and exclusion criteria within that period was used as the sample for this study. The total sample that met the inclusion and exclusion criteria was 81 breast cancer patients. This number meets the minimum sample size based on the sample size formula for unpaired categorical analytical research, 81 samples. This research has passed ethical review from the Health Research Ethics Committee, Faculty of Medicine, University of Lampung, with No. 4183/UN26.18/PP.05.02.00/2022.

The data collected consists of demographic data and pathological characteristics such as grade, type of cancer, subtype, metastasis status, and results of ER, PR, HER2, and Ki-67 examinations of samples recorded in the medical record. The data that has been obtained is then cleared from duplicate and incomplete data. The

relationship between sample characteristics and the incidence of metastasis and the relationship between breast cancer subtype and the incidence and location of metastasis was tested using the Chi-Square test with a significance level of 95%.

RESEARCH RESULTS

Sample Characteristics

During the study period, the target population was 186 breast cancer patients. One hundred five patients did not meet the inclusion and exclusion criteria, such as patients conducting the IHC test, incomplete IHC data, and borderline HER2 results, leaving only 81 patients who met the inclusion and exclusion criteria.

The results of this study indicate that breast cancer is more commonly diagnosed in patients aged ≥50 years. When first diagnosed, most breast cancer patients are at high grade (III). 14 Invasive ductal carcinoma and luminal B subtype are the most common breast cancers. Metastases were found in 35.8% of samples, and the lung was the most common location for metastases (Table 1).

TABLE 1
Characteristics of breast cancer patients

Characteristics		Frequency	%
Age	<50 years	37	45.7
	≥50 years	44	54.3
Grades	Low (I–II)	18	22.2
	High (III)	63	77.8
Type	*Invasive ductal carcinoma*	73	90.1
	Invasive lobular carcinoma	3	3.7
	Mixed invasive carcinoma	5	6.2
Subtype	Luminal A	17	21
	Luminal B	41	50.6
	HER2-enriched	9	11.1
	TNBC	14	17.3
Metastatic Status	Metastasis	29	35.8
	Non Metastatic	52	64.2
Metastasis Location	Brain	1	3.4
	Lungs	11	37.9
	Heart	9	31
	Bone	7	24.1
	Other	1	3.4
Estrogen Receptor (ER) Status	Negative	27	33.3
	Positive	54	66.7
Progesterone Receptor (PR) Status	Negative	32	39.5
	Positive	49	60.5
HER2 status	Positive	34	42
	Negative	47	58
Ki-67 Status	>20%	64	79.1
	<20%	17	20.9

TABLE 2
Relationship between patient characteristics and the incidence of metastasis

Characteristics		Metastasis		Non Metastatic		*p*
		n	%	n	%	
Age	<50 years	12	41.4	25	48.1	0.56
	≥50 years	17	58.6	27	51.9	
Grades	Low (I–II)	9	31	9	17.3	0.15
	High (III)	20	69	43	82.7	
Type	*Invasive ductal carcinoma*	26	89.7	47	90.4	0.18
	Invasive lobular carcinoma	2	6.9	1	1.9	
	Mixed invasive carcinoma	1	3.4	4	7.7	
Estrogen Receptor (ER) Status	Negative	14	48.3	13	25	0.03
	Positive	15	51.7	39	75	
Progesterone Receptor (PR) Status	Negative	15	51.7	17	32.7	0.93
	Positive	14	48.3	35	67.3	
HER2 status	Positive	8	27.6	26	50	0.05
	Negative	21	72.4	26	50	
Ki-67 Status	< 20%	6	20.7	11	21.2	0.96
	> 20%	23	79.3	41	64.2	

TABLE 3
Relationship between breast cancer subtypes and the incidence of metastasis

Subtype	Metastasis		Non-metastatic		*p*
	n	%	n	%	
TNBC	10	34.5	4	7.7	0.01
Luminal B	9	31	32	61.5	
Luminal A	6	20.7	11	21.2	
HER2+	4	13.8	5	9.6	

TABLE 4
Relationship between breast cancer subtype and metastatic location

Subtype	Metastasis Location					*p*
	Brain	Lungs	Liver	Bone	Other	
Luminal A	0	2	4	0	0	0.39
Luminal B	0	3	2	4	0	
HER2+	0	2	2	0	0	
TNBC	1	4	1	3	1	

TABLE 5
Time to breast cancer metastasis

Subtype	Metastasis (Year 2)						
	1	2	3	4	5	6	7
Luminal A	2	0	1	0	1	1	1
Luminal B	2	1	5	0	0	0	1
HER2+	1	2	0	0	0	1	0
TNBC	4	1	4	0	1	0	0

Relationship between patient characteristics and metastatic events

In this study, a significant relationship was found between ER status and the incidence of metastasis ($p<0.05$). However, other characteristics, such as age, grade, type of cancer, PR status, HER2, and Ki-67, were not significantly related to the incidence of metastasis ($p>0.05$) (Table 2).

Relationship between Breast Cancer Subtypes and Metastatic Incidence

In this study, breast cancer with the TNBC subtype had the highest rate of metastasis, and the lowest was the HER2+ subtype. The results of the Chi-Square test showed a significant relationship between the breast cancer subtype and the incidence of metastasis ($p<0.05$) (Table 3).

Relationship between Breast Cancer Subtypes and Metastasis Locations

The results of this study show that the lung organ is the most frequent location of metastasis in TNBC subtype breast cancer. The luminal A subtype has the most metastases in the liver, while the luminal B subtype has the most bone metastases. HER2+ subtype breast cancer is found to metastasize to the lungs and liver with the same frequency. The Chi-Square test results did not show a significant relationship between breast cancer subtype and metastasis location (Table 4).

Time of Breast Cancer Metastases

The time of breast cancer metastases is calculated from the initial diagnosis until the time metastases occur, identified through the results of radiological examinations (chest x-ray, ultrasound, and CT scan). Breast cancer with the TNBC subtype experienced more metastases in the first year than other subtypes (Table 5).

DISCUSSION

Breast cancer is a very heterogeneous type of cancer. Based on the type of hormone receptor, this cancer is classified into four subtypes: luminal A, luminal B, HER2+, and TNBC. This study discovered that the breast cancer subtype had a significant relationship with the incidence of metastasis (Table 3). This finding aligns with several previous studies, which also found a significant relationship between breast cancer subtypes and metastasis.[15,16] This can be caused by the high heterogeneity of breast cancer, where each subtype has a different type of gene and, of course, will express different proteins. These gene and protein expression differences will influence each subtype's metastasis patterns.[15]

In this study, TNBC was the subtype that experienced the most metastases, followed by luminal B, luminal A, and HER2+ subtypes. These results align with previous studies' results, which also found that TNBC is the subtype with the highest frequency of metastasis and distant metastasis compared to other subtypes.[9,17,18] Several factors cause patients with the TNBC subtype to have a higher metastasis rate than other subtypes. First, TNBC does not have a specific therapeutic target, so TNBC is more challenging to treat.[19] This condition will certainly increase the potential for TNBC to metastasize. Second, TNBC is known to have a higher proliferation rate than other subtypes.[20] High cell proliferation will increase the opportunity for tumor cells to leave their initial location and spread to other organs via the bloodstream and lymphatic system. Third, TNBC has a unique microenvironment that is different from other subtypes. The microenvironmental conditions in TNBC allow interaction with various cells around it, thus enabling it to trick the immune system and spread cancer cells to other organs.[21]

The most common metastatic location for breast cancer is the lung, liver, bone, and brain. Another location is the contralateral breast. These results align with the results of other research conducted at RSUP Dr. Sardjito for the 2013–2018 period, who found that the lung was the most common location for breast cancer metastases, namely 12.7%, followed by bone (12.3%), pleura (8.8%), liver (5.5%), and brain (1.9%).[18]

This study found no significant relationship

between breast cancer subtype and metastatic location (Table 4). These findings align with previous research at RSUP Dr. M. Djamil Padang, who also did not find a significant relationship between breast cancer subtype and metastasis location.[9] However, several other studies reported different results, which showed that breast cancer subtype had a significant relationship with metastasis location.[10–12] This difference in results can be caused by differences in the research's location. Sample characteristics such as different races and ethnicities can also influence research results. Another factor that can cause differences in research results is the limited and different number of samples in each study.[22]

This study also found a relationship between ER status and the incidence of metastasis. The metastatic group had a higher frequency of negative ER status than the non-metastatic group (48.3% vs. 25%). These results align with previous research, which found that cancer with negative ER had a higher frequency of metastasis than ER positive (26.1% vs. 25.2%).[18] The results of this study are in accordance with the theory, which states that breast cancer with hormone receptors (26.1% vs 25.2%). ER or PR) positive are often less aggressive, low stage, and have a low risk of metastasis and recurrence, so this type of tumor has a good prognosis.[14]

The results of this study also show that most breast cancers with the TNBC subtype metastasize in the first to third year after the diagnosis of breast cancer is made. In the second year, breast cancer with the HER2+ subtype has the highest frequency of metastases compared to other subtypes. Breast cancer that is slow to metastasize is the luminal A and luminal B subtypes. The results of this study are in accordance with the theory, which states that breast cancer with the TNBC subtype has the fastest onset of metastasis (<0.5 years) compared to other subtypes. The luminal subtype has a late onset of metastasis.[7]

This study is the first study to examine the relationship between molecular subtypes of breast cancer and metastasis patterns in local community populations in Lampung Province. This research has several limitations, including that the sample in this study only came from RSUD Dr. H. Abdul Moeloek Lampung, so we cannot provide a complete picture of the distribution of breast cancer subtypes and metastasis patterns in Lampung Province. Another limitation is that this study used a cross-sectional design, so the course of cancer from initial diagnosis to data collection was not observed. Apart from that, the number of samples used was still small due to the small number of breast cancer patients at RSUD Dr. H. Abdul Moeloek, who could carry out a complete IHC test.

CONCLUSION

Breast cancer subtype was significantly associated with the incidence of metastasis but not with the location of metastasis. The breast cancer subtype that most frequently metastasizes is the TNBC type, with the most common location of metastasis is the lung. Therefore, screening for metastases in breast cancer patients with the TNBC subtype, especially at the most common metastatic locations, is necessary as an early detection effort of breast cancer metastases.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal DMV, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2021;71(3):209–49. https://doi.org/10.3322/caac.21660
2. Pangribowo S. 2019. Cancer Burden in Indonesia, Indonesian Ministry of Health Data and Information Center.
3. Ministry of Health of the Republic of Indonesia. 2022. Most Common Breast Cancer in Indonesia, Ministry of Health Targets Equalization of Health Services [Internet]. Available from:https://www.kemkes.go.id/article/view/22020400002/kanker-payudara-paling-besar-di-indonesia-kemenkes-targetkan-pemerataan-jasa-kesehatan.html
4. Metavivor. 2022. Metastatic Breast Cancer StatisticsNo Title. Metastatic Breast Cancer Research, Support and Awareness [Internet]. Available forms:https://www.metavivor.org/mbc-prep/metastatic-breast-cancer-statistics
5. American Cancer Society. 2019. Breast Cancer Facts & Figures 2019–2020, Atlanta: American Cancer Society.
6. Van Uden DJP, Van Maaren MC, Strobbe LJA, Bult P, Van Der Hoeven JJ, *et al*. Metastatic behavior and overall survival according to breast cancer subtypes in stage IV inflammatory breast cancer. Breast Cancer Res. 2019;21(1):19. https://doi.org/10.1186/s13058-019-1201-5
7. Chikarmane SA, Tirumani SH, Howard SA, Jagannathan JP, Dipiro PJ. Metastatic patterns of breast cancer subtypes: What radiologists should know in the era of personalized cancer medicine. Clin Radiol. 2015;70(1):1–10. https://doi.org/10.1016/j.crad.2014.08.015
8. Yang H, Wang R, Zeng F, Zhao J, Peng S, *et al*. Impact of molecular subtypes on metastatic behavior and overall survival in patients with metastatic breast cancer: A single-center study combined with a large cohort study based on the surveillance, epidemiology and end results database. Oncology Letters. 2020;20(4):1–3. https://doi.org/10.3892/ol.2020.11948
9. Helmi AF, Khambri D, Rustam R. The Relationship of Breast Cancer Subtypes with the Event of Metastasis in. Biosecientia Medicina: Journal of Biomedicine & Translational Research. 2021;1(1):399–405. https://doi.org/10.32539/bsm.v5i4.410
10. Akrami M, Tahmasebi S, Zangouri V, Hosseini S, Talei A. Metastatic Behavior of Breast Cancer Subtypes. Multidisciplinary Cancer Investigation. 2017;1(1):102. https://doi.org/10.21859/mci-supp-102
11. Gong Y, Liu YR, Ji P, Hu X, Shao ZM. Impact of molecular subtypes on metastatic breast cancer patients: A SEER population-based study. Sci Rep. 2017;7(2):1–10. https://doi.org/10.1038/srep45411
12. Wu Q, Li J, Zhu S, Wu J, Chen C, Liu Q, *et al*. Breast cancer subtypes predict the preferential site of distant metastases: A SEER based study. Oncotarget. 2017;8(17):90–6. https://doi.org/10.18632/oncotarget.15856
13. Tagliabue G, Fabiano S, Contiero P, Barigelletti G, Castelli M, Mazzoleni G, *et al*. Molecular subtypes, metastatic pattern and

patient age in breast cancer: An analysis of Italian Network of Cancer Registries (AIRTUM) data. J Clin Med. 2021; 10(24):1–13. https://doi.org/10.3390/jcm10245873
14. Takaltar UV, Advani S. Prognostic indicators in breast cancer. Science Forecast. 2018;1(1):1–3.
15. Guo Y, Arciero CA, Jiang R, Behera M, Peng L, Li X. Different breast cancer subtypes show different metastatic patterns: A study from a large public database. Asian Pac J Cancer Prev. 2020; 21(12):3587–3593. https://doi.org/10.31557/APJCP.2020.21.12.3587.
16. Kast K, Link T, Friedrich K, Petzold A, Niedostatek A, Schoffer O, *et al*. Impact of breast cancer subtypes and patterns of metastasis on outcome. Breast Cancer Res Treat. 2015; 150(3):621–9. https://doi.org/ 10.1007/s10549-015-3341-3
17. Jamnasi J, Gondhowiardjo S, Djoerban Z, Siregar NC, Poetiray EDC, Tunggono AP. Risk factors for distant metastasis in breast cancer patients. Indonesian Radiotherapy & Oncology. 2016;7(2):55–9. https://doi.org/10.32532/jori.v7i2.46
18. Anwar S, Avanti WS, Nugroho AC, Choridah L, Dwianingsih EK, Harahap WA, *et al*. Risk factors of distant metastasis after surgery among different breast cancer subtypes: A hospital-based study in Indonesia. World Journal of Surgical Oncology. 2020;18(1):1–16. https://doi.org/10.1186/s12957-020-01893-w
19. Perales GIU, Facio SKS, Dominiguea CNS, Huerta SC, Maldonado GEM, Flores PR, *et al*. Genetic alterations of triple negative breast cancer (TNBC) in women from northeastern Mexico. Oncol Lett. 2019; 17(3):3581–3588. https://doi.org/10.3892/ol.2019.9984
20. Pillai SKK, Tay A, Nair S, Leong CO. Triple negative breast cancer is associated with EGFR, CK5/6 and c-KIT expression in Malaysian women. BMC Clinic Pathol. 2012; 12(18):1–8. https://doi.org/10.1186/1472-6890-12-18
21. Yu T, Di G. Role of tumor microenvironment in triple-negative breast cancer and its prognostic significance. Chin J Cancer Res. 2017; 29(3):237–252. https://doi.org/10.21147/j.issn.1000-9604.2017.03.10
22. Wiguna N, Manuaba I. Characteristics of immunohistochemical examination in breast cancer patients at Sanglah General Hospital for the period 2003–2012. Udayana Medika E-Journal. 2014;3(7):1–13.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 277–282

OPEN ACCESS

Original Article

Comparison of Clinical Response between Combine Chemotherapy 5 Fluorourasil - Platinum Based and Ifosfamid - Taxane - Platinum Based in Recurrent Nasopharyngeal Carcinoma

Rio Sanjaya[1], Willy Yusmawan[1], Dwi Antono[1], Dwi Marliyawati[2], Kanti Yunika[2]

[1]Departement of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, University of Diponegoro / Dr Kariadi Hospital, Semarang, Indonesia
[2]Departement of Otorhinolaryngology-Head and Neck Surgery Diponegoro National Hospital Semarang, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.926

Accepted: February 13th, 2023
Approved: August 10th, 2023

Author Affiliation:
Departement of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, University of Diponegoro / Dr. Kariadi Hospital, Semarang, Indonesia

Author Correspondence:
Rio Sanjaya
Dr. Sutomo Street No.16, Semarang, Central Java 50244,
Indonesia

E-mail:
riosanjaya24@gmail.com

Abstract

Background : Recurrence of Nasopharyngeal Carcinoma (NPC) is the emergence of a tumor remission after administration of chemoradiation based on symptoms and several examinations. The combination of chemotherapy in recurrent NPC still gives good results. The combine of regimens used is still varied and not much study has been done to assess the clinical response. The objectives of this study was to compare the clinical response between administration of combination 5 Fluorouracil-Platinum based (5-FU) and Ifosfamide-taxan-platinum based (IFO) in recurrent NPC.
Methods : This observational study used electronic medical record (ERM) data at the ENT oncology clinic at Dr. Kariadi General Hospital for the period January 2020–January 2022. The number of samples that suited to the inclusion and exclusion criteria was 44 subjects divided into two groups of 22 subjects respectively. The chi-square test was used to assess differences in alteration of clinical symptoms, tumor mass size, neck lymph node enlargement, tumours stage reduction, and the effect of confounding factors on response to therapy in both groups.
Results : The highest number of patients with recurrent NPC were aged ≥45 Years old and male (75%). WHO type 3 is the most common (95.5%) and ECOG status 1 (95.5%). There was no significant difference administration of the combination of 5-FU with IFO in alteration of clinical symptoms (p=0.500), shrink tumor size (p=0.347), reduction of neck lymph node size (p=0.164), and reduction tumor staging (p=0.347). There was no relationship from confounding factors to clinical response between the administration of the two groups.
Conclusion : Administration of 5 Fluorouracil-platinum based combination chemotherapy did not provide a better clinical response in terms of clinical symptoms, changes in primary tumor size, neck lymph node size, and decreased tumor stage compared to the Ifosfamide-taxane-platinum based combination based on recurrent NPC.

Keywords : recurrent nasopharyngeal carcinoma, 5-flourouracil, ifosfamide, response to therapy.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignancy of squamous cell on nasopharyngeal epithelium layer mucosa. The NPC belongs to the top five of frequent malignancies after cervix cancer, breast cancer, lymph node cancer, and cutaneus cancer.[1–3] NPC patients are rarely diagnosed at an early stage due to unspesific symptoms and lack of awareness from the patients about the signs and complaints. It is causes patients delay to get the treatments and presented with advance stage and is a challenge in determining the modality of therapy for the patients.[2,4,5]

Recurrency in NPC are arrising of tumors once remission-phase after administration of chemoradiation based on the symptoms and by several examinations such as nasopharyngeal endoscopy and radiological imaging.[1] There are several modalities used to treat the NPC, including radiotherapy, chemotherapy, brachytherapy, surgery, targeted therapy, and immunotherapy. Radiotherapy or chemotherapy use to first-line therapy in the early stages or locoregional diseases gives a 5-year survival rate of 85–90%, but 8–10% of patients fail into recurrency and distant metastasis.[6–8]

First-line chemotherapy of taxane and platinum-based gives good results and its can administered by adjuvant, neo-adjuvant, and concurrent.[6,8] However NPC with locoregional/distant metastases or recurrent cases combination two or more of chemotherapy regiments still an option as either curative or palliative therapy.[6] In the study, it was stated that the combination ifosfamide (IFO), 5Fluorouracyl (5FU), and Leucovorin in NPC recurrent gave an overall response rate of 44%.[7] The National Cancer Management Committee in 2015 published the guidelines for the management of Nasopharyngeal Cancer which states that 5-FU combination chemotherapy is an option in recurrent/metastatic NPC therapy.[6] Consideration of effectiveness and efficiency in the administration 5-FU and IFO is very helpful in the management of recurrent, and distant metastatic of NPC. So it is expected that patients do not drop-out of treatment caused by duration of treatment and side effects of chemotherapy drugs. Clinical response monitoring of combination 5-FU and IFO in ENT department Dr. Kariadi hospital Semarang has never been before.

Assessment of the effectiveness of NPC management determined based on re-evaluation of the symptoms, physical examination, and radiology imaging. Monitoring of clinical response assessed at least 4 weeks after complete of therapy.

In this study, the author wants to know the comparison in clinical response between 5FU-platinum based combination with Ifosfamid-platinum-based-taxane combination in recurrent NPC patients at Dr. Kariadi Hospital Semarang.

METHODS

This study is a retrospective observational study. The data was taken from medical records at Dr. Kariadi hospital for the period January 2020 until January 2022. Samples that suited the inclusion criteria and exclusion criteria were 44 subjects. The first group were patients with recurrent NPC administered by IFO combination and the next group were patients who administered by 5-FU combination for 22 samples each groups. Inclusion criteria were patients with recurrent cases who have completed previous chemotherapy with taxane and platinum-based, NPC patients with recurrent cases who have undergone external radiotherapy, histopathology type WHO 2 and WHO 3, age 18–65 years, and patient performance status ECOG 1 or ECOG 2, have a filed medical record. While the exclusion criteria were patients with severe systemic diseases (hypertension, renal failure, diabetes mellitus, and tuberculosis), patients with a history of malignancy of other organs. Patients drop-out treatment.

The variables assessed were therapeutic response from 5-FU chemotherapy and IFO including clinical symptoms, primary tumor size, size of neck lymph-nodes enlargement, and tumour stage with confounding variables include age, gender, initial tumour stage, and histopathological type.

Clinical response assessment includes improvement of clinical symptoms. Improvement if there is improvement of the complained symptoms even though only 1 symptom, there is no improvement if there is no improvement of the complained symptoms or other new symptoms appear. Changes in the size of the primary tumor, assessed the size of the tumor remision or remains/enlarged. Changes in the size of the enlarged neck lymph-node, assessed the size of the neck lymph-node remision or remains/enlarged. Decrease in tumor stage, assessed decrease in tumor stage or still remains. Confounding variables assessed include age, ≤45 years and ≥45 years. Gender, distinguished male or female. Histopathological type, assessed by WHO 2 and WHO 3. Performance status, which is assessed ECOG 1 and ECOG 2.

Data analysis using Chi-square test using SPSS software version 25.0. This research has been ethically approved by the Health Research Ethics Committee (KEPK) No. 1227/ EC/ KEPK-RSDK/ 2022 and research approval from Dr. Kariadi Hospital No: P/02.01/I.II/ 6811/2022.

RESULTS

The subjects obtained for the period January 2020–January 2022 which were used as research samples were obtained as follows (Table 1).

Patients with NPC recurrent is 68.2% of patients

TABLE 1
Characteristic of subjects

Variable		Chemotherapy		Total (%)
		Ifosfamide	5-FU	
		n	n	
Age	< 45 years old	8 (57.1)	6 (42.9)	14 (31.8)
	≥ 45 years old	14 (46.7)	16 (53.3)	30 (68.2)
Gender	Female	8 (72.7)	3 (27.3)	11 (25)
	Male	14 (42.4)	19 (57.6)	33 (75)
Histopathological Types	WHO 3	21 (50)	21 (50)	42 (95.5)
	WHO 2	1 (50)	1 (50)	2 (4.5)
Performance status	Performance status	21 (50)	21 (50)	42 (95.5)
	Negative	1 (50)	1 (50)	2 (4.5)

TABLE 2
Changes in clinical symptoms

Chemotherapy	Clinical symptoms		Total (%)	*p*
	Improve	None		
	n (%)	n (%)		
Ifosfamide	22 (50)	0 (0)	22 (50)	0.500[£]
5-FU	21 (47,7)	1 (2,3)	22 (50)	
Total	43 (97,7)	1 (2,3)	44 (100)	

Description : [£]Fisher's Exact

TABLE 3
The comparison in changes the size of the primary tumor of the nasopharynx

Chemotherapy	Nasopharyngeal Tumor		Total (%)	*p*
	Remision	Remain/Enlarged		
	n (%)	n (%)		
Ifosfamide	16 (36.4)	6 (13.6)	22 (50)	0.347[¥]
5-FU	12 (27.3)	10 (22.7)	22 (50)	
Total	28 (63.6)	16 (36.4)	44 (100)	

Description : [¥] Continuity Correction

aged ≥45 years. The youngest age was 18 years old and the oldest was 65 years old. Male patients predominance than female as much as 75%. Patients with WHO histopathological type 3 are at most 95.5% and 95.5% of patients with ECOG 1 status.

Improvement in clinical symptoms there was *Ifosphamide* chemotherapy and 5-FU chemotherapy there was no difference remarkably (p = 0.500) (Table 2).

Changes in the size of the primary tumor there was *Iphosphamide* chemotherapy and 5-FU chemotherapy no remarkably difference (p = 0.347) (Table 3).

Changes in the size of the neck lymph-nodes administration of *Ifosfhamid*e chemotherapy and 5-FU chemotherapy found no remarkably difference (p = 0.164) (Table 4).

Decreased stage there was *Iphosphamide*

TABLE 4
The Comparison in size changes neck lymph-node

Chemotherapy	Lymph-node enlargement		Total (%)	*p*
	Remision	Remain/Enlarged		
	n (%)	n (%)		
Ifosfamide	19 (43.2)	3 (6.8)	22 (50)	0.164¥
5-FU	14 (31.8)	8 (18.2)	22 (50)	
Total	33 (75)	11 (25)	44 (100)	

Description : ¥ Continuity Correction

TABLE 5
Differences in tumor stage changes

Chemotherapy	Tumor Stage		Total (%)	*p*
	Decrease	None		
	n (%)	n (%)		
Ifosfamide	16 (36.4)	6 (13.6)	22 (50)	0.347¥
5-FU	12 (27.3)	10 (22.7)	22 (50)	
Total	28 (63.6)	16 (36.4)	44 (50)	

Description : ¥ Continuity Correction

chemotherapy and 5-FU chemotherapy was found there was no remarkably difference (p = 0.347) (Table 5).

In Our study the relationship of confounding factors such as age, sex, histopathological type, and *performance* status to changes in clinical response. In statistical analysis, there was no relationship of confounding factors to changes in clinical response in patients who receiving chemotherapy (Table 6).

DISCUSSION

This study found that the IFO group there was a change in remission of primary tumor size, neck lymph-nodes size, decreased tumor stage, and improvement in clinical symptoms greater than the 5-FU group with more than 50%. Statistically there is no significant difference to the clinical response to chemotherapy IFO with 5-FU. The National Cancer Management Committee has issued guidelines for the management of nasopharyngeal cancer where the use of a combination of 5-FU and cisplatin in cases of metastasis/recurrence as a curative treatment or as a palliative treatment. This guide notes that the side effects and toxicity of chemotherapy may cause patients to discontinue treatment or discontinue treatment.[6] Previous studies, the administration of chemotherapy combination of ifosfamide, 5-fluorouracil, and leukovorin gives the value of overall response rate (ORR) reached 56% with a 1-year survival probability rate reached 51%.[9] other studies stated the administration of ifosfamid-doxorubicin combination chemotherapy gives results of 15% to achieve a complete response with ORR reaching 68%.[10,11]

Previous studies have not compared the therapeutic response between ifosfamid-taxane-platinum based with 5FU-platinum based. Several studies that explain administered chemotherapy IFO and 5-FU, both effective and give good results as chemotherapy in recurrent NPC.[6] Administration of IFO and 5-FU combination therapy in several studies was able to provide good response rate when side effects and drug toxicity can be controlled.[10,11] based on the results of this study, the selection of the type of chemotherapy ifosfamid can be a better choice by also considering the length of hospital stay and minimally side effects.

This study shows that the most age range of patients with recurrent NPC is 45 years. Previous research at Dr. Kariadi obtained the average age of NPC patients was 44 years.[4] peak incidence of NPC in the age range of 40–49 years.[2] Incidence of recurrency NPC there are not many studies that discuss it demographically, but the 5-year cumulative rate of recurrent NPC into neck regional is around 12–22%.[13] Incidence at a younger age are suspected to be related to genetic factors and exposure to carcinogenic substances from the environment

TABLE 6
The relationship of confounding factors to clinical symptoms

Variable		Chemotherapy				Total (%)
		Ifosfamide		5-FU		
		n	%	n	%	
Age	< 45 years old	8	57,1	6	42,9	0.746¥
	≥ 45 years old	14	46,7	16	53,3	
Gender	Male	14	42,4	19	57,6	0.164¥
	Female	8	72,7	3	27,3	
Nasopharyngeal tumors	Remision	16	57,1	12	42,9	0.347¥
	Remains/enlarged	6	37,5	10	62,5	
Lymph-node enlargement	Remision	19	57,6	14	42,4	0.164¥
	Remains/enlarged	3	27,3	8	72,7	
Stage changes	Remision	16	57,1	12	42,9	0.347¥
	None	6	37,5	10	62,5	
Hystopatological type	WHO 2	1	50	1	50	0.756£
	WHO 3	21	50	21	50	
ECOG	ECOG 1	21	50	21	50	0.756£
	ECOG 2	1	50	1	50	
Clinical symptoms	Improvement	22	51,2	21	48,8	0.500£
	None	0	0	1	100	

Description : ¥ Continuity Correction; £ Fisher's Exact

earlier.[14–16] As a prognostic factors, age is very influential on the survival rate and tolerance of chemoradiation treatment, so it can affect the recurrence factor of the disease.[17]

Characteristics of patients with recurrent NPC in this study 75% predominantly male This characteristic is similar to previous studies which stated that men have a higher recurrence potential than women.[13] Male tend to be more frequent distant metastases, thereby reducing survival rates due to genetic variation influenced by hormonal changes.[14] Males carried the VEGF-2578 allele gene that is associated with larger tumor size and higher tumor stage.[14,18]

This study patients with recurrent NPC with histopathological type WHO 3 more than WHO 2 and did not find histopathological type WHO 1. Previous studies found that the most histopathological types were WHO 3.[2,4,16,19] Factors that affect the NPC keratinization subtype include unhealthy lifestyles such as smoking. The research conducted by Naomi *et al* stated that there was no relationship between the degree of histopathology and the clinical stage in NPC. The study mentioned that NPC WHO 3 sub-type most often occurs recurrences due to high-incidence factors related to endemic areas.[14,20]

This study did not find the relationship of several confounding factors such as age, gender, histopathology sub-type, and performance status to the assessed clinical response. In this study the dominant age above 45 years, the dominant male with the most histopathology type is WHO 3 and ECOG performance status 1. Improvement of clinical response from chemotherapy management in patients with recurrent NPC is only affected by the type of chemotherapy were administered.

CONCLUSION

Administration of 5 fluorouracil-platinum based combination chemotherapy did not provide better clinical response of clinical symptoms, changes in primary tumor size, neck lymph-nodes size, and decreased tumor stage compared with Ifosfamid-taxane-platinum based combination on recurrent NPC. There was no association of confounding factors on clinical

response between the two groups.

Acknowledgements

The author would like to express his gratitude to all who have supported the implementation of this study and to the reviewers who also provide corrections until the publication of this study.

Conflict of Interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Nasopharyngeal Carcinoma. Int J Nasopharyngeal Carcinoma. 2020; 02(04): 2019–21.
2. Diva P, Suta D, Andi K, Saputra D, Wulan S, Sutanegara D. Profil Penderita Kanker Nasofaring di Rumah Sakit Umum Pusat Sanglah Denpasar Periode Januari – Desember Tahun 2014. E-Jurnal Med. 2019;8(2):1–14
3. Mott FE, Ferrarotto R, Nguyen T, Phan J. Nasopharyngeal carcinoma outcome with induction chemotherapy followed by concurrent chemoradiotherapy. Oral Oncol. 2018;81(April):75–80.
4. Gondhowiardjo SA, Meidania L, Senoaji F, Sekarutami SM. Nasopharyngeal Carcinoma Profile in dr. Cipto Mangunkusumo Hospital Year 2013. Radioter Onkol Indones. 2020;10(1):8–11.
5. Wei WI, Chua DT. Neoplasms of the Nasophaynx. in: Wackym A, Snow Jr JB. Ballenger's Otorhinolaryngology Head and Neck Surgery. Connecticut: People's Medical Publishing House-USA; 2016. 4395–417.
6. Komite Penanggulangan Kanker Nasional Kemenkes RI. Panduan Penatalaksanaan Kanker Nasofaring. Kementeri Kesehat Republik Indones Kom Penanggulangan Kanker Nasional. 2015;1–56.
7. Chua DTT, Kwong DLW, Sham JST, Au GKH, Choy D. A phase II study of ifosfamide, 5-fluorouracil and leucovorin in patients with recurrent nasopharyngeal carcinoma previously treated with platinum chemotherapy. Eur J Cancer. 2000;36(6):736–41.
8. Tsao SW, Tsang CM, Lo KW. Epstein-barr virus infection and nasopharyngeal carcinoma. Philos Trans R Soc B Biol Sci. 2017;372(1732).
9. Dede DS, Aksoy S, Cengiz M, Gullu I, Altundag K. Ifosfamide and doxorubicin combination chemotherapy for recurrent nasopharyngeal carcinoma patients. Asian Pacific J Cancer Prev. 2012;13(5):2225–8.
10. Siti-Azrin AH, Norsa'adah B, Naing NN. Prognostic factors of nasopharyngeal carcinoma patients in a tertiary referral hospital: a retrospective cohort study. BMC Res Notes. 2017;10(1):705.
11. Huang YC, Chang PMH, Chen MH, Chu PY, Tzeng CH, Chang SY, *et al*. A Study using ifosfamide and etoposide in patients with cisplatin-refractory recurrent or metastatic head and neck squamous cell carcinoma. Jpn J Clin Oncol. 2011;41(5):630–6.
12. Adham M, Kurniawan AN, Muhtadi AI, Roezin A, Hermani B, Gondhowiardjo S, *et al*. Nasopharyngeal carcinoma in indonesia: Epidemiology, incidence, signs, and symptoms at presentation. Chin J Cancer. 2012;31(4):185–96.
13. Airoldi M, Cortesina G, Giordano C, Pedani F, Bumma C. Ifosfamide in the treatment of head and neck cancer. Oncology. 2003;65:37–43.
14. Trimonika U, Yusmawan W, Marliyawati D. Perbandingan Respon Klinis Penderita Karsinoma Nasofaring yang Mendapat Kemoterapi Cisplatin Neoadjuvant dengan Concurrent. Diponegoro Med J (Jurnal Kedokt Diponegoro). 2018;7(2):574–85.
15. Xiao G, Y C, X Q, Wang W, Wang Y. Influence of gender and age on the survival of patients with nasopharyngeal carcinoma. BMC Cancer. 2013;13:226–34.
16. Susetiyo KA, Kusumastuti EH, Yusuf M, Falerina R. Clinicopathological profile of nasopharyngeal carcinoma in 2016–2019 at Dr . Soetomo General Hospital. 2022;52(1):7–12.
17. Li J, Lu T, Huang Y, Han F. Clinical Characteristics of Recurrent Nasopharyngeal Carcinoma in High-Incidence Area. 2012;2012.
18. Hashim D, Boffetta P. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Head and Neck Cancers. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Head and Neck Cancers. 2021.
19. Fadhlia, Ferawati, Irnawati. Management of Nasopharyngeal Cancer in Dr. Zainoel Abidin General Hospital Banda Aceh. Int J Nasopharyngeal Carcinoma. 2019;1(02):504.
20. Naomi SM, Dewi YA, Agustina H. Association between Histopathological Grading and Clinical Staging in Nasopharyngeal Carcinoma Hubungan Derajat Histopatologi dengan Stadium Klinis pada Karsinoma Nasofaring. Departemen Telinga Hidung Tenggorokan-Kepala Leher. 2018;2(2):730–7.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 283–288

OPEN ACCESS

Original Article

The Effectiveness of Skin Barrier Acrylate Terpolymer on Medical Adhesive Related to Skin Injury (MARSI) in Children at Pediatric Intensive Care Unit Dr. Cipto Mangunkusumo Hospital

Juanda Mutifa,Nani Nurhaeni, Efa Apriyanti

Nursing Master Program University of Indonesia, Depok Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.928

Accepted: May 10th, 2023
Approved: August 08th, 2023

Author Affiliation:
Nursing Master Program
University of Indonesia, Depok
Indonesia

Author Correspondence:
Juanda Mutifa
Prof. DR. Sudjono D. Pusponegoro Street,
Pondok Cina, Beji, Depok, West Java16424,
Indonesia

E-mail:
Mutifa.irwan@gmail.com

Abstract

Background : For a long time, the use of medical adhesives in invasive device installation procedures can cause medical adhesive related to skin injury (MARSI) in children; in order to minimize the risk of MARSI incidents, so that a skin barrier is needed before applying the adhesive. The purpose of this study is to determine the effectiveness of acrylate terpolymer skin barrier against medical adhesive related to skin injury (MARSI) prevention in children who are treated at the intensive care unit.
Methods : This study used a true experimental design which involved 46 children; it was divided into an intervention group of 24 respondents and a control group of 22 respondents who were treated by using medical adhesive due to the procedure for inserting an endotracheal tube and nasogastric tube. Samples were taken by using random sampling technique. The risk level of skin injury was assessed by using the Braden Q scale and the MARSI incidents were observed by using the observational format.
Results : The results showed that the acrylate terpolymer skin barrier was effective in reducing the MARSI in children who were treated at the intensive care unit with having a p-value of 0.03 (α <0.05). The use of an acrylate terpolymer skin barrier can be recommended to minimize the incidence of MARSI in children.
Conclusion : The use of acrylate terpolymer skin barrier significantly minimizes the incidence of MARSI in children.

Keywords : Skin Barrier, MARSI, Skin injury, Children

INTRODUCTION

PICU as an intensive care service which has various superior facilities and infrastructures, as well as the competent human resources in the field of intensive nursing. Firstly, PICU facilities and infrastructures are equipped by the continuous patient monitoring devices, both invasive (inserted directly into the body) and non-invasive (only attached to the body surface).[7] PICU is also equipped by life support equipment, namely a ventilator machine which is a breathing assistance machine.[15] Children care in PICU services requires the medical devices to support children life. Medical devices are placed in the PICU for various indications, ranging from prevention (eg, sequential compression), treatment or therapeutic (eg, tubing, surgical drains, nasogastric tube (NGT), oropharyngeal tube (OGT), endotracheal tube (ETT) and for diagnostic purposes) (eg sphygmomanometer, thermometer). NGT and ETT are often associated with the risk of skin injury (skin injury) as a result of the fixation technique performed.[16]

MARSI has many causes and it is related to the development of the patients disease, the knowledge, and the nursing staff experience.[14] Medical Adhesive Related Skin injury (MARSI) is a dermatological disorder in which erythema or other skin disorders are including vesicles, bullae, erosions or tears, appear and persist for 30 minutes or more after adhesive removal.[4] The repeated release may result in changes to skin barrier function and it increases the likelihood of MARSI. Skin irritation and abrasions are caused by MARSI, it can create conditions under the film for infection.[9] MARSI is known to have a significant effect on the quality of life of patients.[16] MARSI can occur in the pediatric population at intensive care units who frequently use medical adhesives.[15]

The skin barrier is a protective part between the skin and the adhesive, thereby reducing the risk of adhesive trauma.[5] The skin barrier is a very influential part of skin integrity and the outer skin barrier.[9] It is really needed and protected, so that it is not damaged and it has a functions properly. Damaging to the skin barrier, it can be triggered by internal and external factors, including medical adhesives.[2] The skin barrier is a protective layer between the epidermis and the adhesive which can reduce the risk of Medical Adhesive Related Skin Injury (MARSI), as well as protect the skin from body fluids, exudate, urine and feces.[3] Skin barriers are available in the form of acrylate terpolymers in water or organic solvents in the form of liquids and silicone barriers, and it is in the form of tissues, creams, applicators or sprays too. Liquid skin barriers are available in formats, such as foam applicators, wet wipes and sprays.[8] An alcohol-free skin barrier is highly recommended because alcohol can cause pain when it is applied to sore skin, broken skin, irritated skin, and the skin around wounds.[18] Skin damage to children will cause discomfort and affect the treatment process. Based on Consensus AWHONN (Association of Women Health, Obstetric and Neonatal Nurses) in 2007 recommended that medical adhesive choice and skin barrier application are as alternative to reduce MARSI.[16]

The high incidents of medical adhesive related skin injury (MARSI) to children who are treated at intensive care becomes a phenomenon to be studied because it is one patients safety indicators in hospital. The insidents of MARSI need to get a serious concern from the health workers to ensure the patients safety during the treatment at hospital. The aim of this study is to know the effectivity of giving skin barrier acrylate terpolymer towards the incidents of medical adhesive related skin injury (MARSI) in children who are treated at intensive room. Besides that, the researcher also want to know the relationship of respondents characteristic, the risk of *skin injury* and the *injury* and adhesive of substitution frequency against MARSI incidents.

METHODS

The design of this study was a true experimental with having a post-test control group design approach. Independent variable of this study was skin barrier acrylate terpolymer, while the dependent variable was the incidence of medical adhesive related skin injury (MARSI). The study involved 46 samples which had fulfilled for the criteria inclusion: the children with having the age of 1 month – 18 years old, installed of ETT and or NGT, treated at PICU Dr Cipto Mangunkusumo Hospital with the minimum length of stay were 3 days and it did not experience of MARSI. Then the respondents were divided into the intervention group and the control group by using a random sampling method. The total number of respondents obtained was 23 respondents from the intervention group and 23 respondents from the control group with an age range of 1 month to 18 years. The data collection technique used in this study was the anxiety level observation format of the Braden Q scale to assess the risk of skin injury which had been tested for validity and reliability by the previous researchers and an observation sheets to assess the MARSI category.[17] The data collection process was carried out on the third day of treatment by assessing the incidence of MARSI in the intervention group and the control group by a wound consultant (post-test). Data analysis was performed by using statistical tests with univariate and bivariate analysis methods. This research determines the Mann Whitney test for unpaired group data analysis because the data was not the requirements of the Chi Square test.

RESULTS

Univariate

Table 1 shows that the average of data distribution is based on the characteristics of the respondents age in the

TABLE 1
Characteristics of Respondents Age in the Intervention and Control Group

Body mass index	Average	Median (Minimum – Maximum)	IK 95%
Age			
Intervention	79.96	75.96 (4–207)	47.88–112.04
Control	47.68	49.16 (3–157)	25.89–69.48

TABLE 2
Characteristics of Respondents by Gender, Main Diagnosis, Installation Area of Acrylate Terpolymer Skin Barrier, Adhesive Replacement, Risk of Skin Injury Intervention and Control Group

Variable		Intervention group		Control Group	
		N	%	N	%
Gender	Boy	18	75	4	18.1
	Girl	6	25	18	81.9
Skin Barrier Installation Area	ETT	9	37.5	12	54.5
	NGT	15	62.5	10	45.5
Main Diagnostics	Medical diagnosis	15	62.5	18	81.9
	Surgical diagnosis	9	37.5	4	18.1
Risk of Skin Injury	No Risk	0	0	0	0
	Low Risk	13	54.2	7	30.4
	Moderate Risk	3	13	7	30.4
	High Risk	6	26.1	7	30.4
	Very High Risk	2	8.6	1	4.3
MARSI	Yes	3	12.5	9	40.9
	No	21	87.5	13	59.1

intervention group who has value of 79.9 months with an age range of 4 to 207 months, and the value of the confidence interval (CI) is 47.88–112.04. In the control group has a mean value of 47.6 months with an age range of 3 to 167 months and a CI value 25.89–69,48.

Table 2 explains that the analysis of univariate gender on intervention group is dominated by boys which are 18 people (75%) and in control group are 18 girls (81.9%). For the most installation area of skin barrier acrylate terpolimer on intervention group is on the NGT area 15 people (62.5%) and fixation area of ETT is on control group 12 people (54.5%). The main diagnosis of the most respondents is from intervention and control group which is medical diagnosis with the amount of 15 respondents (62.5%) for intervention group and 18 respondents (81.9%) for control group. The risk's characteristic of skin injury to 46 respondents in this study is dominated by respondents with having a low risk of skin injury which are 20 respondents. Those low risks of skin injury for 13 respondents (54.2%) from intervention group and 7 respondents (30.4%) from control group. On the tabel explains that the risk of skin injury: low risk and moderate risk; the moderate risk gets the same result for 7 respondents (30.4%). The distribution of MARSI category can be seen from the frequency of MARSI incidents on intervention group which is 21 respondents (87.5%) who do not experience MARSI after using skin barrier acrylate terpolymer. For control, there are 9 repsondents (40.9%) who get having MARSI while 13 respondents (59.1%) is not.

Data showed on Table 3, it can be explained that the replacement of skin barrier is assesed during 3 days of observation period after giving intervention of skin barrier acrylate terpolimer installation on intervention

TABLE 3
Variable Identification of Skin Barrier Replacement and Skin Injury Risk in the Intervention and Control Group)

Variable	N	Minimum	Maximum	Means	Median	SD
Replacement Frequency Skin Barrier (Control group)	22	3	6	4.05	4.00	0.899
Replacement Frequency Skin Barrier (Intervention Group)	24	3	6	3.83	3.00	1.007

TABLE 4
Differences in MARSI Incidence between the Control Group and the Intervention Group

Variable	Mean / Mean Ranking	Z Count	P value
The MARSI event			
Control Group	26.91	-2.168	0.030
Intervention Group	20.38		

*Mann Whitney, *Sig <0.05

TABLE 5
The Relationship between Age, Gender, Frequency of Adhesive Replacement, Risk of Skin Injury and Area of Installation of Skin Barrier Acrylate Terpolymer Against MARSI

Variable	N	Correlation Coefficient (r)	P value
Age	46	-0.207	0.167
Gender	46	0.070	0.643
Adhesive Replacement Frequency	46	0.216	0.149
Risk of skin injury	46	0.071	0.637
Installation Area Skin barrier acrylate terpolymer	46	-0.048	0.754
Main diagnosis	46	0.015	0.923

*Spearman, *Sig <0.05

group, and the installation is appropriate to hospitals standard : skin barrier hidrokoloid on control group. The replacement of skin barrier to respondents is conducted every day, with the number of adhesive replacement is obtained 3, 4, 5, and 6 times. From the analysis result is obtained the most replacement frequency of skin barrier for 3 times; in which 13 respondents (54.2%) are on intervention group. In control group is obtained the most total replacement result which is the same is 3 and 4 times with 8 respondents (34.7%).

Bivariate

Analysis bivariate using the Mann Whitney test explains that the effectiveness of giving skins barrier acrylic terpolymer to the MARSI incidents inchildren which are treated at intensive room.

Table 4 describes the results of the Mann Whitney statistical test, the MARSI incidents explained that both intervention and control group showed in first group (intervention), the average was 20.38 this value was lower than the mean of the second group (control) was 26.91. The sig value in this test is 0.030 this value is smaller than the critical limit of 0.05 there is a significant difference between the two group.

Table 5 explains that there is no significant relationship between the variables of age, gender, frequency of adhesive replacement, risk of skin injury and the area of installation of the acrylate terpolymer skin

barrier to the incidence of MARSI. In this study, it can be concluded that there were no variable characteristics of the respondents who contributed to MARSI incidents in children who are being treated at the PICU Dr. Cipto Mangunkusumo Hospital.

DISCUSSION

Characteristics of Respondents

Based on the analysis result is the average of respondents age for intervention group which is 79.96% (75.96) months and for control group is 47.68% (49.16) months. The homogenity test result of respondents age show that all research variables have a same variety, it is proven by the sig value > p value 0.05; it means that the obtained data is the same or homogenous. Some studies are related to the insident number of skin injury to children is in United States which reported approximately to 1.4%,[17] in Spain with having the same of incidents number to children from 23 hospitals are 3.31%, in which 1.79% happened at pediatric general care unit especially for children, and 9.39% happened at pediatric intensive care unit. The highest insidents number of skin injury was happened to children with having the age of 1 year (4.77%) then the age of 1–3 years (2.89%). The majority of gender of each intervention group is boy and for control group is girl.[12]

In theory, it is not found that gender influences to damage skin integrity. The study was observed by Alfiyanti (2012) stated that there was no significant relationship of gender with the insidence of pressure sores in treated children at PICU. These studies showed that the factor of gender do not influence to the damage sk integrity.[1] The study conducted by Wang *et al*, found that the significant distinction on gender, age, long hospitalization, oedema, infection, score of Braden Q, and erythema or skin injury.[19]

In this study, the main diagnosis of patients is categorized into 2 large groups: medical and surgical diagnosis. The majority of children diagnosis on each group is medical. In this study, the installation area of medical adhesive and the installation of skin barrier at once are fixation area of ETT and or NGT. For the highest of installation area of skin barrier acrylate terpolimer is on intervention group which is NGT area 15 people (62.5%) and fixation area of ETT on control group 12 people (54.5%). This study result is appropriate to the study of Kim *et al*, (2019) who had a study of MARSI at pediatric intensive care unit. The purpose of using fixation in this study are: fixation of CVC, fixation of ESD, fixation of NGT, fixation of ETT, fixation of urinary catheter, fixation of NTT, fixation of line artery, fixation of blindfold, fixation of iv peripheral, and etc. From this study, it can be obtained the main reason of using medical adhesive, which is fixation of ETT, surgical wound dressing, fixation of urinary catheter, fixation of nasal cannula. It is also reported for the common of fixation area are face area, chest area, and legs area. Another study evaluated the daily usage of medical adhesive at 2 non-intensive of inpatient care unit is medical-surgical unit and heart unit. The study result reports that the highest daily usage of Medical Adeshive is for electrode of EKG, (90.3 cases per day), dressing IV peripheral (35.6 cases per day) and surgical dressing (13.6% case per day). The conclusion of Medical Adhesive usage at pediatric intensive and non-intensive care units are quite high needed a proper skin care.[6]

The Characteristics of Respondent with MARSI Incidents

This study also analysis the connection characteristics of respondent and the variable confounders of MARSI incidents; it is derived from the bivariate test results by using the Spearman test. The analysis results states that there are no significant relationship with having the P value <0.05. It means that the age variable of gender, diagnosis main, area installation, category MARSI, frequency replacement adhesive and risk skins injuries relate to significant with MARSI incidents in children treated at PICU of Cipto Mangunkuusmo Hospital. The study results are obtained that the factor uses decontamination during CVC and early detection by nurses in assessing risk skin allergies to the use of adhesives when changing dressings can affect skin injury incident.[13] While the factors of age, gender, medical diagnosis and area installation adhesive do not give contribution on incident skins injury.

Another researches that support to this research is study to find out MARSI incidents in oncology patients which consists of 156 attached respondents of peripheral IV catheter and they are given intervention of risk assessment, risk prevention and management risk of MARSI on group intervention; it is proven effective in controlling MARSI incidents in oncology patients with peripheral IV catheters. While the characteristics of respondents are age, gender, medical diagnosis, frequency of adhesive replacement does not affect to MARSI insidents.[20]

The Effectiveness of Skin barrier Acrylate Terpolymer to MARSI Incidents

The bivariat test of this study conducted to get know the effectiveness of skin barrier acrylate terpolimer usage againts MARSI incidents by conducting the data analysis of intervention and control group with using Mann Whitney test. From the test, it is known that there is significant relationship between the use of skin barrier acrylate terpolimer to MARSI incidents in children at intensive room installed by ETT and or NGT with having the value of p Value < 0.030. The supporting reearches for this study is the study to know MARSI incidents in children who treated at PICU. This study involves to

232 patients with MARSI category such as skin tear, skin stripping, tension injury, blisters, dermatitis contact and maceration which are given an adhesive dressing treatment made from acrylate that is proven to be effective in the wound healing process.[19] Another parallel researches with the study conducted to 98 patients of ICU who installed by central venous catheter (CVC) and it is maintained by using skin barrier acrylate terpolimer to be effective to protect skin, improve skin power, maintain skin integrity, and reduce the incidents of skin tears to patients who installed of CVC at ICU with having the value (P value 0.01). In this study, the reasercher categorizes regularly in perpheral skin care to patients who installed of CVC to avoid the occurance of MARSI.

CONCLUSION

Based on study result and the discussion of the effectivity skin barrier acrylate terpolimer againts medical adhesive related skin injury (MARSI) incidents in children who treated intensive room at Dr. Cipto Mangunkusumo Hospital, so it can be concluded that there is a significant distinction to MARSI incidents between control and intervention group with the p value 0.030 means that the administration of skin barrier acrylate terpolimer is effective in avoiding MARSI incidents to children who treated at intensive room Dr. Cipto Mangunkusumo Hospital.

