VOL 55 NO 2 (2023)

ACTA MEDICA INDONESIANA

The Indonesian Journal of Internal Medicine

2023

A Publication of The Indonesian Society of Internal Medicine

e-ISSN: 2338-2732
p-ISSN: 0125-9326

We Need Epidemiological Study from Our Own Population

Laurentius Aswin Pramono*

Department of Public Health and Nutrition, School of Medicine and Health Sciences Atma Jaya Catholic University of Indonesia & Department of Internal Medicine, St Carolus Hospital, Jakarta, Indonesia.

Corresponding Author:
Laurentius Aswin Pramono, MD. Department of Public Health and Nutrition, School of Medicine and Health Sciences Atma Jaya Catholic University of Indonesia, Jl. Pluit Selatan Raya no. 19, Jakarta, Indonesia. Email: l.aswin.pramono@gmail.com, aswin.pramono@atmajaya.ac.id.

Epidemiological data is a valuable source for decision-making in a clinical setting or from a public health perspective.[1] It serves not only direct purposes by supporting evidence-based treatment but also indirectly contributes to guidelines and policies in healthcare services. Currently, there remains a pressing need for further epidemiological or population-based studies to be conducted in Indonesia. The availability of health data and information specifically from the Indonesian population is still limited and highly sought after. It is common for us to depend on epidemiological data from foreign countries, but this practice can introduce bias into our decision-making process due to the disparities between their conditions and our own.

Indonesia possesses a distinct socio-demographic and health landscape, setting it apart from other countries. The diverse range of diseases, risk factors, healthcare access, health equity, and geographical characteristics all contribute to the uniqueness and variability of health problems within the nation.[2] Specific regions across the Indonesian archipelago encounter health issues that are distinct to their locations. Infectious diseases, particularly tropical diseases, and nutrient deficiencies continue to present significant challenges in numerous provinces throughout Indonesia.[2-4] Variations are observed across different areas and timeframes of study. These dynamic and variable factors make population studies particularly intriguing. It is the responsibility of clinicians, researchers, and epidemiologists to delve into the intricacies of the population and study its health problems comprehensively.

One of the prevailing epidemiological and clinical concerns related to micronutrient deficiency in Indonesia is iodine deficiency, which requires immediate attention.[5,6] Despite its current lack of significant national focus, iodine deficiency disorders (IDD) remain a crucial global issue, including within Indonesia. IDD stands as the most prevalent preventable cause of brain damage and hampers human growth and development.[5] It contributes to thyroid complications such as hypothyroidism, hyperthyroidism, and an elevated risk of goiter, thyroid nodules, and thyroid cancer. Furthermore, iodine-deficient areas experience an increased susceptibility to autoimmune thyroid diseases.

Over the years, the awareness regarding iodine deficiency problems has dwindled due to the successful implementation of global salt iodization and fortification programs. However, it is crucial to continually evaluate these nationwide initiatives and conduct further studies to generate attention, disseminate information, and provide ongoing support.[7] Surprisingly, 30% of the global population, including Indonesia, still faces the risk of iodine deficiency disorders (IDD).[8] Collaboration among epidemiologists, clinicians, public health stakeholders, and the government is essential to support all programs, including updated clinical and epidemiological studies, discussions, and policy updates regarding IDD.

In this issue, we present a population study conducted in Magelang Regency, which is

situated in the Central Java Province. The study focuses on examining the iodine intake status and thyroid profiles of women of childbearing age. The article is authored by a team of endocrinologists from Kariadi Hospital in Semarang, led by Nugroho H. Notably, this team has a rich research history spanning several decades, dating back to the 1970s, under the guidance of the esteemed late Professor R Djokomoeljanto, a prominent endocrinologist from Universitas Diponegoro in Semarang. Central Java Province, specifically Magelang Regency, is recognized as one of the areas in Java Island and Indonesia with high endemicity of iodine deficiency disorders (IDD). Numerous studies focusing on public health and nutritional epidemiology of IDD have been carried out in this region.[9] As a matter of fact, Magelang Regency holds a prominent position as the hub for IDD studies in Indonesia.

Nugroho H et al.[10] assessed iodine levels, dietary intake, goitrogenic food consumption, urinary iodine concentration, FT4, TSH, and total goiter rate in women of childbearing age. This study comprehensively examines iodine and thyroid status in a specific population. Senggi Village in Magelang Regency was chosen due to its geographical, climatic, topographical, and land material characteristics, which pose a moderate risk for iodine deficiency. The region's soil is encompassed by the eruption-affected Merapi Mountain, heightening the vulnerability of residents to iodine deficiency disorders. In a prior study conducted in this area, a prevalence of 6% for congenital hypothyroidism was observed.[10]

The study found that women of childbearing age in Senggi had adequate iodine and thyroid status but showed an increased total goiter rate and low urinary iodine concentration. The iodine content in the freshwater source, table salt, and daily dietary intake was also found to be low. The study did not find any associations between iodine status, daily goitrogen intake, and salt iodine concentration. Adequate iodine status and a significant total goiter rate may indicate residual goiter from previous severe endemic iodine deficiency disorders or a higher rate of autoimmune thyroid disease or thyroiditis.[10] This phenomenon can be further studied in the same or other populations.