REFERENCES

1. Alfiyanti, D., Nurhaeni, N., & Eryando, T. Pengaruh Perawatan Kulit Berdasarkan Skor Skala Braden Q terhadap Kejadian Luka Tekan Anak di Pediatric Intensive Care Unit (PICU) RS Tugurejo dan RS Roemani Semarang. Prosiding Seminar Nasional, 1(1); 2012
2. Arisanty, I. P. Konsep Dasar Manajemen Perawatan Luka. Penerbit Buku Kedokteran. ISBN 978-979-044-387-7; 2016
3. Barton, A. Prevention of medical adhesive-related skin injury (MARSI) during vascular access. British Journal of Nursing. 2021;30(6):1–7. https://doi.org/10.12968/bjon.2021.30.Sup2.1
4. Black J. M., Cuddigan J. E., Walko M. A., *et al*. Medical Device Related Pressure Ulcers in Hospitalized Patients. Int Wound J. 2010;7: 358–365.
5. Bryant RA. Types of Skin Damage And Di-Erential Diagnosis. In: Bryant R, Nix D, eds. Acute and Chronic Wounds: Current Management Concepts. 4th ed. St Louis, MO: Elsevier Mosby. 2012: 83–107.
6. Ferreira, D. H., Teixeira, M. L. O., Branco, E. M. S. C. Nursing Care in The Prevention of Adhesive-Related Skin Injuries in Surgical Wounds. Cienc Cuid Saude. 2017;16(2). https://doi.org/ 10.4025/Cienccuidsaude.V16i2.33421.
7. Fumarola S, Allaway R, Callaghan R, Collier M, Downie F, Geraghty J, Kiernan S, Spratt F. Overlooked and Underestimated: Medical Adhesive-Related Skin Injuries. Best Practice Consensus Document on Prevention. J Wound Care 29(Suppl 3c). 2020:S1–S24.
8. George M, Pal U, Guduri V, Smith G. Use of a barrier film (3M Cavilon No Sting Barrier Film) to reduce local skin complications around peripherally inserted central catheter lines: a randomised prospective controlled study. WCET J. 2016;36(4):8–13.
9. Habiballah, L. Prevalence of Neonate Adhesive Skin Injuries in a Jordanian Intensive Care Unit. Nursing Children and Young People. 2017;29(10): 42–46. https://doi.org/ 10.7748/ncyp.2017.e966.
10. Handayani, S., Budiman, A., & Adawiah, R. The Damages of Medical Records in the Outpatient Room in Dr. R. Soeharsono Lv. III Hospital Banjarmasin. Formosa Journal of Sustainable Research. 2022;1(5): 671–680.
11. Hsu MY. Skin-related Damage Care. The New Concepts of Wound Care. 3rd ed. Taipei City, Taiwan, Republic of China: Farseeing; 2017:217–50.
12. Kim, M. J., Jang, J. M., Kim, H. K., Heo, H. J., Jeong, I. S. Medical Adhesives-Related Skin Injury in A Pediatric Intensive Care Unit: A Single-Center Observational Study. Journal of Wound, Ostomy and Continence Nursing. 2019;6(11): 491–6. https://doi.org/ 10.1097/WON.0000000000000592.
13. Kutzscher, L. Management of irritant contact dermatitis and peripherally inserted central catheters. Clinical Journal of Oncology Nursing. 2012;16(2). https://doi.org/10.1188/12.CJON.E48-E55
14. LeBlanc, K., Baranoski, S., Christensen, D., Langemo, D., Sammon, M. A., Edwards, K., ... & Regan, M. International Skin Tear Advisory Panel: a tool kit to aid in the prevention, assessment, and treatment of skin tears using a Simplified Classification System©. Advances in skin & wound care. 2019;26(10): 459–476.
15. Marcato, J. O, Santos, A. S., Oliveira, A. J. F., Costa, A. C. L., Regne, G. R. S., Trindade, R. E., Noronha, K. V. M. S., Andrade, M. V. Medical Adhesive-Related Skin Injuries in The Neonatology Department of a Teaching Hospital. British Association of Critical Care Nurses. 2021. https://doi.org/ 10.1111/Nicc.12621.
16. Mcnichol, L., Lund, C., Rosen T., Gray, M. Medical Adhesive and Patient Safety: State of The Science: Consensus Statement for The Assessment, Prevention, and Treatment of Adhesive-Related Skin Injuries. J Wound Ostomy Continience Nurs. 2013;40 (4): 365–380.
17. Noonan, C., Quigley, S., & Curley, M. A. Q. Using the Braden Q Scale to Predict Pressure Ulcer Risk in Pediatric Patients. Journal of Pediatric Nursing. 2011;26(6): 566–575. https://doi.org/10.1016/j.pedn.2010.07.006
18. Voegeli, D. Moisture-Associated Skin Damage: Aetiology, Prevention and Treatment. British Journal of Nursing. 2021;21(9). https://doi.org/10.12968/bjon.2012.21.9.517.
19. Wang, D., Xu, H., Chen, S., Lou, X., Tan, J., Xu, Y. Medical Adhesive-Related Skin Injuries and Associated Risk Factors in a Pediatric Intensive Care Unit. Advances in Ski& Wound Care. 2019;32(4): 176–182. https://doi.org/ 10.1097/01.ASW.0000553601.05196.fb.
20. Zhao, Y., Bian, L., & Yang, J. Intervention efficacy of MARSI nursing management on skin injury at peripherally inserted central catheter insertion site on oncological patients. International Wound Journal. 2022;12 :2055–2061. https://doi.org/10.1111/iwj.13805

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 289–294

OPEN ACCESS

Original Article

Correlation between Testosterone Level with HBA1C Level as Glycemic Control Marker among Type 2 Diabetes Mellitus Patient

Nina Tristina, Imas Nurhayati, Raja Iqbal Mulya Harahap, Sylvia Rachmayati

Department of Clinical Pathology,, Faculty of Medicine Universitas Padjadjaran,
Hasan Sadikin Hospital Bandung, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.941

Accepted: March 14th, 2023
Approved: August 14th, 2023

Author Affiliation:
Department of Clinical Pathology,
Faculty of Medicine Universitas Padjadjaran,
Hasan Sadikin Hospital Bandung, Indonesia

Author Correspondence:
Raja Iqbal Mulya Harahap
Pasteur Street No.38, Sukajadi, Bandung,
West Java 40161, Indonesia

E-mail:
rajanafiah@gmail.com

Abstract

Background : Type 2 Diabetes Mellitus could cause various complications due to formation of advanced glycation end products (AGEs). The AGEs could destroy many organs into cellular level, one of them is testis, then causing testosterone production deficiency, and hypogonadism. Meanwhile, the AGEs formation in vivo will depend on on mean glucose level in T2DM patient. HbA1C is one of the most common parameter used to asses glycemic control among T2DM patient. This research was conducted to find out the correlation between serum total testosterone with HbA1C level among T2DM patient
Methods : Research subject was collected from Outpatient Polyclinic of Internal Medicine Departement Hasan Sadikin Hospital. HbA1C examination was conducted with turbidimetry method, meanwhile total testosterone level was performed with ELISA method. The examination of research parameter was done at Clinical Laboratory Installation of Hasan Sadikin Bandung.
Results : During sample collection periode, 70 patients was collected and fulfilled the inclusion criteria, 18 of 70 subjects has low testosteron level with Mean (SD): 424.48 (204.82) ng/mL. Correlationntesting between the variables showed r = -0.619 , and p-value <0.001, which means strong and significant correlation between total testosterone and HbA1C among T2DM patient.
Conclusion : There was strong and significant correlation between total testosterone with HbA1C level among T2DM patients, further research could be conducted with prospective cohort method or using free testosterone examination.

Keywords : Diabetes Mellitus, Glycemic, HbA1C, Testosterone

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases which stills become a health problem in the world, including Indonesia. Data from the International Diabetes Federation (IDF) in 2021 shows that globally there are 415 million people with DM in the world. Indonesia is ranked 7th with DM sufferers reaching 10 million people. World Health Organization (WHO) predicts an increase in the number of DM patients at Indonesia in 2030 to around 21.3 million people. Based on the 2019 Basic Health Research (Riskesdas) data, proportion of the Indonesian population aged ≥15 years who were diagnosed with diabetes mellitus (DM) was 6.9 percent.[1] Based on the American Diabetes Association (ADA) and Indonesian Endocrinology Association (PERKENI) in 2021, establishment of DM diagnosis can be made based on the classic symptoms of DM, high blood glucose level, and hemoglobin A1c (HbA1c). Patients who were diagnosed with Type 2 Diabetes Mellitus (T2DM) must be managed comprehensively by controlling food intake, regular exercise, and other pharmacological interventions for the therapy. Pharmacological interventions in T2DM includes oral hypoglycemic drugs (OHO), insulin injections, or even combination of both. Regularity and adherence of T2DM patients to therapeutic management is the key to control blood glucose and preventing complications.[2,3]

Various current studies show that complications of T2DM could also cause hormonal disorders, such as testosterone deficiency in adult men with T2DM. Testosterone is the main androgen hormone in males which takes role in the formation of sexual and reproductive characteristics. This hormone also has other biological roles in the body such as increasing muscle mass, strength, and bone matrix, stimulating erythropoiesis, and supporting cognitive function and emotional stability. Testosterone deficiency can cause clinical symptoms called hypogonadism, which symptoms includes impaired sexual function and reproduction.[4] Impaired sexual function in T2DM patients was also associated with other complications of neuropathy and vasculopathy. However, it is now known that testosterone deficiency due to T2DM plays an important role in the pathogenesis of sexual dysfunction (such as erectile dysfunction) and reproduction (infertility). Therefore, testosterone deficiency in T2DM patients can lead to decreased quality of life.[4,5]

Glycated Hemoglobin (HbA1c) examination is currently used to monitor the control of blood glucose levels in the past 2–3 months and also reflects adherence of patients to the therapy. Hemoglobin-A1c (glycated hemoglobin, glycohemoglobin) is a part of hemoglobin formed as a result of a non-enzymatic glycation reaction between the N-terminal valine of the β chain of hemoglobin A (Hb-A) and glucose. This reaction is continuous and irreversible so that HbA1c can be used as a glycemic control parameter. Based on the Indonesian Endocrinologic Association consensus, results of HbA1c examination can be grouped into some categories, that is: good glycemic control (HbA1c <6.5%), moderate (HbA1c 6.5–8%), and poor (HbA1c >8%).[1,6] Regarding glucose homeostasis, testosterone plays a role in maintaining normoglycemia by increasing insulin sensitivity and glucose uptake in target cells, especially skeletal muscle, adipose and liver. Bad glycemic control, indicated by high HbA1c levels, may be related to low testosterone levels in men with T2DM. Testosterone deficiency in men with T2DM is often undiagnosed and left without treatment. This study is aimed determine the correlation between total serum testosterone levels and HbA1C as a marker of glycemic control in T2DM patients.[6,7]

METHODS

Subjects of this research were men who had been diagnosed with T2DM by clinician from Endocrinology Clinic of Internal Medicine RSUP Hasan Sadikin, met the inclusion criteria, and willing to participate in the study by signing consent. Subjects will be excluded if suffering from abnormalities in testicles, receiving steroid hormone replacement therapy or receive long-term steroid therapy. Patients who met the inclusion criteria will be asked for informed consent, interviewed according to the case report form, then obtained 2cc of blood for HbA1C examination and 2cc for total testosterone examination. Blood sampling was carried out at 07.00–10.00 AM in the morning

Examination of HbA1c levels in this study using quantitative turbidimetric inhibition immunoassay (TINIA) method. The material used is whole blood EDTA. HbA1c levels are stable for 3 days at 15-25°C, stable for 7 days at 2–8°C, stable for 6 months at (-15)-(-25)°C. In this study, the examination material would be checked every time there is a sample. Examination of total testosterone levels in this study used a competitive ELISA method with serum examination materials. The stability of the test material is 8 hours at 18–25°C, four days at 2–8°C, and can last for 6 months at -20°C. In this study, the examination material will be stored at -20°C until the required number of samples is obtained, then examined simultaneously.[8,9]

Data collected then being analyzed with Statistical Package for the Social Sciences (SPSS) version 20. Normality test was performed on HbA1c and total testosterone level The amount of subjects in this study was more than 50, so the normality test was conducted using Kolmogorov-Smirnov's test. If the normality test shows that the data is normally distributed (p>0.05), these variables will be presented in the mean and standard deviation, then statistical analysis will use Pearson correlation test. If normality test shows that the

data is not normally distributed (p≤0.05), the variable will be presented in the median and range (minimum to maximum values), then the next analysis using Spearman correlation test. The correlation will be stated in r-value. The r-value will be considered very weak if <0.2, weak if 0.2–0.4, moderate if 0.4–0.6, strong if 0.6–0.8, and very strong if >0.8. The correlation will be considered significant, if the p-value is <0.05.

RESULT AND DISCUSSION

During the research subject collecting period, 70 subjects met the inclusion criteria and willing to sign the informed consent. Overview of the characteristics of the research subjects is presented in Table 1 including age, duration of T2DM , body mass index, type of medication, adherence to controls and therapy, HbA1c levels, and total testosterone levels. The results of the normality test showed that data on total testosterone level were normally distributed so that they were presented in Table 1 in the form of mean and standard deviation, while data on HbA1c levels were not normally distributed so that they were presented in Table 1 in the form of median and range.

Total testosterone level is normally distributed, meanwhile HbA1c level is not normally distributed, so thus the correlation measurement between the variables will be performed with *Spearman's correlation test*. The result of the correlation test between HbA1C and testosteron level in confidence interval 95% will be presented in Table 3.

According to previous table, *Spearman's correlation test* showed that there was negative correlation between HbA1c with total testosterone lebel, with r-value : 0.619 and p-value <0.001. The results showed that there were strong and negative correlation that is statistically significant. The sample count in this research refers to previous research that found that the correlation of testosterone and HbA1c is with r = -0.346. If the result is compared to the previous research, r-value obtained in this research is bigger than previous one, so it means that the correlation of those variables in this research could be considered as clinically significant.

The correlation graphics of research subject in total testosterone and HbA1c level is provided in Figure 1. The gradient and dispersion of the data in this research showed negative correlation pattern, it means that there is negative and reversal correlation between total testosterone and HbA1c level, it means that higher HbA1C is correlated with lower testosteron level, and also vice versa.

Factors in obesity that plays role in causing testosterone deficiency are increased leptin and pro-inflammatory cytokines (adipokines). Leptin is a hormone produced by adipocytes. An increase in leptin and adipokines will inhibit the release of GnRH resulting in a decrease in LH secretion and eventually cause a decrease in testosterone production by Leydig cells.[10,11]

TABLE 1
Characteristic of Research Subjects (n=70)

Variable		n
Age	30–49 years old	14 (20.0)
	50–59 years old	18 (25.7)
	60–69 years old	26 (37.2)
	≥ 70 years old	12 (17.1)
Duration of Disease	≤ 5 years	45 (64.3)
	6–10 years	11 (15.7)
	> 10 years	14 (20.0)
Body weight	Underweight and normal	21 (30.0)
	Overweight and obese	49 (70.0)
Type of medication	Oral Hypoglycemic Agent	43 (61.4)
	Insulin	17 (24.3)
	Both	10 (14.3)
Compliance of Therapy	Good	41 (58.6)
	Bad	29 (41.4)

SD ; Standard deviation

TABLE 2
HbA1C and Testosteron Level among Research Subjects

Variable	n
HbA1C level (%)	Median (ranges) = 7.24 (4.77–13)
Good glycemic control	18 (25.7)
Moderate glycemic control	26 (37.2)
Poor glycemic control	12 (17.1)
Total testosterone level (ng/dL)	Mean (SD) = 424.48 (204.82)
Deficiency	18 (25.7)
Normal	52 (74.3)

TABLE 3
Correlations between HbA1C and Testosterone Level Among Research Subjects

Variables	r_s (CI 95%)	p-value
HbA1C and Testosterone level	-0.619	< 0.001*

rs = Spearman Rank Correlation; CI = confidence interval
* statistically significant (p<0,05)

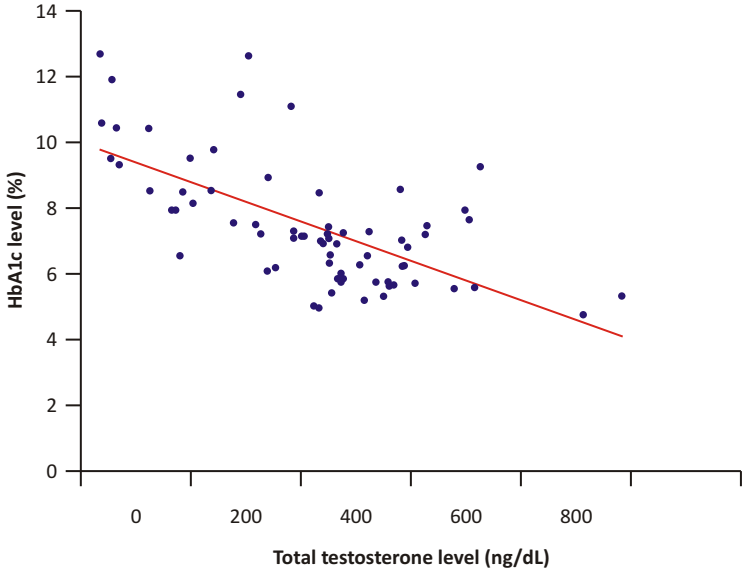


Figure 1. Correlation Graphic between Total Testosterone and HbA1C Level

There were 33.3% (6/18) of testosterone deficient subjects who had testosterone levels <100 ng/dL. All of these subjects were disobedient to control and therapy and also had poor glycemic control. Most of them had already used combination therapy, with a duration of disease varies between 5–13 years. This shows that poor glycemic control reflects non-adherence to control and therapy will make testosterone levels lower. Increasing number of adipose tissue will cause increase in the expression of aromatase which catalyzes the conversion of testosterone to estradiol. Increased estradiol creates a negative feedback on the HPT axis so that testosterone

level will decrease. Fat deposition in the abdomen can also increase testicular temperature that cause testosterone production decreases.[12–14]

Testosterone deficiency has multifactorial causes, such as genetics, age, BMI, and physical activity. Testosterone deficiency is also related to glycemic control, as in this study. Subjects 53, 63 and 66 had low testosterone levels, even though BMI was in the normal category and their age is under 40 years old. These subjects may experience testosterone deficiency due to various other factor. The known risk factors in these subjects are age >50 years and also poor glycemic control, since testosterone decline courd occur after 50 years old in male. The risk factors that were not traced to these subjects were risk of genetics, physical activity, and diet.[14–16]

Insulin receptors are also present on Leydig cells so that insulin binding with insulin receptors on Leydig cells can stimulate testosterone production by Leydig cells. The condition of hyperinsulinemia in insulin resistance can induce the expression of DAX-1, a receptor in the nucleus that will inhibit steroidogenesis in Leydig cells then cause a decrease in testosterone production. Testosterone also has an antioxidant effect that able to prevent pancreatic tissue damage. A study by Phillip (2018), showed that tests on experimental animals given streptozotocin (an alkylating agent that induces damage to the pancreas) showed that in castrated animals (testicles were taken) there was more damage to pancreatic tissue than non-castrated animals. The group that was given testosterone therapy experienced less pancreatic tissue damage compared to group that was not given testosterone therapy.[11] Testosterone plays a role in glucose homeostasis, maintaining normoglycemia by increasing insulin sensitivity and glucose uptake in its target cells, especially in skeletal muscle, adipose and liver. Thus, low testosterone levels play a role in the occurrence of hyperglycemia and were associated with poor glycemic control.[11,16]

Testosterone deficiency in T2DM patients can clinically cause a decrease and impairment in quality of life including some specific symptoms such as impaired sexual and reproductive function, alongside with other non-specific symptoms such as anemia, osteoporosis, decreased stamina, impaired cognitive function, and unstable mood. However, this disorder has not been widely diagnosed in the male population with T2DM since the testosterone level is not routinely screend, then they do not receive therapy. Thus the existence of a negative correlation between HbA1c levels and total testosterone levels in this study could be the basis for further research in Indonesia so screening for testosterone levels can be part of of the therapeutic management of T2DM patients clinically.[11]

CONCLUSION

From this research, it could be concluded that there is strong and statistically significant positive correlation between total testosterone level and HbA1C in Type 2 Diabetes Mellitus patients. Other studies with a larger sample size, which are prospective cohorts, can be conducted to better assess the power of these two variables. Another examination by assesing free testosterone fraction can also be suggested to better assess the testosterone function of the T2DM patients. Another study on focused age group also should be conducted to exclude bias from aging process that could make testosterone lower than normal.

REFERENCES

1. Perkeni. Konsensus pengelolaan dan pencegahan diabetes melitus tipe 2 di Indonesia. 2019:1–12
2. World Health Organization. Country and regional data on diabetes. 2019 From: http://www.who.int/diabetes/facts/world_figures/en/index5.html
3. Powers AC. Diabetes Mellitus. Dalam: Jameson JL, editor. Harrison's Endocrinology. Edisi ke-4. New York: McGraw-Hill Companies; 2017. hlm. 421–35
4. Xia Jw, Tan Sj, Zhang Xl, Jun T, Sun Xk, Ling W. Correlation of serum testosterone with insulin resistance in elderly male type 2 diabetes mellitus patients with osteoporosis. J Diabetes Invest 2017. 2015:1–4
5. Bhasin S, Jameson JL. Disorders of the Testes and Male Reproductive Systems. Dalam: Jameson JL, editor. Harrison's Endocrinology. Edisi ke-2. New York: McGraw-Hill Companies; 2010. hlm. 156–77
6. Maiorino MI, Bellastella G, Esposito K. Diabetes and sexual dysfunction: current perspectives. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2018;7:95–103
7. Pitteloud N, Hardin M, Dwyer AA, Valassi E, Yialamas M, Elahi D, *et al*. Increasing Insulin Resistance Is Associated with a Decrease in Leydig Cell Testosterone Secretion in Men. Clin Endocrinol Metab. 2015;90:263641
8. Roche. Turbidimetric inhibition immunoassay (TINIA) for the in vitro determination of hemoglobin A1c. 2013
9. Roche. Elecsys® Testosterone II Electrochemiluminescence immunoassay (ECLIA) for the in vitro quantitative determination of testosterone in human serum and plasma. Roche Diagnostics Ltd. 2012:1–2
10. Beatrice AM, Dutta D, Kumar M, Shivaprasad KS, Sinha A, Ray S. Testosterone levels and type 2 diabetes in men: current knowledge and clinical implications. Diabetes Metabolic Syndrome and Obesity: Targets and Therapy. 2017;7:481–6
11. Phillips KP, Tanphaichitr N. Mechanisms of obesity-induced male infertility Expert Review of Endocrinology & Metabolism. 2018;5(2):229–51
12. Mammi C, Calanchini M, Antelmi A, Cinti F, Rosano GMC, Lenzi A, *et al*. Androgens and Adipose Tissue inMales: A Complex and Reciprocal Interplay. Int J Endocrinol. 2017:1–8
13. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am J Clin Nutr. 2015;81:555–63
14. Anupam, B., Shivaprasad, C., Sridevi, A. *et al*. Association of total and calculated free testosterone with androgen deficiency symptoms in patients with type 2 diabetes. Int J Impot Res 32,

289–296 (2020). https://doi.org/10.1038/s41443-019-0144-9
15. Saghier EOAE, Shebl SE, Fawzy OA, Eltayeb IM, Bekhet LMA, Gharib A. Androgen Deficiency and Erectile Dysfunction in Patients with Type 2 Diabetes. Clin Med Insight: Endocrinol Diab. 2019;8:55–62
16. Grossmann M, Thomas MC, Panagiotopoulos S, Sharpe K, MacIsaac RJ, Clarke S, *et al*. Low Testosterone Levels Are Common and Associated with Insulin Resistance in Men with Diabetes. J Clin Endocrinol Metab. 2018;93(5):1834–40

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 295–301

OPEN ACCESS

Original Article

Effect of Kinesio Taping on Muscle Spasticity in Post-Stroke Patients Receiving Infrared Therapy and Stretching Exercise : A Quasi-Experimental Study

Andirezeki Riswanti[1], Robby Tjandra Kartadinata[1], Hari Peni Julianti[1], Hindun Zuhdiana[2], Lilik Sigit Wibisono[3]

[1]Physical Medicine and Rehabilitation Faculty of Medicine Diponegoro University / Kariadi Hospital Semarang, Indonesia
[2]Physical Medicine and Rehabilitation Faculty of Medicine Diponegoro University / KRMT Wongsonegoro Hospital Semarang, Indonesia
[3]Physiotherapist / KRMT Wongsonegoro Hospital Semarang, Indonesia

Abstract

Background : Spasticity is one of the symptoms of a stroke. One of the muscles with increased tone is the plantar flexor (66%). Spasticity is commonly treated with infrared therapy and stretching exercises. Kinesio Taping is a skin-based therapeutic procedure that uses elastic tape and can be used with infrared therapy and stretching exercises. Kinesio Taping is predicted to reduce spasticity in the plantar flexor muscle as determined by the Tardieu scale, improving functional walking. The objectives of this study was to demonstrate the efficacy of adding Kinesio Taping on lower extremity muscular spasticity in post-stroke patients who had previously received infrared and stretching exercises.
Methods : This study is a controlled group design with a quasi experimental pre and post test. Post-stroke patients were divided into two groups: the control group (16 patients) and the treatment group (16 patients) who received the addition of Kinesio Taping. Before and after 6 weeks of treatment, the Tardieu scale was measured.
Results : Before and after treatment, there was a significant difference in Tardieu scale (both on quality and angle of resistance) in each group ($p < 0.05$), and there was a significant difference in Tardieu scale in the two groups ($p < 0.05$).
Conclusion : Kinesio Taping has been demonstrated to significantly reduce plantar flexor muscle spasticity in stroke survivors.

Keywords : post-stroke, spasticity, stretching, Kinesio Taping

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.952

Accepted: April 18th, 2023
Approved: July 04th, 2023

Author Affiliation:
Physical Medicine and Rehabilitation
Faculty of Medicine Diponegoro University
Semarang, Indonesia

Author Correspondence:
Andirezeki Riswanti
Dr. Sutomo Street 16, Semarang,
Central Java 50244, Indonesia

E-mail:
andikiki1987@gmail.com

INTRODUCTION

Stroke is the leading cause of disability worldwide and the second leading cause of death after coronary heart disease.[1] Damage to the higher motor neurons occurs in stroke, resulting in symptoms such as spasticity, clonus, hyper reflexes from deep tendon reflexes, muscle weakness, functional difficulties in walking and daily activities. Spasticity, a component of upper motor neuron syndrome, is caused by a lesion in the descending motor pathway caused by a pathological condition such as stroke or brain injury and is defined as a velocity-dependent increase in muscle tone with increased tendon reflexes.[2] According to reports, the prevalence of post-stroke spasticity ranges from 30% to 80%, with disability rates ranging from 2% to 13%.[3] This is caused by limb muscle weakness and poor coordination between the agonist and antagonist muscles.[4] Spasticity is more prevalent in the lower leg extensor muscles (knee and ankle) and upper limb flexor muscles (fingers, wrist, and elbow). Spasticity most frequently occurred at the elbows (79%), wrists (66%), ankles (66%), and shoulders (58%) according to Wissel *et al*.[3] Increased tone, particularly in the plantar flexor muscle, can lead to spastic equinus, which is the primary cause of walking problems caused by decreased ankle dorsiflexion during stance and circumduction during swing.[5]

Heating and stretching are prominent therapy strategies utilized in spasticity management since they are simple to execute and generally inexpensive. Infrared heating is the most commonly utilized and virtually always available in medical rehabilitation services. However, because infrared heating has a short duration, it must be paired with stretching exercises to achieve the best benefits in reducing spasticity.[6] Stretching is currently used to treat spasticity.[7] Dr. Kenzo Kase developed Kinesio Taping, a form of skin therapy that uses an elastic tape, in Japan. Studies have shown that it is effective at providing afferent stimulation in weaker muscles, causing contractions with increased motor unit recruitment, and inducing neuroplasticity. Kinesio Taping has recently emerged as a treatment option for hemiplegic stroke patients. Kinesio taping can help enhance limb function in daily activities. According to Jaraczewska in the journal Yu Chi Huang *et al*, Kinesio Taping when used with other interventions can improve muscle function, joint support, and minimize post-stroke discomfort. According to Yu Chi Huang *et al*. (2019), the inclusion of Kinesio Taping can reduce spasticity and improve hand function.[4] Kinesio Taping, according to Cavalcante J *et al* (2018), is beneficial for relieving spasticity in post-stroke patients.[8] According to the findings of Koseoglu *et al*. (2017), the use of Kinesio Taping on the tibialis anterior muscle may enhance the recovery of lower extremity motor function and can be utilized as an ankle training method for stroke patients.[9] According to a study conducted in Indonesia (at Kandou Hospital/Manado) by Gloria *et al* (2020), Kinesio Taping on the anterior tibialis muscle can be used as a supplement to walking exercise. Walking mobility function improves in post-stroke subjects following 30 minutes of Kinesio Taping's application on the paretic anterior tibialis muscle.[10] Kinesio Taping is a simple, non-invasive, cost-effective therapy that can be used to treat post-stroke patients who have extremity muscle stiffness. The addition of Kinesio Taping to the spasticity of the ankle plantar flexor muscles in post-stroke patients has never been studied before, according to the researchers. As a result, researchers aim to see how adding Kinesio Taping to basic infrared therapy and stretching exercises affects lower extremity muscle spasticity in post-stroke patients, specifically the ankle plantar flexor muscles.

METHODS

The study design was a quasi experimental pre and post test controlled group design in stroke patients at K.R.M.T. Wongsonegoro Hospital Semarang. The study was approved by the Ethics Commission of the Faculty of Medicine, Diponegoro University Semarang, Number 48/EC/KEPK/FK-UNDIP/XII/2022, as well as the Ethics Commission of K.R.M.T Wongsonegoro Hospital Semarang, Number B/3280/070/IV/2022. The research was carried out between April 4 and August 19, 2022. The approach used to collect subjects was consecutive sampling.

The study's inclusion criteria included post-stroke patients with first attack hemiparesis, stroke duration > 6 months – 12 months, 50 to 60 years old, able to stand and walk on their own with or without assistance, no cognitive impairment (MoCA-Ina, score > 26), spasticity in the plantar flexor muscles based on the Tardieu scale has a quality degree of 1–3, and muscle strength (MMT) of the ankle dorso flexor 3–4.

Uncontrolled hypertension (blood pressure >180/110 mmHg), contractures in the ankle joint, pain when walking with a VAS > 3, abnormalities in the lower limbs such as a history of fracture or history of bone surgery in the lower leg, an open wound or non-specific skin disease in the Kinesio Taping installation area, hypersensitivity to Kinesio Taping materials, no history of diabetes mellitus, had medical rehabilitation therapies (thermal modality, stretching exercises) on the lower limbs less than 3 days before the trial, taking medications antispasticity during the past 2 weeks, received botulinum injections and surgical intervention for management of lower extremities spasticity were all exclusion criteria. While the criteria for dropping out included not finishing the study, not participating in stretching exercises >4 times, and not attending the research's introductory and final assessments, and Kinesio Taping was not installed for more than two days

over the study's duration.

The individuals were allocated into two groups after giving their informed consent, and each group's lower extremity spasticity was measured using the tardieu scale (degree of quality of resistance and angle of resistance). Stretching exercises, infrared therapy, and Kinesio Taping interventions were offered to the treatment group. The Kinesio Taping utilized is BSN Medical Kinesio Tape with a width of 5 cm. An allergy test is performed prior to installing Kinesio Taping by placing a piece of Kinesio Taping (±1 cm) on the skin for 24 hours.

Installation with facilitation technique on the tibialis anterior muscle with a 50% of available tension followed by Kinesio Taping inhibition technique on the gastrocnemius muscle with a 25% of available tension (according to the research protocol), provided Kinesio Taping is applied for 4 days then removed for 24 hours before re-application. Kinesio Taping was applied for 6 weeks (Kinesio Taping was applied at least 30 minutes before activity, removal was performed by the patient's family, and installation was performed by the researcher).

Both groups received infrared therapy twice a week for six weeks, with the intensity determined by the patient's tolerance. The type used an infrared that was given perpendicular to the area being treated, with a distance of 50 cm in the treatment area. Stretching exercises are also given to the lower extremities twice a week for six weeks in a row, with the severity of the stretch in the stiff area, the stretch holding time are 10–30 seconds, 2–4 repetitions, and the type is passive static flexibility. Hip, knee, and ankle stretching exercises are performed. For 6 weeks, both groups were given a home regimen of stretching exercises every day with guidebooks overseen via video calls.

Data was obtained using data collection sheets, which were then coded, tabulated, and placed into a computer application. Data analysis includes descriptive analysis as well as hypothesis testing. The data distribution normality test, using the Shapiro Wilk test, revealed that age, gender, BMI, stroke duration, type of stroke, and amount of physical activity were all normally distributed. The paired t-test is used to examine the hypothesis of differences before and after treatment. Because the delta data from both groups was normally distributed, an unpaired t-test was used. All data is processed on a computer using the SPSS® 23.0 software version. In this study, significance was determined by obtaining a p value < 0.05 with a 95% confidence interval.

RESULTS

The study's inclusion and exclusion criteria were met by 33 subjects. The study lasted six weeks. The assessment of

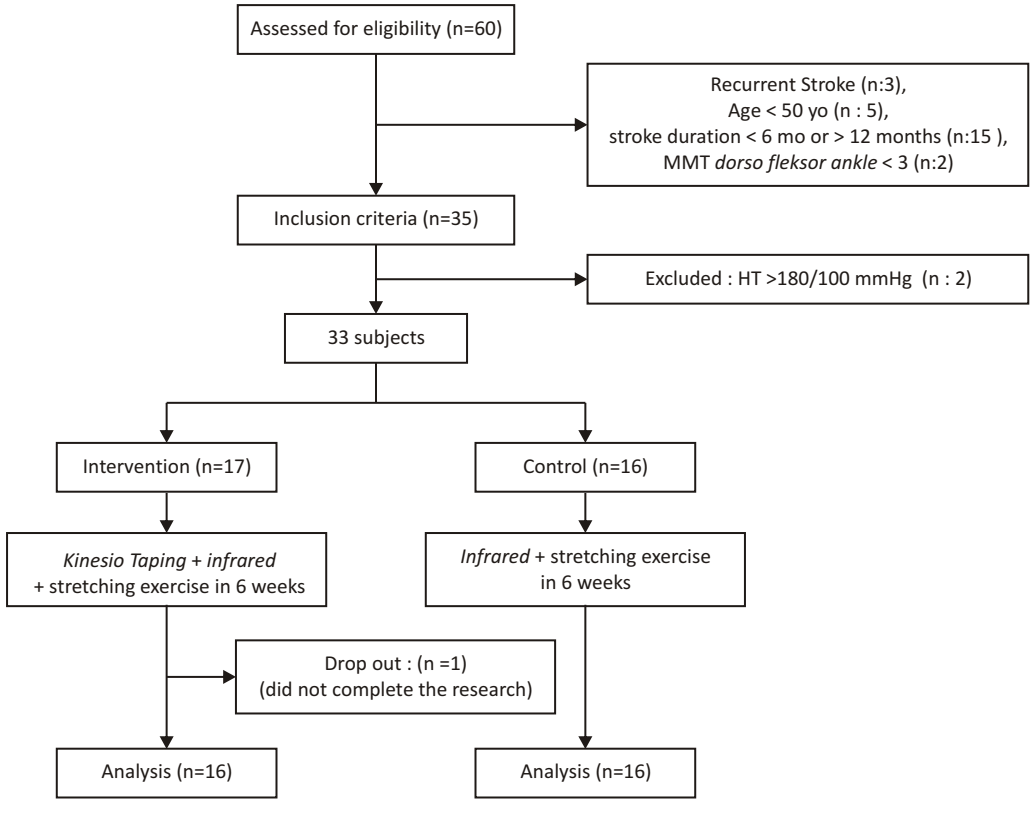


Figure 1. Consort Flow Diagram

TABLE 1
Characteristic of subjects

Variable		Group		p
		Control (16)	Intervention (16)	
Age (years)		59.25 ± 6.49	54.88 ± 7.06	0.078§
Sex	Men	6 (35.3%)	11 (64.7%)	0.156¥
	Women	10 (66.7%)	5 (33.3%)	
Physical activity	Mild	13 (65%)	7 (35%)	0.068¥
	Moderate	3 (25%)	9 (75%)	
Stroke	SNH	16 (51.6%)	15 (48.4%)	0.500£
	SH	0 (0%)	1 (100%)	
Stroke duration		7 (6–12)	8 (6–12)	0.439‡
Degree of quality of plantar fleksor muscle spasticity		1 (1–2)	2 (1–3)	0.483‡
Hemiparesis	Dekstra	6 (54.5%)	5 (45.5%)	1.000¥
	Sinistra	10 (47.6%)	11 (52.4%)	

Explanation : §Independent t; ¥Yates Correction; £Fisher's exact; ‡Mann Whitney
MoCA-INA : *Montreal Cognitive Asessment* Indonesian version; SNH : Stroke Non Hemoragik; SH : Stroke Hemoragik, MMT : *Manual Muscle Testing*

TABLE 2
Degree of quality of muscle resistance

Degree of quality of muscle resistance	Group		p
	Control (16)	Intervention (16)	
Pre treatment	1.50 ± 0.52	1.75 ± 0.68	0.252‡
Post treatment	1.19 ± 0.54	0.88 ± 0.72	0.0177‡*
P	0.019†*	0.0004¥*	
Delta	0.31 ± 0.49	0.88 ± 0.50	0.0042‡*

Explanation : *Signifikan (p < 0,05); ‡Independent t test; †Paired t test; ¥Wilcoxon; ‡Mann Whitney

spasticity was then repeated at the end of the sixth week of the research. One patient from the treatment group dropped out because he did not complete the study. Subject research did not start on the same day, hence the results were not the same for all subjects at the end of the study. The two research groups were given a stretching exercise home program with videos supplied for stretching exercises and were observed using logbooks and video calls. The total number of participants analyzed until the end of the study was 32. There were no adverse effects reported by the patients or identified during the study's evaluation during or after the study.

Data on the characteristic subject baseline evaluation of all the factors described above (Table 1) obtained a p value >0.05, indicating that there was no significant difference between the treatment and control groups in the demographic data.

Table 2 shows that there were significant differences in the pre-treatment and post-treatment degrees of quality of ankle plantar flexor muscle resistance from the paired t-test in the control (value of p = 0.019) and intervention groups (value of p = 0.00004). There was no significant difference in the unpaired t-test during the pre-treatment (value of p = 0.252), but there were significant differences in the post-treatment (value of p = 0.0177) and delta degrees of quality of muscle resistance (value of p = 0.0042).

Table 3 shows that there was a significant difference in the pre-treatment and post-treatment average angle of dorsi flexor ankle muscle from the paired t-test in the control (value of p = 0.025) and intervention groups (value of p = 0.001). There was no significant change in the unpaired t-test during pre-treatment (value of p = 0.794), but there were significant

TABLE 3
The mean angle of muscle resistance

Angle of muscle resistance	Group		p
	Control (16)	Intervention (16)	
Pre treatment	5.94 ± 2.02	6.25 ± 4.28	0.794‡
Post treatment	4.38 ± 3.10	1.88 ± 2.50	0.022‡*
P	0.025†*	0.001†*	
Delta	-1.56 ± 2.39	-4.38 ± 3.59	0.012‡*

Explanation : *Signifikan (p < 0.05); ‡Mann Whitney; ‡Independent t test; *Paired t test

differences in the post-treatment (value of p = 0.022) and delta mean angle of muscle resistance (value of p = 0.012).

DISCUSSION

The effect of infrared therapy and stretching exercises on spasticity

Upper motor neuron lesions occur in stroke patients, causing symptoms such as spasticity. Spasticity can develop in the ankle (66% of the incidence).[3] This can result in a drop foot condition. This syndrome is caused by a weakness of the dorsi flexor ankle muscles, which is followed by an increase in tone of the plantar flexor muscles (gastrocnemius muscles). This causes the feet to be in an unfavorable position, resulting in a reduction in the contact area with the floor surface on the soles of the feet, resulting in a decrease in sensory input received by the plantar mechanoreceptors for posture adjustment.[5] This abnormal gait pattern is caused mostly by difficulty moving the body by supporting the affected side, resulting in a hemiplegic walking pattern.[11]

The Tardieu scale is used for measuring spasticity, and its components measure the degree of quality and the angle of resistance. Because it is assessed subjectively and objectively, this measurement is more valid. The results of this study revealed a reduction in plantar flexor muscle spasticity in the control group who underwent infrared therapy and stretching exercises, as well as a reduction in the degree of resistance quality and the angle of resistance before and after treatment.

These findings support the idea that infrared, as a heat modality with a peak intensity of 1000 nm, can raise the temperature of surface tissue over 40 degrees Celsius. An increase in tissue temperature of up to 42 degrees Celsius reduces the excitation rate of the muscle spindles while increasing the excitation rate of the Golgi tendon organ. Furthermore, heating enhances connective tissue extensibility, with a peak at 40°C to 45°C for 5 to 10 minutes. The process described above shows how heat works to reduce spasticity. The loss of influence on activation of muscle spindles and golgi tendon organs, as well as decreased extensibility of connective tissue, leads in a drop in muscle tone that cannot be maintained optimally by just heating. Continuous stretching exercises promote changes in the organization of collagen fibers as well as changes in the viscoelasticity of collagen fibers, resulting in a decrease in muscle tone.[6]

This is also consistent with the findings of Ghasemi *et al*., who provided stretching exercises 3 times a week for 4 weeks in spastic stroke patients and found a reduction in spasticity as measured by the modified Ashworth scale until two months after the program ended.[12] Ergul *et al*. discovered that stretching exercises performed 3 times a week for 4 weeks on the hamstring, quadriceps, hip adductor, and plantar flexor muscles in patients with multiple sclerosis may reduce spasticity in the lower extremities.[13]

The effect of adding Kinesio Taping on spasticity

The application of Kinesio Taping to the muscles will facilitate the tibialis anterior muscles while inhibiting the plantar flexor muscles, resulting in reduced plantar flexor muscle spasticity. Reducing spasticity improves joint range of motion, resulting in more functional walking in stroke patients. Kinesio Taping is applied with 50% tension to the tibialis anterior muscle and 25% tension to the plantar flexor muscles. In this study, the treatment group that received the addition of Kinesio Taping experienced a reduction in ankle plantar flexor muscle spasticity. However, when compared to the control group, the delta of reduction in resistance quality and the resulting angle of resistance was significantly greater.

This is consistent with the hypothesis that using Kinesio Taping with facilitation techniques, from origin to insertion, can improve muscle performance and increase motor unit recruitment, hence increasing muscular strength. This mechanism is hypothesized to be caused by the elastic rebound qualities of Kinesio Taping influencing the length-to-tone relationship. Taping from the origin to the insertion improves reflex contraction of the muscle spindles and promotes muscular contraction. The concept is based on cutaneous afferent impulses that are hypothesized to influence the excitability of the motor unit as well as the proprioceptive reflex arc. Through

pressure and tension, Kinesio Taping will stimulate skin mechanoreceptors, resulting in physiological changes such as increased muscle activity and recruitment of firing motor units.[14]

Kinesio Taping with inhibited techniques used from insertion to origin through receptors on the skin's surface can provide stimulation to the neuromuscular system by facilitating in the activation of nerve and muscle performance when performing a functional movement. Kinesio Taping can improve muscle and tendon function by stimulating mechanical receptors, namely the Golgi tendon organ in the muscle tendon junction. During movement, the Golgi tendon organ regulates the muscle spindles. Kinesio Taping applied in an inhibitory approach to the ankle plantar flexor muscle through the Achilles tendon will inhibit the Golgi tendon organ, consequently helping to regulate the tone of the ankle plantar flexor muscle. As a result, the ankle plantar flexor muscles' spasticity is decreased. The insertion and origin of Kinesio Taping, as well as the muscle fibers, fascia, and skin above it, are moved away from the center of mass using this inhibitory technique, which inhibits muscle contraction.[15,16] The muscles work better when muscle tone is reduced with Kinesio Taping stretch inhibition of the ankle plantar flexor muscles.

The findings of this study coincide with the findings of Razti *et al* and Roy *et al*. Razti stated that Kinesio Taping with 35% tension will help the wrist extensor muscles due to the effect of skin mechanoreceptors through pressure and stretch, causing physiological changes such as increased muscle recruitment. Furthermore, Kinesio Taping enhances the flow of blood arteries and lymph, which affects muscle function.[17] Furthermore, Yam *et al*. and others who studied the influence of Kinesio Taping on muscle activation reported that 50% Kinesio Taping resulted in significant outcomes.[18] According to Koseoglu *et al*, applying Kinesio Taping with facilitation techniques to the ankle dorso flexor muscles can enhance muscle contractions in stroke patients.[9] The research by Cavalcante *et al*, which demonstrates a reduction in spasticity in the wrist flexor muscles following 6 weeks of Kinesio Taping treatment in post-stroke patients as measured by the modified ashworth scale (MAS).[8]

Kinesio Taping applied to spastic muscles after infrared therapy and stretching exercises will result in optimum tissue extensibility. Subjectively, the subjects reported a reduction in the sensation of being pulled and tight, which is typically felt on the side of pain, after getting Kinesio Taping. This provides weight to the study's objective findings. All of this contributes to a lower delta degree of quality and a greater angle of resistance in the group who received Kinesio Taping. The findings of this study support the research hypothesis, namely that there is a significant difference in a reduction in the average degree of quality and the angle of resistance between the intervention and control groups at the end of the study.

The use of Kinesio Taping was also determined to be safe for post-stroke patients in this study. There was no mention of any potential pain or adverse effects in the literature. Kinesio Taping's strong effectiveness and lack of side effects may be reasons for considering it as a complement in the treatment of stroke spasticity.

CONCLUSION

In post-stroke patients who received Kinesio Taping in conjunction with infrared therapy and stretching exercises, there was a significant difference in improvement in spasticity of the ankle plantar flexor muscles, which was greater than in those who was infrared and stretching exercises alone. Kinesio taping can be applied as a complementary treatment to relieve spasticity in stroke patients who are receiving other treatments. The findings of this study can be used to guide future studies into the long-term effect of Kinesio Taping on spasticity. Following the Kinesio Taping treatment, a follow-up study can be performed to assess the effectiveness of the addition of Kinesio Taping in post-stroke rehabilitation that receives infrared and stretching exercises against spasticity while taking neuroplasticity and the drugs given into consideration.

REFERENCES

1. Kuriakose D, Xiao Z. Pathophysiology and Treatment of Stroke: Present Status and Future Perspectives. 2020;21(20):7609.
2. Bavikatte G, Subramanian G, Ashford S, Allison R, Hicklin D. Early Identification, Intervention and Management of Post-stroke Spasticity: Expert Consensus Recommendations. 2021;13:11795735211036576.
3. Kuo C-L, Hu G-C. Post-stroke Spasticity: A Review of Epidemiology, Pathophysiology, and Treatments. International Journal of Gerontology 2018;12(4):280–4.
4. Huang YC, Chen PC, Tso HH, Yang YC, Ho TL, Leong CP. Effects of kinesio taping on hemiplegic hand in patients with upper limb post-stroke spasticity: a randomized controlled pilot study. European journal of physical and rehabilitation medicine 2019;55(5):551–7.
5. Son J, Rymer WZ. Effects of Changes in Ankle Joint Angle on the Relation Between Plantarflexion Torque and EMG Magnitude in Major Plantar Flexors of Male Chronic Stroke Survivors. 2020;11.
6. Cameron MH. Thermal Agents. Physical Agents in Rehabilitation : An Evidence-Based Approach to Practice. Fifth ed. St Louis, MO: Saunders Elsevier; 2018. p. 509–13.
7. Lecharte T, Gross R, Nordez A, Le Sant G. Effect of chronic stretching interventions on the mechanical properties of muscles in patients with stroke: A systematic review. Ann Phys Rehabil Med 2020;63(3):222–9.
8. Cavalcante J, Silva M, Silva J, Anjos C, Soutinho R. Effect of Kinesio Taping on Hand Function in Hemiparetic Patients. World Journal of Neuroscience 2018;08:293–302.
9. Koseoglu BF, Dogan A, Tatli HU, Sezgin Ozcan D, Polat CS.

Can kinesio tape be used as an ankle training method in the rehabilitation of the stroke patients? Complement Ther Clin Pract 2017;27:46–51.
10. Gloria E Rondonuwu , Lidwina S Sengkey, Marpaung. E. Pengaruh Kinesio Taping Terhadap Fungsi Mobilitas Berjalan pada Pasca Stroke Jurnal Medik dan Rehabilitasi (JMR) 2020;2:1–9.
11. Timmermans C, Roerdink M, Meskers CGM, Beek PJ, Janssen TWJ. Walking-adaptability therapy after stroke: results of a randomized controlled trial. Trials 2021;22(1):923.
12. Ghasemi E, Khademi-Kalantari K, Khalkhali-Zavieh M, Rezasoltani A, Ghasemi M, Baghban AA, *et al*. The effect of functional stretching exercises on functional outcomes in spastic stroke patients: A randomized controlled clinical trial. Journal of bodywork and movement therapies 2018;22(4):1004–12.
13. Ergul M. NMA, Biglarıan A. Effects of Static and Functional Stretching Exercises on Lower Limb Spasticity and Function in People with Multiple Sclerosis: A Randomized Controlled Trial. Turk J Physiother Rehabil 2021;32(3):43–51.
14. Denizoğlu Külli H, Karabulut D, Arslan YZ. The prolonged effect of Kinesio Taping on joint torque and muscle activity. Somatosensory & Motor Research 2022;40:1–7.
15. Sheng Y, Kan S, Wen Z, Chen W, Qi Q, Qu Q, *et al*. Effect of Kinesio Taping on the Walking Ability of Patients with Foot Drop after Stroke. Evidence-based complementary and alternative medicine : eCAM 2019;2019:2459852.
16. Park SJ, Kim T-H, Oh S. Immediate Effects of Tibialis Anterior and Calf Muscle Taping on Center of Pressure Excursion in Chronic Stroke Patients: A Cross-Over Study. 2020;17(11):4109.
17. Roy S, Dixit J, Kumar A, Singh O, editors. The Effect of Kinesiotaping in Improving Fine Motor Skills In Children With Spastic Diplegic Cerebral Palsy2018.
18. Yam TTT, Or PPL, Ma AWW, Fong SSM, Wong MS. Effect of Kinesio taping on Y-balance test performance and the associated leg muscle activation patterns in children with developmental coordination disorder: A randomized controlled trial. Gait & posture 2019;68:388–96.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 302–311

OPEN ACCESS

Original Article

Relationship between Stress Level and Risk of Eating Disorder in Undergraduate Students during the COVID-19 Pandemic

Jessica Clara[1], Titis Hadiati[2], Innawati Jusup[2], Widodo Sarjana A.S.[2]

[1]Faculty of Medicine, Diponegoro University, Indonesia
[2]Department of Psychiatry, Faculty of Medicine, Diponegoro University, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.953

Accepted: April 18th, 2023
Approved: June 27th, 2023

Author Affiliation:
Department of Psychiatry, Faculty of Medicine, Diponegoro University, Indonesia

Author Correspondence:
Widodo Sarjana A.S.
Prof. Sudarto Street, Tembalang, Semarang, Central Java, 50275, Indonesia

E-mail:
Widodosarjana22@yahoo.com

Abstract

Background : The prevalence of undergraduate students' stress before COVID-19 pandemic in Indonesia was 36.7-71.6%, where undergraduate students' age was classified as the age group for the onset of eating disorders. During the COVID-19 pandemic, students must continue their studies. However, modifications of daily routines in pandemic have a negative effect on mental health, increase negative stress (distress), and it could increase the incidence of eating disorders symptoms. The purpose of this study was to find out the relationship between stress level in undergraduate student and the risk of eating disorder they might have during the COVID-19 Pandemic.
Methods : This study used cross sectional study design and conducted on June 2021. The subjects were 110 active students who studied in Faculty of Medicine Diponegoro University who was chosen using consecutive sampling technique. The Perceived Stress Scale-10 questionnaire was used to measure the students' stress level for the past month and the Eating Attitude Test-26 questionnaire was used to determine the students' risk of having an eating disoder. Both questionnaires were selected because it has been proven as reliable questionnaires with high sensitivity and specificity (Cronbach's alpha >0.7).
Results : The result showed that out of 110 students who have been subjects of this study, 25.5% of respondents experienced low stress, 68.2% of respondents experienced moderate stress, and 6.4% of respondents experienced high stress. It also showed that 4.5% of respondents have the risk of having an eating disorder.
Conclusion : There is a significant correlation (p=0.005) between the stress level and risk of eating disorder with very weak positive relationship direction (r=0.097).

Keywords : COVID-19, Eating Disorder, Stress level

INTRODUCTION

Stress is defined as a particular relationship between individual and their environment,[1] where there is an imbalance between demands from the environment and individual's ability to adjust, thus it becomes a source of stress and emotional tension.[2] According to the American Psychological Association (APA), there is a connection between age and perceived stress levels. It is reported that Generation Z (age 10 to 25 in 2021),[3] has the highest stress level of 5.3 out of 10 compared to other generations.[4] This generation involves primary school students up to undergraduate students. In another study, it is specifically stated that the prevalence of stress in undergraduate students in Indonesia was 36.7–71.6%.[5]

In dealing with stress, everyone has their own unique ways to cope. Generally, coping process can be divided into two, problem-focused coping if a person directly looks into solutions of the problem and emotional-focused coping if someone prioritizes to regulate their emotional response to stress.[6] It was written that most of the people who changed their eating behavior as a form of emotional-focused coping felt the effects of stress on their bodies were reduced.[7] Whereas changes in eating behavior, dieting, and weight control behavior are predicted to cause eating disorders in the next 5 years.[8]

Eating disorders are a syndrome associated with pathological eating attitudes and behavior.[9] It is reported that cases of eating disorders continue to increase from year to year, found more in women than men, and cases are more often found in western countries than in eastern countries.[10] However, Indonesia which is an eastern country, ranks fourth in the world after the United States, India, and China for the incidence of eating disorders, although statistical data is not known for sure.[9] It is should be emphasized that the onset of eating disorders are very common in adolescence and young adults with age range of 15–19 years, although it can occur at any age.[11]

Since 2019, the COVID-19 pandemic has brought huge amount of changes in various aspects in our daily life. Previous research has shown that the COVID-19 pandemic affects negatively on mental health by increasing distress and depressive symptoms in adults. The COVID-19 pandemic has also increased the incidence of symptoms and the risk of eating disorders due to modifications in daily routines, including mealtimes, sleep and exercise schedule, and the loss of social support.[12]

As far as the researcher knows, the topic of eating disorders during pandemic in undergraduate students has not been widely studied in Indonesia. In addition, national statistical data about the incidence of eating disorders in Indonesia has also not been regularly reported, let alone published. The purpose of this study was to find out the relationship between stress level in undergraduate student and the risk of eating disorder they might have during the COVID-19 Pandemic.

METHODS

This research is an analytic observational study with cross sectional approach that was conducted in June 2021. The sample was chosen using the consecutive sampling technique, which was the students of Faculty of Medicine Diponegoro University who met the inclusion criteria. The inclusion criteria of this study were students who actively being registered as students of Medical Study Program in Faculty of Medicine Diponegoro University during the COVID-19 pandemic and agreed to be this research's subjects by filling out the informed consent and questionnaire completely. Meanwhile, the exclusion criteria for this study were students who have already been diagnosed with eating disorders, currently undergoing therapy for their eating disorders, whether it was a psychotherapy or pharmacotherapy. After using consecutive sampling technique, the total number of respondents were 110 students. The Perceived Stress Scale-10 (PSS-10) questionnaire was used to measure the students' stress level for the past month and the Eating Attitude Test-26 (EAT-26) questionnaire was used to determine the students' risk of having an eating disoder. Both of these instruments have been validated and translated in Indonesia by Department of Psychology, University of Diponegoro at 2015.

Data processing and analysis was carried out using Lambda and Spearman test.

RESULTS

Table 1 shows characteristics of research subjects. Table 2 shows correlation between stress level and demographic factors. Table 3 shows correlation between the risk of eating disorders and demographic factors. Table 4 shows correlation between stress level and the risk of eating disorders.

DISCUSSION

The purpose of this study was to find out the relationship between stress level in undergraduate student and the risk of eating disorder they might have during the COVID-19 Pandemic. This study found that out of 110 students who have been subjects of this study, 25.5% of respondents experienced low stress, 68.2% of respondents experienced moderate stress, and 6.4% of respondents experienced high stress. From this data, it can be seen that more than half of the respondents experienced moderate stress. This finding is in line with previous research where the majority of undergraduate students at other medical faculties in Indonesia also

TABLE 1
Characteristics of research subjects

Variable		Frequency (%)
Age	Late Teen (17–25 years)	110 (100%)
Gender	Male	31 (28.2%)
	Female	79 (71.8%)
Religion	Islam	69 (62.7%)
	Catholicism	23 (20.9%)
	Protestantism	14 (12.7%)
	Buddhism	2 (1.8%)
	Hinduism	2 (1.8%)
BMI	Underweight (<18.5)	12 (10.9%)
	Normal or Healthy weight (18.5–22.9)	51 (46.4%)
	Overweight at risk (23–24.9)	20 (18.2%)
	Obesity class I (25–29.9)	18 (16.4%)
	Obesity class II (≥30)	9 (8.2%)
GPA	Excellent (IPK 4.00–3.51)	70 (63.6%)
	Good (IPK 3.50–3.01)	39 (35.5%)
	Moderate (IPK 3.00–2.50)	1 (0.9%)
Economic Status	< Rp. 500.000,00	23 (20.9%)
	Rp. 500.000,00 – Rp. 1.000.000,00	24 (21.8%)
	Rp. 1.000.001,00 – Rp. 2.000.000,00	33 (30%)
	> Rp. 2.000.000,00	30 (27.3%)
Isolation Status	Living alone	15 (13.6%)
	Living with family	95 (86.4%)

experienced moderate stress during the COVID-19 pandemic.[13,14] When compared with previous study before the pandemic,[15] it can be said that there was an increase of undergraduate students' stress levels during the COVID-19 pandemic. It was written that majority of respondents considered online learning was not effective and became one of the causes of stress.

This study also showed that 4.5% of respondents have the risk of having an eating disorder. If compared with studies conducted before the COVID-19 pandemic began, they also showed the same findings with this study, where the percentage of respondents who are at risk is lower than the normal respondents.[16,17] From the existing percentages, it can be said that generally, there has been a decrease of respondents who are at risk of developing eating disorders from before the pandemic, beginning of the pandemic, to a year after the pandemic took place. It happens because patients have been able to find adaptive coping strategies for their eating disorders, they are willing to accept the situation and seek therapy for eating disorder symptoms, and have been receiving social support from family during the pandemic period which has lasted for one year.[18]

This study also found that there were no significant relation of undergraduate students' stress level and the risk of eating disorder with subjects' demographic factors such as age, gender, religion, BMI, GPA, economic status, and isolation status.

Relationship between Stress Level and Eating Disorder Risk

During the COVID-19 pandemic, students' stress tends to increase.[19] The causes of increased stress are multifactorial. Some of them are modification into online learning system and drastic changes in social environment during the COVID-19 pandemic which

TABLE 2
Correlation between stress level and demographic factors

Variable		Stress level			p
		Low Stress	Moderate Stress	High Stress	
Age	Late Teen (17–25 years)	28	75	7	constant
Gender	Male	8	20	3	0.798$
	Female	20	55	4	
Religion	Islam	15	51	3	0.134$
	Catholicism	7	14	2	
	Protestantism	3	9	2	
	Buddhism	1	1	0	
	Hinduism	2	0	0	
BMI	Underweight (<18.5)	2	10	0	0.721¥
	Normal or Healthy weight (18.5–22.9)	13	35	3	
	Overweight at risk (23–24.9)	7	12	1	
	Obesity class I (25–29.9)	5	13	0	
	Obesity class II (≥30)	1	5	3	
GPA	Excellent (IPK 4.00–3.51)	16	52	2	0.952¥
	Good (IPK 3.50–3.01)	11	23	5	
	Moderate (IPK 3.00–2.50)	1	0	0	
Economic Status	< Rp. 500.000,00	6	16	1	0.386¥
	Rp. 500.000,00 – Rp. 1.000.000,00	2	20	2	
	Rp. 1.000.001,00 – Rp. 2.000.000,00	11	20	2	
	> Rp. 2.000.000,00	9	19	2	
Isolation Status	Living alone	5	9	1	0.621$
	Living with family	23	66	6	

requires undergraduate students to self-isolate. When the environment changes and humans feel that they lose their sense of control, they tend to feel afraid and insecure. These feelings are amplified by the threat of being infected with the COVID-19 virus.[20] All of these causes have increased undergraduate students' stress level so that stress management is necessary. In terms of managing their stress, humans must go through a process called a coping mechanism, either it is a problem-focused coping or an emotional-focused coping. One form of emotional-focused coping is a change in eating behavior. A bad eating behavior which lasts long enough and is accompanied by persistent food preoccupation, an excessive fear or worry about body shape, or body image distortion can lead a person into having an eating disorder. From these explanation, it can be drawn the reason why someone with stress can be at risk for eating disorders.

This study found a significant relationship between stress levels and the risk of eating disorders (p=0.005) with a very weak relationship strength (r=0.097). The direction between two variables is positive, which means the higher level of stress someone has, their risk of developing an eating disorder is also greater. This finding is in line with previous research.[21] The very weak relationship strength between the two variables can be explained by the theory of coping mechanisms. According to Lazarus and Folkman, problem-focused coping consists of confrontational coping, seeking social support and planning ways to solve problems, while emotional-focused coping consists of ways to control oneself, humor, keeping a distance from the crowd,

TABLE 3
Correlation between the risk of eating disorders and demographic factors

Variable		Risk of Eating Disorders		p
		Normal	At Risk	
Age	Late Teen (17–25 years)	105	5	constant
Gender	Male	31	0	0.154[$]
	Female	74	5	
Religion	Islam	68	1	0.228[$]
	Catholicism	21	2	
	Protestantism	12	2	
	Buddhism	2	0	
	Hinduism	2	0	
BMI	Underweight (<18.5)	12	0	0.098[$]
	Normal or Healthy weight (18.5–22.9)	50	1	
	Overweight at risk (23–24.9)	19	1	
	Obesity class I (25–29.9)	17	1	
	Obesity class II (≥30)	7	2	
GPA	Excellent (IPK 4.00–3.51)	67	3	0,957[$]
	Good (IPK 3.50–3.01)	37	2	
	Moderate (IPK 3.00–2.50)	1	0	
Economic Status	< Rp. 500.000,00	23	0	0.053[$]
	Rp. 500.000,00 – Rp. 1.000.000,00	24	0	
	Rp. 1.000.001,00 – Rp. 2.000.000,00	32	1	
	> Rp. 2.000.000,00	26	4	
Isolation Status	Living alone	15	0	0.365[$]
	Living with family	90	5	

TABLE 4
Correlation between stress level and the risk of eating disorders

Stress Level	Risk of Eating Disorders		
	Normal	At Risk	Total
Low Stress	28	0	28
Moderate Stress	72	3	75
High Stress	5	2	7

Variable	p	r	Description
Stress Level and Risk of Eating Disorders	0.005[*$]	0.097	Significant very weak correlation

seeking emotional support, giving positive words affirmation, praying and doing religious activities. Carver and Weintraub added another type of coping, namely dysfunctional coping which consists of various activities that are not good for someone's wellbeing.[22]

But if we focus on emotional-focused coping, a study has listed several activities that undergraduate students usually chose to reduce stress. From the most desirable, namely listening to the music, socializing with family or friends, sitting alone in a quiet place, exercising, praying or reading the bible, and so on.[23] From the description above, it can be seen that there are several types of coping methods which contain many activities. The subjects in this study were not asked further about their usual coping methods, but it is possible that the majority of respondents did not choose emotional-focused coping mechanism in the form of eating behaviour changes so they are not at risk of developing eating disorders. This lead us to the result which shows very weak relationship between stress levels and eating disorders, even though the majority of respondents experienced moderate stress.

Stress Level and Demographic Factors

The first demographic factor was age where in this study shows homogeneous result, so that there is no comparison category for relationship analysis. However, the existing finding was in accordance with previous study which stated that generation Z (age 10 to 25 in 2021) has the highest stress level compared to other generations.[3] Because all respondents were categorized as Generation Z, this theory explained why more respondents experience moderate stress compared to low stress.

This study also found that there were no significant relationship between gender and stress levels ($p = 0.798$). It can be caused by uneven distribution of male and female respondents, where 71.8% of respondents were women. Although there was no significant relationship, the result of this study were in line with previous research where women tend to have higher stress levels than men. In general, it was women who experienced more chronic stress with stressors from small things in their lives. Kaplan and Sadock also stated that women have twice the risk of experiencing stress compared to men.[24]

While Indonesia has officially recognized six religions, research on the relationship between religion and stress had never been done. This study did not find a significant relationship between those two variables ($p=0.134$). However, research conducted by Ira Darmawanti stated that there was a positive relationship between a person's religiosity and the level of stress they experienced. Religiosity itself was known as a personal aspect of a person's religious life that emphasized personal depth and respect for God.[25] It could be related to the result of this study that whatever religion someone had, it could be used as a coping mechanism. The stress level experienced was not from what type of religion that they had but from how religious they were in practicing their religion. Nevertheless, the level of religiosity was not measured in this study and should be a consideration for future researchers.

BMI was also had no significant relationship with stress levels ($p=0.721$). This finding had same results from previous studies which had also been done on undergraduate students in Faculty of Medicine in Indonesia.[26,27] No significant relationship might be due to the number of factors that could affect the level of stress and a person's BMI, but were not measured in this study. Some factors that needed to be considered were individual's psychosocial aspect, eating habits, and physical activity, which resulted with significant outcomes when those were included from earlier study. It was written that stress could increase someone's appetite and daily food intake which could lead to overweight and obesity.[28] That statement could be associated with this study where seven respondents who experienced severe stress, one of them was overweight and three of them were in stage II obesity.

A study affirmed that the COVID-19 pandemic was a stressor that could be a bad risk for a person's mental health.[29] 71.26% of students who had increased stress and anxiety in this pandemic, only 43.25% of them could overcome it.[30] Those findings were similar to the result of this study, where majority of respondents experienced moderate to high stress. In contrast, the GPA, which was considered as a proof of students' ability in their study period, was found to be higher in students with moderate and high stress. From the GPA, it could be seen that most students could overcome their stress well in term of their studies. The result of this study found that there was no significant relationship between someone's GPA with their stress level ($p=0.952$). Different findings might be caused by the learning system or curriculum which was not exactly the same. Furthermore, pandemic in Indonesia has also lasted for almost a year so that students had quite a long time (two semesters) to adjust themselves with online learning system. This reason was proven by a study that found a significant effect between student's adaptation to learning environment with their GPA ($p=0.04$).[31]

Besides of changes in the learning system, COVID-19 pandemic also impact on the economy aspects that could be a stressor. Previous study said that in general, students from low socio-economic status had higher level of academic stress.[32] However, this study got a different result. Perhaps the amount of pocket money received by students everymonth was not able to represent the students family's economic status because this study did not ask whether there was a change in the amount of pocket money they received before and after

the pandemic period. The result may also be caused by the majority of respondents (57.3%) had considerable pocket money, namely bigger than Rp. 1,000,000.00, where 86.4% of total respondents still lived with their families. Therefore, the economic status in this study did not provide a significant relationship (p=0.386) and it was likely not to be a stressor for students, which has been proven by other study with same sample in previous year.[33]

A study wrote that isolation status during pandemic period could be a risk factor to someone's mental health.[34] In contrast, there was no significant relationship found in this study (p=0.621). This could be caused by the distribution of respondents where 86.4% of students lived with their families. The research data showed that out of 95 respondents who lived with their family, 66 of them experienced moderate stress and 6 of them experienced high stress. Although there was no significant relationship, the result of this study was in accordance with other study, where students who lived with their parents were more likely to feel stressed (70.2%).[35] There might be a problem inside the family that affected students physically and emotionally, thus gave an impact in learning skills which could become the source of academic stress. On the contrary, other study found out that students who lived alone also had their own stressors, namely homesickness.[36] Another study stated that the sources of stress can be different for everyone and their level of stress depends on their perception towards the stressor. So that students who perceive a stressor as a threatening situation, tend to feel more stressful.[33] Therefore, the results of this study is in accordance with previous study, which also stated that the relationship between isolation status and stress levels was not significant.

Risk of Eating Disorders and Demographic Factors

In this study, respondents' age was homogeneous so that the analysis showed constant results. However, respondents' age in this study was in the range of 17–25 years, which could be categorized as late teen according to the Indonesian Ministry of Health. The age category often be the onset of eating disorders, namely teenagers and young adults.[37] It was in accordance that five respondents had a risk of eating disorders in this study.

Furthermore for gender, there was also an insignificant relationship with p value of 0.154. This might be caused by uneven distribution of respondents' gender, where 71.8% of respondents are women. However, other study in Indonesia about eating disorders with almost equal distribution of gender (male 55.8% and women 44.2%) also had insignificant results (p=0.325).[38] It can be said that gender does not have an influence on someone's risk of having eating disorders eventhough the incidence showed more cases of eating disorders in women. Kaplan and Sadocks also stated that eating disorders were indeed more common in women, especially Anorexia Nervosa, Bullimia Nervosa, and Binge Eating Disorder.[39] In this study, five respondents who are at risk were all women.

Eating disorders were usually associated with body image, which was once mentioned that female students were more likely to feel dissastified with their appearance and their body.[40] Especially in women, eating disorders often appeared in their adolescence age because there was a transition in their body caused by puberty so it could change their self-perception. However, questions about body image was not taken in this study, but it could be the reason why five respondents were at risk. In addition, other study mentioned that women usually prefered emotional focused coping as a way to deal with their stress.[24] This theory explained why women have higher risk of eating disorders because one form of emotional focused coping is dietary changes.

About religion, in Indonesia there has never been any research linking it with eating disorders yet. Nevertheless, this study found a nonsignificant relationship between religion and eating disorders (p=0.228). Studies in other countries also found that there was no significant correlation between those two variables but rituals in each religion has been proven to increase the risk of eating disorders, for example the ritual of fasting in the month of Ramadan.[41,42]

In diagnosing eating disorders, BMI was used but this study found insignificant relationship between BMI and eating disorders (p=0.098). Similar results were also found in another study which stated that eating disorders were also influenced by other factors, namely food intake and infection status[43] although these two factors were not included in this study. According to PPDGJ-III pocket book, to diagnose a type of eating disorder, a patient was not only seen from his BMI but also from his behavior before and after eating, patient's body image, as well as changes in hormonal and physiological aspects. Respondents who were at risk in this study, four of them were in the overweight and obese categories. This could be explained with the theory which stated that women who were obese and overweight had higher risk of eating disorders. Possible causes behind the increased risk were immoderate worry about their weight and body shape, low self-esteem, and excessive dieting.[44]

Another demographic factor analyzed in this study was GPA, which was also found insignificant (p=0.957). A study stated that an increase in academic burden during pandemic became a trigger for eating disorders.[45] Despite being at risk for having eating disorders, two respondents still had good GPAs and three other respondents had excellent GPAs. Good academic performance was also found in a study, where students with eating disorders did not have academic obstacles, moreover had 1.35–1.49 times higher GPA than other

students who were not at risk.[46] In contrary, other study showed opposite results, where students who were not at risk had higher GPA.[47] Inconsistent analysis results explained why there was no relation between GPA and the risk of eating disorders. In addition, the psychological aspects of each individual at risk for eating disorders have an influence on attitudes, interests, motivation, and behavior related to academic success, so that it has a measurable impact on academic performance.[47]

Furthermore, respondents' economic status which was assessed based on the amount of monthly pocket money showed an insignificant relationship with eating disorders (p=0.053). This result was not in accordance with previous research which stated that socioeconomic status could trigger eating disorders.[48] It was possible that different findings were caused by difference in respondents' age because undergraduate students in this study did not work so they did not have their own monthly allowance.

The last demographic factor analyzed in this study was isolation status. Previous research found that environment had an impact on a person's mindset which could be related to eating disorders. An environment that focused on the perception of being skinny and exercising excessively, being in a bad family relationship, and being educated with less empathy parenting style could be risk factors for eating disorders.[39] However, this study found a non-significant relationship between isolation status and eating disorders (p=0.365). In this study, two options were given for isolation status, that is living alone and living with family. All respondents who were at risk lived with their families. This could be explained by the previous theory that someone who had poor family support could be more at risk of having eating disorders rather than someone who lived alone. Other study also mentioned that girls felt greater pressure from their parents regarding to food restriction.[49] Female students also reported to receive more negative comments about their body from their parents, which affected their psychological condition.[50] Both of these theories may be experienced by respondents who were at risk because they lived with their families during the COVID-19 pandemic.

Limitation of This Study

This study was concluded when a pandemic took place in Semarang, Indonesia so direct data collection (for example by interviewing) was limited by COVID-19 regulation. Wide inclusion criteria contributed to this study bias and this study have not been able to include other risk factors that may affect the relationship between variables. Further research could consider other sampling methods, include other social risk factors that may affect both variables, and specify inclusion criteria to reduce study bias.

CONCLUSION

Based on the results of the study, it was concluded that there was a significant correlation between the stress level and risk of eating disorder with very weak positive relationship direction. There was no significant relationship between demographic factors of the respondents with their level of stress, nor with the risk of eating disorders.

Ethical Approval

The study has received ethical clearance approval from the Health Research Ethics Comission of the Faculty of Medicine, Diponegoro University with ethical clearance number No. 170/EC/KEPK/FK-UNDIP/V/2021. All research subjects were asked for consent with informed consent questionnaire before the study was conducted. Identity of respondents and all research data will be kept confidentially.

Conflicts of Interest

The authors declare that there was no conflict of interest.

Funding

No specific funding was provided for this article.

Author of Contributions

Conceptualization, Jessica Clara; methodology, Jessica Clara and Widodo Sarjana; writingoriginal draft preparation, Jessica Clara; writingreview and editing, Widodo Sarjana; supervision, Widodo Sarjana, Titis Hadiati, Innawati Jusup.

Acknowledgments

This work was supported by Department of Medicine and Department of Psychiatry, Faculty of Medicine, Diponegoro University.

REFERENCES

1. Shahsavarani AM, Azad E, Abadi M, Kalkhoran MH. Stress: Facts and Theories through Literature Review. Int J Med Rev. 2015;2(2):230–41.
2. Bua Hidayat. Faktor yang dapat menyebabkan insomnia. Univ Diponegoro. 2012;11–35.
3. Anantatmula VS, Shrivastav B. Evolution of project teams for Generation Y workforce. Int J Manag Proj Bus. 2012 Jan 20;5(1):9–26.
4. American Psychological Association. Stress in America™ Generation Z. Stress in America survey. Am Psychol Assoc. 2018
5. Fitasari IN. Faktor yang berhubungan dengan kejadian stres pada Mahasiswa Fakultas Kesehatan Masyarakat Universitas

Airlangga. Media Gizi Indones. 2010;1:13–9.
6. Musradinur. Stres dan cara mengatasinya dalam perspektif psikologi. Jurnal Edukasi. 2016;2(2):183.
7. Park M, Quinn L, Park C, Martyn-Nemeth P. Pathways of the relationships among eating behavior, stress, and coping in adults with type 2 diabetes: A cross-sectional study. Appetite. 2018 Dec 1;131:84–93.
8. Wu XY, Yin WQ, Sun HW, Yang SX, Li XY, Liu HQ. The association between disordered eating and health-related quality of life among children and adolescents: A systematic review of population-based studies. PLoS One. 2019;14(10):1–17.
9. Chairani L-. Body Shame dan Gangguan Makan Kajian Meta-Analisis. Bul Psikol. 2018;26(1):1227.
10. Qian J, Hu Q, Wan Y, Li T, Wu M, Ren Z, *et al*. Prevalence of eating disorders in the general population: a systematic review. Shanghai Arch Psychiatry. 2013;25(4):212–23.
11. Smink FRE, Van Hoeken D, Hoek HW. Epidemiology of eating disorders: Incidence, prevalence and mortality rates. Curr Psychiatry Rep. 2012 Aug 27;14(4):406–14.
12. Holingue C, Kalb LG, Riehm KE, Bennett D, Kapteyn A, Veldhuis CB, *et al*. Mental distress in the United States at the beginning of the covid-19 pandemic. Am J Public Health. 2020.
13. Inama S. Gambaran tingkat stres mahasiswa Fakultas Kedokteran Universitas Sumatera Utara dalam sistem pembelajaran daring pada era pandemi covid-19. 2021.
14. Jannah M. Pengaruh pembelajaran via online selama pandemi covid-19 terhadap tingkat stress mahasiswa tingkat akhir Fakultas Kedokteran Universitas Muhammadiyah Makassar. Jurnal Kedokteran Universitas Muhammadiyah Makasar. 2021.
15. Fitri EW, Titis H, Widodo SA. Hubungan antara tingkat stres dengan tingkat insomnia mahasiswa/i angkatan 2012/2013 program studi pendidikan dokter Fakultas Kedokteran Universitas Diponegoro. Jurnal Kedokteran Diponegoro. 2017;6(2):549–57.
16. Haslinda L, Ernalia Y, Wahyuni S. Citra tubuh, perilaku diet, dan kualitas hidup remaja akhir mahasiswa Fakultas Kedokteran Universitas Riau. Jurnal Ilmu Kedokteran. 2015.
17. Amir E. Hubungan intensitas penggunaan media sosial dengan kejadian gangguan makan : studi pada mahasiswa Fakultas Kedokteran Universitas Diponegoro program studi pendidikan dokter tahun pertama. Universitas Diponegoro. 2019.
18. Schlegl S, Maier J, Meule A, Voderholzer U. Eating disorders in times of the COVID-19 pandemic – Results from an online survey of patients with anorexia nervosa. Int J Eat Disord. 2020;53(11):1791–800.
19. Charles NE, Strong SJ, Burns LC, Bullerjahn MR, Serafine KM. Increased mood disorder symptoms, perceived stress, and alcohol use among college students during the COVID-19 pandemic. Psychiatry Res. 2021 Feb 1;296:113706.
20. Tracy M, Norris FH, Galea S. Differences in the determinants of posttraumatic stress disorder and depression after a mass traumatic event. Depress Anxiety. 2011;28(8):666–75.
21. Kristanti RA. Hubungan antara tingkat stres dengan gangguan makan pada Mahasiswa Preklinik Fakultas Kedokteran Universitas Pelita Harapan. 2020.
22. Saleh Baqutayan SM. Stress and coping mechanisms: A historical overview. Mediterr J Soc Sci. 2015;6(2S1):479–88.
23. Gallagher KM, Jones TR, Landrosh N V., Abraham SP, Gillum DR. College Students' Perceptions of Stress and Coping Mechanisms. J Educ Dev. 2019;3(2):25.
24. Matud MP. Gender differences in stress and coping styles. Pers Individ Dif. 2004 Nov 1;37(7):1401–15.
25. Darmawanti I. Hubungan antara tingkat religiusitas dengan kemampuan dalam mengatasi stres (coping stress). J Psikol Teor dan Terap. 2012 Feb 1;2(2):102.
26. P Kumaladewi R, Wawang SS, Fajar AY. Hubungan Antara Tingkat Stres dengan Indeks Massa Tubuh Mahasiswa Fakultas Kedokteran Universitas Islam Bandung. Pros Pendidik Dr. 2018;4(2):71–6.
27. Kusuma UF. Hubungan stres dengan indeks massa tubuh mahasiswa program studi pendidikan dokter Fakultas Kedokteran Universitas Sriwijaya. 2019.
28. Purwanti M, Putri EA, Ilmiawan MI, Wilson, Rozalina. Hubungan tingkat stres dengan indeks massa tubuh mahasiswa PSPD FK Untan. 2017;3(2):1–10.
29. Bryan CJ, Bryan ABO, Baker JC. Associations among state-level physical distancing measures and suicidal thoughts and behaviors among U.S. adults during the early COVID-19 pandemic. Suicide Life-Threatening Behav. 2020 Dec 24;50(6):1223–9.
30. Wang X, Hegde S, Son C, Keller B, Smith A, Sasangohar F. Investigating mental health of US college students during the COVID-19 pandemic: Cross-sectional survey study. J Med Internet Res. 2020 Sep 17;22(9):e22817.
31. Alviani P. Pengaruh adaptasi lingkungan pembelajaran terhadap kemampuan akademik mahasiswa di program studi pendidikan dokter Fakultas Kedokteran Universitas Abulyatama. Jurnal Health Sains: Vol. 1, No. 6, Desember 2020. 2020;1(6):401–6.
32. Jain P, Billaiya R, Malaiya S. International Journal of Physical Sciences and Engineering A correlational analysis of academic stress in adolescents in respect of socio-economic status. 2017;1(1):2550–6951.
33. Azis MZ, Bellinawati N. Faktor risiko stres dan perbedaannya pada mahasiswa berbagai angkatan di Fakultas Kedokteran Universitas Muhammadiyah Palembang. 2015;2(2):197–202.
34. Guo Y, Cheng C, Zeng Y, Li Y, Zhu M, Yang W, *et al*. Mental health disorders and associated risk factors in quarantined adults during the COVID-19 outbreak in China: Cross-sectional study. J Med Internet Res. 2020 Aug 1;22(8):e20328.
35. Federal U, Cat U, Grande R, Studi D, Santos M. Perceived stresses among male students in University of Dammam, Eastern Saudi Arabia: a comparative study. 2012;8(6):1–4.
36. Shaikh BT, Kahloon A, Kazmi M, Khalid H, Nawaz K, Khan NA, *et al*. Students, stress and coping strategies: A case of Pakistani Medical School. Educ Heal. 2004;17(3):346–53.
37. Lewinsohn PM, Striegel-Moore RH, Seeley JR. Epidemiology and natural course of eating disorders in young women from adolescence to young adulthood. J Am Acad Child Adolesc Psychiatry. 2000;39(10):1284–92.
38. Laila NN. faktor faktor yang mempengaruhi gangguan makan pada remaja di Madrasah Aliyah Pembangunan UIN Jakarta. 2013.
39. Sadock, B. J., Sadock, V. A., & Ruiz P. Kaplan and Sadock's Synopsis of Psychiatry: Behavioral sciences/clinical psychiatry. Eleventh e. Philadelphia: Wolters Kluwer; 2015.
40. Kurniawan MY, Briawan D, Caraka RE. Jurnal Gizi Klinik Indonesia Persepsi tubuh dan gangguan makan pada remaja. 2015;11(03):105–14.
41. Jacoby GE. Essstorung und konfession. Gibt es einen zusammenhang zwischen dem typ der essstorung und einer bestimmten religionszugehorigkeit? PPmP Psychother Psychosom Medizinische Psychol. 1993;43(2):70–3.
42. Abraham NK, Birmingham CL. Is there evidence that religion is a risk factor for eating disorders? Eat Weight Disord. 2008;13(4):12–5.
43. Merita M, Hamzah N, Djayusmantoko D. Persepsi Citra Tubuh, Kecenderungan Gangguan Makan dan Status Gizi Pada Remaja Putri di Kota Jambi. J Nutr Coll. 2020;9(2):81–6.
44. Burrows A, Cooper M. Possible risk factors in the development

of eating disorders in overweight pre-adolescent girls. Int J Obes.
45. Kristanto T, Chen WS, Thoo YY. Academic burnout and eating disorder among students in Monash University Malaysia. Eat Behav. 2016 Aug 1;22:96–100.
46. Claydon E, Zullig KJ. Eating disorders and academic performance among college students. J Am Coll Heal. 2020 Apr 2;68(3):320–5.
47. Adelantado-Renau M, Beltran-Valls MR, Toledo-Bonifás M, Bou-Sospedra C, Pastor MC, Moliner-Urdiales D. The risk of eating disorders and academic performance in adolescents: DADOS study. Nutr Hosp. 2018;35(5):1201–7.
48. Mulders-Jones B, Mitchison D, Girosi F, Hay P. Socioeconomic correlates of eating disorder symptoms in an australian population-based sample. jiménez-murcia s, editor. PLoS One. 2017 Jan 31;12(1):e0170603.
49. Haycraft E, Goodwin H, Meyer C. Adolescents' level of eating psychopathology is related to perceptions of their parents' current feeding practices. J Adolesc Heal. 2014 Feb 1;54(2):204–8.
50. Díaz De León Vázquez C, Santoncini CU. Revista mexicana de trastornos alimentarios mexican journal of eating disorders parental negative weight/shape comments and their association with disordered eating behaviors: A systematic review Comentarios negativos paternos acerca de peso/forma corporal y su asociación con las conductas alimentarias de riesgo: Una revisión sistemática. Rev Mex Trastor Aliment. 2019;10(1):134–47.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 312–318

OPEN ACCESS

Original Article

Comparison between Immunohistochemistry and Modified Giemsa Staining for Identification of *Helicobacter spp* in Stomach Biopsy

Fenny Halim[1], Devia Eka Listiana[2], Vega Karlowee[1], Hermawan Istiadi[1], Awal Prasetyo[1], Meira Dewi Kusuma Astuti[2]

[1]Anatomical Pathology Department, Faculty of Medicine, Diponegoro University, Semarang, Central Java, Indonesia
[2]Department of Anatomical Pathology, dr Kariadi Central General Hospital Semarang, Central Java, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.959

Accepted: May 05th, 2022
Approved: September 14th, 2023

Author Affiliation:
Anatomical Pathology Department,
Faculty of Medicine, Diponegoro University,
Semarang, Central Java, Indonesia

Author Correspondence:
Fenny Halim
Dr. Sutomo Street No.16, Semarang,
Central Java 50244, Indonesia

E-mail:
fennyhalim2017@gmail.com

Abstract

Background : *Helicobacter pylori* is classified as a grade 1 carcinogen by the International Agency for Research on Cancer. Identification of *Helicobacter pylori* infection is crucial for the prevention of malignancy. Immunohistochemistry is more specific and sensitive than modified Giemsa because it based on the antigen - antibody binding so it can exclude other organisms. However, it can be expressed in all species of *Helicobacter* genus. The objectives if this study was to compare the identification methods of *Helicobacter spp* in stomach biopsy between modified Giemsa and immunohistochemistry.
Methods : This research was a cross-sectional study. There were 64 biopsies taken by simple random sampling. They consisted of 32 positive and 32 negative *Helicobacter spp* based on the interpretation of modified Giemsa. Statistical analysis using x2 test.
Results : The number of atypical *Helicobacter spp* was 42.%. The number of samples that received Proton Pump Inhibitor (PPI) therapy was 93.75%. *Helicobacter spp* was positive in 31 samples and negative in 33 samples based on the interpretation of immunohistochemistry staining. There was no significant difference (p=0.617) between the identification results of *Helicobacter spp* using immunohistochemistry compared to the Modified Giemsa at both 400x and 1000x magnification.
Conclusion : Modified Giemsa is still reliable for identifying *Helicobacter spp*, especially in classical form, compared to immunohistochemistry. Due to the administration of PPI, there are a lot of cases with atypical form of *Helicobacter spp* which can be differentiated into coccoid form and intraepithelial located. Immunohistochemistry staining is useful in identify these cases.

Keywords : anti-*Helicobacter pylori* immunohistochemistry; *Helicobacter spp*; *Helicobacter pylori* identification; modified Giemsa; staining methods.

INTRODUCTION

Helicobacter pylori is classified as a grade 1 carcinogen by the International Agency for Research on Cancer.[1] Untreated *Helicobacter pylori* infection is a risk factor for gastric adenocarcinoma and primary B-cell lymphoma. The prevalence of *Helicobacter pylori* infection in 2015 was 22.1% in Indonesia.[2–6] *Helicobacter pylori* identification methods encompass non-invasive methods such as urea breath tests and invasive methods such as biopsies. A histopathological examination after biopsy has benefit of identifying *Helicobacter pylori* and simultaneous evaluation of any related mucosal lesions, such as inflammation, ulceration, atrophy, intestinal metaplasia, dysplasia, and/or malignancy.[7–11] The type of staining used includes routine histochemical staining of Hematoxylin Eosin (HE) followed by additional histochemical staining, immunohistochemistry, as well as FISH and PCR tests.[9,12] There has been controversies on these methods. Histochemical staining such as modified Giemsa is cheaper yet unspecific. Immunohistochemistry is specific to genus *Helicobacter* and not expressed in other organisms. However, there is still potential for cross-reactivity with *Helicobacter heilmannii*.[7] FISH and PCR are specific for *Helicobacter pylori* but are less applicable for daily practice. Boldt and Fan recommend routinely additional modified Giemsa histochemical staining,[13,14] while Glickman, Lash, Prabhu, and Loharamtaweethong recommend routine immunohistochemistry staining,[6,8,15,16] and others recommend HE staining for routine analyses; additional staining can be performed as needed.[2,10,11,17–19]

Modified Giemsa staining is routinely used to identify *Helicobacter spp* in Dr. Kariadi Central General Hospial. In this study we compare the identification methods of *Helicobacter spp* in stomach biopsy between modified Giemsa and immunohistochemistry. We aim for further understanding on the benefit of immunohistochemistry use for *Helicobacter spp* identification in daily practice.

METHODS

This research has been approved by the Health Research Ethics Committee of Dr. Kariadi Central General Hospital (1025/EC/KEPK-RSDK/2022) with research permission number DP.02.01/I.II/1485/2022. This analytical study used a cross-sectional design and was conducted from May to November 2022 in Anatomical Pathology Department of Integrated Laboratory Installation in Dr. Kariadi Central General Hospital. There were 320 gastric biopsies from patients undergoing endoscopic procedures with positive *Helicobacter spp* in 70 biopsies (21.9%) and negative in 250 biopsies (78.1%) using modified Giemsa. Simple random sampling was carried out to obtain 32 positive and 32 negative samples. The modified Giemsa slides used the Kwik-Diff (Shandon™) stain. Formalin- fixed, paraffin-embedded (FFPE) block were cut for immunohistochemistry slides with 4 microns in thickness. Antigen retrieval used citrate buffer pH 9.0 and heated in a decloaking chamber at 96°C for 40 minutes. Immunohistochemistry staining used primary monoclonal antibody anti-*Helicobacter pylori* (Biocare CM 383A, clone BC7, immunogen: whole lysate) with 1 hour incubation at 26.5°C. The positive control was attained from Awal Bros Hospital Batam.

Each slide of HE, modified Giemsa and immunohistochemistry was taken 1 field of 400x and 1000x magnification. Identification of *Helicobacter spp* was carried out by 2 observers blindly. Immunohistochemistry staining positivity defined by brown-stained bacterial structure. The bacterial structure is differentiated into 3 forms: classical form (spiral shaped), atypical coccoid and intraepithelial located.[20] Positivity with modified Giemsa staining defined by blue-stained bacterial structure.

Data analysis used SPSS version 22.0. Because there is no expected sample lower than 5 samples in each cell of the table, so it met the requirements for using the x^2 test. The x^2 was used to analyze the comparation in the identification of *Helicobacter spp* based on immunohistochemistry staining and modified Giemsa and the Kappa test to assess interobserver agreement.

RESULTS

The characteristics of the research sample based on the results of Observer I can be seen in Table 1. The patients' age ranges from 12 to 76 years old, with an average age of 51 years and a standard deviation of 14 years. The sample characteristics based on age group showed that *Helicobacter spp* infection was most found in adults (18–59 years). Based on gender, the results of positive identification of *Helicobacter spp* were found more frequently in men (Table 1).

The statistical analysis of the comparison between *Helicobacter spp* identification using immunohistochemistry and modified Giemsa (Table 2) was no significant difference ($p>0.05$), with Kappain moderate level of interobserver agreement (0.717 at 400x magnification and 0.748 at 1000x magnification). Representative images of *Helicobacter spp* cases based on immunohistochemistry and modified Giemsa can be seen in Figure 1.

The majority of the positive samples shows atypical *Helicobacter spp* (Figure 2). Sixty patients (93.75%) received intravenous or oral proton pump inhibitors such as omeprazole, lansoprazole and esomeprazole, whereas the other 4 patients (6.25%) had no information of proton pump inhibitor history. Those 4 patients had no history of antibiotic use and no previous endoscopic procedures and biopsies.

TABLE 1
Characteristics of the research samples

Variable	IHK (+) positive (n)	MG (+) positive (n)	IHK (-) negative (n)	MG (-) negative (n)	Total (n)	(%)
Age						
Younger than 18 years old	0	0	1	1	1	1.56
18–59 years old	21	23	25	23	46	71.88
60 years old or more	10	9	7	8	17	26.56
Gender						
Female	13	15	15	13	28	43.75
Male	18	17	18	19	36	56.25
Endoscopic finding						
Gastric within normal limits	2	2	3	3	5	7.81
Antral Gastritis	8	8	11	11	19	29.69
Erosive Gastritis	5	5	3	3	8	12.50
Chronic Gastritis	1	0	0	1	1	1.56
Superficial Gastritis	0	0	1	1	1	1.56
Gastroduodenitis	0	1	2	1	2	3.13
Duodenal ulcer	2	3	1	0	3	4.69
Pangastritis	7	8	6	5	13	20.31
Gastric ulcer	6	5	6	7	12	18.75

IHK: Immunohistochemistry; MG: Modified Giemsa

TABLE 2
Differences between the identification of *Helicobacter spp* using immunohistochemistry and modified Giemsa based on the evaluation of observer I

Helicobacter spp		Immunohistochemistry		P*
		Positive	Negative	
Modified Giemsa	Positive	17 (53.1%)	15 (46.9%)	0.617
	Negative	14 (43.8%)	18 (56.3%)	

*statistically significant if P value less than 0.05

DISCUSSION

There has been little data in recent studies about the prevalence of *Helicobacter pylori* in general because latest studies focus on the specific strain of *Helicobacter pylori* using molecular test or immunohistochemistry that specific to evaluate the antibiotic resistance types which is still not applicable to do widely in the daily practice.[21] Some recent articles in Indonesia still cite the large scale study about *Helicobacter pylori* prevalence in 2015.[4,22] The overall sample characteristic of this study consistent with previous study in prevalence, age and gender distribution. *Helicobacter pylori* infection is usually found in childhood and symptoms appear in adulthood.[2,10,17] The reduction in infections in the elderly group in this study was directly proportional to the number of patients in that age group. There was higher prevalence of infection in men. Some researchers have linked lifestyles such as smoking, alcohol consumption, and diet types with *Helicobacter pylori* infection.[23,24] *Helicobacter spp* can

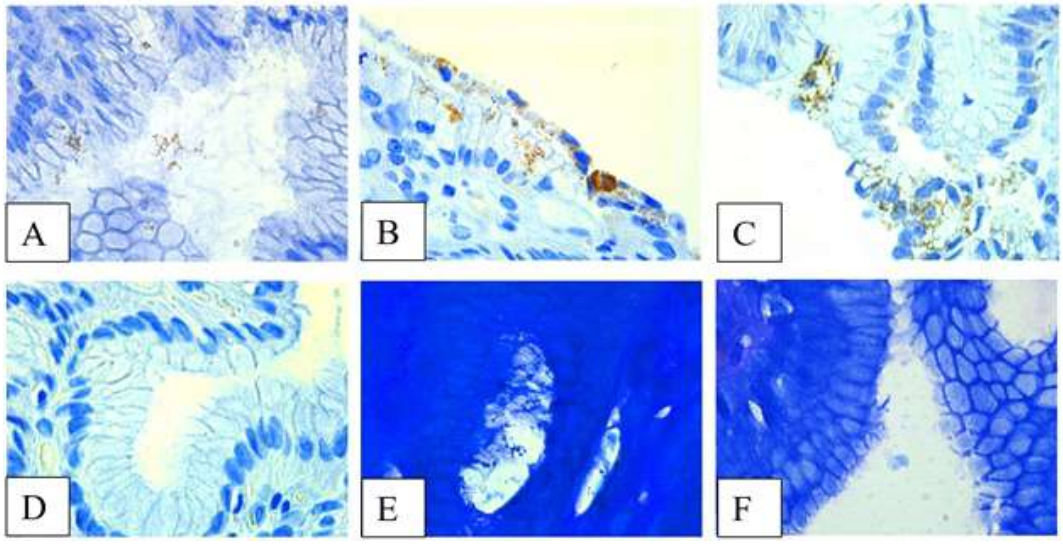


Figure 1. Microscopic figure of immunohistochemistry and modified Giemsa staining in 1000x magnification. A, *Helicobacter spp* in classical spiral form (immunohistochemistry). B, *Helicobacter spp* in atypical coccoid form (immunohistochemistry). C, *Helicobacter spp* are located intraepithelial (immunohistochemistry). D, *Helicobacter spp* negative (immunohistochemistry). E, *Helicobacter spp* positive (modified Giemsa staining). F, *Helicobacter spp* negative (modified Giemsa staining).

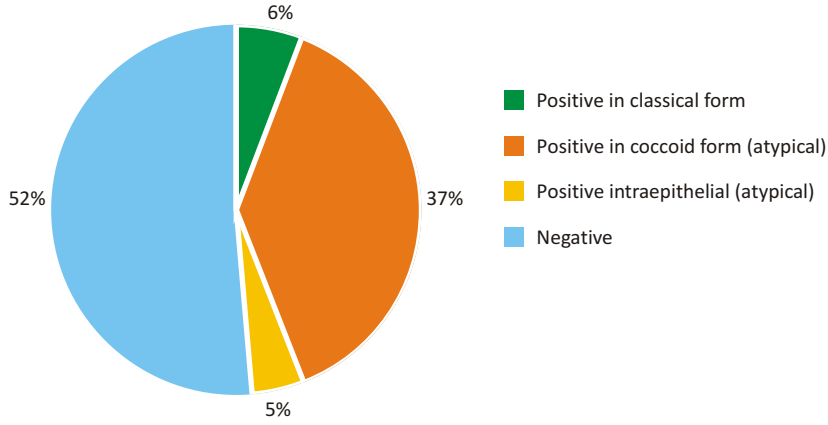


Figure 2. *Helicobacter spp* identification based on the morphology by immunohistochemistry. The positive results were classified as classical form, atypical in coccoid form and atypical in location (intraepithelial).

be found in the normal endoscopic findings, this was in accordance with previous studies which stated that *Helicobacter spp* infection can also be found in endoscopically normal mucosa, redness, and mild gastritis without signs of erosion.[25,26]

The results of the statistical analysis showed no significant difference in the identification of *Helicobacter spp* by modified Giemsa compared to immunohistochemistry. The result of this study is in line with other studies which stated that there was no difference in the identification of *Helicobacter pylori* using immunohistochemistry compared to modified Giemsa,[27,28] but differed from several previous studies which stated that there were significant differences.[8,11] Therefore, routine use of modified Giemsa can still be recommended.

Modified Giemsa staining is reliable to identify classical *Helicobacter spp*. In the normal condition, *Helicobacter pylori* has a classical a spiral or comma shape.[2,29] The classical form can turn to be atypical because of several factors. The atypical form consists of coccoid form and intraepithelial located.[20] When starved of nutrients, *Helicobacter pylori* converts to the coccoid form[30] which is metabolically active, but cannot be cultured. This change can be induced by administration of antibiotics and Proton Pump Inhibitors (PPI). Besides, PPI can affect the histopathological finding including minimal inflammation, atrophic mucosal changes,

changes in the density of bacteria, reduced bacterial colonization of the antrum, and a concomitant increase in bacterial colonization of the corpus, a phenomenon called 'proximal shift'. It can also affect the location of the bacteria that were originally in the mucous layer to become intraepithelial. The number of patients with minimal infection response and atypically shaped bacteria is increasing so that additional staining methods are needed to increase the accuracy of the diagnosis.[8,10–12,30,31]

This study showed that the number of samples of atypical bacteria was higher than in previous studies.[6,8,10,32] This is possibly due to the high number of PPI use prior to endoscopy. A previous study by Nurdin *et al* showed coccoid-shaped bacteria at 26.67% based on immunohistochemistry, although it did not consider the atypical category based on other criterias.[10] Glickman's study showed an atypical number of 10.7% of all samples with positive *Helicobacter pylori* with various methods. The difference may be caused by different criteria for atypical category including rare number of bacteria, minimal inflammation, and location of bacteria.[6]

Modified Giemsa cannot distinguish between *Helicobacter spp* in coccoid forms and cocci bacteria.[7,28,32] False positive results on modified Giemsa may be debris, thick straight rod-shaped bacteria, contaminants from consumed food, or contaminants from water baths that are also stained blue on modified Giemsa. Some studies note that false negatives can occur with modified Giemsa, especially in cases with low bacterial counts or patients undergoing incomplete therapy There is a possibility that the distribution of *Helicobacter pylori* is unequal and focal in the gastric mucosa, especially in cases with low bacterial density. Some small clusters or individual scatters of bacteria may not be sectioned in some slides.[7,11,12] Immunohistochemistry can identify bacteria with an intraepithelial location and coccoid forms because the positive stain colour contrasts with the background and it is specific for *Helicobacter spp* because of the principle of antibody and antigen binding.[7] Immunohistochemistry staining can be helpful in cases of negative bacteria on Hematoxylin Eosin (HE) and modified Giemsa with inflammation, post-therapy, atypical structures, intestinal metaplasia, gland atrophy for efficiency.[7,13,17,33,34]

If only histochemical stains such as Modified Giemsa are available for the identification of *Helicobacter spp* from gastric biopsy, it is necessary to ensure that the bacteria can be detected based on classic morphological features. In daily practice, it is often difficult to diagnose *Helicobacter spp* infection due to the finding of structures resembling atypical bacteria, although statistically there is no significant difference in this study. In such cases, an endoscopy should be performed after discontinuation of the consumption of PPI and antibiotics[33] at least for 2 weeks as in the Urea Breath Test. There should be a consensus with Gastroenterologists and Pathologist regarding patient preparation, criteria for collection, management, delivery of adequate samples for histopathological examination, and optimal Anatomic Pathology diagnosis results for patient management. Although the use of PCR may still be difficult to apply in daily practice, PCR analysis is considered as the gold standard compared to the Urea Breath Test, HE staining, modified Giemsa or immunohistochemistry. Previous studies have shown that immunohistochemistry has the same level of reliability as FISH and real-time PCR.[7,35]

This limitation of this study is on *Helicobacter spp* sampling from the FFPE. The modified Giemsa slides used for this study were readily available slides while the immunohistochemistry slides were newly cut from FFPE borrowed from the archives. The effect of cutting FFPE at different times can cause cutting levels that are too far apart so that there is a large depth level distance and cause differences in results due to sample heterogeneity. Thus, the results of the study may not reflect the actual conditions. This is also found in daily practice and is a common limitation in research.

CONCLUSION

There is no significant difference in identifying *Helicobacter spp* using immunohistochemistry compared with modified Giemsa. This study showed that modified Giemsa is still reliable for identifying *Helicobacter spp*, especially in classical form, compared to immunohistochemistry staining. Due to the administration of PPI, there are a lot of cases with atypical form of *Helicobacter spp* which can be differentiated into coccoid form and intraepithelial located. Immunohistochemistry staining is useful in identify these cases. Further studies are needed to define better comparison between immunohistochemistry and modified Giemsa staining with typical cases of *Helicobacter spp* which has not been treated by PPI. In addition, it is necessary to do research on the use of immunohistochemistry and modification of Giemsa when compared to molecular assays such as PCR as a gold standard.

Acknowledgement

Special gratitude to dr. Devy Serevina, Sp.PA from Awal Bros Batam Hospital who has provided assistance in finding FFPE containing *Helicobacter spp* for positive controls in this study.

REFERENCES

1. Tempera PJ, Michael M, Tageldin O, Hasak S. Gastric Cancer Due to Chronic H. pylori Infection: What We Know and Where We Are Going. Diseases. 2022 Aug 25;10(3):57.

2. Bamanikar S, Khandelwal A, Shah K, Bamanikar A, Buch A. Detection of Helicobacter Pylori in Gastric Biopsies of Patients with Chronic Gastritis: Histopathological and Immunohistochemical Study. Int J Health Sci Res [Internet]. 2018;8:39. Available from: www.ijhsr.org
3. Syam AF, Simadibrata M, Makmun D, Abdullah M, Fauzi A, Renaldi K, *et al*. National Consensus on Management of Dyspepsia and Helicobacter pylori Infection. Vol. 49, Acta Med Indones-Indones J Intern Med. 2017 p. 279–87.
4. Syam AF, Miftahussurur M, Makmun D, Nusi IA, Zain LH, Zulkhairi, *et al*. Risk factors and prevalence of Helicobacter pylori in five largest islands of Indonesia: A preliminary study. PLoS One. 2015;10(11):1–14.
5. Uchida T, Miftahussurur M, Pittayanon R, Vilaichone R, Wisedopas N, Ratanachu-Ek T, *et al*. Helicobacter pylori infection in Thailand: A nationwide study of the CagA phenotype. PLoS One. 2015;10(9):1–13.
6. Glickman JN, Noffsinger A, Nevin DT, Ray M, Lash RH, Genta RM. Helicobacter infections with rare bacteria or minimal gastritis: Expecting the unexpected. Digestive and Liver Disease. 2015 Jul;47(7):549–55.
7. Kocsmár É, Szirtes I, Kramer Z, Szijártó A, Bene L, Buzás GM, *et al*. Sensitivity of Helicobacter pylori detection by Giemsa staining is poor in comparison with immunohistochemistry and fluorescent in situ hybridization and strongly depends on inflammatory activity. Helicobacter. 2017;22(4):1–9.
8. Lash RH, Genta RM. Routine Anti-Helicobacter Immunohistochemical Staining is Significantly Superior to Reflex Staining Protocols for the Detection of Helicobacter in Gastric Biopsy Specimens. Helicobacter. 2016;21(6).
9. Sandhika W. Detection of Helicobacter Pylori Infection in Chronic Gastritis Biopsy Specimen Using Warthin-Starry and Modified Giemsa Stain in Dr Soetomo Hospital Surabaya. Indonesian Journal of Tropical and Infectious Disease. 2019;7(6):150.
10. Nurdin W, Krisnuhoni E, Kusmardi K. Comparison of Helicobacter pylori Detection Using Immunohistochemistry and Giemsa and Its Association with Morphological Changes in Active Chronic Gastritis. The Indonesian Journal of Gastroenterology, Hepatology, and Digestive Endoscopy. 2016;17(1):21.
11. Ginestet F, Guibourg B, Doucet L, Théreaux J, Robaszkiewicz M, Marcorelles P, *et al*. Upfront immunohistochemistry improves specificity of Helicobacter pylori diagnosis. A French pathology laboratory point of view. Helicobacter. 2017 Oct;22(5):e12424.
12. Farouk WI, Hassan NH, Ismail TR, Daud IS, Mohammed F. Warthin-Starry staining for the detection of Helicobacter pylori in gastric biopsies. Malaysian Journal of Medical Sciences. 2018;25(4):92–9.
13. Boldt MS, Pereira RD, Barbosa AJA. Histological identification of H. pylori stained by hematoxylin-eosin and Giemsa: Review for quality control. J Bras Patol Med Lab. 2015;51(2):108–12.
14. Fan CC, Chen CH, Chou C, Kao TY, Cheng AN, Lee AYL, *et al*. A time-saving modified Giemsa stain is a better diagnostic method of Helicobacter pylori infection compared with the rapid urease test. J Clin Lab Anal. 2020;34(4):1–5.
15. Prabhu R K, Jayaraman A. Immunohistochemistry on Helicobacter pylori□: An institutional diagnostic hands-on review. GJRA - Global Journal For Research Analysis. 2017;6(9):155–7.
16. Loharamtaweethong K, Puripat N. Comparison of immunohistochemistry and conventional stains for helicobacter pylori detection in gastric biopsies of patients receiving proton pump inhibitors. Journal of Health Science and Medical Research. 2020;38(4):321–30.
17. Aziz ZW, Saleem SH, Al-Nuaimy HA. Helicobacter pylori in Gastric biopsy: A Histochemical and Immunohistochemical Assessment. Annals of the College of Medicine, Mosul. 2020;41(2):139–47.
18. Pittman ME, Kharar jian A, Wood LD, Montgomery EA, Voltaggio L. Prospective identification of Helicobacter pylori in routine gastric biopsies without reflex ancillary stains is cost-efficient for our health care system. Hum Pathol [Internet]. 2016 Dec;58:90–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0046817716301988
19. Decker L, Routh JK, Snider JS, Hanson JA. Selective staining of gastric biopsies for H. pylori does not affect detection rates or turnaround time and improves cost compared to reflexive staining. Pathol Res Pract. 2017 Jan;213(1):23–6.
20. Riba AK, Ingeneri TJ, Strand CL. Improved Histologic Identification of Helicobacter pylori by Immunohistochemistry Using a New Novocastra Monoclonal Antibody. Lab Med. 2011;42(1):35–9.
21. Miftahussurur M, Syam AF, Nusi IA, Makmun D, Waskito LA, Zein LH, *et al*. Surveillance of Helicobacter pylori Antibiotic Susceptibility in Indonesia: Different Resistance Types among Regions and with Novel Genetic Mutations. PLoS One. 2016 Dec 1;11(12):e0166199.
22. Syam AF, Miftahussurur M, Makmun D, Abdullah M, Rani AA, Siregar GA, *et al*. Management of dyspepsia and Helicobacter pylori infection: the 2022 Indonesian Consensus Report. Gut Pathog. 2023 May 22;15(1):25.
23. Wu W, Leja M, Tsukanov V, Basharat Z, Hua D, Hong W. Sex differences in the relationship among alcohol, smoking, and Helicobacter pylori infection in asymptomatic individuals. Journal of International Medical Research. 2020 May 28;48(5):030006052092603.
24. Xia Y, Meng G, Zhang Q, Liu L, Wu H, Shi H, *et al*. Dietary Patterns are Associated with Helicobacter Pylori Infection in Chinese Adults: A Cross-Sectional Study. Sci Rep. 2016 Aug 30;6(1):32334.
25. Alkhamiss AS. Evaluation of Better Staining Method among Hematoxylin and Eosin, Giemsa and Periodic Acid Schiff-Alcian Blue for the Detection of Helicobacter pylori in Gastric Biopsies. Malaysian Journal of Medical Sciences. 2020 Oct 27;27(5):53–61.
26. Chitkara Y. Upfront Special Staining for Helicobacter pylori in Gastric Biopsy Specimens Is Not Indicated. Am J Clin Pathol. 2015 Jan 1;143(1):84–8.
27. Son JH, Lebwohl B, Sepulveda AR, Lagana SM. Utilization Rate of Helicobacter pylori Immunohistochemistry Is Not Associated with the Diagnostic Rate of Helicobacter pylori Infection. Applied Immunohistochemistry and Molecular Morphology. 2019;27(9):694–8.
28. Patnayak R, Reddy V, Reddy Mk, Rukmangadha N, Jena A, Parthasarathy S. Utility of immunohistochemistry in demonstrating Helicobacter pylori. Oncology, Gastroenterology and Hepatology Reports. 2015;4(1):4.
29. Charitos IA, D'Agostino D, Topi S, Bottalico L. 40 years of Helicobacter pylori: A revolution in biomedical thought. Gastroenterol Insights. 2021;12(2):111–35.
30. Mégraud F, Lehours P. Helicobacter pylori detection and antimicrobial susceptibility testing. Clin Microbiol Rev. 2007;20(2):280–322.
31. Morris GB, Ridgway EJ, Suvarna SK. Traditional stains and modern techniques for demonstrating microorganisms in histology. In: Suvarna SK, Layton C, Bancroft JD, editors. Bancroft's Theory and Practice of Histological Techniques. 8th ed. Sheffield, United Kingdom: Elsevier; 2019. p. 254–77.
32. Buharideen SM, Wijetunge S, Jayamaha T, Sinnadurei A,

Waduge R, Ratnatunga CN. Evaluation of histology as a Helicobacter pylori detection method and analysis of associated problems. Journal of Diagnostic Pathology. 2016;10(2):5.
33. Lee JY, Kim N. Diagnosis of Helicobacter pylori by invasive test: Histology. Ann Transl Med. 2015;3(1):1–8.
34. Kocak C, Kucuk S, Ercihan E, Gundogan M, Sakar C, Uncu A, *et al*. Does anti-Helicobacter pylori immunohistochemical staining has a confirmative role in the definitive diagnosis of negative gastric biopsy samples stained with routine histological stains? Medicine Science | International Medical Journal. 2019;8(4):786.
35. Akeel M, Elhafey A, Shehata A, Elmakki E, Aboshouk T, Ageely H, *et al*. Efficacy of immunohistochemical staining in detecting Helicobacter pylori in Saudi patients with minimal and atypical infection. European Journal of Histochemistry. 2021 Jul 20;65(3).