Nugroho H et al.'s study,[10] along with seven other original papers on anemia in end-stage renal disease, hypovitaminosis D and depression among patients with type 2 diabetes mellitus, mental health status in pulmonary tuberculosis patients, vitamin D levels and handgrip strength in pre-frail older adults, validity and reliability of the Indonesian version of an arrhythmia-specific questionnaire, characteristics of recurrent malaria episodes, and quality of life of patients after kidney transplantation, are featured in our second edition for 2023. This issue presents high-quality studies that provide data and information from our patients and the Indonesian population. We hope this issue will expand our knowledge, strategies, and wisdom for diagnosing, treating, and providing education for our patients in a clinical setting.

In short, IDD represents just a single illustration of the numerous public health and clinical concerns that demand our attention. To effectively address these concerns, gathering data specific to our own population is imperative, enabling the identification of risk factors. This knowledge will empower us to devise and execute appropriate actions. Collaboration among clinicians, researchers, and public health stakeholders is essential to facilitate research, disseminate vital information, establish local guidelines, and shape policies. The collective efforts undertaken in these areas will ultimately shape the future of our nation's health status.

REFERENCES

1. Marks JS. Epidemiology, public health, and public policy. Prev Chronic Dis. 2009;6(4):1-4.
2. GBD 2019 Indonesia Subnational Collaborators. The state of health in Indonesia's provinces, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Glob Health. 2022;10(11):e1632-45.
3. Fauziyah S, Putri SMD, Salma Z, Wardhani HR, Hakim FKN, Sucipto TH, Aquaresta F, Soegijanto S. How should Indonesia consider its neglected tropical diseases in the COVID-19 era? Hopes and challenges (Review). Biomed Rep. 2021;14(6):53.
4. Ernawati F, Syauqy A, Arifin AY, Soekatri MYE, Sandjaja S. Micronutrient deficiencies and stunting were associated with socioeconomic status in

Indonesian children aged 6-59 months. Nutrients. 2021;13(6):1-9.
5. Fitra S, Susanto R, Purwanti A, Utari A. Iodine deficiency profile of Central Java province Indonesia during the year 2011. Int J Pediatr Endocrinol. 2013;2013(Suppl 1):P149.
6. Kusrini I, Farebrother J, Mulyantoro DK. Adequately iodized salt is an important strategy to prevent iodine insufficiency in pregnant women living in Central Java, Indonesia. PLoS One. 2020;15(11):1-13.
7. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol. 2015;3(4):286-95.
8. Hatch-McChesney A, Lieberman HR. Iodine and iodine deficiency: a comprehensive review of a re-emerging issue. Nutrients. 2022;14(17):1-11.
9. Mulyantoro DK, Kusrini I, Hidayat T, Puspitasari C. Assesment of thyroid function and its association with free thyroxin hormone among pregnant women in areas with previous history iodine deficiency in Magelang, Indonesia. J Nutr Sci Vitaminol (Tokyo). 2020;66:S474-8.
10. Nugroho H, Pemayun TDG, Dharmono, Rachmawati B. The iodine status of women of childbearing age in an iodine-repleted area: An epidemiological study in Sengi village on Merapi mountain area. Acta Med Indones – Indones J Intern Med. 2023;55(2):142-9.

The Effect of Anemia and Hypoalbuminemia on Six-Months Hospitalization Risk in End Stage Chronic Kidney Disease Patients Undergoing Hemodialysis: A Retrospective Cohort Study

Octavianus Umboh, Emma Syarifih Moies, Stella Palar*

Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Sam Ratulangi University - Prof. Dr. R. D. Kandou Hospital, Manado, Indonesia.

Corresponding Author:
Octavianus Umboh, MD. Department of Internal Medicine, Faculty of Medicine, Sam Ratulangi University, Prof. Dr. R. D. Kandou Hospital. Jalan Raya Tanawangko, Manado, Indonesia. Email: octavianus.umboh@gmail.com.

ABSTRACT

Background: *Chronic kidney disease (CKD) patients, particularly those who require renal replacement therapy, have a higher risk of hospitalization and mortality compared than the general population. The patients can suffer hypoalbuminemia and anemia due to chronic inflammations, that might affect the risk of hospitalization risk. The aim of this study is to investigate the effect of albumin dan hemoglobin levels on the hospitalization incidence of patients with stage 5 chronic kidney disease who undergo chronic hemodialysis.* ***Methods:*** *This retrospective cohort study enrolled patients aged 18 years and older with end stage kidney disease who underwent regular hemodialysis at the Prof. dr. R. D Kandou Hospital, Manado, Indonesia. Patients with malignancy were excluded. We measured the hemoglobin and albumin baseline level and observed the hospitalization incidence over the next 6 months. We used the Chi Square test with significance level of p-value 0.05, to analyze the association between both anemia and hypoalbuminemia with risk of hospitalization over 6 months of follow up period.* ***Results:*** *We enrolled 202 patients as our participants, most of whom were men (61.8%), with a mean age of 60.21±9.32 years. There were 120 participants (59.4%) being hospitalized during 6-months-follow-up period. The mean level of albumin was 3.29±0.63 g/dl, while the mean hemoglobin level was 9.43±1.75 g/dl. This study found that most of the participants had hypoalbuminemia (62.9%) while 45% had anemia. We found significant associations between hypoalbuminemia and anemia with the risk of hospitalization within 6 months, with p values 0.001 and 0.007, respectively. The relative risk for being hospitalized over 6 months follow up period in patients having anemia was 2.32 (95% CI 1.29-4.17), and for hypoalbuminemia was 2.77 (95% CI 1.54-4.99).* ***Conclusion:*** *Hypoalbuminemia and anemia are associated with increased risk of all causes hospitalization within 6 months in stage 5 chronic kidney disease patients undergoing hemodialysis.*