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 319–323

OPEN ACCESS

Original Article

The Relationship between Obesity and Allergies with Olfactory Disorders in Covid-19 Patients

Yudistira Pratama, Anna Mailasari Kusuma Dewi, Muyassaroh, Riece Hariyati, Willy Yusmawan

Department of Otorhinolaryngology Head Neck Surgery, Faculty of Medicine, Diponegoro University, Semarang, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.745

Accepted: April 14th, 2023
Approved: September 21th, 2023

Author Affiliation:
Department of Otorhinolaryngology Head Neck Surgery, Faculty of Medicine, Diponegoro University, Semarang, Indonesia

Author Correspondence:
Anna Mailasari Kusuma Dewi
Dr. Sutomo Street No.16, Semarang, Central Java 50244, Indonesia

E-mail:
anna_drtht@fk.undip.ac.id

Abstract

Background : The prevalence of olfactory disorders is around 68–85% which occurs in COVID-19 patients with obesity and allergies as risk factors. The abnormalities olfactory pathways can cause by inflammatory response in adipose tissue in obese patients and excessive inflammation due to hyperreactivity of the immune system to allergens in allergic patients. This study aims to analyze the relationship between obesity and allergies to the occurrence of olfactory disorders in COVID-19.
Methods : It was an observational study during pandemic. Subjects were adult COVID-19 patients in the dr. Kariadi Hospital from June to July 2021. Patient with complete medical record ask for olfactory and allergic questionnaire. Patient with nasal tumor were excluded.
Results : We found 100 subjects who meet the criteria. There was a significant difference in smell disturbances between obese and non-obese subjects. (p = 0.019, OR 4.99). There was a significant difference (p=0.001) in complaints of olfactory disorders between allergic and non-allergic subjects, whereas all allergic subjects experienced olfactory disorders.
Conclusion : Obesity and allergies are corelated with impaired smell in COVID-19 patients.

Keywords : COVID-19, olfactory disorders, obesity, allergies

INTRODUCTION

Coronavirus Disease (COVID-19) is a form of inflammation in upper respiratory mucosal.[1] It is known as severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) caused by a large single-stranded RNA virus.[2,3] Symptoms include fever, dyspnea, cough, headache, sore throat, stuffy nose, runny nose, weakness, and loss of smell.[4] Several studies have stated that patients who have certain co-morbidities can increase the severity of COVID-19. One of the most reported cases is the occurrence of olfactory disorders.[4,5] Olfactory disorders are defined as loss of smell such as anosmia (patient loss their ability to smell) and hyposmia (patient loss their ability to smell partially). Pathological processes along the olfactory pathway, such as inflammation, infectious, tumoral, or congenital processes, result in conductive or sensorineural disturbances.[6,7] Olfactory disturbance is one of the clinical manifestations and occurs in the beginning of COVID-19 disease.[7,8]

The actual risk for COVID-19 are obesity and allergies. In obesity activated dendritic cells in vitro express less CD83 (a marker of dendritic cell maturation) and also produce IL-10. IL-10 inhibits the ability of dendritic cells to stimulate CD4+ T cells and downregulates MHC-II, CD86 (co-stimulator signal protein), and antigen presentation to CD4+ T cells. High leptin concentrations in obesity, which are also known to trigger IL-6 and TNF-α production from adipose tissue and increase the risk of viral infections.[9] Hyperactivity of the inflammatory response can cause a cytokine storm that causes systemic inflammation throughout the body. This inflammation or inflammation can cause defects in the olfactory pathways that lead to disturbances in olfactory function. In addition, viral infection through the enzyme converting angiotensin 2 (ACE 2) can cause inflammation of the olfactory submucosa which disrupts olfactory integrity and function.

In allergies, there is type 2 inflammation, and the mediator is eosinophils. IgE-mediated hypersensitivity reactions explain the occurrence of allergic disease. An allergen is captured by an antigen-presenting cell (APC), which is then processed and presented to T-helper lymphocyte cells. This communication takes place due to the presence of specific human leukocyte antigen receptors present on both APCs and specific T-cell receptors. TH2 cells present the allergen or allergy epitope on B lymphocytes, which have B cell receptors for that antigen. All of these receptors must be present for an allergic response to occur. IL-4 and other allergic cytokines can trigger B cells to turn into IgE-producing plasma cells. The IgE travels through the circulatory system and binds to IgE receptors on basophils and mast cells. Re-exposure to specific allergens causes IgE-mediated degranulation of basophils and mast cells. This will release inflammatory mediators such as histamine. Histamine binds to histamine receptors on endothelial cells and vascular smooth muscle causing vasodilation and increasing permeability. So that the symptoms of rhinorrhea, sneezing and stuffy nose arise.[10] The olfactory sensory neuron will suffer if the olfactory mucosa is inflamed.[11] In COVID-19 patients there are also olfactory disturbances caused by excessive inflammation which results in damage to the olfactory neurons. Therefore, in COVID-19 patients who have accompanying allergies, the symptoms of olfactory disturbances can worsen.[5] The objective of this study is to assess the correlation between obesity and allergies with the occurrence of impaired sense of smell in COVID-19.

METHODS

This is an observational study with a cross-sectional design. It was conducted at Dr. Kariadi hospital in Semarang, Indonesia. Subjects are COVID-19 patients who were recorded in medical records from June to July 2021. The sampling method used was consecutive sampling. Adult patients (age 18–60 years) with complete medical record were included. We exclude patient with nasal tumor. The outcome are olfactory disorder, obesity and allergies. The *American Academy of Otolaryngology Head and Neck Surgery* (AAOHNS) questionnaire was use to assess the olfactory disorder in Covid-19. It consists of 17 question about anosmia and dysgeusia. Body mass index from WHO was use to asses obesity, BMI >25 were count as obesity. Patient with history of asthma, food allergy and others allergy or patient who had 2 or more allergic rhinitis symptoms was define as positive allergy. The blood sugar test was collect to determine patient with diabetic and non-diabetic using Indonesian Society of Endocrinology criteria.

Data was analyzed with Fischer's exact test. This research has received permission from the Health Research Ethics Commission, Faculty of Medicine, Diponegoro University/Dr. Kariadi Semarang and the Medical Council of RSUP Dr. Kariadi Semarang No.1038/EC/KEPK-RSDK/2022

RESULTS

COVID-19 patients in June – July 2021 at Dr. Kariadi hospital found as many as 3565 patients. The characteristics of the study from 100 subjects who met the criteria shows in Table 1. The subjects aged were 21–60 years with the median was 36 years. Female patients were more than male (60%: 40%). This study found that patients with olfactory disorders is 89%, obesity is 61%, and allergies is 61%. Most patients didn't have hypertension (92%) and diabetic (88%).

In subjects with obesity, 95.1% of subjects experienced olfactory disorders. There was a significant

TABLE 1
Characteristics of research subjects

Variable		Olfactory disorder	
		Yes	No
Obesity	Yes	58 (95.1)	3 (4.9)
	No	31 (79.5)	8 (20.5)
Allergies	Yes	61 (100)	0 (0)
	No	28 (71.8)	11 (28.2)
Diabetes	Yes	8 (100)	0 (0)
	No	81 (88)	11 (12)
Hypertension	Yes	12 (100)	0 (0)
	No	77 (87.5)	11 (12.5)

TABLE 2
Characteristics of research subjects

Variable		Olfactory disorder		p	r
		Yes	No		
Obesity	Yes	58 (95.1)	3 (4.9)	0.019*	0.236
	No	31 (79.5)	8 (20.5)		
Allergies	Yes	61 (100)	0 (0)	<0.001*	0.402
	No	28 (71.8)	11 (28.2)		

Fisher exact test, * Significant (p < 0.05)

difference (p=0.019) OR 4.99 CI (1.23–20.17) in complaints of smell disorders between obese and non-obese subjects. The obese patients have a risk 4.99 times greater for experiencing olfactory disorders than subjects who are not obese. In the obesity contingency coefficient test on olfactory disorders, it has a weak positive correlation r 0.236 (Table 2).

In subjects with allergies, all subjects experienced olfactory disturbances. There was a significant difference (p=0.001) in complaints of smell disturbances between allergic and non-allergic subjects. In the obesity contingency coefficient test on olfactory disorders, it has a moderate positive correlation r 0.402 (Table 2).

All subjects with diabetes experienced olfactory disturbances. There was no difference (p=0.380) in olfactory complaints between diabetic and non-diabetic subjects. All hypertensive subjects experienced olfactory disorders. There was no difference (p=0.226) in olfactory complaints between hypertensive and non-hypertensive subjects.

DISCUSSION

Prevalence and characteristics of COVID-19 patients in previous studies conducted in several regions obtained almost the same results where COVID-19 patients were dominated by subjects aged 19–40 years who were dominated by women.[12,13,14] This condition indicates that the population detected by COVID-19 is concentrated in the productive age group. Recent studies have shown that the molecular and immune systems in male patient are fundamentally different with female when exposed to COVID-19. Several studies have described the role of ACE2, TMPRSS2, and the immune system in COVID-19 sex dimorphism. ACE2 is an X-linked gene located in the Xp22.22 region with a length of 41.04 kb. ACE2 is one of the X chromosome genes that 'escapes' the X chromosome inactivation mechanism, so the expression level of ACE2 is found higher in female than in male.[15,16,17]

The were 19.4% to 85.6% COVID-19 patients associated with olfactory dysfunction.[20,21] The prevalence

of olfactory dysfunction as the early symptom of COVID-19 are 11.8% to 27%.[21] Based on the initial results of the AAO-HNS "Anosmia COVID-19 Reporting Tool", reporting that nearly 75% suffer from anosmia noted that the event started before the diagnosis of COVID-19. Analysis showed that ability to smell worsened significantly from initial to two weeks after diagnosis but normalized within a month after confirming COVID-19.[22, 23]

The is unclear pathogenesis of the impairment of smell and taste related with COVID-19, the possibility is that the effect of the virus in the nasal epithelium and the central nervous system.[24] SARS-CoV-2 invaded the olfactory epithelium and infect the human central nervous system.[25] This virus enters the central nervous system through the peripheral olfactory or trigeminal nerves. Because of damage of the trigeminal and olfactory nerve can cause smell and taste disturbances. Another pathogenesis because of decreasing reflex sensitivity of sensory neurons cause by SARS-CoV-2 infection.[26]

In patients with obesity, the volume of the olfactory bulb is significantly lower than normal weight. Decreased olfactory bulb volume may be a consequence of obesity caused by metabolic and endocrine disturbances. Olfactory dysfunction is more prominent in severely obese patients than overweight or moderately obese patients. The elevation of leptin in obesity can inhibit olfactory function.[27] The HOMA-IR score asses the effect of insulin resistance on the relationship between BMI and olfactory function. The lower olfactory function associate with high BMI through insulin resistance. The early changes of olfactory function in obesity signing with decreased olfactory bulb volume.[28, 29, 30]

In a previous study, olfactory dysfunction in allergic rhinitis patients found that 50% of allergic rhinitis patients experienced hyposmia. In some cases, allergic rhinitis is related with an elevation of the olfactory threshold.[31] Although it has long been thought that the main cause of olfactory dysfunction in rhinitis is secondary caused by mucosal inflammation or nasal polyps that obstruct airflow across the olfactory epithelium. Other mechanisms include changes in the composition of nasal secretions, recurrent acute viral infection, or direct damage to the olfactory epithelium by an allergic inflammatory infiltrate.[32] Rhinitis has the potential to impair olfactory abilities in several ways. Airway constriction caused by inflammation can alter or block airflow through the nasal cavities, reducing the access of volatile compounds to sensory receptor cells, which are in relatively protected areas of the nasal passages.[33] Alterations in the composition and transport of the aqueous slime layer through which odorants must pass can interfere with access to or removal from receptor sites.[34]

Based on previous research there are other comorbid such as diabetes and hypertension. It showed that the odor recognition score was lower in diabetic patients (68 subjects), either type 1 and type 2 diabetes mellitus compared to 30 controls.[35] Similar results in a epidemiological study among 1900 adults in Sweden, the result showed even though diabetes was not associated with olfactory dysfunction in 1387 adults, it was considered as a risk factor for anosmia with odds ratio (OR) 2.6 and interval 95% confidence (CI) 1.3–5.5.[36] In a longitudinal cohort study of changes in smell and taste perceptions, it was found that individuals with changes in taste and smell perceptions had greater increases in systolic blood pressure and mean arterial pressure compared to individuals without taste and smell perceptions changes.[37] In this study we found there only few patient with diabetic and hypertension

The limitation of this study is that allergies were only evaluated based on the history of the patient's history, and no previous allergy diagnostic tests were carried out. In olfactory disorders only using a questionnaire does not use objective examination. Suggestions for further research are to carry out allergy diagnostic tests, specific Ig E or skin prick test, and examination of the sniffing stick test for olfactory disorders to get accurate results.

CONCLUSION

A relationship was found between obesity and allergies to olfactory disease in COVID-19 patients. Subjects with obesity are at risk of 4.99 times greater for experiencing olfactory disorders than subjects who are not obese.

REFERENCES

1. Baloch S, Baloch MA, Zheng T, Pei X. The Coronavirus Disease 2019 (COVID-19) Pandemic. Tohoku J Exp Med. 2020;250(4):271-8.
2. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020;24:91-8.
3. Tanno LK, Demoly P, Martin B, Berstein J, Morais-Almeida M, Levin M, *et al*. Allergy and coronavirus disease (COVID-19) international survey: Real-life data from the allergy community during the pandemic. World Allergy Organ J. 2021;14(2):100515.
4. da Rosa Mesquita R, Francelino Silva Junior LC, Santos Santana FM, Farias de Oliveira T, Campos Alcantara R, Monteiro Arnozo G, *et al*. Clinical manifestations of COVID-19 in the general population: systematic review. Wien Klin Wochenschr. 2021;133(7-8):377-82.
5. Aziz M, Goyal H, Haghbin H, Lee-Smith WM, Gajendran M, Perisetti A. The Association of "Loss of Smell" to COVID-19: A Systematic Review and Meta-Analysis. Am J Med Sci. 2021;361(2):216-25.
6. Xydakis MS, Dehgani-Mobaraki P, Holbrook EH, Geisthoff UW, Bauer C, Hautefort C, *et al*. Smell and taste dysfunction in patients with COVID-19. Lancet Infect Dis. 2020;20(9):1015-6.
7. Khan AS, Hichami A, Khan NA. Obesity and COVID-19: Oro-Naso-Sensory Perception. J Clin Med. 2020;9(7).
8. Sulistyani, Winarsih DS. Characteristics of anosmia cases in

COVID-19 patients: A systematic review. International Summit on Science Technology and Humanity. 2020;1(1):8.
9. Dugail I, Amri EZ, Vitale N. High prevalence for obesity in severe COVID-19: Possible links and perspectives towards patient stratification. Biochimie. 2020;179:257-65.
10. Sivam A, Jeswani S, Reder L, Wang J, DeTineo M, Taxy J, *et al*. Olfactory cleft inflammation is present in seasonal allergic rhinitis and is reduced with intranasal steroids. Am J Rhinol Allergy. 2010;24(4):286-90.
11. Langdon C, Guilemany JM, Valls M, Alobid I, Bartra J, Davila I, *et al*. Allergic rhinitis causes loss of smell in children: The OLFAPEDRIAL study. Pediatr Allergy Immunol. 2016;27(8):867-70.
12. Setiadi W, Rozi IE, Safari D, Daningrat WOD, Johar E, Yohan B, *et al*. Prevalence and epidemiological characteristics of COVID-19 after one year of pandemic in Jakarta and neighbouring areas, Indonesia: A single center study. PLoS One. 2022;17(5):e0268241.
13. Hidayati D. Profil Penduduk Terkonfirmasi Positif COVID-19 dan Meninggal: Kasus Indonesia dan DKI Jakarta. Jurnal Kependudukan Indonesia. 2020;1(1):8.
14. Iriani D, Dewi AMK, Hariyati R, Santosa YI. Prevalensi, Onset, dan Durasi Gangguan Olfaktori dan Gangguan Gustatori pada Kasus COVID 19. Medica Hospitalia. 2022;9(2):6.
15. Doerre A, Doblhammer G. The influence of gender on COVID-19 infections and mortality in Germany: Insights from age- and gender-specific modeling of contact rates, infections, and deaths in the early phase of the pandemic. PLoS One. 2022;17(5):e0268119.
16. Achidsti A, Sari OK, Ratnasari DP, Ningsih NS, Widyaningrum AR, Maji JS, *et al*. Women's Resilience and Vulnerability in Facing COVID-19 in DKI Jakarta and East Java. Jurnal Kependudukan dan Kebijakan. 2020;28(2).
17. Gemmati D, Bramanti B, Serino ML, Secchiero P, Zauli G, Tisato V. COVID-19 and Individual Genetic Susceptibility/Receptivity: Role of ACE1/ACE2 Genes, Immunity, Inflammation and Coagulation. Might the Double X-chromosome in Females Be Protective against SARS-CoV-2 Compared to the Single X-Chromosome in Males? Int J Mol Sci. 2020;21(10).
18. Cortis D. On Determining the Age Distribution of COVID-19 Pandemic. Front Public Health. 2020;8:202.
19. Davies NG, Klepac P, Liu Y, Prem K, Jit M, group CC-w, *et al*. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med. 2020;26(8):1205-11.
20. Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and Ageusia: Common Findings in COVID-19 Patients. Laryngoscope. 2020;130(7):1787.
21. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, *et al*. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol. 2020;277(8):2251-61.
22. Hopkins C, Alanin M, Philpott C, Harries P, Whitcroft K, Qureishi A, *et al*. Management of new onset loss of sense of smell during the COVID-19 pandemic - BRS Consensus Guidelines. Clin Otolaryngol. 2021;46(1):16-22.
23. Patel A, Charani E, Ariyanayagam D, Abdulaal A, Denny SJ, Mughal N, *et al*. New-onset anosmia and ageusia in adult patients diagnosed with SARS-CoV-2 infection. Clin Microbiol Infect. 2020;26(9):1236-41.
24. Chen L, Zheng S. Understand variability of COVID-19 through population and tissue variations in expression of SARS-CoV-2 host genes. Inform Med Unlocked. 2020;21:100443.
25. Keyhan SO, Fallahi HR, Cheshmi B. Dysosmia and dysgeusia due to the 2019 Novel Coronavirus; a hypothesis that needs further investigation. Maxillofac Plast Reconstr Surg. 2020;42(1):9.
26. Richardson BE, Vander Woude EA, Sudan R, Thompson JS, Leopold DA. Altered olfactory acuity in the morbidly obese. Obes Surg. 2004;14(7):967-9.
27. Getchell TV, Kwong K, Saunders CP, Stromberg AJ, Getchell ML. Leptin regulates olfactory-mediated behavior in ob/ob mice. Physiol Behav. 2006;87(5):848-56.
28. Riera CE, Dillin A. Emerging Role of Sensory Perception in Aging and Metabolism. Trends Endocrinol Metab. 2016;27(5):294-303.
29. Tsai SY, Gildengers AG, Hsu JL, Chung KH, Chen PH, Huang YJ. Inflammation associated with volume reduction in the gray matter and hippocampus of older patients with bipolar disorder. J Affect Disord. 2019;244:60-6.
30. Riviere S, Soubeyre V, Jarriault D, Molinas A, Leger-Charnay E, Desmoulins L, *et al*. High Fructose Diet inducing diabetes rapidly impacts olfactory epithelium and behavior in mice. Sci Rep. 2016;6:34011.
31. Velluzzi F, Deledda A, Onida M, Loviselli A, Crnjar R, Sollai G. Relationship between Olfactory Function and BMI in Normal Weight Healthy Subjects and Patients with Overweight or Obesity. Nutrients. 2022;14(6).
32. Guss J, Doghramji L, Reger C, Chiu AG. Olfactory dysfunction in allergic rhinitis. ORL J Otorhinolaryngol Relat Spec. 2009;71(5):268-72.
33. Suzuki Y, Farbman AI. Tumor necrosis factor-alpha-induced apoptosis in olfactory epithelium in vitro: possible roles of caspase 1 (ICE), caspase 2 (ICH-1), and caspase 3 (CPP32). Exp Neurol. 2000;165(1):35-45.
34. Dalton P. Olfaction and anosmia in rhinosinusitis. Curr Allergy Asthma Rep. 2004;4(3):230-6.
35. Gouveri E, Papanas N. Olfactory Dysfunction: A Complication of Diabetes or a Factor That Complicates Glucose Metabolism? A Narrative Review. J Clin Med. 2021;10(23).
36. Chan JYK, Garcia-Esquinas E, Ko OH, Tong MCF, Lin SY. The Association Between Diabetes and Olfactory Function in Adults. Chem Senses. 2017;43(1):59-64.
37. Liu YH, Huang Z, Vaidya A, Li J, Curhan GC, Wu S, *et al*. A longitudinal study of altered taste and smell perception and change in blood pressure. Nutr Metab Cardiovasc Dis. 2018;28(9):877-83.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 324–333

OPEN ACCESS

Original Article

Factors Affecting Gastric Perforation Patient Outcome with History of Arthritis and Long Term Use of NSAIDs in Dr. Kariadi Semarang Period 2020–2022

Leonardo Cahyo Nugroho[1], Ardi Fauzi[2], Agus Priambodo[3]

[1]General Surgery, Faculty of Medicine, Duta Wacana Christian University Yogyakarta, Indonesia
[2]General Surgery, Faculty of Medicine, Diponegoro University Semarang, Indonesia
[3]Orthopedic Surgery, Faculty of Medicine Diponegoro University Semarang, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.978

Accepted: June 20th, 2023
Approved: October 03th, 2023

Author Affiliation:
General Surgery, Faculty of Medicine,
Duta Wacana Christian University Yogyakarta,
Indonesia

Author Correspondence:
Leonardo Cahyo Nugroho
Dr. Wahidin Sudirohusodo Street No.5-25,
Yogyakarta, Daerah Istimewa Yogyakarta 55224,
Indonesia

E-mail:
leonardocahyo@staff.ukdw.ac.id

Abstract

Background : The incidence of gastric perforation gives a high mortality outcome. The second most common cause of gastric perforation is long-term use of NSAIDs. In cases of arthritis during the COVID-19 pandemic, a conservative therapeutic approach and administration of NSAIDs are preferred. Due to this, researchers want to know the factors affecting gastric perforation cause by NSAIDs.
Methods : An analytic descriptive study with a retrospective cohort study design, using electronic medical records of patients at RSUP Dr. Kariadi Semarang from January 2020 – December 2022. Data collected was in the form of demographics, diagnoses, procedures, preoperative conditions, scoring system, and outcome.
Results : PULP score, one of prognostic factor, has a good level of significance compared to other scoring systems in determining the prognostic mortality of patients with gastric perforation. The combination of variables between the type of NSAIDs and the type of arthritis has a direct correlation with a positive inter-variable power of 86.7% and a significance of 0.049 on patient outcome.
Conclusion : NSAIDs pose a risk of gastric perforation in long-term use. tNSAIDs carry a higher risk inducing gastric perforation than selective NSAIDs.

Keywords : NSAIDs, Gastric Perforation, Arthritis, Scoring System

INTRODUCTION

The incidence of complications from peptic ulcers has not decreased. Bleeding and perforation are the most common complications. In a study conducted by Dadfar A *et al* in Norway, it was stated that the incidence of this complication is more common in women than men, and this risk increases with age > 65 years in the last 3 decades. NSAIDs can cause mucosal injury by inhibiting cyclo-oxygenase (COX)-1 by reducing cytoprotective mucosal prostaglandins and reducing secretion of the protective bicarbonate mucus barrier in the stomach and small intestine.[1]

NSAIDs are recommended as first-line therapy for arthritis to relieve inflammatory pain. In cases of arthritis during the COVID-19 pandemic, conservative therapeutic approaches and administration of painkillers have been widely used. The increase in the incidence of COVID-19 that occurred in 2020 has caused increasing health problems in the community such as postponement of elective surgery cases including in the musculoskeletal field.[3,4] As in a study conducted by Mikko uimonen *et al* it was said that the waiting time for surgery in the musculoskeletal field in Finland during the COVID-19 pandemic was a lengthening of the waiting time between 93 days to 100 days. Due to the limitations of the COVID-19 virus detection and screening system in the pandemic era resulted in limiting doctors' practice time and postponement of elective surgeries to reduce the risk of COVID-19 transmission in face-to-face outpatient sessions or in elective arthritis surgeries.[1,2,5,6]

According to the Indonesian Orthopedic Association in Orthi – Magz – May 2020, surgery is prioritized in orthopedic emergency cases and in patients who have complaints of severe pain in the musculoskeletal system that does not subside with medical administration.[7] Based on the problems above, the author wants to see which factors could affect the outcome of patients with gastric perforation due to NSAIDs and by finding these affecting factors, it is hoped that steps can be taken and consider to prevent gastric perforation.

METHODS

An analytic descriptive study with a retrospective cohort study design, using data sources obtained from patients electronic medical records at RSUP Dr. Kariadi Semarang from January 2020 – December 2022. Demographic data of patients with gastric perforation, the relationship between variables and outcomes, and the power between variables to affect outcomes are presented in the form of tables, graphs and diagrams which were processed using the SPSS ver 23 programming. Discussion of results research is presented using comparisons, literature review and data synthesis.

Patients who were included on this study which have diagnosed with gastric perforation due to long-term uses of NSAIDs and received definitive surgical therapy at Dr. Kariadi Semarang between January 2020 to December 2022. Patients who were excluded were patients who met the inclusion criteria but did not have data completed / insufficient of independent variables needed for data synthesis and patients whose outcome died with the main cause not from gastric perforation and its direct complications. Researchers have obtained research approval with ethical clearance from the Health Research Ethics Committee of RSUP Dr. Kariadi Semarang.

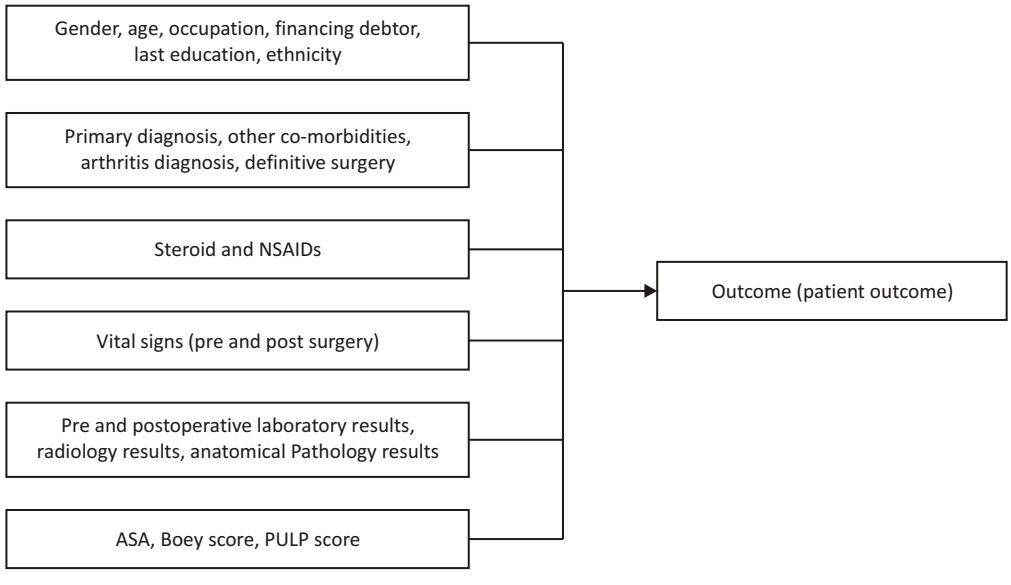


Figure 1. Variables that affects to outcome

RESULTS

Table 1 shows subject demographic caracteristics. Table 2 shows characteristics of independent variables. Table 3 shows characteristics of independent variables and outcome.

DISCUSSION

Gastric perforation is closely related to long-term use of anti-inflammatory drugs. NSAIDs are known to be the second causative factor in gastric perforation after Helicobacter pylori infection in initiating peptic ulceration in the upper GI tract. NSAIDs cause mucosal injury due to cyclo-oxygenase (COX)-1 inhibition along

TABLE 1
Subject Demographic Characteristics

No	Characteristics of Subjects	Type of Characteristics	Frequency	Percentage (%)
1	Gender	Male	4	66.7
		Female	2	33.3
2	Age	< 65 years	5	83.3
		More 65 years	1	16.6
3	Occupation	Housewaives	2	33.3
		Fisherman	1	16.7
		Private employees	2	33.3
		Farmer	1	16.7
4	Debtor	COVID funding	1	16.7
		Private	0	0
		JKN Non PBI	1	16.7
		JKN PBI	4	66.7
5	Last education	Elementary	3	50.0
		Junior High School	1	16.7
		Senior High School	1	16.7
		Non complete elementary	1	16.7
6	Ethnic Group	Java	6	100

TABLE 2
Characteristics of Independent Variables

No	Variable	Characteristic (Factors Affeecting)	Patient Outcome		Significancy
			Live	Death	
Diagnosis					
1	Diagnosis	Peritonitis generalisata ec perforasi corpus gaster	2	3	1.000
		Peritonitis generalisata ec perforasi antrum gaster	1	0	
2	Other Comorbid	None	1	0	1.000
		Comorbid (heart disease, metabolic, kidney disease, liver disease, DM, HT)	2	3	

TABLE 2. Continued

No	Variable	Characteristic (Factors Affeecting)	Patient Outcome		Significancy
			Live	Death	
3	Sepsis	None	3	1	0.400
		Sepsis existance	0	2	
4	Arthritis	OA genu	1	2	0.189
		OA hip	0	1	
		RA genu	12	0	
		RA hip	0	0	
5	Definitive operation	Laparotomy omental plug	2	3	1.000
		Laparotomy omental patch	1	0	
Use of anti-inflammatory types					
6	Use of steroids	No usage history	2	3	1.000
		Has a long history of use	1	0	
7	NSAID type	Traditional NSAID	2	3	0.208
		COX-2 selective inhibitor	1	0	
Additional Examination					
8	Hb pre operation	Not diagnosed with anemia	1	1	0.800
		Diagnosed with anemia	2	2	
9	Leucosyt pre operation	Under 11.000	2	2	0.800
		Above 11.000	1	1	
10	Trombosit pre operation	150.000 – 400.000	3	3	1.000
		Under 150.000 or above 400.000	0	0	
11	Creatinine pre operation	Low (< 1.47)	2	2	1.000
		High (> 1.47)	1	1	
12	Natrium pre operation	Normal	3	0	0.05
		High	0	1	Linier 0.038
		Low	0	2	
13	Kalium pre operation	Normal	1	2	0.513
		High	1	0	
		Low	1	1	
14	Chlorida pre operation	Normal	2	1	0.317
		High	1	1	
		Low	0	1	
15	Hb post operation	Not diagnosed with anemia	0	1	0.317
		Diagnosed with anemia	3	2	

TABLE 2. Continued

No	Variable	Characteristic (Factors Affeecting)	Patient Outcome		Significancy
			Live	Death	
16	Leucosyt post operation	Under 11.000	2	2	1.000
		Above 11.000	1	1	
17	Trombosit post operation	150.000–400.000	2	2	1.000
		Under 150.000 or above 400.000	1	1	
18	Patologic anatomy	Chronic gastritis	3	2	0.208
		Non chronic gastritis	0	1	
14	Chlorida pre operation	Normal	2	1	0.317
		High	1	1	
		Low	0	1	
15	Hb post operation	Not diagnosed with anemia	0	1	0.317
		Diagnosed with anemia	3	2	
16	Leucosyt post operation	Under 11.000	2	2	1.000
		Above 11.000	1	1	
17	Trombosit post operation	150.000–400.000	2	2	1.000
		Under 150.000 or above 400.000	1	1	
18	Patologic anatomy	Chronic gastritis	3	2	0.208
		Non chronic gastritis	0	1	
Physical Examination					
19	Pulse rate pre operation	60–100x/ minute	1	1	1.000
		Below 60 or above 100x/minute	2	2	
20	Systolic pre operation	more than equal to 100	3	1	0.400
		under 100	0	2	
21	RR pre operation	16–22x/ minute	0	0	1.000
		Above 22x/minute	3	3	
22	Temp pre operation	Normal (36–37.5°C)	0	0	1.000
		High (above 37.5°C)	3	3	
23	Pulse rate post operation	60–100x/ minute	3	1	0.400
		Below 60 or above 100x/minute	0	2	
24	Systolic post operation	more than equal to 100	3	1	0.400
		under 100	0	2	
25	RR post operation	16–22x/ minute	3	1	0.400
		Above 22x/minute	0	2	
26	Temp post operation	Normal (36–37.5°C)	3	3	1.000
		High (above 37.5°C)	0	0	

TABLE 2. Continued

No	Variable	Characteristic (Factors Affeecting)	Patient Outcome		Significancy
			Live	Death	
Scoring system					
27	ASA pre operation	ASA 1	0	0	0.400
		ASA 2	0	0	
		ASA 3	2	0	1.000
		ASA 4	1	3	
28	BOEY Score	1 (mortality 10%)	1	0	0.189
		2 (mortality 55,5%)	2	1	
		3 (mortality 100%)	0	2	
29	PULP Score	Low risk (0–7)	3	0	0.05
		High risk (8–18)	0	3	Corelation Spearman 0.001 Linier 0.025

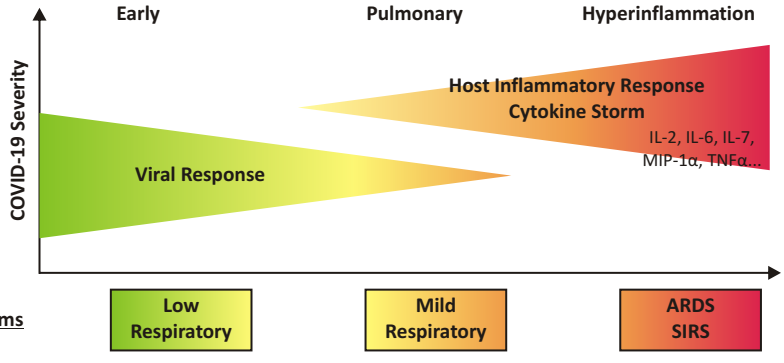
TABLE 3
Characteristics of Independent Variables and Outcome

No	Independent variable	R Square	Significancy
1	Type of NSAID used and type of arthritis	86.7%	0.049
2	Sepsis and other comorbid	55.6%	0.296
3	Operations (omental plug and patch) on the main diagnosis and perforation site	50%	0.354
4	Preoperative leukocytes and Hb	15%	1.000
5	Preoperative sodium, potassium, chloride	91.1%	0.130
6	Preoperative systolic and pulse	66.7%	0.192
7	Hb, leukocytes, and postoperative thrombocytes	33.3%	0.808
8	Preoperative ASA and PA results	55.6%	0.296

with reduced cytoprotective mucosal prostaglandins and reduced secretion of protective mucobicarbonate inhibitors in the stomach and duodenum.[8,9]

In a study conducted by Dadfar A *et al* who conducted a case study in Norway at the beginning of the 2000-2020 decade, it was stated that the incidence of complications due to NSAIDs was more common in women than men and this risk increased with age >65 years in 2 last decade.1 This is different from research at Dr. Kariadi General Hospital for the period 2020–2022 which found that males were more exposed to gastric perforations (66.7%) than females. Age under 65 years also has a higher percentage than those aged 65 years and over at 83.3%. The cut-off age of 65 years in this study was adjusted according to the PULP prognostic score, which said those over 65 years of age had a higher tendency of mortality. This can be confirmed logically because increasing age increases the decline in the function of vital organs which will assume a decrease in life expectancy.

Differences in the type of work, financing status (debtor), and the latest education in this study did not make a significant difference. The author also has not



OA Therapies	Early Pulmonary	Pulmonary / Hyperinflammation
NSAIDs	✓	~
Paracetamol	✓	✓
Corticosteroids	~	~
Opioids	Weak ✓ / ~ strong/IS	Weak ✓ / ~ strong/IS
mAbs	✓	✓

✓ Continue ~ Critical risk/benefit

Figure 2. Classification of COVID-19 disease states and overlaywith OA-associated treatments. The figure shows the escalatingphases of disease progression with COVID-19, with associated symptoms and the relevance of OA treatments with their possible continuation, disontinuation, or cos/benefit depending on available literature data. ARDs, cute respiratory distress syndrome:COVID-19, coronavirus disease 2019; IL, interleukin; IS, immunosuppressive; mAbs, monoclonal antibodies; MIP, macrophage inflammatory protein; NSAISs, nonsteroidal antiinflammatory drugs; OA, osteoarthritis; SIRS, systemic inflammatory response syndrome; TNF, tumor necrosis factor. [Colour figure can be viewed at wileyonlinelibrary.com]

found any literary sources confirming that demographic data on the variables of employment, debtors and education contribute significant significance. This is understandable because the differences in the variables above do not directly provide a potential difference in the pathophysiology of gastric perforation and its output. This also assumes that differences in financing status in the community do not make a significant difference to patient output.

In 70% of patients with a history of long-term use of NSAIDs had abnormalities on endoscopic examination (mucosal erosion, ulceration, and subepithelial bleeding) and only 10% complained of dyspeptic symptoms.[9] Serious complications of peptic ulcer (such as bleeding and perforation) can occur without any previous symptoms. Gastroduodenal peptic ulcer complications increase up to five times in patients who regularly consume NSAIDs. Peptic ulcer bleeding occurs when there is erosion into the subepithelial lining of blood vessels. It occurs more frequently in mucosal capillaries with a smaller caliber and if it occurs in a larger caliber the risk of bleeding is also more massive and rapid, thus giving the clinical presentation of patients with hematemesis melena. The clinical presentation of hypovolemic shock is also common in patients with ulcers and erosions of vessels of large caliber.[10–12]

Mucosal erosion and ulceration that causes bleeding can also cause iron deficiency anemia.[13] This is in accordance with the findings of the preoperative laboratory of patients at Dr. Kariadi General Hospital, Semarang, namely 66.7% had anemia in the iron deficiency category. Increased leukocytes are also present in the majority of patients with gastric perforation, this is in accordance with the theory of perforation development, namely sterile peritonitis becomes bacterial peritonitis in the advanced phase after 24 hours of perforation.

Sometimes deep ulceration does not cause bleeding which is also at risk of perforation. The site of NSAID-induced peptic ulcer perforation is more common in the stomach than the duodenum and is associated with higher and longer-than-recommended doses of NSAIDs.[11,14] This is consistent with the presentation of surgical findings in research at Dr. Kariadi General Hospital Semarang for the period 2020–2022, namely the location of the findings in the

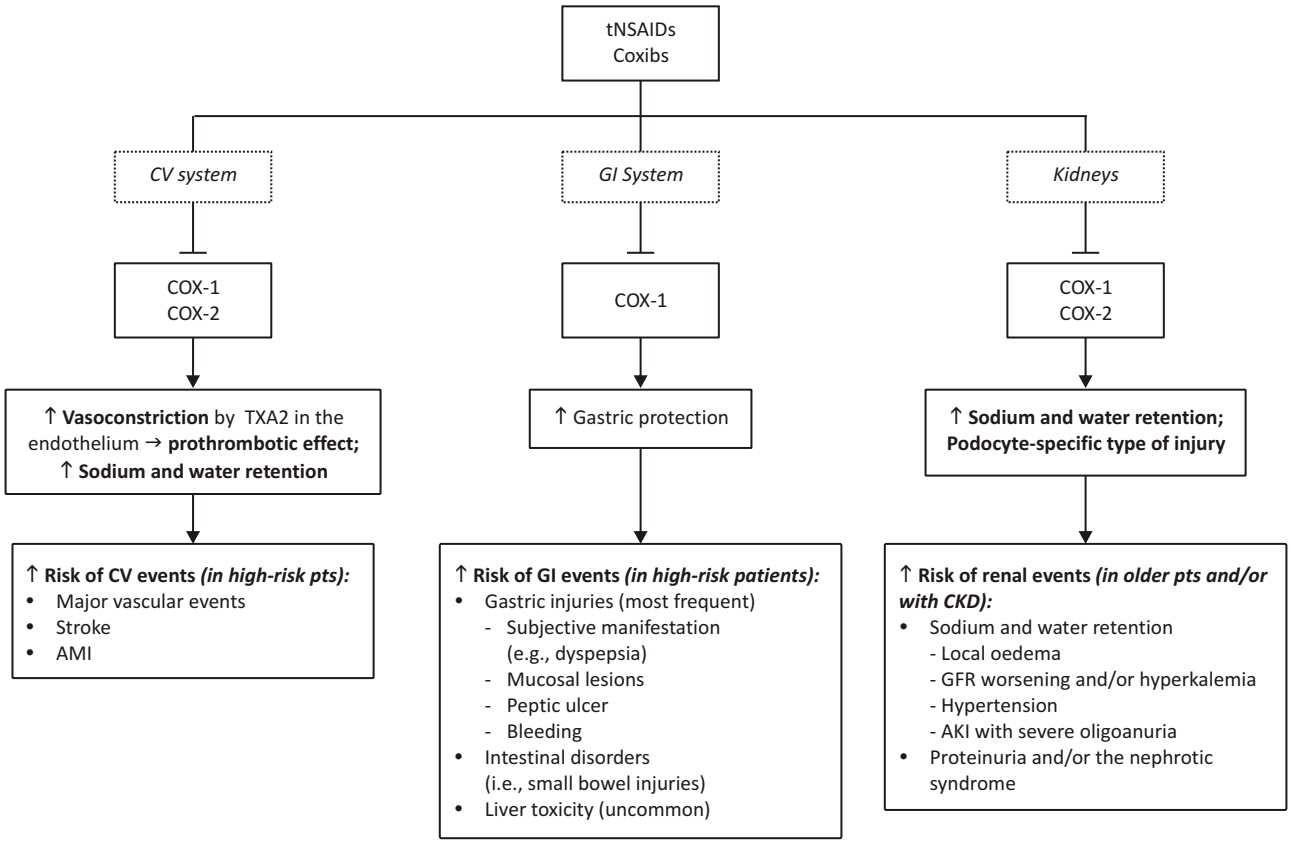


Figure 3.

gastric corpuscle as much as 83.3%. In addition to the clinical presentation of hypovolemic shock, sepsis/septic shock and complications due to gastric perforation are also common in patients who come to the emergency room or are hospitalized.[15,16]

In this study, sepsis was only found in 50% of definitive preoperative cases, possibly because patients who were consulted from the internal medicine department, or came directly to the emergency room, had good initial physical resistance to sepsis. This can be proven in the physical examination of vital signs and initial laboratory results which show that there is no deterioration in the condition to sepsis. In the initial management in a comprehensive and holistic way, tertiary hospitals also make a large contribution compared to hospitals that are not referral centers for the initial preoperative conditions.[17] However, according to the capacity of tertiary hospitals, cases with gastric perforation are often complicated cases. As many as 83.3% of cases of gastric perforation come with comorbid factors such as heart disease, metabolism, kidney disease, liver, DM and hypertension. These comorbid factors will contribute big points for increasing gastric perforation mortality scores such as the BOEY and PULP scores.[14,15,18]

Conservative therapeutic approaches for the treatment of patients affected by arthritis (OA, RA) need to be adjusted so as not to place the patient at further risk.[19] Osteoarthritis (OA) is the most common degenerative joint disease that affects quality of life and causes disability. OA is multifactorial. Common histopathological findings in OA are articular cartilage damage, subchondral bone sclerosis and osteophyte formation, joint cap hypertrophy, and periarticular muscle dysfunction, and synovial inflammation.[6,20,21] Synovitis is actually a hallmark of OA, characterized by increased vascularity, macrophage and lymphocyte infiltration, and villous hyperplasia. At present, there are no studies investigating the potential association between respiratory viral infections and the development of OA, as described for parainfluenza and coronavirus and the incidence of rheumatoid arthritis.[22] Similarly, looking the other way, there is no documentation of an increased risk of respiratory infections for OA patients compared with the general population.[23]

Osteoarthritis (OA) is a leading cause of disability among older adults worldwide. In Italy, the prevalence is 24.9% in women and 16% in men and is highest in people aged > 85 years (63.0% in women and 50.9% in men). The main risk factors for OA are age, sex, obesity and other mechanical factors. The most common lesions are the

joints of the knees, hips and hands. Patients often present with joint pain, joint stiffness, swelling and loss of normal joint function which negatively impact their quality of life. In this study it was found that the majority of arthritis diagnoses were genu OA, this is consistent with previous studies regarding the most common location of OA, namely genu predisposition.[23,24]

The goal of treatment is to relieve inflammatory pain and improve physical function through non-pharmacological and pharmacological interventions. Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line therapy. The workings of a group of heterogeneous chemical agents that inhibit the production of prostaglandins (PG) and thromboboxane A through cyclooxygenase (COX) blockade. Traditional NSAIDs (tNSAIDs), which target COX-1 and COX-2 isozymes to varying degrees, have a consolidated role in the symptomatic treatment of pain in musculoskeletal disorders, but their long-term use is limited by toxicity, especially cardiovascular (CV), gastrointestinal (GI) and kidney toxicity.[15,23,25]

In a study at Dr. Kariadi Hospital in Semarang, it was found that the use of traditional NSAIDs had more presentations than selective COX-2 inhibitors of 83.3%. Although a COX-2 selective NSAID (coxib) was originally introduced as a safer alternative to tNSAIDs, their use is associated with a high risk of cardiovascular (CV) events.[22,26] According to a recent Italian long-term active pharmaceutical covigilance study, NSAIDs were responsible for 8.4% of emergency department visits and 24.4% of emergency department visits resulting in hospitalization.

In practice, drug and patient characteristics influence the choice of therapy. The efficacy profile of NSAIDs has been described by a meta-analysis of randomized controlled trials (RCTs). In 74 RCTs, totaling 58.556 OA patients, there was insufficient statistical evidence to support the superiority of diclofenac 70 mg/day, naproxen 750 mg/day and ibuprofen 1200 mg/day over placebo for pain and improvement of physical function. In contrast, for pain relief, diclofenac 150 mg/day and etoricoxib given at 30 mg/day, 60 mg/day and 90 mg/day had the probability of achieving a minimum clinically important difference compared with placebo C 95%, achieving 100% only. in the case of diclofenac 150 mg/day and etoricoxib 60 mg/day. Notably, a significant linear dose-effect response was found only for celecoxib (P=0.030), diclofenac (P=0.031) and naproxen (P=0.026).[26,27]

For improvement of physical function, minimal clinically significant treatment effect was observed for diclofenac 150 mg/day only. The authors concluded that diclofenac at a dose of 150 mg/day was the best NSAID in terms of improving pain and function in OA, exceeding the maximum doses of commonly used NSAIDs, including ibuprofen, naproxen, and celecoxib. Although etoricoxib at a maximum dose of 60 mg/day is as effective as diclofenac 150 mg/day for the treatment of pain, its estimated effect on physical disability is unclear. Finally, paracetamol has no clinical effect and is not recommended for the symptomatic treatment of OA.[26–28]

However, selection is constrained by patient age, co-morbidities and polypharmacy, and by the benefit/risk balance of the drug, which all together influence cardiovascular risk, gastrointestinal and renal function. While the efficacy profiles of various NSAIDs are described, the differences in safety profiles are not straightforward.[29]

The thing that attracted attention in this study was the finding that preoperative sodium had a significant difference with the occurrence of differences in the output of patients with gastric perforation. The authors have not found any literature studies that can directly prove that there is a relationship between sodium levels and gastric perforation output. Gastric perforation will give systemic effects, one of which will cause electrolyte imbalance, especially in patients with hypovolemic shock and septic shock. This should also be followed by an imbalance between potassium and chloride. However, in this study the levels of potassium and chloride did not make a significant difference to the patient's output. The authors also performed calculations on the gastric perforation prognosis scoring, and according to previous journal literature, PULP scoring has a better significance than other scoring systems.

The type of non-selective NSAID impacts the frequency of GI upset. This is in accordance with the results of multiple regression calculations which state that the combined variables between the type of NSAID and the type of arthritis have a direct correlation with a positive 86.7% inter-variable power and a significant difference in the relationship of 0.049. Results from two previous epidemiological studies confirmed the risk scale for various tNSAIDs (ie ibuprofen, diclofenac, naproxen, ketoprofen, indomethacin, piroxicam, and azapropazone); azapropazone and piroxicam were associated with the highest risk of gastroduodenal bleeding (odds ratios [OR] 23.4–31.5 and 13.7–18, respectively) and with diclofenac and ibuprofen with the lowest (OR 3.9–4.2 and 2). .0–2.9, respectively).[11,30]

CONCLUSION

NSAIDs cause mucosal injury due to cyclo-oxygenase (COX)-1 inhibition along with reduced cytoprotective mucosal prostaglandins and reduced secretion of protective mucobicarbonate inhibitors in the stomach and duodenum.[1,3,4] PULP score has a good level of significance statistical compared to other scoring systems in determining the prognostic mortality of patients with gastric perforation. The type of NSAID (traditional and selective) and the location of arthritis play a role in the

factors affecting of gastric perforation which could lead to increased mortality. The used of non-selective tNSAIDs with the location of genu has a higher effect on the occurrence of ulcers in the gastric mucosa which will lead to gastric perforation incidences. Appropriate considerations need to be declare in administering appropriate long-term anti-inflammatory drugs in patients with arthritis, this is adjusted to the patient's condition, history of other comorbidities and complications that are and may occur. Surgery is the modality therapy of choice for arthritis that cannot be treated with oral medication. Selective NSAIDs in this study are more recommended if patients suffer from arthritis who cannot undergo surgical therapy that requires long-term administration medicine.

REFERENCES

1. Dadfar A *et al*. Epidemiology of perforating peptic ulcer; World Journal of Gastroenterology; 2020
2. Andrew H soll. NSAID- Related Gastrointestinal Complication. Clinical Cornerstone- Upper GI disorder Vol 1 No. 5
3. Kloppenburg M, Kroon FP, Blanco FJ, *et al*. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. Ann Rheum Dis. 2019;78:16–24.
4. Bruye`re O, Honvo G, Veronese N, *et al*. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Semin Arthritis Rheum. 2019;49:337–50
5. Enrico R, Mangiavini L, Vigano M, Brini Teresa A. Management of Osteoarthritis During COVID-19 Pandemic. Clinical Pharmacology & Therapeutics Volume 108 number 4, Milan, Oct 2020
6. Uimonen M, Kuitunen I, Paloneva J, Launonen AP, Ponkilainen V, Mattila VM (2021) The impact of the COVID-19 pandemic on waiting times for elective surgery patients: A multicenter study. PLoS ONE 16(7): e0253875
7. M. Hardian Basuki, Dampak COVID -19 terhadap layanan orthopaedi ; Ortho-Magz-Mei 2020
8. Ross, H. M, Pawlina, W. (2011). Histology (6th ed.). Philadelphia, PA: Lippincott Williams & Wilkins.
9. Mescher, A. L. (2013). Junquiera's Basic Histology (13th ed.). New York, NY: McGraw-Hill Education
10. Kurata JH, Abbey DE. The effect of chronic aspirin use on duodenal and gastric ulcer hospitalizations. J Clin Gastroenterol. 1990;12:260–266.
11. Kurata JH. An assessment of nonsteroid anti- inflammatory drugs as a risk factor in ulcer disease. Ann Intern Med. 1991; 114: 390–398.
12. Laine L, Marin-Sorensen M, Weinstein WM. Nonsteroidal antiinflammatory drug-associated gastric ulcers do not require Helicobacter pylon' for their development. Am J Gastroenterol. 1992;87: 1398–1402.
13. Ekstrom P, Carling L, Wetterhus S, Wingren PE, *et al*. Prevention of peptic ulcer and dyspeptic symptoms with omeprazole in patients receiving continuous non-steroidal anti-inflammatory drug therapy. A Nordic multicentre study. Stand J Gastroenterol. 1996;31:753–758.
14. Stöllberger C, Finsterer J. Nonsteroidal anti-inflammatory drugs in patients with cardio - or cerebrovascular disorders. Vol. 92, Zeitschrift fur Kardiologie. 2003. p. 721–9.
15. Antman EM, DeMets D, Loscalzo J. Cyclooxygenase inhibition and cardiovascular risk. Vol. 112, Circulation. 2005. p. 759–70.
16. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs: An update for clinicians: A scientific statement from the American Heart Association. Vol. 115, Circulation. 2007. p. 1634–42.
17. Hawkey CJ. COX-1 and COX-2 inhibitors. Best Practice and Research: Clinical Gastroenterology. 2001;15(5):801–20.
18. Varga Z, Sabzwari S rafay ali, Vargova V. Cardiovascular Risk of Nonsteroidal Anti-Inflammatory Drugs: An Under-Recognized Public Health Issue. Cureus. 2017 Apr 8;
19. Qureshi O, Dua A. COX Inhibitors. Encyclopedia of Immunotoxicology [Internet]. 2021 Oct 19 [cited 2022 Jan 25];218218. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549795
20. Topper JN, Cait J, Falbt D, Gimbrone MA, Steinberg D. Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: Cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress (atherosclerosis/vascular endothelium/ hemodynamic forces/differential display). Vol. 93, Medical Sciences. 1996
21. Tegeder I. COX-1 and COX-2 in Pain. In: Gebhart Gerald F. and Schmidt RF, editor. Encyclopedia of Pain [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2013. p. 791–4. Available from: https://doi.org/10.1007/978-3-642-28753-4_915
22. Bunimov N, Laneuville O. Cyclooxygenase Inhibitors: Instrumental Drugs to Understand Cardiovascular Homeostasis and Arterial Thrombosis. Vol. 8, Cardiovascular & Haematological Disorders-Drug Targets. 2008.
23. Bruye`re O, Honvo G, Veronese N, *et al*. An updated algorithm recommendation for the management of knee osteoarthritis from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Semin Arthritis Rheum. 2019;49:337–50
24. Rapporto Osservasalute. Osservatorio sulla Salute. 2019. https://www.osservatoriosullasalute.it/osservasalute/rapporto-osservasalute-2019. Accessed 14 Sept 2020
25. Report_XII SIMG 2019.pdf. 2019. https://report.healthsearch.it/Report_XII.pdf. Accessed 14 Sept 2020.
26. Ariani A, Manara M, Fioravanti A, *et al*. The Italian Society for Rheumatology clinical practice guidelines for the diagnosis and management of knee, hip and hand osteoarthritis. Reumatismo. 2019;71: 5–21.
27. Kloppenburg M, Kroon FP, Blanco FJ, *et al*. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. Ann Rheum Dis. 2019;78:16–24.
28. Grosser T, Yu Y, Fitzgerald GA. Emotion recollected in tranquility: Lessons learned from the cox-2 saga. Vol. 61, Annual Review of Medicine. 2010. p. 17–33.
29. Lombardi N, Crescioli G, Bettiol A, *et al*. Italian emergency department visits and hospitalizations for outpatients' adverse drug events: 12-year active pharmacovigilance surveillance (The MEREAFaPS Study). Front Pharmacol. 2020;11:412
30. Scarpignato C, Bjarnason I. Drug-induced small bowel injury: a challenging and often forgotten clinical condition. Curr Gastroenterol Rep. 2019;21: 55.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 334–339

OPEN ACCESS

Original Article

Assessing the Inter-observer Agreement of Electrocardiography Interpretation in the Elderly Surgical Patients: A Cross-Sectional Study

Yudo Murti Mupangati[1,2,3], Henry Setyawan[4], Czeresna Heriawan Soejono[5], Muhammad Hussein Gasem[6], Ignatius Riwanto[3,7]

[1]Doctoral Study Program of Medical and Health Science, Faculty of Medicine, Diponegoro University Semarang, Indonesia
[2]Geriatric Division, Internal Medicine Department Dr. Kariadi Hospital Semarang, Indonesia
[3]Faculty of Medicine, Diponegoro University Semarang, Indonesia
[4]Epidemiology Master Study Program/School of Public Health Diponegoro University Semarang, Indonesia
[5]Geriatric Division, Internal Medicine Department, Faculty of Medicine Indonesia University, Jakarta, Indonesia
[6]Center for Tropical and Infectious Diseases, Dr. Kariadi Hospital and Diponegoro University Semarang, Indonesia
[7]Indonesian Digestive Surgeon Association, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.969

Accepted: May 31th, 2023
Approved: October 10th, 2023

Author Affiliation:
Doctoral Study Program of Medical and Health Science,
Diponegoro University Semarang,
Indonesia

Author Correspondence:
Yudo Murti Mupangati
Dr. Sutomo Street No.16, Semarang.
Central Java 50244, Indonesia

E-mail:
yudomurtidisertasi@gmail.com

Abstract

Background : Electrocardiography (ECG) is an essential objective diagnosis tool, specifically for the elderly who are about to undergo surgery. From the examination results, it is possible to determine the presence of a heart condition that could impair the surgical outcome. Furthermore, the examination is slightly influenced by the subjectivity of observers. The purpose of this study was to evaluate the inter-observer agreement on the reader of a 12-lead ECG on elderly patients subjected to elective surgery.
Methods : A consequential ECG examination was conducted on elderly patients who underwent elective surgery at Dr. Kariadi Hospital Semarang between July and November 2021. Two junior internist observers were independently involved in reading the ECG results in different places. The inter-observer reliability analysis used kappa statistics to determine consistency between observers.
Results : Analysis was carried out on 193 patients aged 60–87 years old, with a prevalence of abnormal ECG was 33.7%. Kappa Conformity Value was 0.864 (95 % CI: 0.790–0.938, p<0.001).
Conclusion : The value of agreement between junior internists in ECG interpretation among elderly surgical patients is good (kappa value >0.8). Even though the observers are junior internist, the result of the interpretation with a high kappa is considered to have reliable validity.

Keywords : Electrocardiography, elective surgery procedure, elderly

INTRODUCTION

The increase in life expectancy leads to a rise in the elderly for surgical procedures, and the cardiovascular system is associated with various structural and functional changes in the heart and blood vessels. Furthermore, the myocardium has increased stiffness due to fibrosis and hypertrophy, and this magnification structure can be seen from the Electrocardiography (ECG) surface.[1,2] ECG is an essential diagnostic tool in medicine, and as a clinician, it is vital to know the general and dangerous patterns.[3]

Preoperative ECG is a routine examination to identify patients' cardiovascular and arrhythmia abnormalities. ECG examination is sometimes influenced by subjectivity in the analysis. Therefore, a study has been conducted to determine the inter-observer agreement on ECG examination in elderly patients, evaluated individually by two junior internist doctors at Dr. Kariadi Hospital Semarang. We choose junior internis to participate in research because they should develop a better understanding of the principle of evidence-based medicine.

MATERIALS AND METHODS

The cross-sectional study included patients aged 60 years or older who underwent elective surgery with general anesthesia at Dr. Kariadi Hospital from June to December 2021. Patients who had undergone outpatient surgery or emergency surgery were excluded. Selection of samples by concurrent sampling obtained 193 subjects.

The ECG machine used to examine subjects was MAC 400, produced by GE Medical Systems Information Technologies China, with the SCT tool series number 11413002 WA. ECG paper printed did not contain an automatic interpretation of the machine. A certified nurse did the ECG recording of 12 leads and independently read by two junior general internists at different places. The ECG reading analysis technique was based on knowledge gained during specialist education. The junior internists were doctors with up to five years of working and experience to become internists.

Furthermore, the data were coded, tabulated, and entered into the computer. The data obtained were checked for completeness and correctness. Statistical and Descriptive analyses were conducted using SPSS and univariate analysis, respectively. Variables that scale to categories were expressed in frequency and percentage distributions. Following the normal distribution, data with a numerical scale were expressed as mean and standard deviation or as median and range when distributed abnormally. The suitability between observations was analyzed using the Kappa test, with its p-value and confidence interval. Ethical clearance was obtained from the health study ethics committee of RSUP Dr. Kariadi with number 842/EC/KEPK-RSDK/2021.

RESULTS

The characteristics of the subjects can be seen in Table 1. Age variables are divided into three groups based on WHO criteria.

TABLE 1
Subjects' Characteristics

Variable		n	%	Median (Minimum–Maximum)
Age (years)	60–70 years old	155	80.3	66 (60–87)
	71–80 years old	32	16.6	
	≥ 81 years old	6	3.1	
Gender	Male	95	49.2	
	Female	98	50.8	
Marital Status	Married	161	8.4	
	Not married	32	16.6	
Education Status	Finished college/university	15	7.8	
	Finished Senior High School	62	32.1	
	Finished Junior High School	18	9.3	
	Finished Elementary School	77	39.9	
	Unfinished Elementary School	3	1.6	
	Non-educated	18	9.3	

TABLE 1. Continued.

Variable		n	%	Median (Minimum–Maximum)
Comorbidities	Hypertension	54	28	
	Liver Disease	12	6.2	
	Hemiplegia	3	1.6	
	Chronic Kidney Disease	4	2.1	
	Peptic Ulcer	2	1	
	COPD	2	1	
	Dementia	1	5	
	Peripheral Vascular Disease	1	5	
	CVD	7	3.6	
	Infark Miocard	8	4.1	
	Congestive Heart Failure	14	7.3	
	Diabetes Mellitus	41	21.2	
	Solid tumor	96	49.7	
Total		193	100.0	

Note: COPD (Chronic Obstructive Pulmonary Disease); CVD (Cerebro Vascular Disease)

TABLE 2
Agreement value between Observer A and Observer B

Variable		Observer B		Total
		Positive	Negative	
Observer A	Positive	119 (61.7%)	9 (4.7%)	128 (66.3 %)
	Negative	3 (1.6 %)	62 (32.1%)	65 (33.7%)
	Total	122 (63.2 %)	71 (36.8%)	193 (100 %)

*Kappa 0,864 (CI 95% 0.790–0.938); p-value < 0.001

The inter-observe agreement value can be seen in Table 2. The observers gave the same result (concordance) as much as 93.8 %, and The observers gave a different result (discordant) of 6.2 %), with a kappa value of 0.864, which is categorized as a good agreement.

In Table 3, the ECG readings obtained are listed, and the differences between observers can be seen in the readings of normal sinus rhythm, RBBB (Right Bundle Brand Block), OMI (Old Myocardial Infarction), LAD (Left Axis Deviation), LAE (Left Atrial Enlargement), and Ischemic anteroseptal.

The results of the ECG abnormality reading between observers A and B can be seen in Figure 1.

DISCUSSION

In this study, the inter-observe agreement had a kappa value of 0.894 (95% CI: 0.790 – 0.938). It is better than Schneiter and colleagues' study, which examined inter-observe suitability in athletes between cardiological and electrophysiological residents with a kappa value of 0.539 (CI 95 % 0.419–0.685). It was also compared to a study conducted between senior internship medical students and cardiological residents with a kappa value of 0.720 (CI 95%: 0.681-0.821). This is likely due to the different levels of education of observers in Schneiter's study.[4] In this research, the quality and homogeneity test of two general internists read the ECG is good with the Levene test 0.556, which means it is homogeneous. This research is almost the same as that conducted by Terho, who obtained a Kappa value of 0.81 to analyze all leads. In Terho's study, the population was young adults, and ECG was read by two people independently without mentioning their education.[5]

TABLE 3
Types of ECG Readings

ECG reading	Observer A n (%)	Observer B n (%)
NSR	109 (56.5)	107 (55.4)
RBBB	9 (4.7)	8 (4.1)
AV Block 1st degree	3 (1.6)	3 (1.6)
OMI	6 (3.1)	7 (3.6)
Sinus Tachycardia	7 (3.6)	7 (3.6)
Sinus Aritmia	1 (0.5)	1 (0.5)
VES	1 (0.5)	1 (0.5)
Non-specific St	7 (3.6)	7 (3.6)
LAD	14 (7.3)	13 (6.7)
Ischaemic anterolateral	6 (3.1)	6 (3.1)
Ischaemic anterior	2 (1.0)	2 (1.0)
LAE	10 (5.2)	11 (5.7)
IVCD	1 (0.5)	1 (0.5)
Atrial fibrillation	2 (10)	2 (1.0)
AV Blok ck 2nd degree	1 (0.5)	1 (0.5)
Bradicardia sinus	4 (2.1)	4 (2.1)
Ischaemic whole-wall	1 (0.5)	1 (0.5)
LVH	1 (0.5)	1 (0.5)
Ischaemic anteroseptal	8 (4.1)	10 (5.2)
Total	193 (100)	193 (100)

Abbreviation: NSR (Normo sinus rhythm); RBBB (Right Bundle Brand Block); OMI (Old Miocard Infark); VES (Ventricle extra systole); LAD (Left Axis Deviation); LAE (Left Atrial Enlargement); IVCD (Intra Ventricular Conducting Defect); AV (Atrio Ventricular); LVH (Left Ventricular Hypertrophy).

From the results, most study subjects were in the age group of 60–70 years. This is slightly different from the study conducted by Yeh *et al*., with the age of the subjects between 65–104 years. The difference is related to the age of older adults and the life expectancy of the Indonesian population based on the Central Statistics Agency of around 70.9 years.[6,7] The gender of the subjects was more women because their life expectancy was slightly longer than males. The female had lower mortality than males because of a low prevalence of most specific systemic variables.[8] Based on marital status, 100% of subjects have been married. This is because the culture in Indonesia that views marriage as mandatory shows a person's level of maturity.[9] The most works recorded are housewives since 50.8% of the subjects belonged to this category. This study focused on the Java tribe because it was conducted on Java Island. Hypertension was found in 28 % of the subjects, possibly due to arterial stiffness in the elderly.[10]

The results of the ECG reading found abnormalities in 43.5% and 44.6% of the elderly subjected to surgery on observers A and B. The two main hypotheses that explain the existence of age-related ECG changes are in the topography of the heart concerning the thorax and diaphragm, as well as the presence of degenerative structural modifications of the conduction system and heart muscle.[1]

Based on the ECG abnormalities, most are LAD, LAE, RBBB, and Ischaemic anteroseptal. In this study, most LAD was likely due to the comorbidity of hypertension based on the study of Romhilt and Estes to diagnose the presence of LVH, changes in ST segments, LAD, and abnormalities of the left atrial.[11]

In addition, RBBB was found with 4.7% in Observer A and 4.1% in Observer B, while LBBB was not found. This funding is in line with a study conducted by

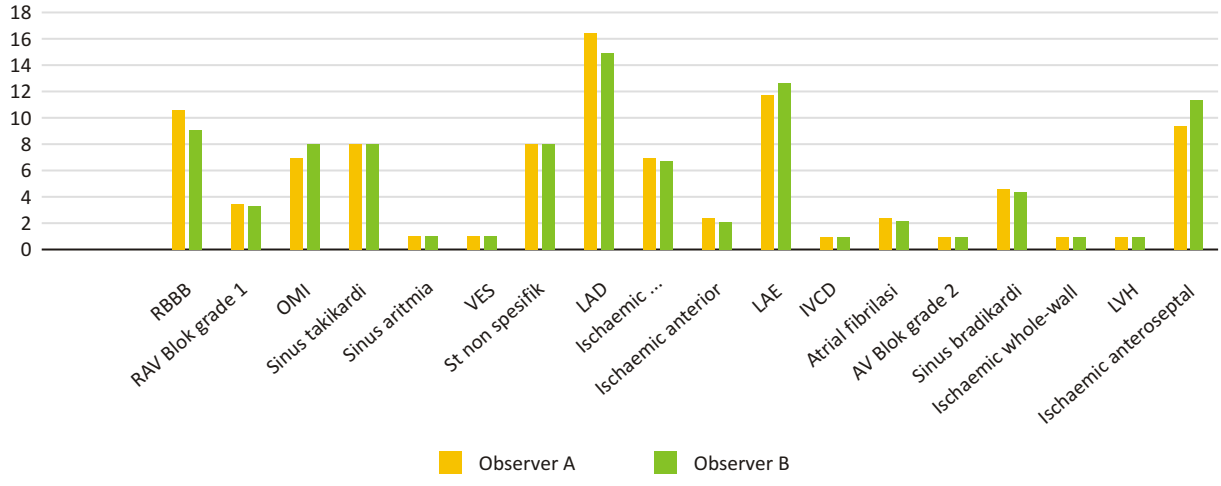


Figure 1. ECG Abnormality Results obtained between Observers A and B
Abbreviation: RBBB (Right Bundle Branch Block), AV (Atrio Ventricular), OMI (Old Miokard Infark), VES (Ventrikel Extra Systolic), LAD (Left Axis Deviation), LAE (Left Atrial Enlargement), IVCD (Intra Ventricular Septal Defect), LVH (Left Ventricular Hypertrophy).

Mihalick and Fisch, where RBBB is more common than LBBB in elderly patients. Generally, Bundle Branch Block is caused by changes in fibro calcification of the conduction system compared to ischemic heart disease.[12] The Baltimore Longitudinal Study of Aging found 3.4% of which is a complete RBBB.[13] In the study of Yeh and friends, 5.05% found complete RBBB.[6]

Observe A found anteroseptal ischemic with 4.1%, and Observe B with 5.2%. The most common cause of ischemic in the elderly is atherosclerosis. Therefore, the elderly with this disease tend to have a prevalence of cardiovascular risk, specifically hypertension, diabetes mellitus, and dyslipidemia.[14] Ishaemic myocardium is a public health problem, and the prevalence increased in the sixth decade. Furthermore, it has been the major cause of death in the elderly, greatly influencing hospitalization and invasive procedures.[15] LVH was obtained in 0.5% of the subjects and has been appointed as a predictor for systolic and diastolic heart failure.[16] Based on Table 3, we can assume that even though kappa is good, ECG readers have the same level of education, different ECG interpretation inter-observer are still found, such as NSR, RBBB, OMI, LAD, LAE, and anteroseptal ischaemic between observe A dan B. Therefore, if any of the above is found in clinical practice, the examining doctor cannot be 100 % sure of the abnormality; it is better if another doctor reads it to make a more objective decision. As regards limitations, this is a study from one central hospital, and it has to be confirmed in a multicentre study on a large scale.

CONCLUSION

This study found that the ECG readings in the elderly to be interpreted by internists had almost similar results. The value of agreement between junior internists in ECG interpretation among elderly surgical patients is good (kappa value >0.8).

Conflict of Interest

All authors have nothing to disclose.

REFERENCES

1. Simova I, Bortolan G, Christov I. ECG attenuation phenomenon with advancing age. J Electrocardiol, 2018;51(6):1029–34.
2. Vicent L, Martínez-Sellés M. Electrocardiogeriatrics: ECG in advanced age. J Electrocardiol. 2017;50(5):698–700.
3. Stephanie Choo CC. Easy Peasy ECG. In: Vaswani A, Khaw HJ, Dougherty SD, Zamvar V, Lang CC, editors. Cardiology in a heartbeat. United Kingdom: Scion Publishing Limited; 2016: 43–54.
4. Schneiter S, Trachsel LD, Perrin T, Albrecht S, Pirrello T, Eser P, *et al*. Inter-observer agreement in athletes ECG interpretation using the recent international recommendations for ECG interpretation in athletes among observers with different levels of expertise. PLoS One. 2018;13(11):1–12.
5. Terho HK, Tikkanen JT, Junttila JM, Anttonen O, Kentta TV, Aro AL, *et al*. Prevalence and Prognostic Significance of Fragmented QRS complewx in Middle-Aged Subjects With and Without Clinical or Electrocardiographic Evidence of Cardiac Disease. Am J Cardiol. 2014;114:141–7.
6. Yeh SSF, Chen CYJ, Wu IC, Hsu CC, Chen TY, Tseng WT, *et al*. Prognostic value and prevalence of complete right bundle branch block in an elderly population: a community-based 10-year prospective study. Aging. 2020;12(19):19073–82.
7. BPS BPPN. Proyeksi Penduduk Indonesia 2010–2035.
8. Al-Taki M, Sukkarieh HG, Hoballah JJ, Jamali SF, Habbal M, Masrouha KZ, *et al*. Effect of gender on postoperative morbidity and mortality outcomes: A retrospective cohort study. American Surgeon. 2018;84(3):377–86.
9. IES. Indonesian Culture. The Cultural Atlas [Internet]. 2021;1:ڤڤڤڤڤ ڤڤ(ڤڤڤڤڤ ڤڤ). Available from:

https://culturalatlas.sbs.com.au/reference
10. Benetos A, Petrovic M, Strandberg T. Hypertension Management in Older and Frail Older Patients. Circ Res. 2019;124(7):1045–60.
11. Macfarlane PW. The influence of age and sex on the Electrocardiogram. Adv Exp Med Biol. 2018;1065(1):93–106.
12. Harkness WT, Hicks M. Right Bundle Brand Block. In: Aboubakr S, Abu-Ghosh A, Sedeh PA, Aeby TC, Aeddula NR, editors. Statpearls. StatPearls Publising; 2023.
13. Baltazar RF. Intraventricular conduction defect:bundle branch block. In: Destifano F, McMillan L, Martz B, editors. Basic and bedside electrocardiography. 1st ed. Philadelphia: Wliter Kluwer; 2009:127.
14. Bjarnason-Wehrens B. Elderly patients with ischaemic heart disease need our attention! Eur J Prev Cardiol. 2018;25(3):276–7.
15. Ochiai ME, Lopes NH, Buzo CG, Pierri H. Manifestação Atípica da Isquemia Miocárdica no Idoso. Arq Bras Cardiol. 2014;102(3):2013–5.
16. Olesen LL, Andersen A. ECG as a first step in the detection of left ventricular systolic dysfunction in the elderly. ESC Heart Fail. 2016;3(1):44–52.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 340–345

OPEN ACCESS

Original Article

The Effect of Sodium Lauryl Sulfate on Orthodontic Elastic Latex's & Non-Latex's Tensile Strength

Indryasari[1], Budi Wibowo[2], Indah Lestari Vidyahayati[1]

[1]Department of Dentistry, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
[2]Dr. Kariadi Hospital/Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.996

Accepted: July 14th, 2023
Approved: October 10th, 2023

Author Affiliation:
Department of Dentistry, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia

Author Correspondence:
Indryasari
Prof. Sudarto Street, Tembalang, Semarang, Central Java, 50275, Indonesia

E-mail:
indryasari65@gmail.com

Abstract

Background : Orthodontic elastic is one of the tools used in orthodontic treatment. Based on the type of material, orthodontic elastics are divided into latex & non-latex. Clinically, orthodontic elastic has decreased tensile strength which can be influenced by various factors including salivary pH and the use of toothpaste. The content of SLS in toothpaste can increase the pH of saliva, causing a decrease in tensile strength. This study aims to analyze the effect of Sodium Lauryl Sulfate on the elastic tensile strength of latex and non-latex orthodontics.
Methods : This is an experimental laboratory research with post-test only control group design. The research samples consisted of 15 samples of orthodontics elastics latex and 15 samples of orthodontics elastics non-latex of AO brand with diameter ¼ inches. The samples were divided into 3 groups with latex and non-latex variations in each group, the samples was soaked for 24 hours. Tensile strength was measured using Imada Motorized Tensile Test MV 110. The statistic used one way Anova test.
Results : One way Anova test showed that there was no significant difference between the control group, detergent toothpaste group and non-detergent toothpaste group with $p = 0.757$ ($p > 0.05$) for latex and $p = 0.382$ ($p > 0.05$) for non-latex.
Conclusion : Detergent and non-detergent toothpaste did not affect the tensile strength of orthodontic elastic latex and non-latex.

Keywords : Tensile strength, sodium lauryl sulfate, orthodontic elastic

INTRODUCTION

According to the World Health Organization (WHO), malocclusion is an anomaly or abnormality that causes complaints, damage, or occlusion dysfunction.[1] The prevalence of malocclusion in Indonesia reached 80% and placed third in oral health problems, following caries and periodontal disease.[2,3] This high prevalence of malocclusion leads to a high demand for orthodontics treatment, especially in adolescents.[4] Orthodontics treatment can be carried out using fixed and removable appliances. One of the main components of fixed orthodontic appliances is orthodontic elastic.[5]

Orthodontic elastics are used to aid in closing interproximal space and provide intermaxillary fixation in bone fracture cases or orthodontic treatment.[6] Its advantages include relatively cheap price, high flexibility, and the ability to return to its original dimension after a significant stretching.[6]

Orthodontic elastic needs to maintain its tensile strength to provide an ideal result. Clinically, orthodontic elastic shows a decrease in tensile strength.[7] This decrease can be affected by the type of material, saliva, potential of Hydrogen (pH), changes in temperature, enzyme, microbes, duration of stretching, food and drink consumption, and the use of oral hygiene products.[7–9]

The most commonly used oral hygiene product is toothpaste. Commercial toothpaste comprises various brands and compositions.[10] The ingredients contained in toothpaste can alter the pH of saliva. Aside from toothpaste, salivary pH can also be affected by diet, stimulation of salivary secretions, salivary flow rate, microorganisms, and buffer capacity.[11,12] Increased salivary pH due to the use of toothpaste is caused by the ingredients contained in toothpaste, including Sodium Lauryl Sulfate (SLS).[13]

SLS is one of the detergents used as an active ingredient in toothpaste, which functions to help release food debris and plaque adhering to the tooth surface. SLS can only be found in toothpaste with detergent.[14] According to Yustika, toothpaste containing SLS can significantly increase salivary pH compared to non-SLS toothpaste.[15]

Choice of toothpaste needs to be considered, due to different oral hygiene needs between individuals, especially in orthodontics appliance users. Orthodontic appliance users need to consider the ingredients contained in toothpaste to minimize the side effects of the interaction between fixed orthodontics appliances and toothpaste ingredients. Many studies related to the effect of toothpaste ingredients such as fluoride and colostrum on orthodontic appliances have been conducted. However, none of the studies directly evaluate the effect of sodium lauryl sulfate on the tensile strength of latex and non-latex orthodontic elastics. This is important to help orthodontic appliance users choose the appropriate toothpaste to minimize frequent replacement of orthodontic elastics.

METHODS

This study uses a laboratory experiment with a post-test-only control group design. It was conducted in the Biochemical Laboratory of the Faculty of Medicine and the Mechanical Engineering Laboratory of Diponegoro University between June and July 2022. The study received ethical clearance from the Health Research Ethical Committee of the Faculty of Medicine of Diponegoro University No. 70/EC/H/FK-UNDIP/VII/2022. The samples were latex and non-latex orthodontic elastics chosen through simple random sampling. They were divided into three treatment groups with a variation of latex and non-latex elastics in each group. The group contained 15 latex and 15 non-latex ¼ inch medium force orthodontic elastics from American Orthodontics with 4.5 oz power. Samples were to be stretched in an acrylic board by a distance of 19.05 mm and immersed for 24 hours at 37°C.

Sample Preparation

The samples were 15 latex and 15 non-latex ¼ inch medium force orthodontics elastics from American Orthodontics with 4.5 oz power. The samples were to be stretched on an acrylic board made by adjusting the stretching distance of the elastics three times its diameter, which was 19.05 mm. The acrylic boards were labeled according to the three treatment groups, the control group, the detergent toothpaste group, and the non-detergent toothpaste group.

Sample Immersion

There were three different immersion solutions : 1) Control group : Artificial saliva; 2) Detergent toothpaste treatment group : Artificial saliva + detergent toothpaste (Pepsodent®); 3) Non-detergent toothpaste treatment group : Artificial saliva + non-detergent toothpaste (Enzim®).

One-point-five grams of detergent and non-detergent toothpaste were prepared and diluted into 25 ml of artificial saliva with a pH of 6.7 in a prepared beaker glass. The solutions in each treatment group were checked for pH with a pH meter (Hanna®) and incubated at 37°C for 24 hours using the Memmert IN55 incubator. The artificial saliva used in this study was formulated according to the Fusayama-Meyer method by mixing KCl (400 mg/L), NaCl (400 mg/L), CaCl2.2H2O (906 mg/L), NaH2PO4.2H2O (690 mg/L), Na2S.9H2O (5 mg/L), and Urea (1000 mg/L).

Measurement of Tensile Strength

Tensile strength measurement requires a puller hook to pull orthodontic elastics. The hook was made using

U-shaped 0.8 mm stainless steel clasps, which were placed into the Imada Motorized Tensile Test MV 110. Tensile strength was measured by placing the samples on the puller hook. The initial strength of latex and non-latex orthodontic elastics was measured in advance before tensile strength measurements in treatment groups. After the samples were placed in the puller hook, the Imada Motorized Tensile Test MV 110 would pull the samples until they broke and the tensile strength was recorded in the device's monitor.

Statistical Analysis

The obtained data were analyzed using the IBM SPSS Statistics version 26. Statistical analyses include the Shapiro-Wilk normality test, Levenne's homogeneity test, and the One-Way ANOVA parametric test.

RESULTS

The initial tensile strength from latex and non-latex orthodontic elastics is presented in Table 1. Table 1 and Table 2 showed that the tensile strength of latex and non-latex elastics experienced a decrease after 24-hour immersion at 37°C. The largest decrease in tensile strength was 24.21%, which was found in the latex elastics immersed in artificial saliva mixed with detergent toothpaste. The mean and standard deviation chart of the tensile strength of orthodontic elastics can be seen in Figure 1.

The analysis shown in Table 3 using the Shapiro-Wilk normality test and Levenne's homogeneity test showed a significance value of p >0.05. This concluded that the data were normally distributed and

TABLE 1
The initial strength of orthodontic elastics

Group	Tensile Strength (MPa)
Latex Orthodontic Elastics	15.95
Non-Latex Orthodontic Elastics	9.13

TABLE 2
Mean and standard deviation (SD) of tensile strength

Group		Sample Size	Mean ± SD (MPa)
Latex	Control	5	12.82 ± 1.44
	Detergent Toothpaste	5	12.09 ± 1.74
	Non-detergent Toothpaste	5	12.71 ± 1.75
Non-Latex	Control	5	8.17 ± 0.35
	Detergent Toothpaste	5	7.93 ± 0.12
	Non-detergent Toothpaste	5	8.09 ± 0.29

TABLE 3
The percentage of orthodontic elastics' tensile strength decreases

Group		Tensile Strength Decrease %
Latex	Control	19.62%
	Detergent Toothpaste	24.20%
	Non-detergent Toothpaste	20.31%
Non-Latex	Control	10.50%
	Detergent Toothpaste	13.14%
	Non-detergent Toothpaste	11.39%

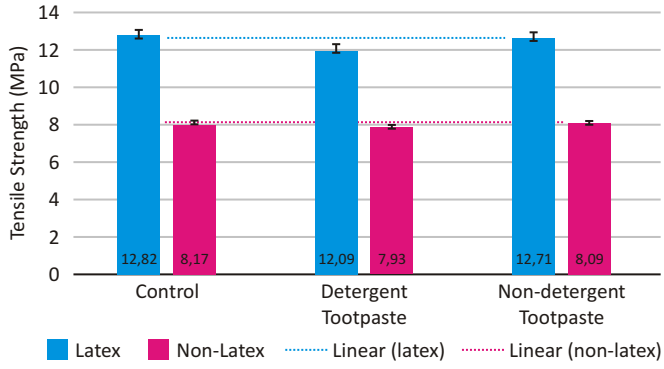


Figure 1. Mean and standard deviation chart of tensile strength.

TABLE 4
Shapiro-Wilk and Levenne's tests

Group		p^a	p^b
Latex	Control	0.449*	0.703*
	Detergent Toothpaste	0.815*	
	Non-detergent Toothpaste	0.061*	
Non-Latex	Control	0.167*	0.307*
	Detergent Toothpaste	0.196*	
	Non-detergent Toothpaste	0.994*	

*Normal/homogenous ($p > 0.05$), [a]Shapiro-Wilk, [b]Levenne's test

TABLE 5
One-Way ANOVA

Group		p
Latex	Control	0.757*
	Detergent Toothpaste	
	Non-detergent Toothpaste	
Non-Latex	Control	0.382*
	Detergent Toothpaste	
	Non-detergent Toothpaste	

*Normal/homogenous ($p > 0.05$), [a]Shapiro-Wilk, [b]Levenne's test

TABLE 6
The results of the pH test

Group	Tensile Strength (MPa)
Artificial Saliva	6.7
Artificial Saliva + Detergent Toothpaste	7.9
Artificial Saliva + Non-detergent Toothpaste	7.6

homogenous. Data were further analyzed with One-Way ANOVA, which was shown in Table 4 with a significance value of p >0.05. This concluded that there were no significant differences in the tensile strength of orthodontic elastics between different treatment groups. The pH results in Table 5 indicated a pH of 6.7 for artificial saliva, 7.9 for artificial saliva + detergent toothpaste, and 7.6 for artificial saliva + non-detergent toothpaste.

DISCUSSION

In its application, orthodontic elastic underwent a decrease in tensile strength.[7] This decrease can be affected by several factors, including solution pH, enzyme, duration of stretching, the use of oral hygiene products, to composition and brand from orthodontic elastics.[7–9,16] Toothpaste is a common oral hygiene product. It is used to clean and control plaque in the oral cavity.[17,18] In general, toothpaste comprises several ingredients, such as abrasive, humectant, bonding agent, water, flavorings and sweeteners, coloring, active ingredients, gel, and surfactant or detergent.[14] These ingredients can affect salivary pH.[15] The measurement in artificial saliva mixed with detergent toothpaste showed an increase in pH to 7.9 and an increase to 7.6 for artificial saliva mixed with non-detergent toothpaste.

The results of One-Way ANOVA revealed a p-value of >0.05, which indicated no significant differences between treatment groups. Sumekar and Suparwitri stated that pH only affects the tensile strength of latex orthodontic elastics after 24 hours of immersion.[7] This was in line with Yuwana, *et al*. who found a significant difference between treatment groups after 48 hours of immersion.[19] The pH obtained between detergent and non-detergent toothpaste solution did not differ much and thus did not cause a significant difference in tensile strength. This result can also be explained by the micelle concentration of SLS which was only 7 mM/L. This concentration is not enough to denature or change the structure of the polypeptide chain in the proteins in latex and non-latex orthodontic elastics.[20]

Detergents with micelle concentration under the critical level could not denature proteins. This is because micelle acts as a denaturant.[20] The ability to denature proteins derived from the amphiphilic nature of detergent. SLS will bind proteins through the interaction between sulfate groups and the positively-charged amino acid side chains, and between alkyl chain and hydrophobic side chains.[20] the micelle concentration in the SLS contained in toothpaste in this study could not be exactly known. This insignificant result could also be caused by thickness differences within the same brand of orthodontic elastics. Thickness differences can cause a difference in the cross-sectional area of orthodontic elastics. This can affect the forces produced by the elastics, thus causing insignificant changes in the tensile strength of orthodontic elastics.[21]

A tensile strength decrease was also found in the control group. This may be due to the effect of stretching and immersion duration. Orthodontic elastics showed a 10–40% decrease in tensile strength from the initial strength after immersion in saliva for 30 minutes to the first 24 hours.[22,23] In non-latex orthodontic elastics, the reduction of tensile strength occurred because the chemical structure of non-latex orthodontic elastics comprised of hydrogen and Van der Waals bond, which is relatively weak in maintaining strength and elasticity from polymers.[7]

CONCLUSION

This article concludes that sodium lauryl sulfate does not affect the tensile strength of latex and non-latex orthodontic elastics. The insignificant difference can be caused by the use of commercially available toothpaste, which leads to uncontrolled and unknown SLS concentrations. This study could not be generalized using other brands of orthodontic elastics due to the different formulas and manufacturing processes of elastics from each brand. This study suggests a further study using measured SLS concentration and variations in orthodontic elastic brands.

REFERENCES

1. Carisa Ka, Yusra Y, Hardja Buntara Mj. Hubungan antara Usia Anak dan Kebutuhan Perawatan Ortodonti Interseptif (Kajian pada Anak Usia 8–11 Tahun di SDN Balekambang 03 Jakarta Timur). J Kedokt Gigi Terpadu. 2019;1(1):15–21.
2. Laguhi Va, Anindita P., Gunawan Pn. Gambaran Maloklusi dengan Menggunakan Hmar pada Pasien di Rumah Sakit Gigi Dan Mulut. E-Gigi. 2014;2(2).
3. Adha Mar, Wibowo D, Rasyid Ni. Gambaran Tingkat Keparahan Maloklusi Menggunakan Handicapping Malocclusion Assessment Record (Hmar) pada Siswa SDN Gambut 10. Dentin J Kedokt Gigi. 2019;3(1):1–9.
4. Herwanda, Arifin R, Lindawati. Pengetahuan Remaja Usia 15–17 Tahun di SMAN 4 Kota Banda Aceh terhadap Efek Samping Pemakaian Alat Ortodonti Cekat. Syah Kuala Dent Soc. 2016;1(1):79–84.
5. Aldira C, Kornialia K, Andriansyah A. Penilaian Tingkat Keberhasilan Perawatan Ortodontik dengan Piranti Lepasan Berdasarkan Indeks Par di RSGM Universitas Baiturrahmah Tahun 2012–2017. J Kesehat Andalas. 2020;8(4):27–32.
6. Krisnaini A, Maulana H, Prasetyarini S. Evaluasi Kehilangan Gaya (Force Decay) Elastik Ortodontik Akibat Perendaman Minuman Berkarbonasi [Internet]. Prosiding The 3th Dentistry Scientific Meeting of Jember. 2017.
7. Sumekar W, Suparwitri S. Perbandingan Kekuatan Tarik Elastik Ortodontik Lateks dan Non Lateks dalam Saliva Buatan dengan Ph dan Waktu yang Berbeda. J Kedokt Gigi. 2013;4(2):169–75.
8. De Carvalho Notaroberto Df, Martins E Martins M, De Andrade Goldner Mt, De Moraes Mendes A, Quintão Cca. Force Decay Evaluation of Latex And Non-Latex Orthodontic Intraoral Elastics: In Vivo Study. Dental Press J Orthod. 2018;23(6):42–7.

9. Csekő K, Maróti P, Helyes Z, Told R, Riegler F, Szalma J, et al. The Effect of Extrinsic Factors on The Mechanical Behavior And Structure of Elastic Dental Ligatures and Chains. Polymers (Basel). 2022;14(1).
10. Puspitasari A, Balbeid M, Adirhesa A. Perbedaan Pasta Gigi Herbal dan Non-Herbal terhadap Penurunan Plaque Index Score pada Anak. E-Prodenta J Dent. 2018;2(1):116–23.
11. Najoan Sb, Kepel Bj, Wicaksono Da. Perubahan Ph Saliva Siswa Ma Darul Istiqamah Manado Sesudah Menyikat Gigi dengan Pasta Gigi Mengandung Xylitol. E-Gigi. 2014;2(2).
12. Putri Me, Restadiamawati R. Pengaruh Pemakaian Kontrasepsi Pil Oral Kombinasi terhadap Ph dan Volume Saliva Serta Angka Leukosit Cairan Sulkus Gingiva. In 2014.
13. Advani S, Sogi S, Hugar S, Indushekar Kr, Kiran K, Hallikerimath S. Remineralization Effects of Two Pediatric Dentifrices and One Regular Dentifrice on Artificial Carious Lesion in Primary Teeth: An In Vitro Study. J Int Soc Prev Community Dent. 2014 May;4(2):96–102.
14. Emiralda Z. Perbedaan Efektivitas Penggunaan Pasta Gigi dengan Kandungan Detergen (Sodium Lauryl Sulfate) dan Non-Detergen terhadap Penurunan Skor Plak. Universitas Syiah Kuala; 2016.
15. Yustika Ad. Studi Perbandingan Penggunaan Pasta Gigi Detergen dan Non-Detergen terhadap Derajat Keasaman (Ph) Saliva Anak Usia 10–12 Tahun di Madrasah Ibtidaiyah Al Ma'arif Kebumen Kecamatan Banyubiru. Universitas Muhammadiyah Surakarta; 2016.
16. Pithon Mm, Macena Ja, Prado Mc, Pinto Hb. Effects of Active Substances in Dentifrices on Force Degradation of Elastomeric Chain Elastics. J Indian Orthod Soc. 2014;48(March):27–32.
17. Wondal Lhd, Anindita Ps, Tambunan E. Perbedaan Pelepasan Ion Nikel (Ni) dan Kromium (Cr) Kawat Ortodonti Stainless Steel pada Perendaman Pasta Gigi Ortodonti dan Non-Ortodonti. E-Gigi. 2018;6(2).
18. Putra Fs, Mintjelungan Cn, Juliatri. Efektivitas Pasta Gigi Herbal dan Non-Herbal terhadap Penurunan Plak Gigi Anak Usia 12–14 Tahun. E-Gigi. 2017;5(2).
19. Yuwana Cp, Christnawati C, Farmasyanti C. The Effect of Immersion Time in Three Kinds of Carbonated Beverages on Orthodontic Elastic Latex's Tensile Strength (In Vitro). Ui Proc Heal Med. 2017;1(1):63–7.
20. Otzen De. Protein Unfolding in Detergents: Effect of Micelle Structure, Ionic Strength, Ph, and Temperature. Biophys J [Internet]. 2002;83(4):2219–30.
21. Kersey Ml, Glover Ke, Heo G, Raboud D, Major Pw. A Comparison of Dynamic and Static Testing of Latex and Nonlatex Orthodontic Elastics. Angle Orthod. 2003;73(2):181–6.
22. Article O. Comparison of Claimed and Measured Forces of Interarch Orthodontic Elastics – An In Vitro Study. 2015;7(2):60–5.
23. Qodcieh Sma, Al-Khateeb Sn, Jaradat Zw, Abu Alhaija Esj. Force Degradation of Orthodontic Latex Elastics: An In-Vivo Study. Am J Orthod Dentofac Orthop [Internet]. 2017;151(3):507–12.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 346–351

OPEN ACCESS

Original Article

The Effect of Suctioning to Oxygen Saturation Improvement towards ICU Patients in Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang

Fince Trisna Anggreni[1], Istha Leanni Muskananfola[2], Akto Yudowaluyo[1]

[1]Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang, East Nusa Tenggara, Indonesia
[2]Nursing Program, Faculty of Health Science, University of Citra Bangsa Kupang, East Nusa Tenggara, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.966

Accepted: May 26th, 2023
Approved: October 11th, 2023

Author Affiliation:
Nursing Program, Faculty of Health Science,
University of Citra Bangsa Kupang,
East Nusa Tenggara, Indonesia

Author Correspondence:
Istha Leanni Muskananfola
Manafe Street No. 17 Kayu Putih Oebobo Kupang,
East Nusa Tenggara, Indonesia

E-mail:
leanni.istha@gmail.com

Abstract

Background : Treated ICU patients may experience consciousness deterioration which leads to loss of cough response and increase of saliva and secretions production which blocks the airway. Therefore, patients need to receive suctioning or mucus suctioning to clear the airway. The success of such procedure can be supervised by measuring the patient's oxygen saturation level before and after the procedure. The objection of this research was to analyze the effect of suctioning to oxygen saturation improvement towards ICU patients in Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang.
Methods : The research was conducted from November to December 2022 in a quantitative form with a pre-experimental layout and one-group pre-posttest design. It involved 30 respondents with accidental sampling technique. The instruments used were suction observation sheets and the oximeter. The gained data were then analyzed using SPSS with the Mc Nemar test.
Results : The results showed that the average value of the patient's oxygen saturation pre-suctioning was 93.73% whilst post-suctioning was 96.23%. The statistical test results show the value of ρ = 0.002, which means that there is an effect of suctioning to oxygen saturation improvement towards ICU patients in Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang.
Conclusion : Suctioning has an effect to improve the oxygen saturation towards ICU patients in Prof. Dr. W. Z. Johannes Hospital Regional Public Hospital Kupang.

Keywords : intensive care unit, oxygen saturation, suction

INTRODUCTION

Intensive Care Unit (ICU) admitted patients are those who experience a critical condition accompanied by a deterioration in consciousness that threatens life.[1,2] In this state, a patient will lose the response to cough, accompanied by increased saliva and secretions production that block the airway. The fulfillment of the patient's oxygen needs is inadequate.[3,4] The obstruction in the patient's airway will hinder the entry of oxygen into the patient's body so that oxygen perfusion to the periphery is also reduced, which can be seen from a decline in oxygen saturation.[5–7] To overcome this condition, one of the actions that can be taken by a nurse is the precise suctioning to clear the obstruction from the patient's airway. The success of this procedure can be monitored from the change in the patient's oxygen saturation level using a pulse oximeter measurement.8 Pulse oximeter detects arterial blood oxygen saturation and its accuracy. Therefore, pulse oximeter readings are very important. Incorrect measurements can lead to patients falling into a situation of undetected hypoxemia or unnecessary use of oxygen therapy, waste of oxygen and inappropriate clinical decision-making.[9–11]

The obtained data from the ICU room in Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang showed that from January to May 2022 there were 187 ICU admitted adult and pediatric. It also showed that from these 187 patients, there were 57 patients, consisted of 46 adult patients and 11 pediatric patients who had consciousness deterioration, ventilator-supported and needed constant observation. Based on treatment standards in Prof. Dr. W. Z. Johannes Regional Public Hopital Kupang, consciousness deteriorated patients with increased accumulation of secretions in the airway are necessary to be treated with suctioning one to two times in every 8 hours or adjusted to the patient's needs if the accumulation of secretions is too much in the patient's airway. The nurse will adjust the pressure on the suction machine, use the right suction catheter, conduct suctioning no longer than 10 and end the procedure by evaluating vital signs which includes observing the patient's oxygen saturation before and after the suctioning procedure.[12,13] Based on the description above, the purpose of this study is to analyze the effect of suctioning to oxygen saturation improvement towards ICU patients in Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang.

RESEARCH METHODS

This is quantitative research with a pre-experimental research layout. This research design is one group pre and post-test design. The population in this study were all ICU admitted patients in Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang from November to December 2022 with the inclusion criteria for the adult patients aged more than 20 years, consciousness-deteriorated patients whom attached to an oropharyngeal airway tube (OPA) or endotracheal tube (ETT) with a Glasgow Coma Scale (GCS) value less than 5, patients who are unable to cough and have oxygen saturation (SpO2) ≤95%. The exclusion criteria determined by researchers for research sampling are pediatric patients who experience consciousness deterioration and patients who are not admitted on the schedule of researchers carrying out tasks in the ICU room. The sampling technique in this study was accidental sampling technique. This sampling technique were chosen because researchers could not predict patients who were admitted to the research location, so patients who were encountered and in accordance with the inclusion criteria that researcher determine will be taken as research sample. Therefore, the number of samples in this study was 30 patients who were treated within a span of two months, from November 2nd to December 30th, 2022. The instruments that were utilized in this research were suction observation sheets and pulse oximeter.

This research was conducted from November 2nd to December 30th, 2022, which was preceded by an ethical clearance from the ethics commission of the Polytechnic of the Ministry of Health Kupang with Number: No.LB.02.03/1/0185/2022. Research data collection was carried out after the researchers explained the aims and objectives of the study and asked for approval from patients' family through informed consent. Researchers observed oxygen saturation before suctioning, then measured the patient's oxygen saturation again shortly after suctioning. However, to see the consistency of changes in oxygen saturation, the researcher monitored patients' condition for two consecutive days of treatment. The first measurement has been done on the first day and the second measurement on the second day of the patient treatment in the ICU room. The results of measuring oxygen saturation before and after suctioning on the second day were taken as research data to continue at the stage of analyzing the effect using statistical tests. The research data were analyzed used SPSS with the Mc Nemar test.

RESULTS

Table 1 shows patients characteristics based on age, gender, additional breathing sounds, breathing equipment and medical diagnosis.

Patients' oxygen saturation before and after suctioning on the 1st observation day in the ICU room at Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang shows in Table 2.

Patients' oxygen saturation before and after suctioning on the 2nd observation day in the ICU room at

TABLE 1
Patients characteristics based on age, gender, additional breathing sounds, breathing equipment and medical diagnosis

Variables		Frequency (n)	Percentage (%)
Age	26-35 years	6	20.0
	36-45 years	8	26.7
	46-55 years	12	40.0
	56-65 years	4	13.3
Gender	Male	18	60.0
	Female	12	40.0
Additional Breath Sounds	Ronchi	25	83.3
	Stridor	4	13.3
	Crackles	1	3.3
Breathing Apparatus	ETT + OPA	21	70.0
	OPA	9	30.0
Medical Diagnosis	Post Craniotomy Surgery	15	50.0
	Stroke	8	26.7
	Sepsis and Metabolic disorders	5	16.7
	PEB and Lung Oedema	2	6.7

TABLE 2
Patients' Oxygen Saturation before and after suctioning on the 1st observation day in the ICU room at Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang

Oxygen Saturation [SpO_2]	Before Suctioning		After Suctioning	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Less than normal (<95%)	19	63.3	7	23.3
Normal (≥95%)	11	36.7	23	76.7
Oxygen saturation average	92.03%		94.70%	

Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang shows in Table 3.

The effect of suctioning to oxygen saturation improvement towards ICU patients in Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang shows in Table 4.

DISCUSSION

Oxygen saturation (SpO_2) of patients before suctioning in the ICU room at Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang

The average measurement result of patient oxygen saturation before suctioning on the first day was 92.03%. On the second day of measurement, the average patient oxygen saturation was 93.73% with details of 17 respondents (56.7%) who had SpO_2 less than normal, while 13 respondents (43.3%) had normal SpO_2. The results of this study are also supported by previous research conducted in the ICU room of RSUD R.A.A. Soewondo Pati on 16 research samples which showed that the average oxygen saturation of patients before receiving suctioning was 93.38% or less than normal.[14]

Oxygen saturation is a value of the amount of oxygen bound to hemoglobin or the percentage of hemoglobin to oxygen in arterial blood vessels. A decline in the value of oxygen saturation can mean a disturbance in the respiratory system such as hypoxia and airway obstruction. The impact of a decline in oxygen saturation

TABLE 3
Patients' Oxygen saturation before and after suctioning on the 2nd observation day in the ICU room at Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang

Oxygen Saturation [SpO_2]	Before Suctioning		After Suctioning	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Less than normal (<95%)	17	56.7	7	23.3
Normal (≥95%)	13	43.3	23	76.7
Oxygen saturation average	93.73%		96.23%	

TABLE 4
The effect of suctioning to oxygen saturation improvement towards ICU patients in Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang

Oxygen Saturation [SpO_2] Before Suctioning	Oxygen Saturation [SpO_2] After Suctioning				N	Percentage (%)	*p* value
	Less than normal		Normal				
	(<95%)	(%)	(<95%)	(%)			
Less than normal (<95%)	7	23.3	10	33.3	17	56.7	0.002
Normal (≥95%)	0	0	13	43.3	13	43.3	
Total	7	23.3	23	76.6	30	100	

that occurs for more than 4 minutes and unmaximized supply of oxygen to the brain results irreversible brain damage and patient's death.[15] The normal value of oxygen saturation is ≥95–100%.[2] Oxygen saturation can be assessed as a component of arterial blood gas/ABGs (SaO_2) or can be measured noninvasively using a pulse oximeter (SpO_2).[2] One of the objectives of monitoring oxygen saturation before suctioning is to obtain data on the patient's vital sign, which is also part of the oxygen assessment. Another purpose of measuring oxygen saturation is to perform early detection of critical patient conditions that can change rapidly at any time, as well as to evaluate the patient's response to oxygenation activities such as suctioning, repositioning or changes in oxygen concentration (O_2) received by the patient.[2]

Oxygen saturation of ICU admitted patients is mostly in the less than normal category (<95%) because above-mentioned are critical and chronic patients who generally experience consciousness deterioration. The patient's unconscious condition makes the patient lose the ability to cough effectively accompanied by increased saliva production. This makes the patient's airway obstructed by secretions both in the mouth, bronchus, trachea and lungs. Increased secretion production and consciousness deterioration make the patient unable to remove secretions so that airway obstruction occurs which worsens the patient's condition and oxygen supply to the periphery.[2] This is in accordance with the results of this study, namely there were 15 patients (50%) who experienced postoperative craniotomy, which made them experienced consciousness deterioration, lost the ability to maintain an effective airway independently which certainly affected the fulfillment of patient oxygen saturation.

Oxygen saturation of ICU admitted patients need to be monitored because they are critical patients.[2] A patient's oxygen saturation value indicates the adequacy of oxygenation or perfusion of the patient's tissues and if a decline in oxygen saturation is found, it can be an indicator of oxygen transport failure. Therefore, measuring oxygen saturation is the easiest way to determine the adequacy of oxygen supply to the patient's body.[2,15]

The researchers argue that ICU admitted patients in Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang had less than normal oxygen saturation was also caused by the disease at the time, namely some had a disease that aggravates their condition as shown in the characteristics. There were 15 patients (50%) who had postoperative craniotomy. Patients also showed symptoms of excessive accumulation of secretions that obstructed the patient's airway as shown by the research data, namely as many as 25 respondents (83.3%) had rhonchi breath sounds. This is in accordance with the theory that supports the results of this study.

Oxygen Saturation (SpO_2) of Patients After Receiving Suction Action in the ICU room of Prof. Dr. W. Z. Johannes Kupang

The result of measuring the average oxygen saturation of patients after receiving suctioning on the first day was 94.70%. On the second day of measurement, the average oxygen saturation was 96.23% with details of 7 respondents (23.3%) who had SpO_2 less than normal, while 23 other respondents (76.7%) had normal SpO_2. The results of this study are supported by previous research conducted on 40 research sample in the ICU room of An-Nisa Tangerang Hospital which stated that the average oxygen saturation of patients after receiving suction action was in the normal category with an average of 97.25%.[2]

The patient's oxygen saturation needs to be measured after suction because oxygen saturation is an indicator that the patient's oxygen needs are being met.[16] When a patient receives suctioning, there is a process of suctioning mucus that was blocking the patient's airway. Therefore, the results of measuring oxygen saturation after suctioning are expected to show signs that suctioning has an impact on the patient's airway.[2] A patient's oxygen saturation that is less than normal may change to normal after suctioning because secretions, saliva build-up or other fluids have been cleared from the patient's airway.[17]

However, not all patients showed changes in oxygen saturation to normal after suctioning. This is proven by the results of the research which showed that there were still 7 patients (23.3%) who had oxygen saturations less than normal. The researcher believes that these patients' oxygen saturation was also influenced by their clinical condition, namely these patients had a chronic disease that could make the oxygen supply inadequate to the peripheral tissue.

The Effect of Suction Measures on Increasing Oxygen Saturation (SpO_2) Patients in the ICU Room of Prof. Dr. W. Z. Johannes Kupang

The results showed that there was an effect of suctioning on improving patient oxygen saturation due to changes in the average value of oxygen saturation pre- and post-procedure. Before the suctioning was conducted, the results showed that the average oxygen saturation was lower than after the suctioning. This is supported by the results of statistical tests that show a value of $\rho = 0{,}002$ ($\rho < \alpha$ (0,05)) which means that there was a significant effect of giving suctioning on improving patient oxygen saturation. Table 4 also shown that before receiving suctioning there were 17 respondents who had SpO_2 less than normal, but after receiving suctioning, 10 respondents (33.3%) had normal SpO_2, and the rest still had SpO_2 less than normal.

The results of this study are supported by research in the ICU room of Ulin Banjarmasin Hospital in 2020 which stated that there were changes in patient oxygen saturation after receiving suctioning. The patient's oxygen saturation increased to normal, and the frequency of suctioning given to patients would provide better results and lead to normal saturation values.[18] The results of other studies have also been carried out in the ICU room of the Bogor City Hospital in 2019 and showed evidence that sufficient suctioning intensity of 4–6 times a day or 1–2 times every 8 hours of care given to 20 patients had maintained the patient's oxygen saturation remained normal, while patients who received suctioning too often or insufficiently would fall into a state of hypoxemia.[13,19]

Suctioning received by patients who are bedridden and consciousness deteriorated in the ICU is an important procedure to clear the patient's airway from the accumulation of secretions and saliva in the airway.[20] An airway that is patent and free of accumulated secretions and saliva will prevent bacterial infection.[21] Suctioning is a collaborative and invasive procedure that can be performed by nurses for patients who need it. Suctioning is accepted by a number of patients in the ICU because these patients experience clinically critical conditions so that they experience prolonged bed rest with a level of total care needs. In this state, patients cannot fulfill their needs independently, one of which is freeing the airway from accumulated mucus or saliva.[21]

Suctioning that is performed correctly and at the right frequency for the patient will have an impact on oxygen saturation improvement for the patient. However, improper suctioning or not in accordance with standard operating procedures in terms of frequency can have a harmful impact on patients, namely increasing intracanal pressure, infection and even oxygen desaturation.[8] A decrease in oxygen saturation can occur in patients who receive suctioning too often, because when the mucus suctioning procedure is conducted, it will not only remove fluid or mucus in the patient's airway, but is accompanied by suctioning oxygen from the patient's airway.[19]

The researchers argues that suctioning does have an effect on improving patients' oxygen saturation, especially towards unconscious patients. However, suctioning also has a negative impact on patients if the nurse on duty does not perform suctioning according to applicable operational standards.

CONCLUSION

Based on the results of the study, it is concluded that there is an effect of suctioning to oxygen saturation improvement towards ICU patients in Prof. Dr. W. Z. Johannes Regional Public Hospital Kupang.

REFERENCES

1. Sudiarti PE. Konsep dasar keperawatan kritis. In: Munandar A, editor. Keperawatan Kegawatdaruratan dan Keperawatan Kritis. Bandung: Media Sains Indonesia; 2022. p. 239–50.
2. Sari RP, Ikbal RN. Tindakan suction dan perubahan saturasi oksigen pada pasien penurunan kesadaran di ruangan ICU rumah sakit. JIK-Jurnal Ilmu Kesehatan [Internet]. 2019 Oct 24 [cited 2023 Oct 10];3(2):85–90. Available from: http://www.jik.stikesalifah.ac.id/index.php/jurnalkes/article/view/223
3. Susila IMDP. Penatalaksanaan masalah-masalah dalam keperawatan kritis. In: Munandar A, editor. Keperawatan Kegawatdaruratan dan Keperawatan Kritis. Bandung: Media Sains Indonesia; 2022. p. 319–36.
4. Mazlan MZ, Mohd Zaini RH, Hassan SK, Ali S, Che Omar S, Wan Hassan WMN. Significance of a clean-tip catheter closed suctioning system in a high-setting ventilated, super morbidly obese patient with profuse respiratory secretions. Respir Med Case Rep. 2017;21:129–31.
5. Min S, Sorin C, Carino G. Patient with recent covid-19 infection presenting with acute upper airway obstruction. Chest. 2021 Oct 1;160(4):375–82.
6. Septimar ZM. Pengaruh tindakan penghisapan lendir (suction) terhadap perubahan saturasi oksigen pada pasien kritis di ICU. Jurnal Ilmu Kesehatan Masyarakat [Internet]. 2018 Mar 20 [cited 2023 Jun 25];7(01):10–4. Available from: https://journals.stikim.ac.id/index.php/jikm/article/view/47
7. Balfour-lynn IM, Wright M. Acute infections that produce upper airway obstruction. In: Kendig's Disorders of the Respiratory Tract in Children. 9th ed. 2019. p. 406–420e2.
8. Destiana Ri. Hubungan tingkat pengetahuan dan sikap perawat terhadap pelaksanaan tindakan suction pada pasien di ruang ICU RSUD Siti Fatimah Az-Zahra Palembang Tahun 2022. Prosiding Seminar Nasional Penerapan Hasil Penelitian dan Pengabdian Kepada Masyarakat di Era Digitalisasi. Palembang: Stikes Mitra Adiguna;2022.
9. Bangash MN, Hodson J, Evison F, Patel JM, Johnston AMD, Gallier S, *et al*. Impact of ethnicity on the accuracy of measurements of oxygen saturations: a retrospective observational cohort study. e-Clinical Medicine. 2022 Jun 1;48:101–8.
10. Swenson KE, Hardin CC. Pathophysiology of hypoxemia in covid-19 lung disease. Clin Chest Med. 2023 Jun 1;44(2):239–48.
11. Satici MO, Islam MM, Satici C, Uygun CN, Ademoglu E, Altunok İ, *et al*. The role of a noninvasive index 'Spo2/ Fio2' in predicting mortality among patients with covid-19 pneumonia. Am J Emerg Med. 2022 Jul 1;57:54–9.
12. RSUD Prof. Dr. W. Z. Johannes Kupang. Data pasien di ruang ICU RSUD Prof. Dr. W. Z. Johannes Kupang tahun 2022. Kupang; 2022.
13. Shrimpton AJ, Brown JM, Cook TM, Penfold CM, Reid JP, Pickering AE. Quantitative evaluation of aerosol generation from upper airway suctioning assessed during tracheal intubation and extubation sequences in anaesthetized patients. Journal of Hospital Infection. 2022 Jun 1;124:13–21.
14. Setiyo Wulan E, Nurul Huda N. Pengaruh tindakan suction terhadap saturasi oksigen pada pasien yang dirawat di ruang ICU RSUD R.A.A. Soewondo Pati. Jurnal Profesi Keperawatan (JPK) [Internet]. 2022 Jan 25 [cited 2023 Jun 25];9(1):22–33. Available from: https://jprokep.jurnal.centamaku.ac.id/index.php/jpk/article/view/115
15. Nizar AM, Haryati DS. Pengaruh suction terhadap kadar oksigen pada pasien koma di ruang ICU RSUD Dr. Moewardi Surakarta. Jurnal Keperawatan Global. 2017;2(2):62–9.
16. Susanti E, Okstoria MR, Wijayanti S, Damayanti H, Putra HE, Chipojola R, *et al*. Clinical determinants of oxygen saturation and length of hospitalisation of covid-19 patients: a cross-sectional study in Indonesia. Enferm Clin. 2023 Mar 1;33:S38–44.
17. Marchese GA, Crystal J, Louro LF. Incidence of severe hypoxemia in anesthetized horses undergoing emergency exploratory laparotomy. J Equine Vet Sci. 2022 Sep 1;116:104–26.
18. Hammad, Rijani MI, Marwansyah. Perubahan kadar saturasi oksigen pada pasien dewasa yang dilakukan tindakan suction endotrakeal tube di ruang ICU RSUD Ulin Banjarmasin. Bima Nursing Journal [Internet]. 2020;1(2):82–8. Available from: http://jkp.poltekkes-mataram.ac.id/index.php/bnj/index
19. Astuti W, Sulistyo FA. Hubungan intensitas tindakan suction dengan perubahan kadar saturasi oksigen pada pasien yang terpasang ventilator di ruang ICU RSUD Kota Bogor. Jurnal Ilmiah Wijaya [Internet]. 2019;11:2301–4113. Available from: www.jurnalwijaya.com.
20. Afenigus AD, Mulugeta H, Bewuket B, Ayenew T, Getnet A, Akalu TY, *et al*. Skill of suctioning adult patients with an artificial airway and associated factors among nurses working in intensive care units of Amhara region, public hospitals, Ethiopia. Int J Afr Nurs Sci. 2021 Jan 1;14.
21. Kristiani AH, Riani S, Supriyono M. Analisis perubahan saturasi oksigen dan frekuensi pernapasan pada pasien dengan ventilator yang dilakukan suction di ruang ICU RS Mardi Rahayu Kudus. Jurnal Perawat Indonesia. 2020;4(3):504–14.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 352–358

OPEN ACCESS

Original Article

The Influence of Inflammatory Factors (IL-6, CRP, NLPR, D-Dimer, LDH) on the PaO2/FiO2 Ratio, in Patients with Severe and Critical Degrees of COVID-19

Yulia Octaviany Harnoto[1], Ali Assagaf[1], Dewi Indah Noviana Pratiwi[2], Mohamad Isa[1], Ira Nurrasyidah[1], Erna Kusumawardhani[1]

[1]Department of Pulmonology and Respiratory Health, Faculty of Medicine, University of Lambung Mangkurat, Ulin Hospital, Banjarmasin, Indonesia
[2]Department of Clinical Pathology, Faculty of Medicine, Lambung Mangkurat University, Ulin Hospital, Banjarmasin, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.1014

Accepted: August 09th, 2023
Approved: October 19th, 2023

Author Affiliation:
Department of Pulmonology and Respiratory Health, Faculty of Medicine, University of Lambung Mangkurat, Ulin Hospital, Banjarmasin, Indonesia

Author Correspondence:
Yulia Octaviany Harnoto
Ahmad Yani Street No. 43, Banjarmasin, South Kalimantan 70233, Indonesia

E-mail:
yulia.octaviany@gmail.com

Abstract

Background : Several types of inflammatory biomarkers that are important in severe and critical Covid-19 infections include: levels of IL-6, C-reactive protein (CRP), lactate dehydrogenase (LDH), D-Dimer and neutrophil-lymphocyte platelet ratio (NLRP), which are independent variables. Meanwhile, the severity of Covid-19 infection can be determined by measuring the PaO2 /FiO2 ratio. However, the relationship between the PaO2/FiO2 ratio as the dependent variable is not yet known. The aims of this study was to analyze the relationship between PaO2/FiO2 ratio and inflammatory biomarkers in COVID-19 patients

Methods : An analytic observational study with a retrospective, cross-sectional approach. The research sample consisted of PCR-confirmed severe and critical COVID-19 patients who were treated in the isolation room of the Ulin Hospital in Banjarmasin from AugustDecember 2021, who met the inclusion and exclusion criteria. Data analysis used the Spearman test to see the relationship between the PaO2/FiO2 ratio and various inflammatory markers.

Results : 52 severe and critical patients were observed according to the research flow. The number of male and female subjects (32/20) was found. The mean age was 55.38 years. The correlation test found that: there was no significant relationship between the PaO2/FiO2 ratio and IL-6 ($p = 0.964$), but there was a negative correlation between the PaO2/FiO2 ratio and: a) CRP ($p = 0.038$), b) LDH ($p<0.001$), c) NLPR ($p = 0.013$), and d) D-dimer ($p<0.001$). The inflammatory biomarkers NLPR, LDH, and D-dimer are important independent variables for the severity of COVID-19, namely the PaO2/FiO2 ratio.

Conclusion : There are a significant correlation between the PaO2/FiO2 ratio to measure the severity of Covid-19 and several inflammatory biomarkers CRP, LDH, NLPR and D-dimer.

Keywords : COVID-19, PaO2/FiO2 ratio, NLPR, LDH, D-dimer

INTRODUCTION

The most frequent coronavirus 2019 (COVID-19) complication is acute respiratory distress syndrome (ARDS). Patients with SARS-CoV-2 illness can cause cytokine levels increases, which are indicative of the viral load and cause lung injury.[1,2] PaO2/FiO2, which is the ratio of arterial partial pressure of oxygen to inspired oxygen, can define ARDS and indicate the severity of low tissue oxygenation.[3] Some research exploring the relationship of various biomarkers to the severity of COVID-19, such as the Neutrophil Lymphocyte Platelet Ratio (NLPR), C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH), D-Dimer, and Interleukin-6 (IL-6).[4–7] Decreased CD4+ and CD8+ T cells level in SARS-CoV-2 infection can increase several ratios, such as NLPR.[7] Increased inflammation in COVID-19 causes CRP, LDH and d-dimer to increase, so that they can describe COVID-19's severity.[8–10] Also, IL-6 levels will increase sharply in individuals infected with SARS-CoV-2 because it is involved in cytokine release syndrome (CRS), and this cytokine is involved in the differentiation and formation of B lymphocytes and also T lymphocyte differentiation and proliferation. Excess IL-6 can harm organs by increasing the permeability of vessels and decreasing myocardial contractility. The movement of fluid and blood cells in the alveoli causes ARDS, which can lead to death.[4,11,12]

COVID-19 causes many acute respiratory disorders, which can increase mortality. We suspect that PaO2/FiO2 is related to NLPR, CRP, LDH, D-dimer, and IL-6 because they both describe the severity of COVID-19 patients. So far, there is still no research on the relationship between PaO2/FiO2 and inflammatory biomarkers in COVID-19 patients. The aim of this study was to analyze the relationship between PaO2/FiO2 with NLPR, CRP, LDH, D-dimer and IL-6 in patients with severe and critical COVID-19.

MATERIALS AND METHODS

Study Design and Participants

This research is an analytic observational study with a retrospective study, with cross-sectional approach. It was carried out at the Ulin Hospital in Banjarmasin from February to March 2023. Our study population was all patients with severe and critical degrees of COVID-19 confirmed by PCR and being treated in the isolation room of the Ulin Hospital in Banjarmasin during the period AugustDecember 2021, and our study sample was all patients with severe and critical degrees of COVID-19 confirmed by PCR and being treated in the isolation room of the Ulin Hospital in Banjarmasin during the period August–December 2021, which meets the inclusion and exclusion criteria. The research sample in this study used a purposive sampling technique with a minimum sample size of 33 people.

Inclusion Criteria: 1) COVID-19 patients are over 18 years old; 2) Patients with severe and critical degrees of COVID-19 confirmed by PCR at Ulin Hospital, Banjarmasin; 3) COVID-19 patients who underwent routine blood tests (blood gas analize, IL-6, CRP, LDH, and D-Dimer) when admitted to hospital at Ulin Hospital in Banjarmasin during the August–December 2021 period.

Exclusion Criteria: 1) Patients with incomplete medical record data; 2) Patients with blood hematological malignancies.

COVID-19 patients was classified by Indonesian Pulmonary Doctors Association (2021) with the following criteria:

- Severe: Patients with confirmed COVID-19 who have oxygen saturation <94% in room air, PaO2/FiO2 ratio <300 mmHg, respiratory rate > 30 breaths per minute, or pulmonary infiltration > 50%.
- Critical: Patients with confirmed COVID-19 who have respiratory failure (ARDS), septic shock, and multi-organ dysfunction.

Measurement Method

All study subjects who met the inclusion criteria were measured for the ratio of PaO2/FiO2 using the i-STAT1 tool. Then measurements of IL-6, NLPR, CRP, LDH, and D-dimer were assessed in each study subject. IL-6 examination was carried out using the specification iCHROMA-II, NLPR with the specification SYSMEX XN-1000, as well as examination of CRP, LDH, and D-dimer using the ARCHITECT C-4000.

Statistic analysis

Data analysis was performed using SPSS computer software version 26.0. Gender, age, PaO2/FiO2 ratio, NLPR, CRP, LDH, D-dimer, and IL-6 were presented as mean PaO2/FiO2 ratio, NLPR, CRP, LDH, D-dimer, and IL-6 are presented as mean SD and median. The normality test was assessed using the Shapiro-Wilk test. The relationship between the PaO2/FiO2 ratio and NLPR, CRP, LDH, D-dimer, and IL-6 was the Spearman correlation test. A multiple linear regression analysis test was used to determine the independent variables that affect the ratio of PaO2/FiO2.

Ethical Clearance

Each action in this study was carried out only after information was provided and with parental consent. This research with human subjects was carried out in accordance with the ethical guidelines of each institution. In accordance with ethical guidelines, the Ethics Commission of the Research and Development Agency at the Ulin Hospital in Banjarmasin and the Faculty of Medicine at the University of Lambung Mangkurat endorsed this research protocol.

RESULTS

This study consisted of 52 samples from patients with severe and critical degrees of COVID-19 confirmed by PCR and being treated in the isolation room of the Ulin General Hospital in Banjarmasin during the period of August to December 2021 who met the study criteria.

Subject Characteristics

There were more male than female, namely 32 male subjects (61.5%) vs. 20 female subjects (38.5%). The median age of the patients was 57.50 years, with a range between 25 and 80 years for the youngest and oldest patients, respectively, with a mean age of 55.38 years (Tabel 1).

Relationship of PaO2/FiO2 Ratio with NLPR, CRP, LDH, D-dimer, and IL-6

Based on Table 2, NLPR, CRP, LDH, and D-dimer have a negative correlation with the PaO2/FiO2 ratio with p-value 0.013; 0.038; <0.001; <0.001, respectively. NLPR has a weak correlation with the ratio of PaO2/FiO2 (rs: -0.334); CRP has a weak correlation with the ratio of PaO2/FiO2 (rs: -0.289); LDH has a moderate correlation to the ratio of PaO2/FiO2 (rs: -0.580); and D-dimer has a moderate correlation to the PaO2/FiO2 ratio (rs: -0.538). IL-6 did not correlate with the PaO2/FiO2 ratio ($p > 0.05$).

Multiple Linear Analysis

Using multiple linear regression analysis and the backward method, a multivariate model of the relationship between the PaO2/FiO2 ratio in severe and critical COVID-19 patients with inflammatory biomarkers was obtained in the Table 3. This study has a t-table value of 1.676. In the partial test on model 3, which consists of 3 independent variables in the regression model, it can be seen that NLPR has a t value of -2.932 and a t count greater than the t table, so it can be concluded that partially NLPR has an influence on the ratio of PaO2/FiO2. LDH has a calculated t value of -4.163, and t calculated is greater than t table, so it can be concluded that LDH partially has an effect on the ratio of PaO2/FiO2. D-Dimer has a t count of -1.781; the t count is greater than the t table, so it can be concluded that partially D-Dimer has an effect on the ratio of PaO2/FiO2.

The F table of this research is 2,574. With the backward method, CRP and IL-6 are removed. After being removed, we then assessed three other inflammatory biomarkers, namely NLPR, LDH, and D-dimer. In model 3, F count > F table (11.089 > 2.574), so it can be concluded that NLPR, LDH, and D-dimer together have an influence on the PaO2/FiO2 ratio (Table 4).

Multiple linear regression equation as follows:

$$\gamma = 366.668 - 10.478X_2 - 0.145X_4 - 4.357X_5$$

TABLE 1
Characteristics of Research Sample

Characteristics		n	Mean ± SD	Median
Sex	Female	20		
	Male	32		
Age		52	55.38 ± 13.69	57.5
PaO2/FiO2 Ratio		52	186.73 ± 131.76	148.71
NLPR		52	3.85 ± 4.15	2.06
CRP		52	108.08 ± 71.43	99.05
LDH		52	863.92 ± 427.58	767.5
D-Dimer		52	3.28 ± 6.15	1.31
IL-6		52	35.87 ± 57.24	16.5

TABLE 2
Relationship of PaO2/FiO2 Ratio with NLPR, CRP, LDH, D-dimer, and IL-6

Variable		NLPR	CRP	LDH	D-dimer	IL-6
PaO2/ FiO2 Ratio	Spearman's rho	-0.344	-0.289	-0.580	-0.538	-0.006
	p-value	0.013	0.038	<0.001	<0.001	0.964

TABLE 3
Partial test results for the backward method

Model		B	t	Sig
1	Constant	363.049		
	NLPR	0.438	-2.423	0.019
	CRP	-8.919	-1.224	0.227
	LDH	-0.276	-3.359	0.002
	D-dimer	-0.124	-2.109	0.040
	IL-6	-6.336	1.364	0.179
2	Constant	352.241		
	NLPR	0.356	-2.799	0.007
	LDH	-10.035	-3.885	<0.001
	D-dimer	-0.137	-2.108	0.040
	IL-6	-6.368	1.129	0.265
3	Constant	366.668		
	NLPR	-10.478	-2.932	0.005
	LDH	-0.145	-4.163	<0.001
	D-dimer	-4.357	-1.781	0.081

TABLE 4
Analysis of variance for the backward method

Model	F	Sig.
1 (NLPR,CRP,LDH,D-dimer,IL-6)	7.320	<0.001
2 (NLPR,LDH,D-dimer, IL-6)	8.683	<0.001
3 (NLPR, LDH, D-dimer)	11.089	<0.001

The value of -10,478 in the above model means that for every addition of X2 (NLPR) by one unit, Y (PaO2/FiO2 ratio) will decrease by 10,478 units; the value of - 0.145 in the above model means that for every addition of X4 (LDH) by one unit, Y (PaO2/FiO2 ratio) will decrease by 0.145 units; the value of -4,357 in the above model means that for every addition of X5 (D-Dimer) by one unit, Y (PaO2/FiO2 ratio) will decrease by 4,357 units.

DISCUSSION

Males were found to be more prevalent than female in our study. This is due to the fact that female are more likely to produce larger amounts of antibodies against influenza vaccinations that have been inactivated. Female are also have immune systems that are twice as powerful as those of male. Because estrogen increases the action of vitamin D in female, infections will reduce more slowly than in male. On the other hand, male sex hormones are considered to boost ACE2 receptor activation, which might stimulate the virus to enter, making them more vulnerable to COVID-19 and worsening the prognosis of the illness.[13] The subjects in our research had a median age of 55.38 years, with the range of 25 years and 80 years. A person's ability to produce T and B cells declines with age, and their body's innate immune system becomes less effective. Finally, during an infection, the cells responsible for innate immunity go dormant. As a result, eliminating viruses is less likely to be successful and raises the risk of setting off a dysregulated immune response, in which highly active immune cells generate a plethora of cytokines, leading to a cytokine storm that will worsen the situation.[14,15]

The study revealed a negative correlation between NLPR and the PaO2/FiO2 ratio. The NLPR tends to decrease when the PaO2/FiO2 ratio rises, and there is a

statistically significant correlation between the two variables. It is the same with other studies by Syahrini H. *et al*., which showed that there was a significant relationship between neutrophils, lymphocytes, and platelets and the degree of severity of COVID-19 (16), and also research by Haryati H. *et al*., showed a substantial correlation between NLPR and COVID-19 patient outcomes ($p<0.005$). In patients who died (75.4%) had a higher rise in NLPR (≥0.037) than those who survived (23.6%). The NLPR defines how neutrophils, lymphocytes, and platelets interact with acute immunological processes to cause immunoembolism.[17]

The pathogenesis of inflammatory injury to the kidney, cardiovascular system, gastrointestinal tract, and lung, with necrosis and subsequent apoptosis of these tissues, are influenced by dysregulation of neutrophil activation by the release of cytotoxic chemicals, including reactive oxygen species (ROS) and proteinases such as leukocyte elastase. Neutrophils alone may not be the dominant component affecting the PaO2/FiO2 ratio's outcomes. In addition, the pathogenicity of SARS CoV-2, which harms type II alveolar cells, the cytokine storm (TNF-alpha, IL-1, IL-6, and L-8), and neutrophil products (ROS and MMP) are further probable causes of epithelial and endothelial damage in the lungs. All organs, including the lungs, experience increasing neutrophil recruitment and activation as a result of the cytokine storm. Increased neutrophil counts result in the activation and release of neutrophil elastase, as well as ROS and MMP, which damage the lung's alveoli-capillary membrane and diffusely injure the alveoli. Both the beginning of acute lung injury (ALI) and the progression of ARDS are characterized by these two mechanisms.[18]

One of the key laboratory indicators that may be utilized to help with diagnosis and prognosis in COVID-19 patients is lymphopenia. The primary immune cells that respond to viral infections are lymphocytes. The amount of systemic inflammation is thought to be adversely associated with the lymphocyte count. Increased systemic inflammation resulted in a considerable reduction in CD4+ T cells, an increase in CD8+ suppressor T cells, and a rise in lymphocyte death.[19,20] Thrombocytopenia has been reported in hospitalized patients with COVID-19, and lower platelet counts are associated with poorer clinical outcomes.[21] Research by Zaid Y. *et al*., showed higher platelets in the COVID-19 group with ARDS ($159.90x10^3/L$) compared to the COVID-19 group without ARDS ($194.55x10^3/L$).[21] Low platelet counts cause platelet counts to aggregate, platelet-leukocyte complexes to form, and the release of chemicals that support cell adhesion and inflammation. Increased adhesion molecules and pro-inflammatory factors have a detrimental effect on patient survival. Platelet count and ARDS mortality are closely correlated, as shown by platelet-mediated thrombosis and enhanced capillary-endothelial barrier permeability.[22]

An inflammatory biomarker that can be used to gauge the severity of COVID-19 is C-reactive protein (CRP).[23] Our research showed that there was a weak negative correlation between the PaO2/FiO2 ratio and CRP. Research regarding the direct relationship between the PaO2/FiO2 ratio and CRP is still rare. Our result are in line with the research of Erika P. *et al*., indicated a significant negative correlation between the PaO2/FiO2 ratio and CRP. Due to an aberrant inflammatory condition, CRP in COVID-19 patients may be a manifestation of lung injury and may indicate respiratory distress as measured by the PaO2/FiO2 ratio. The creation of a cytokine storm is thought to be one of the key contributors, despite the fact that the precise mechanism of SARS-CoV-2 in ARDS is not well understood.[24]

In metabolic processes, lactate dehydrogenase is crucial because it participates in the incomplete conversion of pyruvate, the glycolysis product, to lactate in the absence of an adequate oxygen supply. A shortage of oxygen in biochemical or tissue processes, or multiorgan failure, is indicated by elevated LDH activity. A rise in LDH activity might be a sign of cell death, hypoxia, or injury.[9] Our findings indicated a weakly negative correlation between the PaO2/FiO2 ratio and LDH. According to our research, LDH tends to decrease when the ratio of PaO2/FiO2 rises. The link between the PaO2/FiO2 ratio and LDH in severe or critical COVID-19 patients have not been studied. However, Zinelu A *et al*., showed that patients with more severe COVID-19 had a lower PaO2/FiO2 ratio than patients with less severe COVID-19 ($p=0.002$). In the severe group, the PaO2/FiO2 ratio was 25251, whereas it was 31466 in the mild to moderate group.[12] PaO2/FiO2 may be used to determine how much COVID-19 pneumonia lesions have affected the overall lung tissue by measuring LDH. The SARS-CoV-2 virus can induce cytotoxicity and a cytokine storm. After being infected with COVID-19, several cells also perish, which ultimately results in the production of extracellular LDH and an instantaneous rise in serum LDH. In other words, the LDH level will rise and the PaO2/FiO2 ratio will decrease if there is more cell damage, such as a bigger pneumonia lesion.[25]

The COVID-19 virus has been linked to hemostatic conditions. Numerous investigations have also discovered a considerable rise in D-dimer levels among patients with severe illnesses and those who did not survive.[26] The same conclusion is drawn from our study. The PaO2/FiO2 ratio and D-dimer have a moderately strong negative correlation that is statistically very significant. Patients with severe and critical COVID-19 might experience hypoxia, which can activate clotting. Numerous studies also suggested that hypoxemia might result in venous and arterial thrombosis. This physio-pathological process appears to be influenced by Virchow's triad of hypercoagulability, endothelial damage, and stasis. Hypoxia-inducible transcription

factors (HIF), which control the genes that govern coagulation and fibrinolysis, can also be activated by local and systemic hypoxia brought on by various risk factors (such as cancer, high altitude, immobility following serious trauma or surgical intervention, etc).[27,28]

Our finding demonstrated a negative correlation between IL-6 and the PaO2/FiO2 ratio. However, there was no statistically significant correlation between the two variables. However, it still seems that a rise in IL-6 will lead to a fall in the PaO2/FiO2 ratio. The association between the PaO2/FiO2 ratio and IL-6 in COVID-19 has not yet been studied. We speculate that there may be a correlation between the PaO2/FiO2 ratio and IL-6, which is connecting to the development of ARDS and extensive inflammatory activity and reduce the PaO2/FiO2 ratio. Gu Y *et al*.'s[4] research backs up our theory, they showed that COVID-19 patients who died from ARDS had high IL-6 and a low PaO2/FiO2 ratio ($p < 0.0001$). When infection occurs, the downstream JAK signaling pathway will bind to transmembrane or soluble IL-6R through IL-6. However, if IL-6 is excessive, it can cause organ damage, such as increased vascular permeability and decreased myocardial contractility revealed that in severe COVID-19 patients, IL-6 level, an important cytokine upstream of the inflammatory cytokine cascade, are raising prior to ARDS, followed by acute phase proteins level elevating, such as CRP. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6 are examples of pro-inflammatory cytokines that can be promptly released by pathogenic Th1 cells after SARS-CoV-2 activation.[4,22,29]

After doing a multiple linear regression analysis between the ratio of PaO2/FiO2 and IL6, NLPR, CRP, LDH, and D-dimer As a consequence, only NLPR, LDH, and D-dimer, three independent factors, influence the PaO2/FiO2 ratio in severe and critical COVID-19 patients. There hasn't been any research done yet that compares different biomarkers as independent factors impacting the PaO2/FiO2 ratio. Neutrophils are thought to be the first cell type to be drawn to inflammatory areas. Neutrophils will transform into various phenotypes with different cell activities after they have reached the location of the inflammation. Additionally, neutrophils can attempt to modify innate and adaptive immune responses directly or indirectly through cytokines, chemokines, and other immune cells.[30] Although initially only neutrophils can be shown to be present, it is likely to affect NLPR. We further speculate that LDH may be present in large quantities across all organs and be intricately linked to the existence of the SARS-CoV02 infection, making LDH an independent factor influencing the PaO2/FiO2 ratio. Increased LDH activity can also be a sign of multiple organ failure, tissue oxygen deprivation, or oxygen deprivation in metabolic processes.[9] Another independent factor that might impact the PaO2/FiO2 ratio is D-dimer. Infection with SARS-CoV-2 increases the likelihood of developing ARDS, which affects lung oxygenation. One of the causes of a thrombus, which is indicated by an increase in D-dimer, is hypoxia. Numerous cellular and molecular signaling pathways are impacted by oxygen deprivation, which results in thrombus development.[30]

The strength of this study is that it is the only study that directly analyzes the relationship between the PaO2/FiO2 ratio and IL-6, LDH, CRP, NLPR, and D-dimer in severe and critical COVID-19 patients. It is hoped that this research can explain the relationship between the PaO2/FiO2 ratio and IL-6, LDH, CRP, NLPR, and D-dimer in patients with severe and critical degrees of COVID-19. However, our study has several limitations. First, the sample size of our study was small. Second, it did not separate the severe group from the critical group. Third, we only assessed the relationship of severity with COVID-19 inflammatory biomarkers, without separating mild or moderate degrees. Fourth, we did not analyze factors that had received medical intervention for concomitant diseases or comorbidities during treatment.

CONCLUSION

There are a significant correlation between the PaO2/FiO2 ratio to measure the severity of COVID-19 and several inflammatory biomarkers CRP, LDH, NLPR and D-dimer

Conflicts of interest

There is no conflicts of interest.

Authors' contributions

YOH designed, typed, and compiled the manuscript; AA, DIN, MI, IN, and EK participated in supervising this manuscript. All authors read and approved the final version of the manuscript.

Acknowledgements

We appreciate the facilities and assistance provided by the staff of the Department of Pulmonology and Respiratory Health, Lambung Mangkurat University, Banjarmasin.

REFERENCES

1. Aslan A, Aslan C, Zolbanin NM, Jafari R. Acute respiratory distress syndrome in COVID-19: possible mechanisms and therapeutic management. Pneumonia [Internet]. 2021;13(1).
2. Majidpoor J, Mortezaee K. Interleukin-6 in SARS-CoV-2 induced disease: Interactions and therapeutic applications. Biomed Pharmacother [Internet]. 2022;145:112419.
3. Bonaventura A, Mumoli N, Mazzone A, Colombo A,

Evangelista I, Cerutti S, *et al*. Correlation of SpO2/FiO2 and PaO2/FiO2 in patients with symptomatic COVID-19: An observational, retrospective study. Intern Emerg Med. 2022;17(6):1769–75.
4. Gu Y, Wang D, Chen C, Lu W, Liu H, Lv T, *et al*. PaO2/FiO2 and IL-6 are risk factors of mortality for intensive care COVID-19 patients. Sci Rep [Internet]. 2021;11(1):1–8.
5. Stringer D, Braude P, Myint PK, Evans L, Collins JT, Verduri A, *et al*. The role of C-reactive protein as a prognostic marker in COVID-19. Int J Epidemiol. 2021 May 17;50(2):420–9.
6. Eljilany I, Elzouki AN. D-dimer, fibrinogen, and il-6 in covid-19 patients with suspected venous thromboembolism: A narrative review. Vasc Health Risk Manag. 2020;16:455–62.
7. Ghobadi H, Mohammadshahi J, Javaheri N, Fouladi N, Mirzazadeh Y, Aslani MR. Role of leukocytes and systemic inflammation indexes (NLR, PLR, MLP, dNLR, NLPR, AISI, SIR-I, and SII) on admission predicts in-hospital mortality in non-elderly and elderly COVID-19 patients. Front Med. 2022;9.
8. Ade Saputro T, Vita Purwaningsih N, Watoyani T, Aliviameita A. Correlation between Corona Viruses Disease (Covid-19) and C-Reactive Protein (CRP) in Patients at Haji Hospital Surabaya Hubungan Corona Viruses Disease (Covid-19) dan C-Reactive Protein (CRP) pada Pasien di Rumah Sakit Umum Haji Surabaya. 2022;5(1).
9. Fialek B, Pruc M, Smereka J, Jas R, Rahnama-Hezavah M, Denegri A, *et al*. Diagnostic value of lactate dehydrogenase in COVID-19: A systematic review and meta-analysis. Cardiol J. 2022;29(5):751–8.
10. Riandini HM, Syarani F, Bihar S, Eyanoer PC. Original Article The Associations between Severity of Symptoms , D-Dimer and Incidence of ARDS In COVID-19. 2022;2(3):143–7.
11. Rumaratu SPH, Putra NPP, Sugiri YJ, Djajalaksana S, Listyoko AS, Al Rasyid H. The Effect of N-Acetylcysteine as Adjuvant Therapy of Hypoxemia in COVID-19 Patients, Assessed by Interleukin-6 Level and PaO2/FiO2 Ratio. J Respirologi Indones. 2022;42(3):226–36.
12. Zinellu A, De Vito A, Scano V, Paliogiannis P, Fiore V, Madeddu G, *et al*. The PaO2/FiO2ratio on admission is independently associated with prolonged hospitalization in COVID-19 patients. J Infect Dev Ctries. 2021;15(3):353–9.
13. Statsenko Y, Zahmi F Al, Habuza T, Almansoori TM, Smetanina D, Simiyu GL, *et al*. Impact of Age and Sex on COVID-19 Severity Assessed From Radiologic and Clinical Findings. 2022;11(February).
14. Hu C, Li J, Xing X, Gao J, Zhao S, Xing L. The effect of age on the clinical and immune characteristics of critically ill patients with COVID-19: A preliminary report. PLoS One [Internet]. 2021;16(3 March):1–11.
15. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-Mediated Inflammatory Responses: From Mechanisms to Potential Therapeutic Tools. Virol Sin [Internet]. 2020;35(3):266–71.
16. Syahrini H, Fadjari TH, Dalimoenthe NZ. Neutrophil-Lymphocyte Ratio (NLR) and Lymphocyte-Monocyte Ratio (LMR) as Covid-19 Screening Parameters. Indones J Med Lab Sci Technol. 2022;4(1):10–23.
17. Haryati H, Wicaksono B, Syahadatina M. Complete blood count derived inflammation indexes predict outcome in COVID-19 patients: a study in Indonesia. J Infect Dev Ctries [Internet]. 2023;17(3):319–26.
18. Agustama A, Utariani A, Kriswidyatomo P, Surya Airlangga P, Pujo Semedi B. Correlation of Neutrophil Elastase to D-Dimer, Pao2/Fio2 Ratio and SOFA Score In COVID-19 Patients. Int J Res Publ. 2022;93(1):251–7.
19. Parthasarathi A, Basavaraja CK, Arunachala S, Chandran S, Venkataraman H, Satheesh A, *et al*. Comorbidities influence the predictive power of hematological markers for mortality in hospitalized COVID-19 patients. Adv Respir Med. 2022;90(1):49–59.
20. Yanti B, Agustika R, Zulfikar T. Correlation Between Lymphocyte and Clinical Severity of Covid-19 in Banda Aceh, Indonesia. Malaysian J Public Heal Med. 2022;22(1):213–9.
21. Zaid Y, Guessous F, Puhm F, Elhamdani W, Chentoufi L, Morris AC, *et al*. Platelet reactivity to thrombin differs between patients with COVID-19 and those with ARDS unrelated to COVID-19. Blood Adv. 2021;5(3):635–9.
22. Wang R, Dai H. Association of platelet count with all-cause mortality from acute respiratory distress syndrome: A cohort study. J Clin Lab Anal. 2022;36(5):1–7.
23. Fazal M. C-Reactive Protein a Promising Biomarker of COVID-19 Severity. Korean J Clin Lab Sci. 2021;53(3):201–7.
24. Erika P, Domenica Z, Paolo I, Luca R, Giulia L, Alessandro D, *et al*. Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in CoVID-19 patients. Clin Chim Acta. 2020 Oct 1;509:135–8.
25. Kojima K, Yoon H, Okishio K, Tsuyuguchi K. Increased lactate dehydrogenase reflects the progression of COVID-19 pneumonia on chest computed tomography and predicts subsequent severe disease. Sci Rep [Internet]. 2023;13(1):1–10.
26. Mubarak R, Esa T, Widaningsih Y, Bahrun U. D-Dimer Analysis in COVID-19 Patients. Vol. 28, Indonesian Journal of Clinical Pathology and Medical Laboratory. 2021. p. 5–9.
27. Loffredo L, Pignatelli P, Pirro M, Ceccarelli G, Oliva A, Maggio E, *et al*. Association between - PaO 2 / FiO 2 ratio and thrombotic events in COVID-19 patients. 2023;(0123456789).
28. Leonora Trisna G, Utariani A, Pujo Semedi B. Relationship of Ferritin, Interleukin-8, and D-Dimer Levels with PaO2/FiO2 Ratio and Mortality in ARDS COVID-19. Int J Res Publ. 2021;92(1):106–15.
29. Herold T, Jurinovic V, Arnreich C, Lipworth BJ. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. 2020;(January).
30. Rosales C. Neutrophil: A cell with many roles in inflammation or several cell types? Front Physiol. 2018;9(FEB):1–17.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 359–363

OPEN ACCESS

Original Article

Effectiveness of Sucralphate and Platelet-Rich Plasma Combinations for Vascular Endothelial Growth Factor (VEGF) Expression in Diabetic Ulcer Healing

Victor Jeremia Syaropi Simanjuntak[1], Renni Yuniati[2], Yan Wisnu Prajoko[3], Heri Nugroho Hario Seno[4], Tri Nur Kristina[5]

[1]Master of Biomedical Science Study Program, Faculty of Medicine Diponegoro University, Semarang, Indonesia
[2]Department of Dermatology & Venereal Diseases, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
[3]Department of Surgery, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
[4]Department of Internal Medicine Faculty of Medicine Diponegoro University, Semarang, Indonesia
[5]Department of Microbiology Faculty of Medicine Diponegoro University, Semarang, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.862

Accepted: November 28th, 2022
Approved: October 30th, 2023

Author Affiliation:
Master of Biomedical Science Study Program, Faculty of Medicine Diponegoro University, Semarang, Indonesia

Author Correspondence:
Victor Jeremia Syaropi Simanjuntak
Dr. Sutomo Street No.16, Semarang, Central Java 50244, Indonesia

E-mail:
vjeremia71@gmail.com

Abstract

Background : Diabetic ulcer is one of the most feared chronic infections due to Diabetes Mellitus because it can lead to amputation and death. The aims of this study was to prove the effectiveness of sucralfate and platelet-rich plasma (PRP) combination for Vascular Endothelial Growth Factor (VEGF) expression in diabetic ulcer healing.
Methods : This research is an experimental study of Phase I Clinical Trial with post-test only group design. There were 20 patients with diabetic ulcers divided into two groups, namely the treated group that was given sucralfate and PRP therapy and the control group was given standard therapy of normal saline drainage and gauze covered. Parameters were VEGF expression levels, wound area after being given therapy, and side effect from the treatment. Data on VEGF expression levels were obtained by means of examination with the Quantikine Human VEGF-ELISA Quantikine, R&D System, Inc, Minneapolis. The measurement of the wound area was assessed based on several criteria, namely grade 0 (no change), grade 1 (wound size reduced to less than of the previous wound), grade 2 (wound size was reduced to less than of the previous wound, but granulation was visible), and grade 3 (wound has closed completely).
Results : In unpaired t-test, the mean VEGF expression was 98.18+10.96 in the treatment group and 66.69+23.79 in the control group which showed significant difference in VEGF expression levels ($p = 0.003$). In Mann-Whitney test, the mean wound area was 0.68+0.40 in the treatment group and 0.77+0.67 in the control group which showed that there was not any significant difference in wound area ($p = 0.152$). There were no side effects in both study group.
Conclusion : The combination of sucralfate and PRP can increase VEGF levels significantly in diabetic ulcer patients but does not show a different effect in reducing wound area compared to standard treatment. The combination did not cause any side effects in the study subjects, as well as those using standard treatment.

Keywords: sucralfate, platelete-rich plasma topical, VEGF expression, wound area, side effect, diabetic ulcer

INTRODUCTION

Diabetic ulcer is an injury to all layers of the skin, can be in the form of necrosis or gangrene that can occur in any part of the body, due to peripheral neuropathy or peripheral arterial disease in patients with diabetes mellitus (DM). Diabetic ulcer can be followed by bacterial invasion resulting in infection and decay, especially in the distal lower limbs. Diabetic ulcer can cause disability (amputation) and death.[1,2] The incidence of diabetic ulcer continues to increase worldwide. The study by Leone *et al* estimated that 15% of DM patients will experience complications of diabetic ulcer.[3] The prevalence rate of diabetic foot ulcer differs in each country, but is estimated to be between 4–27% worldwide.[4] The prevalence of diabetic ulcer sufferers in the United States is 15–20%.[5] The data from Dr. Cipto Mangunkusumo showed the mortality rate of DM patients was 16% and the amputation rate due to foot ulcers was 25%.[6] The main goal of diabetic ulcer management is wound closure. Several treatments for diabetic ulcers are debridement, reduction of the burden on the wound area, management of infection and wound care with topical dressings or dressings on the ulcer area.[7] There are various innovative topical dressings to heal diabetic foot ulcers, one of which is sucralfate.[8,9] Study by Nagalakshmi *et al*, showed that topical sucralfate is a more effective modality than conventional dressings and debridement.[10] Sucralfate induces proliferation of dermal fibroblasts and keratinocytes. Sucralfate increases fibroblasts by increasing prostaglandin E2 synthesis in basal keratinocytes, increasing stimulation of interleukin-1 and interleukin-6 release from fibroblasts.[11] Besides sucralfate, platelet-rich plasma (PRP) is another non-invasive technique that can be used to treat diabetic ulcers. Demands for PRP is increasing because of its potential to induce and accelerate tissue healing.[12] PRP is derived from a person's blood, where after centrifugation, a plasma fraction is obtained with a higher concentration of platelets than in circulating blood. Platelets play an important role in the wound healing process because they have hemostatic functions and their cytokines and growth factors. There are several growth factors that are known to be involved in the wound healing process, one of which is vascular endothelial growth factor (VEGF).[13] VEGF plays a role in the process of angiogenesis or neovascularization in the wound healing process.[17] Based on the research by Carter *et al*, the use of PRP in the form of a gel applied to wounds can accelerate wound healing and reduce the incidence of infection in patients.[14] As well as the study by Vilela *et al*, which stated that PRP was clinically proven to give good results in wounds.[15] PRP has also been shown to be safe and efficient in the treatment of diabetic foot ulcers, and provides a faster healing time.[16] In a study conducted by Renni *et al*, regarding the administration of topical sucralfate and topical Platelet-rich plasma in rats with diabetic ulcers, it was shown that the combination of sucralfate and PRP supported each other to improve wound healing. Sucralfate contributes to the inflammatory phase by inducing prostaglandin E2 thereby increasing wound protection and increasing the production of growth factors in the proliferative phase. Meanwhile, PRP contributes to every phase of wound healing by releasing various growth factors.[18]

Previous studies have shown that the use of sucralfate or platelet-rich plasma can accelerate healing in diabetic ulcers. This study aims to prove the effectiveness of the use of a topical combination of sucralfate and platelet-rich plasma in healing diabetic ulcers using VEGF expression parameter so that it is expected to be used as a new, safer and more efficient alternative modality in the management of diabetic ulcers.

METHODS

This study is an experimental study of Phase I Clinical Trial with post-test only control group design which was conducted from January to March 2022 at Kariadi Hospital and the Central Laboratory of the Faculty of Medicine, Diponegoro University, Semarang. The research subjects were patients with type 2 diabetes mellitus who were more than 18 years old, diagnosed with Wegner's diabetic ulcers 1 to 2 who visited the Outpatient Room for Skin and Venereal Diseases and Internal Medicine, RSUP Dr. Kariadi Semarang, and willing to participate in the research and fill out the informed consent form.

The research subjects were selected by consecutive sampling, based on the patient's arrival at Kariadi Hospital Semarang who met the criteria until the minimum sample size was met (20 research subjects) they divided into two groups, the treatment group (administered sucralfate and PRP) and the control group who received standard therapy (normal saline drainage, covered with gauze, and antibiotics). Subjects have received written informed consent and ethical clearance form has passed the ethical review of the Health Research Ethics Committee of Kariadi Hospital Semarang with the number: 590/EC/KEPK-RSDK/2020.

Data on VEGF expression levels were obtained by means of examination with the Quantikine Human VEGF-ELISA Quantikine, R&D System, Inc, Minneapolis. The measurement of the wound area was assessed based on several criteria, namely grade 0 (no change), grade 1 (wound size reduced to less than of the previous wound), grade 2 (wound size was reduced to less than of the previous wound, but granulation was visible), and grade 3 (wound has closed completely). Data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows version 16 program.

RESULTS

Table 1 shows the characteristic data and laboratory results for all research subjects.

Table 2 shows the normality test for VEGF data and wound area was carried out using the Saphiro-Wilk test. From the test results, the data on VEGF expression were normally distributed ($p > 0.05$). Meanwhile, in the normality test of wound area, the data was not normally distributed ($p < 0.05$).

Based on the t test, the results showed that the VEGF expression in the treatment group was significantly lower than the control group ($p=0.003$) (Table 3).

Based on the Mann-Whitney test, the results showed that there was no significant difference in wound area between the treatment and control groups, and there was no significant reduction in wound area in either the treatment or control groups (Table 4).

DISCUSSION

The results of this study showed that the combination of sucralfate and PRP succeeded in increasing VEGF levels significantly compared to controls. This study is in line with the research conducted by Yuniati *et al*. regarding the use of sucralfate and topical PRP in the healing process of diabetic ulcers in rats, where the number of macrophages, VEGF, and PDGF levels all increased significantly.[18]

In this study, it was found that there was no significant difference in the area of the wound in the two

TABLE 1
Characteristics of research subjects

Characteristics		Groups		*p* value
		Treatment (n=10)	Control (n=10)	
Mean age (years)		52 ± 6.89*	57.20 ± 10.27*	0.200
Sex	Male	4 (40)	3 (30)	0.66
	Female	6 (60)	7 (70)	
Lab Value	Hemoglobin	13.30 ± 1.59*	12.65 ± 1.05*	0.731
	Blood Sugar Level	194.40 ± 42.23*	212.30 ± 101.75*	0.621
	Ureum	34.10 ± 22.32*	35.30 ± 19.54*	0.900
	Creatinin	1.07 ± 0.22*	1.36 ± 0.37*	0.609
	HbA1c	7.29 ± 0.94*	7.03 ± 0.64*	0.210

TABLE 2
Normality test for VEGF data and wound area

	Statistics	df	Sig.
VEGF	.158	20	.200
Wound Area	.334	20	.000

TABLE 3
Comparison of mean VEGF levels of the 2 study groups

Categories	Mean VEGF ± SD*		*p*
	Treatment Group	Control Group	
VEGF After treatment	98.18 ± 10.96	66.69 ± 23.79	0.003*

TABLE 4
Comparison of the average area of diabetic wounds from the 2 study groups

Categories	Mean of Wound Area ± SD*		*p* value
	Treatment Group	Control Group	
Before treatment	2.77 ± 2.03	2.14 ± 2.12	0.325
After treatment	2.09 ± 1.63	1.37 ± 1.45	0.173
p	0,353	0.190	
Difference between before and after treatment	0.68 ± 0.40	0.77 ± 0.67	0.152

study groups. There is slightly different from other studies related to the administration of PRP monotherapy to decrease wound area. In a study conducted by Tripathi *et al*, there was a significant difference in wound area in the PRP-treated group compared to the control group. In the study by Harry *et al*, it was also found that there was a significant difference in the reduction in wound area in the PRP-administered group and the control group. In patients with Wagner grade 1, there was an average reduction in wound area of 33.8% in the PRP-treated group and an average reduction of 18.6% in the control group. Meanwhile, in patients with Wagner grade 2, there was an average reduction in wound area of 31.9% in the PRP group and 19.27% in the control group.[45]

The difference between the results of this study and these studies could be due to the difference in the duration of the research conducted on the research subject, which in this study was carried out for 20 days while the studies varied between 3-4 weeks. This study also used research subjects with variations in Wagner grades I and II wounds and did not differentiate the outcomes based on these grades, which is also a limitation of this study.

CONCLUSION

The combination of sucralfate and PRP can increase VEGF expression significantly in diabetic ulcer patients but does not show a different effect in reducing wound area compared to standard treatment. The combination did not cause any side effects in the study subjects, as well as those using standard treatment.

Conflict of intereset

The author declares there is no conflict of interest regarding publication of the current study.

Acknowledgement

This paper and the research behind it would not have been possible without the exceptional support of my supervisor. Their enthusiasm, knowledge and exacting attention to detail have been an inspiration and kept my work on track.

REFERENCES

1. Alavi A, Sibbald RG, Mayer D, Goodman L, Botros M, Armstrong DG, *et al*. Diabetic foot ulcers: Part I. Pathophysiology and prevention. J Am Acad Dermatol. 2014 Jan;70(1):1.e1–18; quiz 19–20.
2. Wang A, Xu Z, Ji L. [Clinical characteristics and medical costs of diabetics with amputation at central urban hospitals in China]. Zhonghua Yi Xue Za Zhi. 2012 Jan;92(4):224–7.
3. Leone S, Pascale R, Vitale M, Esposito S. [Epidemiology of diabetic foot]. Le Infez Med. 2012;20 Suppl 1:8–13.
4. Abdissa D, Adugna T, Gerema U, Dereje D. Prevalence of Diabetic Foot Ulcer and Associated Factors among Adult Diabetic Patients on Follow-Up Clinic at Jimma Medical Center, Southwest Ethiopia, 2019: An Institutional-Based Cross-Sectional Study. J Diabetes Res [Internet]. 2020 Mar 15;2020:4106383. Available from: https://pubmed.ncbi.nlm.nih.gov/32258165
5. Flahr D. The effect of nonweight-bearing exercise and protocol adherence on diabetic foot ulcer healing: a pilot study. Ostomy Wound Manage. 2010 Oct;56(10):40–50.
6. Setati S, Alwi A, Simadibrata S. Kaki Diabetes: Books of Science of Internal Medicine. Jakarta: Interna Publishing; 2014.
7. Rosyid FN. Etiology, pathophysiology, diagnosis and management of diabetics' foot ulcer. Int J Res Med Sci. 2017;5(10):4206.
8. Singer AJ, Clark RA. Cutaneous wound healing. N Engl J Med. 1999 Sep;341(10):738–46.
9. Santilli SM, Valusek PA, Robinson C. Use of a noncontact radiant heat bandage for the treatment of chronic venous stasis ulcers. Adv Wound Care. 1999 Mar;12(2):89–93.
10. Nagalakshmi G, Amalan AJ, Anandan H. Clinical Study of Comparision Between Efficacy of Topical Sucralfate and Conventional Dressing in the Management of Diabetic Ulcer. 2017;5(3):236–8.
11. McGee GS, Davidson JM, Buckley A, Sommer A, Woodward SC, Aquino AM, *et al*. Recombinant basic fibroblast growth factor accelerates wound healing. J Surg Res. 1988 Jul;45(1):145–53.
12. Anitua E, Alkhraisat MH, Orive G. Perspectives and challenges in regenerative medicine using plasma rich in growth factors. J Control Release. 2012 Jan;157(1):29–38.
13. Grazul-Bilska AT, Johnson ML, Bilski JJ, Redmer DA, Reynolds LP, Abdullah A, *et al*. Wound healing: the role of growth factors. Drugs Today (Barc). 2003 Oct;39(10):787–800.

14. Carter MJ, Fylling CP, Parnell LKS. Use of platelet rich plasma gel on wound healing: a systematic review and meta-analysis. Eplasty [Internet]. 2011/09/15. 2011;11:e38–e38. Available from: https://pubmed.ncbi.nlm.nih.gov/22028946
15. Villela DL, Lu V. Evidence on the use of platelet-rich plasma for diabetic ulcer: A systematic review. 2010;28 (April):1116.
16. Driver VR, Hanft J, Fylling CP, Beriou JM. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy Wound Manage. 2006 Jun;52(6):68–70, 72, 74 passim.
17. Singer AJ, Tassiopoulos A, Kirsner RS. Evaluation and Management of Lower-Extremity Ulcers. Vol. 378, The New England journal of medicine. United States; 2018. p. 302–3.
18. Yuniati R, Innelya I, Rachmawati A, *et al*. Application of Topical Sucralfate and Topical Platelet-Rich Plasma Improves Wound Healing in Diabetic Ulcer Rats Wound Model. Journal of Experimental Pharmacology. 2021:13. 797–806.
19. Sidawy A, Perler B, AbuRahman. Rutherford's Vascular Surgery and Endovascular Therapy: 9th edition: Elsevier: 2019.
20. DeFronzo R. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard lecture 2009. Diabetologia. 2010;53(7):1270–1287.
21. Mills JL, *et al*. The Society for Vascular Surgery lower extremity threatened limb classification system: risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg. 2014;59:220–223.
22. Katz DE, Friedman ND, Ostrovski E, *et al*. Diabetic foot infection in hospitalized adults. J Infect Chemother. 2016;22:167–173.
23. Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. N Engl J Med. 2017 Jun;376(24):2367–75.
24. Clayton W, Elasy TA. A Review of the Pathophysiology, Classification, and Treatment of Foot Ulcers in Diabetic Patients. Clin Diabetes [Internet]. 2009 Apr 1;27(2):52 LP – 58. Available from: http://clinical.diabetesjournals.org/content/27/2/52.abstract
25. Charles H, Chung K, Gosain A, *et al*. Grabb and Smith's Plastic Surgery: 7th edition. Wolters Kluwer. 2014.
26. Rosyid F, Dharmana E. Suwondo A, *et al*. VEGF: Strukture, Biological Activities, Regulations and Role in The Healing of Diabetic ulcers. International Journal of Research in Medical Sciences. 2018 Jul;6(7):2184–2192.
27. Brem H, Tomic-Canic M. Cellular and Molecular Basics of Wound Healing in Diabetes. Journal of Clinical Investigation. 2007 May:117(5):1219–1222.
28. Philip B, Arber K, Tomic-Canic M, *et al*. The Role of Vascular Endothelial Growth Factor in Wound Healing. Journal of Surgical Researc. 2009:153:347–358
29. David O. Bates O, Pritchard J. The Role of Vascular Endothelial Growth Factor in Wound Healing. International Journal of Lowe Extremity Wounds. 2003:2(107)
30. Wild T, Rahbarnia A, Kellner M, Sobotka L, Eberlein T. Basics in nutrition and wound healing. Nutrition. 2010 Sep;26(9):862–6.
31. Jain A. A new classification of diabetic foot complications: a simple and effective teaching tool. J Diabet Foot Complicat [Internet]. 2012;4(1):1–5. Available from: http://jdfc.org/2012/volume-4-issue-1/a-new-classification-of-diabetic-foot-complications-a-simple-and-effective-teaching-tool/
32. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Harkless LB, Boulton AJ. A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. Diabetes Care. 2001 Jan;24(1):84–8.
33. Masuelli L, Tumino G, Turriziani M, Modesti A, Bei R. Topical Use of Sucralfate in Epithelial Wound Healing: Clinical Evidence and Molecular Mechanisms of Action. Recent Pat Inflamm Allergy Drug Discov. 2009;4(1):25–36.
34. McCarthy DM. Sucralfate. N Engl J Med. 1991 Oct;325(14):1017–25.
35. Yeh BK, Eliseenkova A V, Plotnikov AN, Green D, Pinnell J, Polat T, *et al*. Structural basis for activation of fibroblast growth factor signaling by sucrose octasulfate. Mol Cell Biol. 2002 Oct;22(20):7184–92.
36. Konturek SJ, Brzozowski T, Majka J, Szlachcic A, Bielanski W, Stachura J, *et al*. Fibroblast growth factor in gastroprotection and ulcer healing: interaction with sucralfate. Gut. 1993 Jul;34(7):881–7.
37. Hu Y, Guo S, Lu K. [The effect of bFGF and sucralfate on cell proliferation during continuous tissue expansion]. Zhonghua zheng xing wai ke za zhi = Zhonghua zhengxing waike zazhi = Chinese J Plast Surg. 2003 May;19(3):203–6.
38. Ebner R, Derynck R. Epidermal growth factor and transforming growth factor-alpha: differential intracellular routing and processing of ligand-receptor complexes. Cell Regul. 1991 Aug;2(8):599–612.
39. Sánchez-Fidalgo S, Martín-Lacave I, Illanes M, Motilva V. Angiogenesis, cell proliferation and apoptosis in gastric ulcer healing. Effect of a selective cox-2 inhibitor. Eur J Pharmacol. 2004 Nov;505(1–3):187–94.
40. Burch RM, McMillan BA. Sucralfate induces proliferation of dermal fibroblasts and keratinocytes in culture and granulation tissue formation in full-thickness skin wounds. Agents Actions. 1991 Sep;34(1–2):229–31.
41. Akhundov K, Pietramaggiori G, Waselle L, Darwiche S, Guerid S, Scaletta C, *et al*. Development of a cost-effective method for platelet-rich plasma (prp) preparation for topical wound healing. Ann Burns Fire Disasters. 2012;25(4):207–13.
42. Suthar M, Gupta S, Bukhari S, Ponemone V. Treatment of chronic non-healing ulcers using autologous platelet rich plasma: a case series. J Biomed Sci. 2017 Feb;24(1):16.
43. Vinay KT, Parijat G. Management of diabetic foot ulcers with platelet rich Plasma : A clinical study. National Journal of Clinical Orthopaedics. 2008;2(3): 09–11
44. Tripathi VK, Gupta P. Management of diabetic foot ulcers with platelet rich plasma: A clinical study. National journal of clinical orthopaedics. 2018 Jun 7;2(3):09–11
45. Harry A, Uma S, Sivaram. Role of platelet rich plasma in treatment of diabetic foot ulcer. Indian journal of Applied Research. 2017 May;7(5):601–602
46. El-rahman MAA, Al-Hayeg OMI, Aboulyazid ABM, Gaafar AM. the role of platelet-rich plasma in the treatment of diabetic foot ulcers. Al-Azhar Med. J. 2020; 49(3):1369–1376

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 364–369

OPEN ACCESS

Original Article

Risk Factors of Mortality in Probable Covid-19 Cases in RSUP Dr. Kariadi Semarang

Yui Prashandika[1], Setyo Gundi Pramudo[2],
Sigid Kirana Lintang Bhima[3], Tuntas Dhanardhono[3]

[1]Faculty of Medicine, Diponegoro University, Semarang Indonesia
[2]Department of Internal Medicine, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
[3]Department of Forensic and Medicolegal Studies, Faculty of Medicine, Diponegoro University, Semarang, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.957

Accepted: April 18th, 2023
Approved: November 07th, 2023

Author Affiliation:
Faculty of Medicine, Diponegoro University, Semarang Indonesia

Author Correspondence:
Yui Prashandika
Prof. Sudarto Street, Tembalang, Semarang, Central Java, 50275, Indonesia

E-mail:
yprashandika@gmail.com

Abstract

Background : On February 19th, 2021, City of Semarang recorded 164 death cases of probable COVID-19. A study of patients who died from COVID-19 found that the death cases occured mostly in patients with comorbidities, such as hypertension, diabetes, heart disease, renal disease, chronic lung disease, and malignancy. The definitions of probable COVID-19 by WHO is a suspected case with radiological features leading to COVID-19 infection. The purpose of this study was to prove pneumoniae, chronic lung disease, heart disease, hypertension, DM, renal disease, and malignancy as risk factors of mortality in probable COVID-19 patients.
Methods : This study used analytic observational design with cross-sectional study approach. Consecutive sampling technique was used with minimum sample of 57 probable COVID-19 medical records. The collected data was analyzed using the SPSS program with univariate, bivariate, and multivariate analysis.
Results : The majority of probable COVID-19 patients died with a number of 65 subjects (91.5%), while the probable COVID-19 patients that survived are only 6 subjects (8.5%). Risk factors like pneumoniae (p=0.151; PR=0.9; 95%CI[0.78–1.03]), chronic lung disease (p=0.764; PR=1.09; 95%CI[1.02–1.18]), heart disease (p=0.591; PR=1.03; 95%CI[0.88–1.20]), hypertension (p=0.254; PR=1.08; 95%CI[0.95–1.23]), DM (p=0.361 PR=1.06; 95%CI[0.93–1.21]), renal disease (p=0.523; PR=1.10; 95%CI[1.02–1.19]), and malignancy (p=0.523; PR=1.10; 95%CI[1.02–1.19]) have not been proven to be risk factors for death in patients probable of COVID-19 at Dr. Kariadi General Hospital, Semarang.
Conclusion : Pneumoniae, chronic lung disease, heart disease, hypertension, diabetes mellitus, kidney disease, and malignancy have not been proven to be risk factors for death in patients probable of COVID-19 at Dr. Kariadi General Hospital, Semarang.

Keywords : Mortality, probable COVID-19, Risk factors

INTRODUCTION

Indonesia became one of the countries with high COVID-19 cases, while COVID-19 was determined as a nonnatural disaster in the form of disease outbreak by BNPB (Badan Nasional Penanggulangan Bencana). On February 19th, 2021, Semarang City recorded 30.167 confirmed cases, 107 suspect cases, and 24 probable cases with 164 probable COVID-19 deaths.[1] Several studies of patients who died from COVID-19 found that the death cases occured mostly in patients with comorbidities, such as hypertension, diabetes, heart disease, renal disease, chronic lung disease, and malignancy.[2–4] Death due to COVID-19 by WHO is defined as a death resulting from clinically compatible illness in a probable or confirmed COVID-19 case. The definition of probable COVID-19 by WHO is a patient who met the clinical criteria of suspect case and had been contacted with probable or confirmed case, or associated with COVID-19 cluster; a suspect case with chest imaging showed suggestive findings of COVID-19 disease; a person with recent onset of anosmia (loss of smell), or ageusia (lost of taste) with no other identified cause; Death in an adult with respiratory distress who had contacted with probable, confirmed case, or associated with COVID-19 cluster.[5]

The high death rate of probable COVID-19 in Semarang City became the reason this study was conducted. The purpose of this study was to prove pneumoniae, chronic lung disease, heart disease, hypertension, DM, renal disease, and malignancy as risk factors of mortality in probable COVID-19 patients.

METHODS

This research was conducted at RSUP Dr. Kariadi Semarang from March–June 2021 (4 month) with an analytic observational design with cross-sectional study approach. The consecutive sampling technique was used with minimum sample of 57 probable COVID-19 medical records between July 2020 – March 2021 period, obtained from the medical records section of RSUP Dr. Kariadi Semarang. Inclusion criteria was patients with diagnosis of probable COVID-19. Exclusion criteria were patients with confirmed diagnosis of COVID- 19, patients with status other than probable COVID-19, patients without medical records, and incomplete medical record data.

Data analysis was carried out using a computer with SPSS 26 statistical analysis program. Data analysis consisted of univariate, bivariate, and multivariate analysis. Univariate analysis was done to find out and describe each independent variables (risk factors). Analysis bivariate was done using Chi-Square 2x2 test to determined significancy of the dependent variable (probable COVID-19) and independent variables (risk factors). The variable is significant if $P < 0.05$. Significant P value from bivariate analysis was then further tested using multivariate analysis with logistic regression test, and calculating the estimated risk of death namely prevalence ratio (PR) and 95%CI. This research has obtained approval from RSUP Dr. Kariadi Semarang and the KEPK Ethics Committee of the Faculty of Medicine Diponegoro University through letter number 109/ EC/ KEPK/ FK-UNDIP/ IV/ 2021.

RESULTS

Medical record research samples that met the inclusion and exclusion criteria from the medical records section of RSUP Dr. Kariadi Semarang were 71 samples. From the univariate analysis (Table 2), it was found that the majority of probable COVID-19 patients died with a number of 65 subjects (91.5%), while the probable COVID-19 patients that survived were only 6 subjects (8.5%). Meanwhile the comorbid risk factors data showed that the majority of patients with probable COVID-19 had pneumonia as their comorbidity in 39 cases (54.9%), followed by hypertension in 27 cases (38.0%), Diabetes Mellitus in 23 cases (32.4%), heart disease in 16 cases

TABLE 1
Probable COVID-19 Patients

Variables	Frequency	%
Deaths		
Yes	65	91.5
No	6	8.5
Patients died with risk factors		
Pneumoniae	34	52.3
CPOD	3	4.6
Heart Disease	15	23.1
Hipertension	26	40
DM	42	33.8
Kidney Disease	10	7
Malignancy	12	7
Pasien survived with risk factors		
Pneumoniae	5	83.3
CPOD	0	0
Heart Disease	1	16.7
Hipertension	1	16.7
DM	1	16.7
Kidney Disease	0	0
Malignancy	0	0

TABLE 2
Bivariate Analysis

Variables	Mortality			
	Yes		No	
	n	%	n	%
Pneumoniae	334	52.3	5	83,3
COPD	3	4.6	0	0
Heart Disease	15	23.1	1	16.7
Hipertension	26	40.0	1	16.7
DM	22	33.8	1	16.7
Kidney Disease	7	10.8	0	0
Malignancy	7	10.8	0	0

TABLE 3
Estimated Risk

Variables	PR (95% CI)	*p*
Pneumoniae	0.9 (0.78–1.03)	0.151
COPD	1.09 (1.02–1.18)	0.764
Heart Disease	1.03 (0.88–1.20)	0.591
Hipertension	1.08 (0.95–1.23)	0.254
DM	1.06 (0.93–1.21)	0.361
Kidney Disease	1.10 (1.02–1.19)	0.523
Malignancy	1.10 (1.02–1.19)	0.523

(22.5%), kidney disease and malignancy in 7 cases (9.9%), and chronic lung disease in 3 cases (4.2%). The results of the bivariate analysis (Table 2 & 3) have not been proven to be risk factors for death in patients probable of COVID-19 at Dr. Kariadi General Hospital, Semarang. The risk factors for comorbid pneumoniae and the death of probable COVID-19 patients was (p=0.151; PR=0.9; 95%CI[0.78–1.03]), chronic lung disease (p=0.764; PR=1.09; 95%CI[1.02–1.18]), heart disease (p=0.591; PR=1.03; 95%CI[0.88–1.20]), hypertension (p=0.254; PR=1.08; 95%CI[0.95–1.23]), DM (p=0.361 PR=1.06; 95%CI[0.93–1.21]), renal disease (p=0.523; PR=1.10; 95%CI[1.02–1.19]), and malignancy (p=0.523; PR=1.10; 95%CI[1,02–1,19]). Multivariate logistic regression analysis was not necessary because the results of the bivariate analysis were all insignificant.

DISCUSSION

Medical record research samples that meet the inclusion and exclusion criteria from the medical records section of RSUP Dr. Kariadi Semarang were 71 samples. From the univariate analysis, it was found that the majority of probable COVID-19 patients died with a number of 65 subjects (91.5%), while the probable COVID-19 patients that survived were only 6 subjects (8.5%). This finding was in line with the data on probable COVID-19 cases in Semarang City which had always been dominated by death cases, for example the data on August 1st 2021 was dominated by death cases of 390 patients, while only 155 people survived with probable COVID-19.[1] Based on one of WHO criterias for probable COVID-19 diagnosis, "COVID-19 is a death not otherwise explained in an adult with respiratory distress; a suspect case with chest imaging showed suggestive finding of COVID-19 disease and had a positive antigen test result".[5] The rapid antigen test was not recommended for clinical diagnosis in detecting COVID-19 infection because the number of virus particles (viral load) determines the test results, hence to confirm the diagnosis of COVID-19 infection, an RT-PCR examination must be carried out.[6,7] Therefore, a probable case of COVID-19 is identical to death and has

been treated the same as a confirmed COVID-19 patient because of the same clinical manifestations with confirmed COVID-19 case, although it cannot be confirmed whether the patient is infected with COVID-19.

Relationship of Pneumoniae Risk Factors with Probable COVID-19 Death

From univariate analysis results of probable COVID-19 patients at RSUP Dr. Kariadi Semarang, pneumoniae was found in 54.9% of the 71 patients. A literature examining mortality in COVID-19 pneumoniae patients by Rong Hui *et al*. found 179 patients treated at the Wuhan Pulmonary Hospital, 43 (24%) of them were diagnosed with probable COVID-19 with clinical manifestations of pneumonia.[8] This difference finding was due to the fact that radiological examination results at RSUP Dr. Kariadi Semarang came out faster than the results of the RT-PCR swab examination, which gave the patients at RSUP Dr. Kariadi Semarang the probable COVID-19 status due to clinical manifestations that supported the diagnosis of COVID-19 in the form of pneumonia based on radiological examinations, even though the results of the RT-PCR swab have not been released. Thus, this method caused high number of probable COVID-19 patients with pneumonia in RSUP Dr. Karidi Semarang. However the results of bivariate analysis showed that the risk factors for comorbid pneumonia were insignificantly related in causing death in patients with probable COVID-19 at RSUP Dr. Kariadi Semarang. A study literature conducted at a hospital in Wuhan, China on 41 confirmed COVID-19 patients found that 100% of these patients had pneumonia.[9] Immunodeficiency conditions made it easier for pathogens to enter the human body and caused infection. Pathogens that reached the trachea could come from the oropharynx, inhalation, and insertion of an endotracheal tube. The entry of pathogens stimulated the activation of inflammatory mechanisms so that plasma fluid and capillary blood cells entered the lung membranes (alveoli). The accumulation of plasma fluid in the alveoli had an impact on decreasing air perfusion so that oxygen saturation decreased, making the patient had difficulty breathing. This pathophysiology explained how pneumonia could increase the severity of COVID-19, which could increase mortality rate up to 70%.[10] A journal that examined the causes of death in 208 pneumonia patients generally found that pneumonia deaths were caused by respiratory failure, sepsis/bacteremia, and cardiac arrhythmias.[11] Even though a probable diagnosis of COVID-19 did not necessarily lead to COVID-19 infection, the most common comorbidity in patients with a probable diagnosis of COVID-19 was pneumoniae even though the results of the study did not show significant results. Pneumoniae generally had a risk of causing death and the prognosis could be worsen if the patient is infected with COVID-19.

Relationship of Chronic Lung Disease Risk Factors with Probable COVID-19 Death

From univariate analysis results, chronic lung diseases comorbid were only found in 4.6% of total sample. This was in line with the results of a study on post-mortem diagnosis in patients with probable COVID-19 by Syamsun, *et al* who found that the sum of the comorbid findings of Diabetes Mellitus, kidney disease, and COPD from 33 patients who died with probable COVID-19 status was not more than 6%.[12] From bivariate analysis results, chronic lung disease was proven to be insignificant in causing death in probable COVID-19 patients at RSUP Dr. Kariadi Semarang, while according to Jaber S., *et al*. chronic lung disease increased the severity and mortality rate in COVID-19 patients and increases even more if the patient was a smoker.[13] COPD, which often occurs in smokers, the risk of mortality increases due to an increase in the expression of ACE2 receptor which is the entry point for the SARS-CoV2 virus. This makes it easier for COPD patients to be infected with COVID-19.[14] The contradiction of this study results with previous theory could be cause by the number of probable COVID-19 patients at RSUP Dr. Kariadi Semarang. The data showed very few chronic lung disease cases as comorbid, so it cannot be concluded whether chronic lung disease caused death in probable COVID-19 patients at Dr. Kariadi Semarang.

Relationship of Heart Disease and Hypertension Risk Factors with Probable COVID-19 Death

A study by J.Li, *et al* examined that within the total of 596 COVID-19 patients, 215 patients had cardiovascular disease as comorbid, 176 of them had hypertension.[15] The results of the univariate analysis of heart disease comorbidities in patients with probable COVID-19 at RSUP Dr. Kariadi Semarang was 22.5%. In previous study conducted by James SI, *et al* regarding the comparison of heart disease in positive and probable COVID-19 patients, it was found that out of 56 respondents, 7 patients (12.5%) with probable COVID-19 had heart disease.[16] This finding was in line with the results of this study that heart disease did not dominate the patients with probable COVID-19 at RSUP Dr. Kariadi Semarang. This was because the diagnosis of heart disease was mostly enforced by the results of physical examination and thoracic X-ray more than by an EKG, so heart disease was less detectable. Meanwhile, hypertension comorbidity also did not dominate in probable COVID- 19 patiens (38% of the 71 cases of probable COVID-19 at RSUP Dr. Kariadi Semarang). This was in line with the research of Badrul Munir, *et al*. who examined neurological manifestations in 4 hospitalized

patients with probable COVID-19 and found that 25% of probable COVID-19 patients suffered a stroke because they had comorbid risk factors including hypertension.[17]

From the results of the bivariate analysis, heart disease did not cause death in patients with probable COVID-19 at RSUP Dr. Kariadi Semarang significantly, as well as hypertension. This was in line with the results of a study, which found that risk factors for cardiovascular disease were not significant in causing death in COVID-19 patients. The incidence of death in COVID-19 patients with cardiovascular disease comorbid was more due to age and the use of ACE-i drugs that increase ACE-2 receptor expression.[18,19]

Although hypertension comorbidities were not significant in causing death in patients with probable COVID-19, hypertension is generally a life-threatening risk because it can increase the risk the number of serious conditions such as heart attack, stroke, heart failure, peripheral arterial disease, aortic aneurysm, kidney disease, etc.

Relationship of DM Risk Factors with Probable COVID-19 Death

In this study, the results of the univariate analysis of comorbid diabetes mellitus risk factors did not dominate the total results (33.8%), while the results of the bivariate analysis also did not significantly cause death in probable COVID-19 patients at the RSUP Dr. Kariadi Semarang. However, a study said that the incidence of Diabetes Mellitus significantly increased the incidence of death in COVID-19 infection due to uncontrolled hyperglycemia disrupting cytokine production, failure in recognizing pathogens, dysfunction of immune cells (neutrophils, macrophages, and NK cells), and inhibition of antibodies and leukocyte recruitment. These made it easier for a person to be infected with pathogens and cause worsening of the disease, so it can be concluded that diabetics are generally more susceptible to various kinds of infections.[18,20,21] The discrepancy between the results of this study and the theory could be caused by the fact that in this study the term probable COVID-19 was used where the patient was not necessarily infected/confirmed by COVID-19, so further research was needed with research subjects with confirmed COVID-19.

Relatioship of Renal Disease Risk Factor with Probable COVID-19 Death

The risk factors for kidney disease comorbid from the univariate analysis in this study were obtained as much as 10.8%. Meanwhile from bivariate analysis, kidney disease was not significant in causing the death of probable COVID-19 at RSUP Dr. Kariadi Semarang. The COVID-19 virus can directly damage podocytes and proximal tubular cells through attachment to the ACE2 receptor and the activity of serine protease enzyme trans cell membrane, which made the kidney a target organ of the COVID-19 virus.[22] A meta-analysis comparing the incidence of mortality in patients with/without comorbid renal disease showed that COVID-19 patients with Acute Kidney Injury (AKI) significantly had worsened condition and died. This was because the ACE-2 receptors were widely expressed in proximal tubular epithelial cells in podocytes, the entry of blood carrying SARS-CoV2 into the kidneys causing attachment between the virus and ACE-2 receptors in podocyte proximal tubular epithelial cells.[23] Acute Kidney Injury in general can cause hypoperfusion in the kidneys. If it is not treated, there will be damage in tubular epithelial cells accompanied by impaired kidney function.[10] This was in accordance with the panelist literature study that there was no literature showing a significant relationship between probable COVID-19.

Relationship of Malignancy Risk Factors with Probable COVID-19 Death

In patients with probable COVID-19 at RSUP Dr. Kariadi Semarang, malignancy does not dominate in comorbid patients with probable COVID-19 (10.8%). This was in line with a study on risk factors and outcomes of COVID-19 patients with blood malignancies by Jose luis pinana, *et al*. It was found that out of 388 patients with blood malignancies, only 21 (5.4%) patients were found with probable COVID-19 status.[24] From the results of the bivariate analysis of the risk factors for comorbid malignancy in this study, it did not have significant effect on causing death in probable COVID-19 patients at RSUP Dr. Kariadi Semarang. In general, malignancy as a comorbidity increases the risk of death because antitumor therapy / chemotherapy inhibits the process of cell division to prevent tumor growth, as well supressing the immune system. So that chemotherapy causes immunosuppression which facilitates the occurrence of infection.[19] A meta-analysis study reported that from 109 COVID-19 patients with malignancy, 32 of them died. Blood malignancies such as leukemia and lymphoma had higher risk of death than solid tumors (50% vs 26.1%). This was because blood malignancies cause dysregulation of T cells so it worsened patient's condition, making them more susceptible to infection.[19] Although from 7 patients with probable COVID-19 at RSUP Dr. Kariadi Semarang all died, the diagnosis of probable COVID-19 still did not necessarily lead to COVID-19 infection. So it cannot be said that malignancy was correlated in causing death of probable COVID-19 patients at RSUP Dr. Kariadi Semarang and further examination should be done.

Limitation of The Research

This study had several limitations. This study used a sample from only one hospital, namely Dr. Kariadi Semarang, so it could not represent the population of probable COVID-19 patients in the city of Semarang. There were few previous literature studies that discussed the relationship between probable COVID-19 and comorbidities, so that researchers had difficulty comparing the data. Definition of heart disease, kidney disease, and chronic lung disease has broad meaning. Also, other risk factors found during the study were not included as risk factors.

CONCLUSION

Pneumoniae, chronic lung disease, heart disease, hypertension, diabetes mellitus, kidney disease, and malignancy have not been proven to be risk factors for death in patients probable of COVID-19 at Dr. Kariadi General Hospital, Semarang.

Acknowledgment

Researcher would like to thank Virgagenie Maisra as Resident of Forensic Medicine and Medicolegal, Faculty of Medicine, Diponegoro University who had supported and assisted this research.

REFERENCES

1. Pemerintah Kota Semarang. Kota Semarang Siaga Corona [Internet]. 2021. Available from: https://siagacorona.semarangkota.go.id/halaman/covid19
2. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, *et al*. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. BMJ. 2020;368.
3. Tian J, Yuan X, Xiao J, Zhong Q, Yang C, Liu B, *et al*. Clinical characteristics and risk factors associated with COVID- 19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol [Internet]. 2020;21(7):893–903. Available from: http://dx.doi.org/10.1016/S1470–2045(20)30309-0
4. Pathania AS, Prathipati P, Abdul BAA, Chava S, Katta SS, Gupta SC, *et al*. COVID-19 and cancer comorbidity: Therapeutic opportunities and challenges. Theranostics. 2020;11(2):731–53.
5. World Health Organization W. WHO COVID-19: Case Definition. 2020;(December):2020.
6. Scohy A, Anantharajah A, Bodéus M, Kabamba-mukadi B, Verroken A, Rodriguez-villalobos H. Low performance of rapid antigen detection test as frontline testing for COVID-19 diagnosis. J Clin Virol. 2020;129(January):1–3.
7. Organization. WH. Laboratory testing strategy recommendations for COVID-19. World Heal Organ [Internet]. 2020;(March). Available from: https://apps.who.int/iris/bitstream/handle/10665/331509/WHO-COVID-19-lab_testing-2020.1-eng.pdf
8. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, *et al*. Predictors of mortality for patients with COVID-19 pneumonia caused by SARSCoV-2: A prospective cohort study. Eur Respir J. 2020;56(3).
9. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, *et al*. Comorbidity and its Impact on Patients with COVID-19. SN Compr Clin Med. 2020;2(8):1069–76.
10. Sudoyo AW, Setiyohadi B, Alwi I, Simadibrata M, Setiati S. Buku Ajar Ilmu Penyakit Dalam Jilid II. Edisi V. JAKARTA: Interna Publishing; 2009.
11. Zhang ZX, Yong Y, Tan WC, Shen L, Ng HS, Fong KY. Prognostic factors for mortality due to pneumonia among adults from different age groups in Singapore and mortality predictions based on PSI and CURB-65. Singapore Med J. 2018;59(4):190–8.
12. Syamsun A, Kadriyan H, Andiwijaya FR, Hunaifi I, Lestarini I, Sari SK, *et al*. Postmortem diagnosis characteristics of probable covid-19 victims by rapid molecular testing. IOP Conf Ser Earth Environ Sci. 2021;712(1).
13. Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, *et al*. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: A rapid systematic review and meta- analysis. PLoS One [Internet]. 2020;15(5):1–13. Available from: http://dx.doi.org/10.1371/journal.pone.0 233147
14. Leung JM, Yang CX, Tam A, Shaipanich T, Hackett TL, Singhera GK, *et al*. ACE-2 expression in the small airway epithelia of smokers and COPD patients: Implications for COVID-19. Eur Respir J. 2020;55(5).
15. Li J, Guo T, Dong D, Zhang X, Chen X, Feng Y, *et al*. Defining heart disease risk for death in COVID-19 infection. Qjm. 2020;113(12):876–82.
16. Si J, Fallon A, Df W, Hanlon OR. Cardiac magnetic resonance in COVID- 19 positive and probable cases: A report from a high volume CMR centre in Ireland. 2021;22:159–60.
17. Munir B, Rianawati SB, Kurniawan SN, Santoso WM, Arisetijono E, Candradikusuma D, *et al*. Neurological Manifestation on Hospitalized Patient with Probable Covid-19 in Saiful Anwar Hospital Indonesia (Serial Cases). MNJ (Malang Neurol Journal). 2020;6(2):51–5.
18. Rastad H, Karim H, Ejtahed HS, Tajbakhsh R, Noorisepehr M, Babaei M, *et al*. Risk and predictors of in-hospital mortality from COVID-19 in patients with diabetes and cardiovascular disease. Diabetol Metab Syndr [Internet]. 2020;12(1):1–11. Available from: https://doi.org/10.1186/s13098-020- 00565-9
19. Meng. Cancer history is an independent risk factor in hospitalized COVID-19 patients. J Hemato. 2020;0:1–11.
20. Berbudi A, Rahmadika N, Tjahjadi AI, Ruslami R. Type 2 Diabetes and its Impact on the Immune System. Curr Diabetes Rev. 2019;16(5):442–9.
21. Corona G, Pizzocaro A, Vena W, Rastrelli G, Semeraro F, Isidori AM, *et al*. Diabetes is most important cause for mortality in COVID-19 hospitalized patients: Systematic review and meta-analysis. Rev Endocr Metab Disord. 2021;22(2):275–96.
22. Pan X wu, Xu D, Zhang H, Zhou W, Wang L hui, Cui X gang. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. Intensive Care Med. 2020;46(6):1114–6.
23. Wang B, Luo Q, Zhang W, Yu S, Cheng X, Wang L, *et al*. The Involvement of Chronic Kidney Disease and Acute Kidney Injury in Disease Severity and Mortality in Patients with COVID-19: A Meta-Analysis. Kidney Blood Press Res. 2021;46(1):17–30.
24. Piñana JL, Martino R, García-García I, Parody R, Morales MD, Benzo G, *et al*. Risk factors and outcome of COVID-19 in patients with hematological malignancies. Exp Hematol Oncol [Internet]. 2020;9(1):1–16. Available from: https://doi.org/10.1186/s40164- 020-00177-z

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 370–376

OPEN ACCESS

Case Report

Case Series Report: Subarachnoid Hemorrhage and ICU Management

Retnaningsih[1], Dodik Tugasworo[1], Yovita Andhitara[1], Rahmi Ardhini[1], Aditya Kurnianto[1], Daynuri[2], Erlangga Pradipta Harianto[3]

[1]Neurology Department, Dr. Kariadi General Center Hospital Semarang, Indonesia
[2]Neurology Program Study, Faculty of Medicine, Diponegoro University Semarang, Indonesia
[3]Faculty of Medicine, Diponegoro University Semarang, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.745

Accepted: December 26th, 2022
Approved: September 21th, 2023

Author Affiliation:
Neurology Department,
Dr. Kariadi General Center Hospital Semarang,
Indonesia

Author Correspondence:
Retnaningsih
Dr. Sutomo Street No.16, Semarang,
Central Java 50244, Indonesia

E-mail:
retnanku_icu@yahoo.com

Abstract

Background : Subarachnoid hemorrhage is a neurological syndrome with complex systemic complications. Rupture of an intracranial aneurysm causes acute extravasation of arterial blood under high pressure into the subarachnoid space and often into the brain parenchyma and ventricles. Bleeding triggers a complex series of events, which can ultimately lead to early brain injury, delayed cerebral ischemia, and systemic complications.
Cases : There were six cases of subarachnoid hemorrhage. Some patients come clinically with severe headache and loss of consciousness. The patient has been treated quickly and aggressively and even put on a ventilator for complications of respiratory failure, support for shock and management of aneurysm clipping and EVD. Rapid and precise diagnosis in the management of patients with SAH is of paramount importance, within the first few hours after the onset of SAH. The risk for early neurologic damage and high rates of severe long-term complications necessitated aggressive early management.
Conclusion : Rapid diagnosis and attentive management of patients with SAH are essential, as early deterioration is possible within the first few hours after the onset of SAH. The risk for early neurologic damage and high rates of severe long-term complications necessitated aggressive early management. Prevention and Management of Complications. The most common complications were pneumonia, aspiration, respiratory failure/distress, sepsis and imbalance electrolyte (hyponatremia). Approximately 50% of deaths after SAH are due to medical complications.

Keywords : Subarachnoid hemorrhage, aneurysm, vasospasm, early brain injury

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a mechanical disorder of the intracranial vascular system that causes blood to enter the subarachnoid space.[1] SAH due to aneurysm rupture is a neurological syndrome with complex systemic complications.[1,2] Rupture of an intracranial aneurysm causes acute extravasation of high-pressure arterial blood into the subarachnoid space, brain parenchyma, and ventricles.[3,4] Hemorrhage triggers a series of complex events that can ultimately cause early brain injury, delayed cerebral ischemia, and systemic complications.[5] Although patients with severe SAH (World Federation of Neurosurgical Societies grade 4 and 5) have a higher risk of early brain injury, delayed cerebral ischemia, and systemic complications, early and aggressive management in this patient population has reduced overall mortality rates from over 50% to 35% in the past four decades.[6] Management of SAH poses a unique challenge for neurointensivists, requiring good intensive care unit (ICU) care and neurosurgical intervention techniques. This article discusses several case illustrations of SAH in the neurological ICU and related management given.

CASE REPORT

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Onset	7 day(s) prior to admission	5 day(s) prior to admission	1 day(s) prior to admission	4 day(s) prior to admission	1 day(s) prior to admission	5 day(s) prior to admission
Chronology	Patient had weakness on the left limb and limited mobility for 3 days prior to admission. The patient also complained of headache, drooling, and slurred speech. The patient was then taken to Panti Wilasa Hospital and diagnosed with hemorrhagic stroke. The patient experienced a decreased level of consciousness and was immediately treated with surgery in the Emergency Department at RSDK Hospital. The patient received postoperative care in the Intensive Care Unit.	One day ago, the patient experienced a sudden onset of decreased level of consciousness after daytime activities. The family then brought the patient to RSDK, where a head CT scan revealed intracranial hemorrhage. The patient underwent hematoma evacuation surgery and received postoperative care in the RSDK ICU for recovery after a basal skull craniotomy. .	One day ago, a patient experienced sudden severe headache described as throbbing accompanied by vomiting while engaging in photocopy activity. The patient then took paracetamol to relieve the pain and the symptoms improved. However, during rest, the patient suddenly felt weakness on the right side and experienced a decrease in consciousness.	-4 days ago, the patient complained of severe headache with throbbing pain and vomiting, but remained conscious. The patient then experienced a sudden decrease in consciousness. --A CT scan was performed, revealing intracranial hemorrhage. The patient was then referred to RSDK for further management. -The patient's hypertension was uncontrolled.	-1 day ago, the patient suddenly experienced a decrease in consciousness. Headache (+), seizure (+). -The patient then underwent a head CT scan which revealed intracranial hemorrhage. -The patient was subsequently admitted to the ICU. -DM (-), uncontrolled hypertension, taking amlodipine. -The patient has been experiencing severe headaches for 1 month, accompanied by dark shadows in the right eye.	5 days ago, the patient experienced sudden vertigo and severe headache. The patient felt like the surrounding environment was spinning, with the vertigo occurring frequently and with unpredictable duration. The patient also experienced weakness on the right side of the body and vomiting. -The patient also complained of severe headache throughout the head. According to the family, the patient's speech was incoherent and had difficulty communicating. The patient also felt nauseous and had dry mouth. Urination and bowel movements were within normal limits. -There is a history of uncontrolled hypertension.
GCS and Vital sign	GCS E1M1Vet, BP 133/75, pulse 72x/mins, RR 12x/mins, temp	GCS E1M1Vet, BP 67/46, pulse 88x/mins, RR 12x/mins, temp	GCS E1M1Vet, BP 141/86, pulse 107x/mins reguler, RR 14x/mins,	Moderately ill, GCS E4M6V5, BP 186/75, pulse 78x/mins, RR	Severely ill GCS E4M6V5, BP 151/71, pulse 81x/mins, RR	Severely ill. GCS E4M6V4, BP 117/64 pulse 82x/mins, RR

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
	36.3°C, SpO2 100% assisted with ventilator mode pressure A/C RR 12 PEEP 5 FiO2 60%.	36°C, SaO2 94% assisted with ventilator mode PSIMV PS 5 PEEP 5 FiO2 30%.	temp 36.8°C, SpO2 100% assisted with ventilator SIMV PEEP 5 FiO2 50%, volume 500cc.	22x/mins, temp 36.8°C, SpO2 100% with NRM 7 lpm	20x/mins, temp 36.4°C, SpO2 100% nasal canule 3 lpm	18x/mins, SpO2 97%
Neurological Deficit	Decreased level of consciousness, spastic bilateral hemiparesis, more severe on the left side. Central paresis of the left Nerve VII	Decreased level of consciousness, spastic bilateral hemiparesis, more severe on the right side. Central right-sided facial nerve palsy.	Decreased level of consciousness, bilateral spastic hemiparesis, with more severe symptoms on the right side. Central right-sided paresis of the facial nerve (N VII).	Neurologic deficit-	Right-sided nasal hemianopsia	Right spastic hemiparesis Central right-sided facial nerve palsy (N. VII)
BGA	pH7.435 pCO2 35.7mmHg PO2 102.6mmHg HCO3 17.8 AaDO2 286.8mmHg PFR: 171 Moderate ARDS	pH7.090 pCO2 78.9 PO2 78.2 BEecf-6.4 BE (B)-7.2 SO2c89.6 HCO3 23.4 A-aDO247.7 *PFR 260* Mild ARDS	H(T) 7.376 PCO2(T) 51.3 PO2(T) 130.0 HCO3- 28.9 TCO2 30.4 BE (B) 3.5 SO2c 98.3 A-aDO2 92 PFR 280 Mild ARDS	FIO2 33.0 pH(T) 7.421 PCO2(T) 31.6 PO2(T) 145.4 HCO3- 20.3 TCO2 21.3 SO2c 99.0 A-aDO2 52.9 PFR 439	BGA pH 7.423 pCO2 36.9 PO2 137.1 HCO3 26.5 FIO2 32.0 PFR 428	pH7.328 pCO243.5 PO278.4 FIO2 32.0 pH(T) 7.330 PCO2(T) 43.3 PO2(T)77.9 HCO3- 22.3 TCO223.7 BE (B)-3.5 SO2c94.8 A- aDO298.3 PFR 243 Mild ARDS
Lab	Hemoglobin12.1 Leukocyte 10.600 Procalsitonin0.12 CRP 14.84	Hemoglobin11.2 Leukocyte14.4 CRP 0.26 Natrium 130	-prokalsitonin 3.67 -Leukocytosis 20.300 - CRP 21.08	Leukocyte 14.400 CRP 0.26 Hiponatremia126 Routine urine test: Yeast Cell 1085.4 YEAST: (+)	Leukocyte 21.900 CRP 1.73 ROUTINE URINE TEST YEAST (+) HYPHA (+)	Hemoglobin 11.1g/dL Leukocyte 13.900 CRP 27.62
Grading SAH	Fisher gr IV, WFNS gr 3 Hunt and Hess 5	Fisher gr IV, WFNS gr 3 Hunt and Hess 5	FISHER grade II, WFNS grade 1 Hunt and Hess 3	FISHER grade II, WFNS grade 1 Hunt and Hess 1	FISHER gr III WFNS 1. Hunt and Hess 3	FISHER gr III WFNS 1. Hunt and Hess 3
Radioimaging	Result of Head CT Angiography on 09/06/2021 - The image shows a saccular aneurysm in the proximal right posterior communicating artery with the dome towards the posterolateral direction (length 5.1 mm, width 9 mm, dome 6 mm) that receives supply from the right internal carotid artery at segment C7 (neck 3.2 mm) and the right posterior communicating	The MSCT angiography of the head revealed a saccular aneurysm on the left internal carotid artery segment 7 (size ± AP 0.88 x CC 0.71 x LL 0.85 cm) with a narrow neck (neck size ± 0.34 cm) and a dome directed towards the superolateral left. Suspected ruptured anterior communicating artery aneurysm with subarachnoid hemorrhage.	MSCT ANGIOGRAPHY OF THE HEAD WITH CONTRAST (12/9/2021) FINDINGS: There is a saccular aneurysm seen in the left anterior cerebral artery, segment A1 (size ± AP 0.32 x CC 0.35 x LL 0.39 cm) with a narrow neck (neck size ± 0.16 cm) and dome directed towards the anterosuperior aspect on the left. Intracerebral hemorrhage is observed along	MSCT angiography of the head showed a saccular aneurysm at the branching of the left anterior cerebral artery (A1) and anterior communicating artery (size: AP 0.22 x CC 0.30 x LL 0.53 cm) with a wide neck (visualized neck size + 0.2 cm) and dome towards the anterosuperiorme dial right. There was subarachnoid hemorrhage in the anterior cerebral interhemispheric fissure, Sylvian	The MSCT angiography of the head showed a decreased subarachnoid hemorrhage, intraventricular hemorrhage in the posterior horns of the lateral ventricles and the fourth ventricle, infarction in the right temporoparietal lobe, cerebral edema with signs of increased intracranial pressure, communicating hydrocephalus, pneumocephalus	A head CT scan showed subarachnoid hemorrhage, lacunar infarction in the right and left external capsule, obstructive hydrocephalus, no signs of increased intracranial pressure at present, and right mastoiditis. The CT angiography of the head showed no signs of aneurysms, AVMs, or other vascular abnormalities, subarachnoid hemorrhage,

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
	artery (neck 1.9 mm) accompanied by a daughter saccular aneurysm with the dome towards the posteromedial direction (neck 4.1 mm, dome 6.1 mm) - Dilatation of the left and right posterior communicating arteries with hypoplasia of the left and right posterior cerebral arteries in the segment.		with perifocal edema in the left frontotemporal lobe, which is compressing the left lateral ventricle and causing midline shift to the right (± 0.6 cm). Intraventricular hemorrhage is also present. Subarachnoid hemorrhage is detected. There is a subdural hemorrhage in the left frontoparietotemporal region. Signs of increased intracranial pressure are apparent.	fissure bilaterally, cortical sulci of the frontal and temporal lobes bilaterally, and cavum septum pellucidum. There was also intraventricular hemorrhage in the left lateral ventricle, old infarction in the left corona radiata and anterior limb of internal capsule, ventriculomegaly, and signs of increased intracranial pressure.	in the right frontal region, and subgaleal hematoma in the right frontotemporal region.	intraventricular hemorrhage, hydrocephalus, signs of increased intracranial pressure, or right mastoiditis.
BGA						
Surgical Procedure	The patient underwent craniotomy for hematoma evacuation and also had an external ventricular drain (EVD) placed.	The patient underwent a post craniotomy of the skull base procedure which involved wrapping of the ruptured giant aneurysm located in the left ICA-MCA and placement of an EVD for management of subarachnoid hemorrhage.	Post clipping of ruptured aneurysm at left A. Com (12/9/21) with intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and intraventricular hemorrhage (IVH) complications, EVD was performed.	Subarachnoid hemorrhage due to the rupture of an aneurysm in the IC-Acom (Internal Carotid-Anterior Communicating) artery, and underwent a clipping surgery to address the issue fixed with VP shunt	Spontaneous subarachnoid hemorrhage due to a ruptured IC-Pcom aneurysm on the right side, with a WFNS score of 1 and a Fisher grade III. The patient underwent a craniotomy for clipping of the aneurysm and also had a lumbar drain placed.	Spontaneous subarachnoid hemorrhage (SAH) due to a ruptured IC Pcom aneurysm on the right side. The aneurysm was subsequently clipped, and the patient underwent a ventriculostomy (EVD) procedure.
Complications	Mild hyponatremia (132) Obstructive hydrocephalus Bronchopneumonia Azotemia (urea level of 94) Seizures Respiratory arrest and cardiac arrest Declared deceased	Bronchopneumonia Hypoalbuminemia Electrolyte imbalance (hypernatremia)	Bronchopneumonia Sepsis Electrolyte imbalance	Electrolyte imbalance UTI	UTI	Electrolyte imbalance UTI

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
	Mild hyponatremia (132) Obstructive hydrocephalus Bronchopneumonia Azotemia (urea level of 94) Seizures Respiratory arrest and cardiac arrest Declared deceased	Bronchopneumonia Hypoalbuminemia Electrolyte imbalance (hypernatremia)	Bronchopneumonia Sepsis Electrolyte imbalance	Electrolyte imbalance UTI	UTI	Electrolyte imbalance UTI
Condition progression	After 6 days of hospitalization, the patient experienced dyspnea followed by 3-5 minutes of generalized tonic-clonic seizures, and subsequently had cardiac arrest. Upon examination, respiratory failure was observed with a heart rate of 120 beats per minute, blood pressure of 87/65 mmHg, SpO2 of 89%, and cold extremities. On the 6th day of hospitalization, the patient was declared deceased.	The patient experienced seizures, fever, desaturation, and eventually cardiac arrest.	On the 40th day of treatment, the patient experienced desaturation, cardiac arrest, and was pronounced dead.	The patient is currently neurologically intact and experiences intermittent headache.	The patient was discharged with improvement. Headache subsided, neurologically intact.	Patient discharged with improvement. Headache present, fully conscious.

DISCUSSION

Subarachnoid hemorrhage (SAH) is a complex neurovascular syndrome with profound systemic effects and is associated with high disability and mortality. Although there has been a decline in mortality rates in the past three decades due to better management strategies, unfortunately, the 30-day mortality and pre-hospital mortality rates remain high. Assessment of onset, initial GCS, Hunt and Hess score, and patient complications play an important role in determining the patient's prognosis outcome.[1] Prevention and management of complications play an important role. The most common complications include pneumonia, aspiration, respiratory failure/distress, sepsis, and electrolyte imbalances (hyponatremia).[3–6] Around 50% of deaths after SAH are caused by medical complications.[5]

In the first, second, and third cases, a long onset assessment, poor initial GCS score, Hunt and Hess score >3, and complications such as blood pressure, hypoxia, fever, and other signs of systemic inflammation associated with mortality suggest the possibility of early brain injury as the cause of poor patient prognosis.[7] The initial GCS upon arrival at the hospital and the Modified Fischer Scale are strong indicators for assessing the severity level at the onset of SAH and also predicting in-hospital mortality, the loss of consciousness at the onset reflects the occurrence of transient intracranial circulation cessation, which is associated with poor outcomes, and the presence of cerebral edema at the onset of SAH.[7–10] Referral factors in the process of transferring patients to tertiary referral hospitals also play a role in determining the mortality rate of patients with SAH, using the Hunt and Hess grading which has been consistently used epidemiologically (Hunt and Hess Table).[11,12] In cases one, two, and three, patients have undergone stabilization management for ABC, TTV, prevention of vasospasm, prevention of rebleeding, and monitoring of clinical signs of increased ICP. They have also received ventilator support for respiratory failure,

TABLE 1
Hunt and Hess

Grading Hunt and Hess grade	Total Mortality	Study Population (%)	Mortality Rate (%)
Mild-moderate headache	12/342	19.5	3.5
Severe headache or cranial nerve palsy	6/186	15.5	3.2
Drowsiness, confusion, or weakness on one side of the body (focal neurological deficit)	30/319	26.6	9.4
Stupor	42/173	14.4	23.6
Coma	127/180	15.0	70.5
Total	216/1200	100.0	18.0

IHK: Immunohistochemistry; MG: Modified Giemsa

support for shock, and EVD management.[2] However, in accordance with the poor initial GCS and Hunt and Hess grade, and increased ICP that impaired the patient's level of consciousness, respiration, and cardiovascular system function, severe disturbances occurred.

In cases of subarachnoid hemorrhage, 66.6% of deaths are determined by brain death and 33.3% are determined by cardiac death. Subarachnoid hemorrhage has a 50% mortality rate during hospitalization. Factors that influence mortality include pre-operative GCS values that are related to Hunt and Hess grading, with Hunt and Hess values > 3 resulting in death in all cases.[13]

In the fourth, fifth, and sixth cases, rapid and accurate diagnosis and management of SAH patients become a very important concern.[2] A good initial GCS upon arrival at the hospital with a score of >13 and a Hunt and Hess score of <3 indicate a good prognostic value. The occurring complications can be well managed. The outcome of SAH can vary significantly, from full recovery to severe disability or death, depending on the severity of the initial bleeding and the potential complications that usually occur within the first 2 weeks after the bleeding. The level of consciousness is considered the most important early predictor of outcome.[1] Patients with a normal level of consciousness have a low risk of mortality. Patients treated with a low level of consciousness have a higher risk of mortality and disability, namely with a Glasgow Coma Scale (GCS) score less than 13, with Hunt and Hess grades 4 and 5.[10] In cases four, five, and six, patients have undergone stabilization management including airway, breathing, and circulation (ABC), monitoring of vital signs, prevention of vasospasm, prevention of rebleeding, and monitoring of increasing signs of intracranial pressure (ICP). Ventilator support was provided for respiratory failure, and shock support was given. In case four, aneurysm clipping and VP Shunt were performed, in case five, aneurysm clipping and lumbar drain were performed, and in case six, aneurysm clipping and EVD were performed.[14,15] Case four, five, and six had a good initial GCS and Hunt and Hess score <3, so the patients showed improvement with mild headache symptoms. The assessment of onset, initial GCS, Hunt and Hess, and patient complications plays an important role in determining the patient's prognosis outcome.[1]

It is still important to note, however, that this report is comprised of a limited sample size of six cases, and thus the prognosis outcome is subject to compounding health factors and statistical variations. Nevertheless, the cases provided shows the significance of prompt and proper initial assessment, while immediate patient management and emergent complications during and after procedure play a significant role to the patients' prognosis outcome.

CONCLUSION

From the 6 cases included in this research, the patients in cases 1, 2, and 3, all of whom showed moderate to severe reduction of consciousness evident by the higher Hunt and Hess score, experienced an increase in mortality. Patients in cases 4, 5, and 6 which showed comparatively lower score experienced a decrease in mortality. The initial assessment of patient's condition is subject to both the severity and extent of symptoms prior to receiving treatment. Nevertheless, in all cases, the first few hours after the onset of SAH carries the risk of early neurological damage and high rates of poor long-term outcomes,[9,16] which underline the need for aggressive early management. The assessment of onset, initial GCS, Hunt and Hess grade and patient complications play an important role in the outcome of the procedure and prognosis of the patient.[17] During the procedure, stabilization of ABC (airway, breathing, circulation) is

crucial in the initial management and control of blood pressure is important to prevent further bleeding, with the use of anti-fibrinolytic drugs and therapy for coagulopathy potentially necessary in some cases.[18] Multimodal monitoring using transcranial doppler, CT angiography, DSA, MRI/MRA, and SPECT.[19,20] In summary, the top priority in the management of SAH is early identification, with the severity measured by all grading parameters used in this report (Hunt and Hess, FISHER, and WFNS) showing a close link to the prognosis outcome. Furthermore, the considerations during patient management proper management are ICP control, complications, and prevention and management of DCI.[14]

REFERENCES

1. Naidech AM, Janjua N, Kreiter KT, Ostapkovich ND, Fitzsimmons BF, Parra A, *et al*. Predictors and impact of aneurysm rebleeding after subarachnoid hemorrhage. Arch Neurol. 2005;62(3):410–6.
2. de Oliveira Manoel AL, Goffi A, Marotta TR, Schweizer TA, Abrahamson S, Macdonald RL. The critical care management of poor-grade subarachnoid haemorrhage. Crit Care 2016 201. 2016 Jan 23;20(1):1–19.
3. Lehmann L, Bendel S, Uehlinger DE, Takala J, Schafer M, Reinert M, *et al*. Randomized, double-blind trial of the effect of fluid composition on electrolyte, acid-base, and fluid homeostasis in patients early after subarachnoid hemorrhage. Neurocrit Care. 2013 Feb;18(1):5–12.
4. Alimohamadi M, Saghafinia M, Alikhani F, Danial Z, Shirani M, Amirjamshidi A. Impact of electrolyte imbalances on the outcome of aneurysmal subarachnoid hemorrhage: A prospective study. Asian J Neurosurg. 2016 Mar;11(1):29.
5. Marupudi NI, Mittal S. Diagnosis and Management of Hyponatremia in Patients with Aneurysmal Subarachnoid Hemorrhage. J Clin Med. 2015 Apr 21;4(4):756.
6. Wilson RD. Mortality and Cost of Pneumonia After Stroke for Different Risk Groups. J Stroke Cerebrovasc Dis. 2012 Jan;21(1):61.
7. Claassen J, Vu A, Kreiter KT, Kowalski RG, Du EY, Ostapkovich N, *et al*. Effect of acute physiologic derangements on outcome after subarachnoid hemorrhage. Crit Care Med. 2004 Mar;32(3):832–8.
8. Rivero Rodríguez D, Scherle Matamoros C, Cúe LF, Miranda Hernández JL, Pernas Sánchez Y, Pérez Nellar J. Predictor's of mortality in patients with aneurysmal subarachnoid haemorrhage and reebleding. Neurol Res Int. 2015;2015.
9. Marcolini E, Hine J. Approach to the diagnosis and management of subarachnoid hemorrhage. West J Emerg Med. 2019;20(2):203–11.
10. Hop JW, Rinkel GJE, Algra A, Van Gijn J. Initial Loss of Consciousness and Risk of Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage. Stroke. 1999;30(11):2268–71.
11. Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. Neurology. 1998 May 1;50(5):1413–8.
12. Stegmayr B, Eriksson M, Asplund K. Declining Mortality From Subarachnoid Hemorrhage. Stroke. 2004 Sep 1;35(9):2059–63.
13. Lantigua H, Ortega-Gutierrez S, Schmidt JM, Lee K, Badjatia N, Agarwal S, *et al*. Subarachnoid hemorrhage: who dies, and why? Crit Care. 2015 Aug 31;19(1).
14. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Haemorrhage. Cerebrovasc Dis. 2013;35(2):93–112.
15. Dey M, Jaffe J, Stadnik A, Awad IA. External Ventricular Drainage for Intraventricular Hemorrhage. Curr Neurol Neurosci Rep. 2012 Feb;12(1):24.
16. Rosen RD, Sapra A. TNM Classification. StatPearls NCBI. 2022 Feb 17;
17. Martin-Schild S, Albright KC, Tanksley J, Pandav V, Jones EB, Grotta JC, *et al*. Zero on the NIHSS Does NOT Equal the Absence of Stroke. Ann Emerg Med. 2011 Jan;57(1):42.
18. Ding R, Logemann JA. Pneumonia in stroke patients: A retrospective study. Dysphagia. 2000 Apr 1;15(2):51–7.
19. Perrini P, Montemurro N, Caniglia M, Lazzarotti G, Benedetto N. Wrapping of intracranial aneurysms: Single-center series and systematic review of the literature. 2015 Nov 2;29(6):785–91.
20. Saber Tehrani AS, Kattah JC, Kerber KA, Gold DR, Zee DS, Urrutia VC, *et al*. Diagnosing Stroke in Acute Dizziness and Vertigo: Pitfalls and Pearls. Stroke. 2018;49(3):788.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 377–381

OPEN ACCESS

Case Report

Rare Case of Inguinal Endometriosis Lump : Case Report and Literature Review

Indra Adi Susianto[1,2], Edward Hartono[1,2], Barkah Fajar Riyadi[1], Siti Amarwati[3], Alberta Widya Kristanti[2], Aprilia Karen Mandagie[2], Mohammad Haekal[4]

[1]Department of Obstetrics and Gynecology Anugerah Women and Children Hospital Semarang, Indonesia
[2]Medical Faculty of Soegijapranata Catholic University Semarang, Indonesia
[3]Department of Patology Kariadi Hospital Semarang, Indonesia
[4]Harapan Kita National Women and Children Health Center Jakarta, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.1019

Accepted: August 16th, 2023
Approved: October 25th, 2023

Author Affiliation:
Medical Faculty of
Soegijapranata Catholic University
Semarang, Indonesia

Author Correspondence:
Indra Adi Susianto
Pawiyatan Luhur Street IV/1, Bendan Duwur, Gajahmungkur, Semarang, Central Java 50234, Indonesia

E-mail:
indraadisusianto@unika.ac.id

Abstract

Background : Endometriosis is usually found in intrapelvic structures such as the ovaries, peritoneum, gynecological organs and the pouch of Douglas. We report an unusual case of endometriosis in the right inguinal region.
Cases : A 36-year-old woman with a history of laparoscopic surgery for endometriosis 4 years ago complained of catamenial pain and a mass in the right inguinal region, and her symptoms fluctuated with the menstrual cycle. An indistinct firm mass palpable in the right inguinal region. Ultrasound examination revealed a 2 × 1 cm mass in front of the pubic area on the lower edge of the rectus abdominis muscle. In a patient with an inguinal subcutaneous mass who complains of periodic changes in symptoms, endometriosis should be considered in the differential diagnosis.
Conclusion : The low incidence of inguinal endometriosis is one of the considerations in the different diagnosis of painful inguinal hernias in the inguinal area in women with childbearing age. The diagnosis of endometriosis can be demonstrated clearly on High-Definition Ultrasound by trained personnel. Surgery is the optional treatment and is curative in this case.

Keywords : Endometriosis; extra pelvic endometriosis; Inguinal subcutaneous Lump ; Inguinal Endometriosis, Inguinal Hernia

INTRODUCTION

Endometriosis means that the functional endometrial gland suffers from a benign pathological disorder it that grows on the outside part of the uterine cavity. We can usually find endometriosis in intrapelvic structures such as the uterus, tubes, ovaries, peritoneum, and pouch of Douglas. The case of endometriosis in the subcutaneous area which is not the same as previous surgical access is hard to find, whereas some cases appear to show the same symptoms as soft tissue tumors.

We make a report on a rare endometriosis case where an endometriosis lump grows in the right inguinal area which resembles a soft tissue tumor or inguinal hernia.

CASE REPORT

A 36-year-old woman with history of laparoscopic cystectomy for endometriosis cyst 4 years ago. Currently single. The patient first experienced pain as well as felt a mass in the right part of the inguinal area 6 months ago. The local doctor's initial examination, it was stated that the patient had thrombophlebitis and was treated with NSAIDs and antibiotics. She felt the pain was gradually increasing and the size of the mass was getting bigger, especially during menstruation, the patient visited the outpatient polyclinic at Brawijaya Hospital, Jakarta, and continued to RSIA Anugerah Semarang.

Physical and supporting examination showed a hard and inelastic lump on the right side of the groin area. The lump is 3 × 2 cm in size and it has fixed mobility. The color of the skin above the mass is normal. Ultrasound examination of the pelvic and pelvis area within normal limits. High-definition General Electric S10® imaging which is taken during the period of menstruation has revealed a mass, with the size of 4 × 3 cm, in the subcutaneous tissue, which is in the front part of the right superior pubic ramus. This mass presented iso-signal intensity with areas of partial high signal intensity with uneven margins and firmly attached to the surrounding lump (Fig. 1), suggesting a desmoid mass, or other soft tissue tumor.

Treatment

We performed excision through the groin using the Erbe VIOs® electrocautery under spinal anesthesia in the operating room. The hard, elastic mass can be found in the subcutaneous area (Fig. 2). A band-like structure in the specimen was then observed macroscopically (Fig. 3,4). Next, we enucleated the mass with wide margins, considering malignancy and recurrence cases due to endometriosis. Histological examination revealed a glandular structure including cylindrical epithelium in the densely fibrous mass; these epithelia showed a little nuclear atypia, and they were confirmed positive for estrogen (Fig. 5). The endometriosis diagnosis was also confirmed microscopically, in which bands of densely fibrous tissue around the gland appeared.

The patient was treated at RSIA Anugerah Semarang with a distinctive diagnosis of right inguinal hernia. Four years earlier she had undergone bilateral cystectomy due to endometriosis and there was no recurrence for endometriosis after surgery. Assisted by a digestive surgeon, a cut is made in the inguinal line at the oblique aponeurosis to reveal the superficial ring at its apex. Exploration then exposed a cystic, bluish mass, with the diameter of 2 cm, attached to a round ligament and

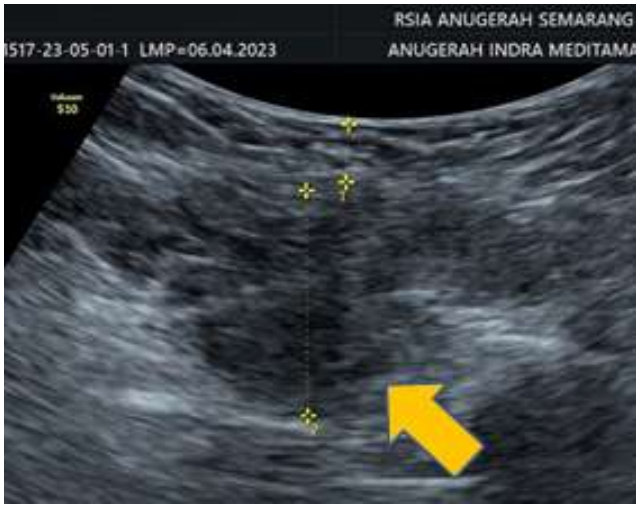


Figure 1. We can see mass in the subcutaneous Lump in front of the right superior pubic ramus with iso-signal intensity with an area of partial high signal intensity with uneven edges and firmly attached to the surrounding Lump.

Figure 2. A hard, elastic tumor is seen under the subcutaneous Lump accompanied by hypervascularization

Figure 3. The diagnosis of endometriosis is confirmed microscopically, where a band-like structure of dense fibrous tissue around the gland (arrows) appears.

Figure 4. We enucleated the mass with wide margins, considering cases of malignancy and recurrence due to endometriosis.

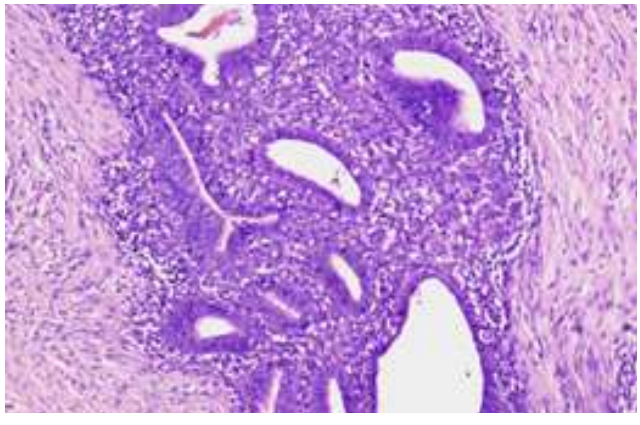


Figure 5. Histological examination revealed a glandular structure consisting of a cylindrical epithelium in dense fibrous tisuue; this epithelium shows minimal nuclear atypia.

Figure 6. No hernia sac was found in the inguinal canal. Subcuticular suturing was performed after control of bleeding from inguinal endometriosis implantation.

which was full of dark fluid.

Outcome

The mass is determined in histopathological way to originate from the endometrium. It is proven that there was no hernia sac found in the inguinal canal. The patient can go home the next day without any problems and complications (Fig. 6).

The patient was free from pain after surgery and there was no recurrence either form physical examintaion and ultrasound screening in 24 months after surgery.

DISCUSSION

Endometriosis is an ordinary gynecological pathology that happens to 8–15% women in childbearing age, and it appears in the fourth decade of life. It is marked by the development of ectopic endometrial mass, which is under hormonal stimulation of the ovaries assuming the functional and proliferative aspects characteristic of normal endometrium.[1–4]

Endometriosis recurrence can occur in 10% of women even though they have had children. Many patients suffering endometriosis are asymptomatic, but some prove to experience infertility, menstrual irregularities, menorrhagia, lower abdominal pain, or flank pain. The onset of symptoms and outgrowth of endometriosis due to exposure to the estrogen hormone against endometrial mass that is in extra pelvic. Therefore, an increase in the intensity of symptoms associated with periodic menstruation may occur. Patients currently complain that the intensity of symptoms increases continually in the period of menstruation, even though endometriosis is commonly discovered in intrapelvic structures such as the ovaries, pelvic peritoneum or pouch of Douglas, extra pelvic endometriosis is relatively uncommon.[2,3] Extra pelvic endometriosis can indeed come up in the ileum, jejunum,

pleura, lungs, and peripheral nerves and can even occur in pleura, which is known as catamenial pneumothorax. Surgical scars following laparotomy, section or part of the trocar insertion from the laparoscope are also potential sites for endometriosis to grow.[3–5]

In the recent case, the patient has never had a laparotomy or surgery around the inguinal region before. Extra pelvic endometriosis, which occurs in the inguinal subcutaneous tissue , is uncommon. Candiani *et al* shared that the occurrence of inguinal endometriosis was 0.6% in all extra pelvic cases. Therefore, in the inguinal region it is difficult to diagnose a soft endometriotic mass as extra pelvic endometriosis. Clausen and Nielsen reported that, the largest series of endometriosis in the groin area, are, in fact, 30 cases. From 27 cases, out of 30 ones, the lesion is located on the right part. In different literature, the right part is predominant, and two-thirds of all cases occur around the round ligament. The same thing, the lesion in this case is on the right part, and the structure of ligament is observed in the surgical specimen. Hagiwara *et al* shared that there are two cases of inguinal subcutaneous endometriosis attached to the round ligament of the uterus. Previous literature states that there is a persistence between the lesion and the right part of round ligament of the uterus, but has there has nothing to do with inguinal hernias.[6–10]

In the prior reports, endometriosis usually appeared as a high-signal intensity lesion on MRI images, due to methemoglobin deposits. On T2 MRI images, the intensity of high signal is normal; nevertheless, diffuse hemosiderin deposition that reflects cyclic bleeding may result in the appearance of low signal intensity. Dimming or losing the variable of signal intensity on T2-weighted images is an image that often occurs in endometriosis. In the recent case, the mass exhibits iso-signal intensity in both the T1 and T2 weighted images. Furthermore, the masses show areas of high partial signal intensity in the T2-weighted images. Because the endometriosis features on MRI varies, it is considered difficult for the diagnosis of endometriosis by MRI. Also, the clinical history involving periodic pain cycles and MRI can indicate the possibility of endometriosis. Proliferation of fibrous tissue, a glandular structure composed of columnar epithelium, and a positive immunohistochemical reaction to estrogen can suggest an endometriosis diagnosis.[11,12]

Overall, a patient suffering an inguinal subcutaneous mass, who complains of continual changes in symptoms, the diagnosis of inguinal endometriosis should be considered as a distinctive diagnosis other than an inguinal hernia.

CONCLUSION

The exception of inguinal endometriosis should not eliminate it from the clinical Pathway in the case of fertile women suffering a painful mass in the area of ingunial, especially if the ingunial mass is related to size and tenderness with menstrual variability.

Endometriosis is a disease marked by the appearance of endometrial tissue that functions in places excluding the uterine cavity. Pelvic lesions are the most frequent site of occurrence, yet endometriosis also occurs at extra pelvic location, and in these cases, a patient's symptoms are opted by localization and not by lesion size. Extra pelvic endometriosis manifesting as a hernia is often unnoticed by digestive surgeons, whereas a correct preoperative diagnosis is made in only 38%.[6,7]

After surgery, thorough gynecological monitoring and assessment is mandatory seeing that additional intraperitoneal localization may be considered and the differential diagnosis of inguinal masses in cases of recurrent endometriosis.

REFERENCES

1. Antonio Simone Laganà *et al*. Diagnosis and Treatment of Endometriosis and Endometriosis-Associated Infertility: Novel Approaches to an Old Problem. J. Clin. Med. 2022. 11, 3914. https://doi.org/10.3390/jcm11133914
2. Laganà, A.S.; Garzon, S.; Götte, M.; Viganò, P.; Franchi, M.; Ghezzi, F.; Martin, D.C. The Pathogenesis of Endometriosis: Molecular and Cell Biology Insights. Int. J. Mol. Sci 2019. 20, 5615. [CrossRef] [PubMed]
3. Bianco, B.; Loureiro, F.A.; Trevisan, C.M.; Peluso, C.; Christofolini, D.M.; Montagna, E.; Laganà, A.S.; Barbosa, C.P. Effects of FSHR and FSHB Variants on Hormonal Profile and Reproductive Outcomes of Infertile Women with Endometriosis. Front. Endocrinol. 2021. 12, 760616. [CrossRef] [PubMed]
4. Scioscia, M.; Scardapane, A.; Virgilio, B.A.; Libera, M.; Lorusso, F.; Noventa, M. Ultrasound of the Uterosacral Ligament, Parametrium, and Paracervix: Disagreement in Terminology between Imaging Anatomy and Modern Gynecologic Surgery. J. Clin. Med. 2021. 10, 437. [CrossRef] [PubMed]
5. Noventa, M.; Scioscia, M.; Schincariol, M.; Cavallin, F.; Pontrelli, G.; Virgilio, B.; Vitale, S.G.; Laganà, A.S.; Dessole, F.; Cosmi, E.; *et al*. Imaging Modalities for Diagnosis of Deep Pelvic Endometriosis: Comparison between Trans-Vaginal Sonography, Rectal Endoscopy Sonography and Magnetic Resonance Imaging. A Head-to-Head Meta-Analysis. Diagnostics 2019. 9, 225. [CrossRef] [PubMed]
6. A. Bergamini, G. Almirante, G. Taccagni, G. Mangili, P. Vigano, M. Candiani. Endometriosis-associated tumor at the inguinal site: report of a case diagnosed during pregnancy and literature review. J Obstet Gynaecol Res, 40 (4).2014. pp. 1132–1136
7. H. Niitsu, H. Tsumura, T. Kanehiro, H. Yamaoka, H. Taogoshi, N. Murao. Clinical characteristics and surgical treatment for inguinal endometriosis in young women of reproductive age. Dig Surg, 36 (2).2019. pp. 166–172
8. M. Kamio, T. Nagata, H. Yamasaki, M. Yoshinaga, T. Douchi. Inguinal hernia containing functioning, rudimentary uterine horn and endometriosis. Obstet Gynecol, 113 (2 Pt 2).2009. pp. 563–566
9. Hagiwara Y, Hatori M, Moriya T, Terada Y, Yaegashi N, Ehara S, Kokubun S. Inguinal endometriosis attaching to the round ligament. Australas Radiol. 2007. 51(1):91–94.
10. Y. Uno, S. Nakajima, F. Yano, K. Eto, N. Omura, K. Yanaga.

Mesothelial cyst with endometriosis mimicking a Nuck cyst. J Surg Case Rep, 2014.
11. Haga T, Kumasaka T, Kurihara M, *et al*. Immunohistochemical analysis of thoracic endometriosis. Pathol int 2013. 63:429–34. [PubMed] [Google Scholar]
12. Haga T, Kumasaka T, Kurihara M, *et al*.Immunohistochemical analysis of thoracic endometriosis.Pathol int 2013. 63:429–34.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 382–386

OPEN ACCESS

Case Report

Lucio's Phenomenon in Lepromatous Leprosy Patient: A Rare Case Report

Irma Amalia[1], Agnes Sri Widayati[2], Holy Ametati[1], Yosep Ferdinand Rahmat Sugianto[1], Sri Windayati[2]

[1]Department of Dermatovenereology, Medical Faculty of Diponegoro University / Central General Hospital of Kariadi Semarang, Indonesia
[2]Department of Dermatovenereology, Medical Faculty of Diponegoro University / Tugurejo General Hospital Semarang, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.998

Accepted: July 10th, 2023
Approved: October 30th, 2023

Author Affiliation:
Department of Dermatovenereology, Medical Faculty of Diponegoro University/ Central General Hospital of Kariadi Semarang, Indonesia

Author Correspondence:
Irma Amalia
Dr. Sutomo Street No.16, Semarang, Central Java 50244, Indonesia

E-mail:
irmamalia@gmail.com

Abstract

Background : Lucio's phenomenon is a rare leprosy reaction, characterized by severe necrotic cutaneous lesions that generally occur in patients with untreated or inadequately treated lepromatous leprosy (LL). The objectives of this study was to describe and comprehend the diagnosis and management of Lucio's phenomenon in leprosy patients

Case : Male, 34 years old with extensive wounds on both arms and legs. About 3 years earlier, the patient felt burning heat in both hands and feet followed by loss of eyebrows and eyelashes, and a change in the shape of the nose. The patient had not received previous therapy. Physical examination showed that the patient appeared anaemic, leonine facies, megalobuli, madarosis, saddle nose, thickening of the ulnar and posterior tibial nerves, deformities of the fingers and toes, and amputations of several fingers. The dermatological status showed multiple ulcers of irregular shape and varying sizes with pus and necrotic tissue. Reitz serum test revealed a bacterial index of +3 with a morphological index of 90%, and routine blood showed hypochromic microcytic anaemia and leucocytosis. The patient received corticosteroid therapy, anti-leprosy combination therapy, antibiotics, iron tablets and wound care.

Discussion : Lucio's phenomenon consists of skin lesions that range from painful red-black patches to flaky blisters and ulcerations. These lesions usually occur on the lower extremities, and may extend proximally and distally. The lesions improved after administration of corticosteroids and anti-leprosy. Delayed diagnosis leads to significant disability and community transmission of the disease. The later the diagnosis, the more serious the disease becomes and can lead to death due to sepsis. Early diagnosis and appropriate treatment are important.

Conclusion : Early detection is crucial in order to deliver therapy earlier and prevent disease worsening.

Keywords : Lucio's phenomenon, Leprosy, Leprosy Reaction

INTRODUCTION

Lucio's phenomenon is a rare leprosy reaction. This phenomenon was first described by Lucio and Alvarado in Mexico in 1852, so it was called the Lucio's phenomenon. This condition often occurs in untreated or inadequately treated lepromatous leprosy. It can be life-threatening in some severe conditions. Lucio's phenomenon is very common in America, particularly in Mexico, although some cases have also been reported in Europe and Asia. Precipitating factors include pregnancy, stress, or infection. Lucio's phenomenon is difficult to diagnose, especially in non-endemic areas, causing delays in identifying the disease and starting time for treatment. Lucio's phenomenon is a type III hypersensitivity reaction associated with the deposition of immune complexes produced by antigen binding from the destruction of the bacilli with antibodies.[1–3]

The diagnosis is based on anamnesis, physical examination and Reitz serum and histopathology. Patient with Lucio's phenomenon usually presents with cutaneous ulceration in extremities. The symptom usually begins with redness that develop into ulcer and spread to the other parts of the body which not accompanied by fever and neuritis. It's also important to ask the patients if they had any contact with people who have leprosy or if they have ever been treated for leprosy.[1,3]

Lucio's phenomenon appears as dark red spots and becomes sores with necrotic tissue and associated deformities. These lesions will cause atrophic scars with a border of hyperpigmentation. Lesions are most often found on the hands, arms, legs and feet and rarely on the face and chest. One of supporting examinations for Lucio's phenomenon is skin slit smear examination. Examination of acid-fast bacilli (AFB) in the form of a skin slit smear stained with Ziehl-Nielsen staining taken from both ear lobes and skin lesion. Lucio's phenomenon showed a very positive bacterial and morphological index.[1,3]

In addition to skin slit smear examination, histopathology examination can also be performed. Histopathological finding shows colonization of endothelial cells by acid fast bacilli; endothelial proliferation of medium vessels of the mid-dermis with venous congestion; and neutrophil infiltration, ischemic epidermal necrosis, and necrotizing vasculitis of small vessels of the superficial dermis.[1,3,4]

The management of Lucio's phenomenon uses anti-leprosy regimen for multibacillary infection and systemic steroids. According to World Health Organisation (WHO) guidelines, multidrug therapy (MDT) for multibacillary leprosy was initiated for 18 months. High doses of corticosteroids (starting at 1 mg/kgBB equivalent to prednisone) should also be started and slowly tapered down over a period of months. After two weeks of treatment, the ulcers usually start healing. Bacterial and morphological index from skin slit smear examination are also performed to evaluate the treatment results. Management should be given at an early stage to reduce the occurrence of physical disability to death.[1,3,4]

CASE

A man, 34 years old, with the chief complaint of extensive and difficult to heal wounds on both forearms and both lower legs for 6 months ago. It was started as red-black spots which increased in number and became a wide and deep ulcer like a crater, with irregular edges, and painful. The ulcer occurred on both lower legs, then spread to the forearms to the fingers on both hands and feet (Figure 1). There was no fever and joint pain.

About 4 years ago, the patient complained of burning sensation in both arms and legs. The patient's eyebrows and eyelashes are falling out. The patient had never undergone treatment before. History of the similar complaints in the family was denied.

Physical examination showed anaemic conjunctiva, madarosis, megalobuli, *facies leonine, saddle nose*, deformities of the fingers and toes, and the amputate of the 4th and 5th fingers of the right and left hands. Nerve examination showed thickening of the ulnar nerve, posterior tibial nerve, and ulnar nerve paralysis. Dermatological status revealed hyperpigmented macules on the face, trunk and back, multiple ulcers on both arms and both legs with irregular shapes and varying sizes accompanied by pus, crusts and necrotic tissues (Figure1).

Complete blood investigation showed hypochromic microcytic anaemia (Hb: 5.3 mg/dL) and leucocytosis (15.35 x 103/ µL). Microbiological examination with Reitz serum on the earlobes showed a bacterial index of +3 and a morphological index of 90%. Whereas Reitz serum on skin lesions showed a bacterial index of +1 and a morphological index of 90%.

Based on anamnesis and physical examination, a diagnosis of Lepromatous Leprosy with Lucio's phenomenon was made. The management of this patient were rifampicin tablet 600 mg/2 weeks, clarithromycin tablet 500 mg/24 hours, methylprednisolone tablet 16 mg/2 hours, vitamin B complex tablet/12 hours, vitamin B12 tablet/8 hours, folic acid tablet/8 hours, iron tablet/8 hours, and zinc tablet 20 mg/24 hours. The treatment was given for a month then the patient was asked to control. Patients also received topical therapy in the form of 0.9% NaCl compress every 12 hours for 10 minutes, before applying cream to ulcers, 2% fusidic acid cream topical/12 hours on ulcers, and 1% silver sulfadiazine cream topical/12 hours on ulcers. After 30 days post treatment, the ulcer started to heal leaving a central achromic scar, surrounded by hyperpigmented

Figure 1. First day observation, before treatment

borders. Rifampicin and clarithromycin were continued for 18 months. After a month of administration, methylprednisolone was tapered off slowly according to the patient's clinical improvement.

DISCUSSION

The clinical manifestations of this patient match the diagnosis of Lepromatous Leprosy with Lucio's phenomenon. Lucio's phenomenon is a rare variant of the leprosy reaction, which is often found in the lepromatous version where it occurs due to unresponsiveness of the immune system causing unlimited proliferation of *Mycobacterium leprae*. As many as 0.7% of cases (16 cases) of a total of 843 cases of leprosy reactions in Indonesia. Lucio's phenomenon consists of skin lesions that range from painful red-black patches to flaky blisters and ulcerations.[5]

These lesions usually occur on the lower extremities, and may extend proximally and distally. The upper extremities, trunk and face may also be affected. Patients with Lucio's phenomenon usually do not have fever or neuritis.[1,6-9] Lucio's phenomenon usually occurs 1-3 years after disease onset and is common in patients with untreated or inadequately treated lepromatous leprosy and borderline type.[1,9-12]

The characteristics of lepromatous leprosy show the appearance of progressive skin thickening, thickened earlobes, rough facial lines and a concave shape. Facies leonine which may be accompanied by madarosis, iritis,

Figure 2. Observation day 30, after administration of anti-leprosy and corticosteroids

keratitis, and megalobuli. Furthermore, deformities can occur in the nose, called saddle nose. Peripheral nerve fibers experience thickening, hyaline degeneration, or fibrosis.[7,13]

Lucio's phenomenon begins as a bluish-red plaque, with a slight induration of the skin with an erythematous halo, usually on the extremities, but can also appear on other areas of the body. The lesions are ill-defined and painful with irregular or triangular shape. After a few days, the lesions will become purplish in the centre. Central haemorrhagic infarction may occur with or without blister formation. Subsequently, the lesion becomes a necrotic eschar, which detaches easily, and an ulcer with an irregular shape develops. The classic sign of Lucio's phenomenon is a jagged-edged necrotic ulcer with geometric shape.[7,9,10]

The results of supporting investigations in this patient are also consistent with the characteristics of Lucio's phenomenon in the literature. The Lucio's phenomenon characteristically shows very positive bacteriological and morphological index. The most common abnormalities found in laboratory tests are

anaemia, hypocalcaemia, hypoalbuminemia, leucocytosis, neutrophilia, and increased erythrocyte sedimentation rate. The classic clinical features of Lucio's phenomenon in this patient support the diagnosis of Lucio's phenomenon.[1,3]

Histopathological examination was performed in patients with atypical clinical features. Histopathological features will show colonization of endothelial cells by acid-fast bacilli, ischemic epidermal necrosis, necrotizing vasculitis of small vessels in the superficial dermis, endothelial proliferation of medium-sized vessels in the middle dermis with passive venous congestion and neutrophil infiltration.[9]

The principle of management in cases of Lucio's phenomenon is by administering high doses of corticosteroids equivalent to prednisone 1 mg/kg/day and starting anti-leprosy therapy. Rifampicin should not be given as monotherapy because resistance may develop. Rifampicin 600 mg or 1200 mg once a month was well tolerated. One of the new leprosy drugs, clarithromycin, is known to be very effective against infection *M. leprosy* in humans and has several advantages, namely providing clinical improvement, high bactericidal activity, good tolerance, and rarely causes side effects. Previous research stated that the combination regimen of rifampicin 600 mg per month and clarithromycin 500 mg per day for 3 months resulted in a significant reduction of acid-fast bacilli, a significant increase in healing, and no significant drug side effects were found.[1,9]

High doses of corticosteroids are tapered every month seeing clinical improvement in patients. Supportive care, such as wound care, is important in the management of these patients, to prevent secondary infection to sepsis. Plasmapheresis therapy can be an option if there is no improvement in the reaction.[13–15]

Evaluation of these patients showed a significant improvement. After 30 days post treatment, the ulcer started to heal and leave a central achromic scar, surrounded by hyperpigmented macules. In accordance with the literature that the ulcer will heal within a period of 2-4 weeks and leave a superficial atrophic scar.[7,10]

CONCLUSION

Lucio's phenomenon is a rare leprosy reaction that usually occurs in untreated leprosy. Early detection is needed to prevent morbidity and concomitant complications. This case was established based on clinical manifestations and investigations that support the diagnosis of Lucio's phenomenon. Administration of high-dose corticosteroid therapy and anti-leprosy showed clinical improvement in the patient.

REFERENCES

1. Sharma P, Kumar A, Tuknayat A, *et al*. Lucio Phenomenon: A Rare Presentation of Hansen's Disease. J Clin Aesthet Dermatol. 2019; 12(12): 35–8.
2. Kamath, S., Vaccaro, S. A., Rea, T. H., & Ochoa, M. T. (2014). Recognizing and managing the immunologic reactions in leprosy. Journal of the American Academy of Dermatology, 71(4), 795–803.
3. Frieda, Kariosentono H, Ellistasari EY. Lucio Phenomenon: A Rare Type of Leprosy Reaction. J Commun Dis. 2022;2022(253):253–7.
4. Frade MAC, Coltro PS, Filho FB, Horácio GS, Neto AA, da Silva VZ, *et al*. Lucio's phenomenon: A systematic literature review of definition, clinical features, histopathogenesis and management. Indian J Dermatol Venereol Leprol. 2022;88(4):464–77.
5. Prakoeswa CRS, Lubis RS, Anum Q, Argentina F, Menaldi SL, Gunawan H, *et al*. Epidemiology of Leprosy in Indonesia: a Retrospective Study. Berk Ilmu Kesehat Kulit dan Kelamin. 2022;34(1):29–35.
6. Herath S, Navinan MR, Liyanage I, *et al*. Lucio's phenomenon, an uncommon occurrence among leprosy patients in Sri Lanka. BMC Res Notes. 2015;8:672–8.
7. Peixoto AB, Leal FRP, Rodrigues NC, *et al*. Lucio's Phenomenon: Case Study of an Exceptional Response to Treatment Exclusively with Multibacillary Multidrug Therapy. An Bras Dermatol. 2013; 88(6 Suppl 1): S93–6.
8. Lemus-Barrios GA, Hoyos-Pulgarin JA, Jimenez-Canizales CE, dkk. Lucio's Phenomenon: A Report of Two Cases and Review of the Literature. Case Rep Intern Med. 2019; 6(2): 15–9.
9. Kar HK, Chauhan A. Leprosy Reactions: Pathogenesis and Clinical Features. In: Kumar B, Kar HK, editor. IAL Textbook of Leprosy. 2nd ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2017: 416–37.
10. Rocha RH, Diniz LM, Cabral ANF, dkk. Lucio's Phenomenon: Exuberant Case Report and Review of Brazilian Cases. An Bras Dermatol. 2016; 91(5 Supl 1): S60–3.
11. Pardo SS, Cabeza LD, Diaz AO, dkk. Hansen's Disease with Lucio's Phenomenon in a Country in the Post Elimination Era: A Case Report. Case Rep Intern Med. 2017; 4(4): 6–9.
12. Suvirya. A Case of Diffuse Lepromatous Leprosy with Lucio's Phenomenon. QJM-Int J Med. 2020: 138–9.
13. Kumar B, Dogra S. Case Definition and Clinical Types of Leprosy. Dalam: Kumar B, Kar HK, editor. IAL Textbook of Leprosy. Edisi ke-2. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2017: 236–53.
14. Prakoeswa CRS, Herwanto N, Agusni RI, dkk. Lucio's Phenomenon of Leprosy LL Type on Pregnancy: A Rare Case. Lepr Rev. 2016; 87: 526–31.
15. Hubaya K, Riyanto P. Treatment of leprosy patients using combination of rifampicin-clarithromycin for 3 months in tugurejo general hospital Semarang. Clin Exp Dermatol Ther. 2017;9:1–5.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; vol 10 (3) : 387–391

OPEN ACCESS

Case Report

Concomitant Colon Adenocarcinoma and Tuberculous Lymphadenitis

Albertus Magnus Arya Abisatya[1], Ajeng Andini Prameswari[1], Agung Rahmat Fauzi[1], Aji Pratama Febrianto[1], Alexander Steven Nugroho[1], Hendrata Erry Andisari[2], Pandu Harijono[2], Redemptus Yudadi[2]

[1]Medical Faculty of Hang Tuah Surabaya, Indonesia
[2]Navy Central Hospital of Dr. Ramelan Surabaya, Indonesia

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v10i3.1007

Accepted: August 07th, 2023
Approved: November 08th, 2023

Author Affiliation:
Navy Central Hospital of Dr. Ramelan Surabaya, Indonesia

Author Correspondence:
Redemptus Yudadi
Gadung Street No.1, Jagir, Wonokromo, Surabaya, East Java 60244, Indonesia

E-mail:
r.yudadi@yahoo.com

Abstract

Background : Colon involvement in tuberculosis infection is a rare event. The coexistence of colon carcinoma and tuberculous lesions of the colon is less frequently reported. Carcinoma and tuberculosis of the colon can occur at the same site or at different sites. The occurrence of two pathologies at the same site is much less common.
Case Presentation : A 52 year old woman complained of difficulty defecating, an enlarged stomach, pain and decreased appetite and weight loss within one month. On clinical examination, the abdomen appeared convex, slightly distended, and tenderness in the left lower iliac quadrant. Radiological examination supported the diagnose of partial obstructive ileus. The patient was diagnosed with adenocarcinoma of the ascending colon until the hepatic flexura was confirmed through surgery and histopathological examination. On histopathological examination, adenocarcinoma of the colon was found to coexistence with tuberculous lymphadenitis of the colon.
Conclusion : The etiological and pathophysiological relationship between tuberculous lymphadenitis and colon cancer is still under debate, but surgeons need to be aware of this occurrence, to choose treatment and avoid post-operative worsening.

Keywords : colon adenocarcinoma, tuberculous lymphadenitis

INTRODUCTION

Gastrointestinal tuberculosis is the third most common form of extrapulmonary tuberculosis (EPTB) with the most common site of infection being the ileocaecal junction, followed by the jejunum and colon. Colon involvement in tuberculosis is a rare event even in regions where TB is endemic, including India, accounting for approximately 3-4% of intestinal TB cases. Coexistence of colon carcinoma with tuberculous lesions in the small intestine has been reported, but coexistence of colon carcinoma with TB is rarely reported. Carcinoma and TB can occur at the same site or at different sites in the large intestine. The occurrence of two pathologies in the same site is relatively rare. Some studies say that this coexistence occurred by chance, while other studies show cause and effect where TB is a precursor to coexistence.[1,2]

Coexistence of TB with many other carcinomas has been reported in the literature. Kaplan *et al* stated that TB is most often seen in patients with Hodgkin's disease, lung cancer, lymphosarcoma and reticulum cell sarcoma.[3] The coexistence of tuberculosis and colon carcinoma not only influences the diagnosis and management plan but also influences the complication rate, prognosis and follow-up plan.

This paper reports a case of a patient with concomitant colon carcinoma and colon tuberculosis.

CASE PRESENTATION

A 52 year old female patient presented with chief complaints of constipation but occasionally experienced diarrhea, since a year before admission. On the day he was admitted to the hospital, he complained that the feces mixed with fresh blood in large quantities so that the patient fainted and was taken to the Emergency Department. The patient could still fart, complained of an enlarged and painful stomach for the last one year and was getting worse three days before admission. The patient complained of nausea and vomiting, decreased appetite and weight loss of 10 kg in the last month. The patient did not complain of shortness of breath or coughing.

History of diabetes mellitus, hypertension, chronic intestinal disease or tuberculosis was denied. On physical examination, the abdomen appeared convex and slightly distended, weak bowel sounds were heard in the right upper quadrant, and tenderness in the left lower iliac quadrant. A plain abdominal radiograph revealed early sign of ileus obstruction. Chest x-ray examination did not reveal cavities, foci of pain and perihilary lymphadenopathy.

The differential diagnosis of this case is ulcerative colitis. Colon cancer and ulcerative colitis have some similar symptoms, such as gastrointestinal bleeding, abdominal pain in the left lower quadrant, and weight loss.

On 25 February 2020, the patient underwent an extended hemicolectomy dextra procedure. Considering systemic factors, namely hypoalbuminemia and local dilatation of the ileum, it was decided to perform an end ileostomy and install an intra-abdominal drain. During the operation, a tumor mass was found in the ascending colon up to the hepatic flexura (staging: T4), multiple enlarged lymph nodes in the mesocolon to the base around the superior mesenteric vein (staging: N2), no nodules/tumors were palpable on the surface of the liver (staging: M0), the uterus has the impression of a small

Picture 1. BOF/LLD on admission showed an early sign of ileus obstruction

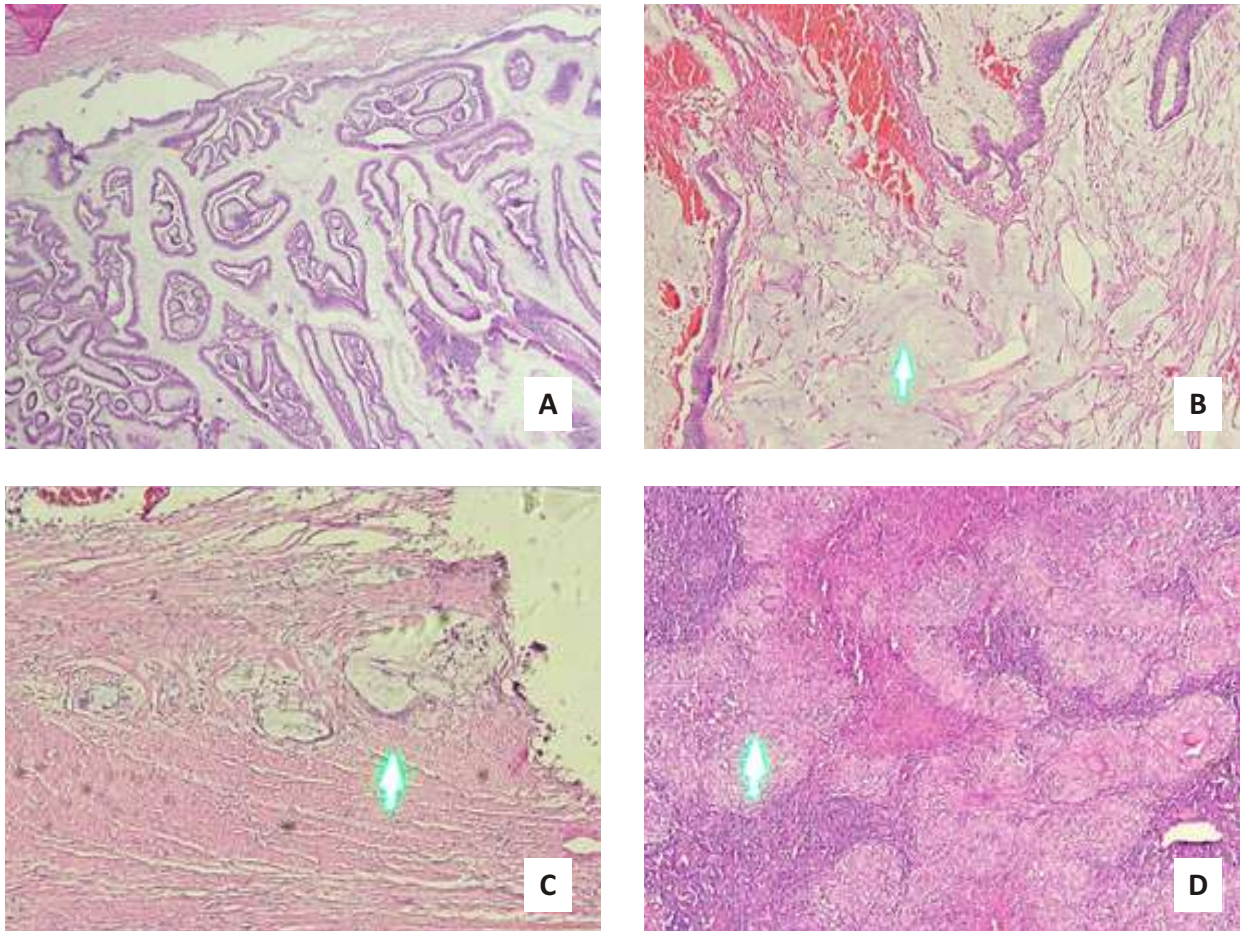


Figure 2. (A) Sections of colon tissue with tumor growth, contain proliferation of epithelial cells arranged in a glandular structure. It grows infiltratively to subserosal (pT3). **(B)** Tumors are partly composed of mucin components. **(C)** Lymphovascular space invasion (LVSI), **(D)** Among the areas of necrosis, groups of epithelioid-shaped histiocytes were found that formed granulomas (arrows), with a distribution of datia langerhans cells.

uterine myoma and dilated small bowel (bowel obstruction). The operation lasted 1 hour 45 minutes, the patient's post-operative status was alive. After the operation a histopathological examination of the tumor tissue was carried out.

Histopathological results showed well-differentiated adenocarcinoma in the ascending colon up to the flexura hepatica measuring (11 x 4.5 x 4) cm3, the tumor grew from the mucous layer to the serosa, and invaded the blood vessels. From the results of the post-operative histopathological examination, only 5/6 lymph nodes were found with tuberculous granulomatic lymphadenitis, the standard for achieving radicality was 12 lymph nodes. In this case, it is possible that the colon lymph node dissection was incomplete, due to the inflammatory condition around the lesion.[4]

The patient took anti-tuberculosis drugs for 9 months and chemotherapy for 12 sessions. On 30 April 2021, an ileostomy closure surgery was performed.

The patient's condition was stable when he was discharged from the hospital. Complaints of pain from surgical wounds are reduced and surgical wounds are dry. After the ileostomy closure operation, the patient can fart and defecate, and return to activities without using a stoma bag.

DISCUSSION

Colon tuberculosis is a rare extrapulmonary tuberculosis, namely only 3–4% of cases of extrapulmonary tuberculosis. The incidence of abdominal tuberculosis accompanied by colon cancer is even rarer, and the relationship between the two is still debatable today. The simultaneous occurrence of abdominal tuberculosis with colon cancer may be just a coincidence, but there could be a link between the two diseases, abdominal tuberculosis could be a factor responsible for the incidence of colon cancer.[5,6]

Bayle (1810) first reported abdominal tuberculosis occurring simultaneously with colon cancer which was

described as a "cavitation cancereuse" which is classified as one of six types of tuberculosis.[7] The relationship between abdominal tuberculosis and malignancy has been widely reported in various organs of the body by several authors. Kaplan's study in 1974 revealed that only 4 (0.0006%) tuberculosis patients had neoplastic complications out of 6472 colon cancer patients.[8,9]

According to several researchers from India, the relationship between tuberculosis and colon cancer is a coincidental, on the grounds that there are very few cases of abdominal tuberculosis co-occurring with colon cancer. This explanation may still be true in some cases where the site of malignancy or neoplasm is located far from the site of tuberculosis infection. However, this opinion can still be refuted, especially if the occurrence of these two diseases is in close proximity or even in the same place, for example in this case report, where the location of the cancer is in the ascending colon at the flexura hepatica and the location of tuberculous lymphadenitis is not far from the location of the tumor.[10]

Several diseases such as ulcerative colitis, Crohns disease, and schistosomiasis are considered predisposing factors for the growth of tissue malignancies. Chronic inflammation damages the intestinal mucosal lining, initiating a process of cell metaplasia and dysplasia that causes neoplastic changes. Some evidence shows that pulmonary tissue that experiences injury/scarring infection as a result of tuberculosis bacteria plays a role in initiating the growth of lung cancer, generally adenocarcinoma which originates from the peripheral parts of the lungs. Tuberculosis that occurs simultaneously with colon cancer can be argued that ulcerative lesions due to intestinal tuberculosis can be a precursor to malignancy in the colon and this possibility is supported by a research in Japan, where 17 of 26 cases of abdominal tuberculosis occuring simultaneously with colon adenocarcinoma were found to have tumors located in the ascending colon or the right side of the colon is the most frequent predilection site for abdominal tuberculosis, namely in the ileocaecal region. These findings strengthen the suspicion that colon malignancy begins with tuberculous lesions.[11]

On the other hand, factors that interfere with host immunity are believed to be responsible for increased activation of tuberculosis infection, both exogenously and endogenously. Severe weight loss or malnutrition associated with advanced malignant disease is one of the factors that interfere with host immunity, this can support the argument that the occurrence of carcinoma can cause dormant tuberculous lesions to become active and re-infection endogenously occurs. Locally produced tumor peptides or tumor antigens can also accelerate granuloma growth and cause tuberculosis bacteria to proliferate. This argument can explain the incident in this case report, where an elderly woman who did not have a clear history of active tuberculosis, both pulmonary and extrapulmonary, experienced colon cancer along with abdominal tuberculosis, but could have previously had latent tuberculosis but it is difficult to prove, for example no clear history of a positive Mantoux test.[12]

To date, no literature can explain clearly the relationship between the incidence of intestinal tuberculosis and colon cancer, the pathophysiological relationship between the two is still unclear and debatable. In-depth and long-term research is needed to determine whether or not there is a possibility that tuberculous lesions in the intestinal mucosa can initiate colon cancer or whether systemic lesions from advanced cancer can be an active factor in tuberculous lesions.

CONCLUSION

A case of coexistence of colon adenocarcinoma with tuberculosis in a 52 year old female patient has been reported. The diagnosis was made post-operatively. The patient's condition was improved after surgery, administration of anti-tuberculosis drugs and chemotherapy. Further research is needed to conclude whether the carcinoma was induced by tuberculosis, or whether it was a coincidence that occurred simultaneously.

Consent

Written informed consent for article publication was obtained directly from the patient's family. The approval sheet can be shown to the Editor.

Confilct of Interest

There is no conflict of interest. If this is found at a later date, the author is fully responsible for this matter.

Source of Funding

Self-funded.

Ethical Clearance

Obtained from the Health Research Ethics Sub-Committee of Rumkital, Dr. Ramelan Surabaya.

REFERENCES

1. Chakravartty S, Chattopadhyay G, Ray D, Choudhury CR, Mandal S. Concomitant tuberculosis and carcinoma colon: Coincidence or causal nexus. Saudi J Gastroenterol. 2010;16(4):292–4.
2. Khaniya S, Koirala R, Shakya VC, Adhikary S, Regmi R, Pandey SR, *et al*. Anorectal tuberculosis coexisting with adenocarcinoma: An unusual association. Cases J. 2009;2(9):2–4.
3. Peter AND. Tuberculosis Complicating Neoplastic. 1971;850–8.

4. Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, *et al*. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19 3:329–59.
5. Ramamoorthy S, Srinivas BH, Badhe BA, Jinkala S. Coexistence of malignancy and tuberculosis. Int J Clin Exp Pathol. 2023;16(1):1–7.
6. Chaudhary P, Bhadana U, Lal R. A Retrospective Cohort Study of Coexistence of Carcinoma and Tuberculosis of Colon: 12-Year Experience. Indian J Surg Oncol. 2021;12(1):61–6.
7. Bayle GL. Recherches sur la phthisie pulmonaire. Gabon; 1810.
8. Kaplan MH, Armstrong D, Rosen P. Tuberculosis complicating neoplastic disease. A review of 201 cases. Cancer. 1974;33(3):850–8.
9. Park SM, Kim JH, Chong Y, Kang WK. Concurrent ascending colon adenocarcinoma and ileocecal tuberculosis: A case report. Med (United States). 2022;101(21):E29430.
10. Khemchand AK, Singh K, Vaiphei K, Kaman L. Synchronous colonic malignancy and tuberculosis: a rare histologic surprise. Int Surg J. 2020;7(10):3505.
11. Tanaka K, Kondo S, Hattori F, Yamashita Y, Matsuda M, Itoh K, *et al*. A case of colonic carcinoma associated with intestinal tuberculosis, and an analysis of 26 cases reported in Japan. Gan No Rinsho. 1987;33(9):1117–23.
12. Rahman D, Rabby J, Saadat M. Co-existent Caecal Adenocarcinoma and Tuberculosis: A Rare Case Report. J Histopathol Cytopathol. 2022;6(1):62–6.

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; Vol 10 (3)
November 2023

AUTHOR GUIDELINE

Medica Hospitalia: *Journal of Clinical Medicine* is a scientific journal published by RSUP Dr. Kariadi and accepts articles written in English expected becoming a media conveying scientific inventions and innovations in medical or health allied fields toward practitioners and academicians.

ORIGINAL ARTICLE

Research manuscript should adhere guidelines as follow:

Title :
1. Is neither too long nor too short, approximately 12–14 words
2. Describes research design
3. Contains no abbreviation unless standard

Abstract :
1. Is well structured (background, aim, method, result, conclusion)
2. Consists of maximum 250 words
3. Consists of 3-8 keywords
4. Is presented in English

Introduction :
1. Consists of 2 paragraphs/parts. The first paragraph consists of research background (research justification): what have been known and what need to be added. The second paragraph consists of hypothesis or research aim.
2. Is supported by relevant and strong references

Methods :
1. Explains research design, settings and time
2. Explains population and sample, sampling technique, sample size (equation doesn't need to be enclosed), inclusion and exclusion criteria.
3. For clinical trial, explains randomization and conceal allocation, and Kappa test if conducted and detailed investment
4. Thoroughly explains method, instrument, measurement technique and data collection
5. Explains data analysis with proper tests according to data, significance and confidence interval
6. Explains computer program (software) used
7. Explains ethical clearance and informed consent

Results :
1. Is presented in a logical sequence
2. Presents subject characteristics (in a table). For clinical trial, subject characteristic of each group before trial are presented
3. Explains subjects who drop out and the reasons. If possible, provides consort diagram
4. Maximum 3-4 tables
5. Provides hypothesis without commentary

Discussion :
1. Discusses all relevant findings and its association with practice. There is no redundant repetition of findings already presented in the results section.
2. Is compared with previous study findings.
3. Mentions research strengths/weaknesses and its impact on findings.

Conclusion :
1. Should answer research question
2. Should be based on research findings, not quotation
3. Can provide suggestion for future research

References :
1. Uses Vancouver style (see *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*) www.icjme.org

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2023; Vol 10 (3)
November 2023

Authors and institutions :

1. Present complete name of authors without academic title along with office/institution/work place address under the title
2. Provide correspondences
   The main author provides a statement explaining that article has never been published nor sent for publication to other journals and has already been approved by all co-authors evidenced by a statement sheet. All sent articles are reviewed by profession groups (peer reviewers) and editors. All articles should provide ethical clearance issued by Ethical Review Board and 2 sheets of inform consent form already signed in "pdf" format.

CASE REPORT

Title :
1. Is neither too long nor too short, approximately 12-14 words
2. Contains no abbreviation unless standard

Abstract :
1. Is well structured (background, aim, case report, discussion, conclusion)
2. Consists of maximum 250 words
3. Consists of 3-8 keywords
4. Is presented in English

Introduction :
1. Consists of 2 paragraphs/parts. The first paragraph consists of research background (justification of the case report). The second paragraph consists of aim of case report emphasizing diagnose/pathogenesis/therapy.
2. Is supported by relevant and strong references

Case report :
1. Presents short case involving medical history, physical examinations, and investigations.
2. Stresses new or rare cases or new therapies or procedures
3. Provides patient's picture (if necessary), investigations such as radiology or laboratory or others as needed. Pictures/photos size minimum 300 dpi.
4. Obtains patients' or families' informed consent for publication for patients with easily identified features. Editors may conceal physical features considered unnecessary.
5. Contains maximum four photos/pictures for each article.

Discussion :
1. Provides epidemiology data showing that rare cases occur or new procedures are conducted.
2. Provides relevant discussion according to aim of the case report emphasizing diagnose/pathogenesis/therapy comparing/relating to other cases and providing LoE (Level of Evidence).

Conclusion and suggestion :
1. Are in line with the aim of case report.
2. Suggestion consists of improvement for case management.

Reference :
1. Uses Vancouver style (see *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*). www.icjme.org

Author and institution :
1. Complete name of authors and office/institution/workplace address are presented under the title.

Contact Person : Aziz Alfarisy, S.Hum 024 8413476 EXT: 8088/ HP: 08995457412
Email : medicahospitalia@rskariadi.co.id atau medica.hospitalia@yahoo.com

SERTIFIKAT

Direktorat Jenderal Pendidikan Tinggi, Riset dan Teknologi
Kementerian Pendidikan, Kebudayaan, Riset dan Teknologi Republik Indonesia

Kutipan dari Keputusan Direktorat Jenderal Pendidikan Tinggi, Riset dan Teknologi
Kementerian Pendidikan, Kebudayaan, Riset, dan Teknologi Republik Indonesia

Nomor 105/E/KPT/2022
Peringkat Akreditasi Jurnal Ilmiah Periode 1 Tahun 2022

Nama Jurnal Ilmiah

Medica Hospitalia : Journal of Clinical Medicine

E-ISSN: 26857898

Penerbit: RSUP Dr. Kariadi Semarang

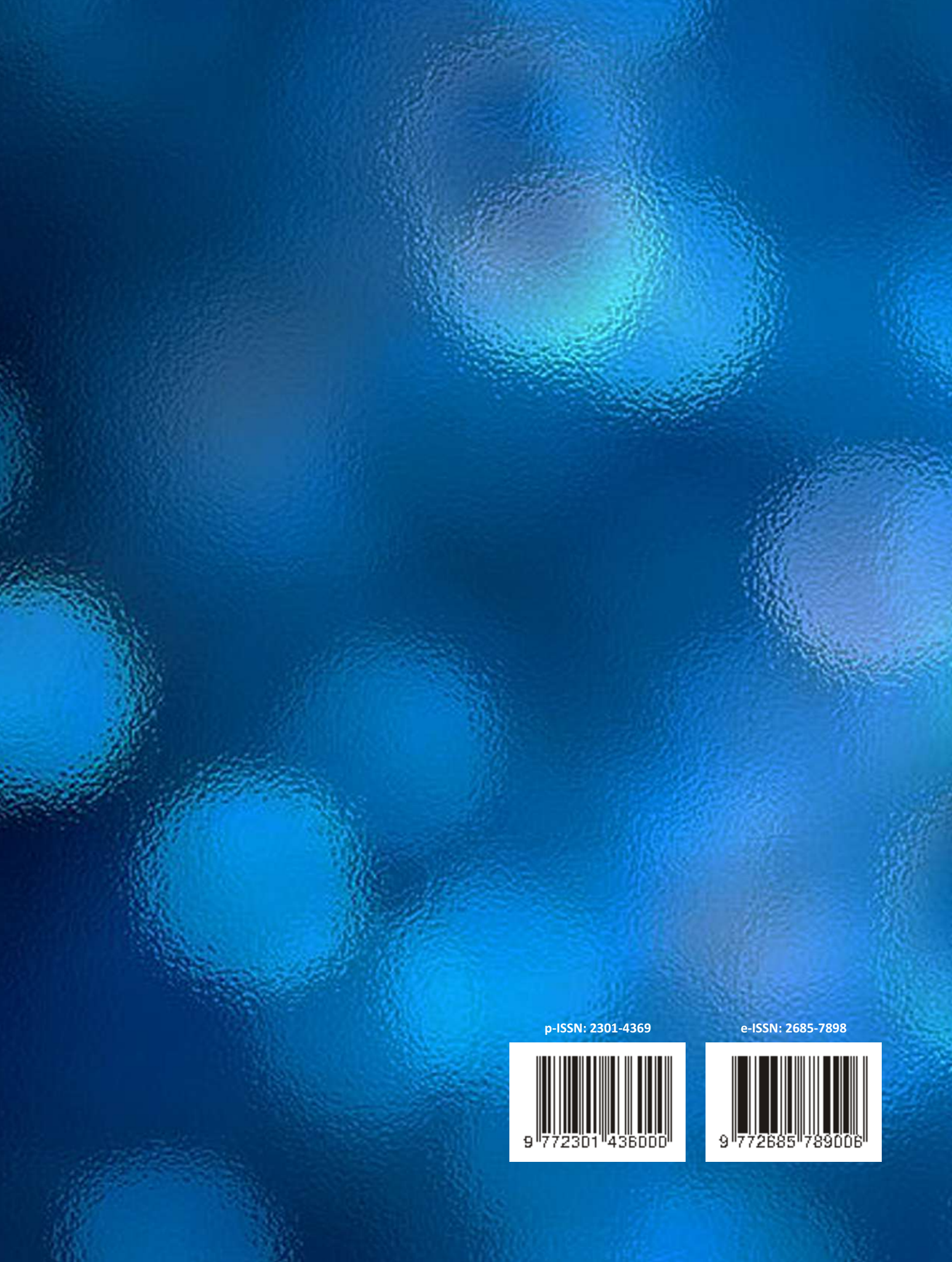
Ditetapkan Sebagai Jurnal Ilmiah

TERAKREDITASI PERINGKAT 3

Akreditasi Berlaku selama 5 (lima) Tahun, yaitu
Volume 8 Nomor 2 Tahun 2021 Sampai Volume 13 Nomor 1 Tahun 2026

Jakarta, 07 April 2022
Plt. Direktur Jenderal Pendidikan Tinggi,
Riset, dan Teknologi

Prof. Ir. Nizam, M.Sc., DIC, Ph.D., IPU, ASEAN Eng
NIP. 196107061987101001



p-ISSN: 2301-4369

e-ISSN: 2685-7898