Keywords**:** *anemia, hypoalbuminemia, chronic kidney disease, hemodialysis, hospitalization.*

INTRODUCTION

Chronic kidney disease (CKD) is defined as an abnormality in the structure or function of the kidneys that occurs over a three-month period. Chronic kidney disease is a progressive disease that affects more than 10% of the world's population.[2] According to the Basic Health Research of the Republic of Indonesia in 2018, the prevalence of CKD among the Indonesian population was 0.38%. This number was higher than the prevalence of CKD in 2013, which was 0.2% nationwide. Chronic kidney disease mostly found in a population between the ages of 65 and 74 years old, and it is more common in

men.[3] Obesity, hypertension, and type 2 diabetes mellitus, are akso risk factors of CKD.[4] The failure of the excretion function of the kidneys leads to an accumulation of uremic particles, which act as oxidants and causes a chronic inflammatory condition.[5]

The classification of CKD can be assessed based on the glomerular filtration rates (GFR) which classify it into five stages. The patients with end stage CKD (stage 5) requires renal replacement therapy (hemodialysis).[1] Hemodialysis is one of the renal replacement therapies methods. It uses a special device to eliminate uremic toxins and regulate the body's electrolyte fluids.[6] According to the data published by the Indonesian Ministry of Health in 2018, only 19.3% of patients with end stage CKD underwent hemodialysis therapy [3]. In fact, if the treatment is not carried out properly, it can increase the risk of complications, for example, anemia. Anemia is caused by a decreased in the level of erythropoietin produced by the kidneys, with is followed by decreased GFR.[7] Some laboratory parameters, including albumin and hemoglobin levels, can be used to evaluate the progression of of CKD, predicting its clinical outcomes, evaluating response to treatment, as well as predicting of the prognosis.[8]

To date, most of the published studies on this topic were conducted in Japanese ,Taiwanese, and Singaporean populations, which may have different profile compared with Indonesian patients in terms of ethnicity, lifestyle, socioeconomic level and health system[9,10] The differences in socioeconomic status level between CKD patients in developed countries compared with those in emerging countries such as Indonesia, may play significant role particularly in nutritional status and dietary intake. Those factors may have effects on hemoglobin and albumin levels. The optimal management of anemia in CKD requires intravenous iron preparation and erythropoietin stimulating agent, which may not always available in all Indonesian hospital, and may thus be unmeet need. Based on those considerations, we want to investigate the effect of albumin dan hemoglobin levels on hospitalization, especially for patients with stage 5 chronic kidney disease undergoing hemodialysis in Indonesia;

Therefore, we aimed to investigate the impact of anemia and hypoalbuminemia on risk of hospitalization over 6 months follow up period in patients with stage 5 chronic kidney disease undergoing hemodialysis. We believe the findings may serve as evidence for the importance of hypoalbuminemia and anemia management to reduce risk of hospitalization over the next 6 months in CKD patients.

METHODS

Study Design and Participants

This is a retrospective cohort study. The study enrolled CKD patients undergoing regular hemodialysis at the Prof. dr. R. D Kandou Hospital, Manado, Indonesia. We screened eligible patients and collected data on their albumin and hemoglobin levels. We enrolled patients aged 18 years or older who underwent regular hemodialysis for at least 3 months with a duration of 8-10 hours per week (divided into two sessions). We excluded patients with malignancy. Patients who met the inclusion criteria and agreed to sign the informed consent form would be asked several questions, including age, sex, education, occupation, and ethnicity. Interviews were conducted by trained interviewers. If the patient did not show up for follow-up or the routine HD schedule, we contacted patient's family member following to find out the reason for the patient's absence, whether the patient had died, been admitted to the hospital, or been converted to CAPD therapy or a kidney transplant. If the patient is admitted to the hospital, the investigator searched the time of admission, as well as the primary and secondary diagnoses. For the next 6 months, we observed the hospitalization incidence as recorded in medical record. (January 1 to June 30, 2021). We did not include hospitalization caused by elective procedure (e.g. hospitalization for arteriovenous fistula operation). Hypoalbuminemia was defined as albumin level lower than 3.5 g/dL. Meanwhile, anemia was defined as hemoglobin level below 10g/dL. We used flowcytometry, method to measure hemoglobin level, and dye bromcresol green to measure the albumin serum level. Both

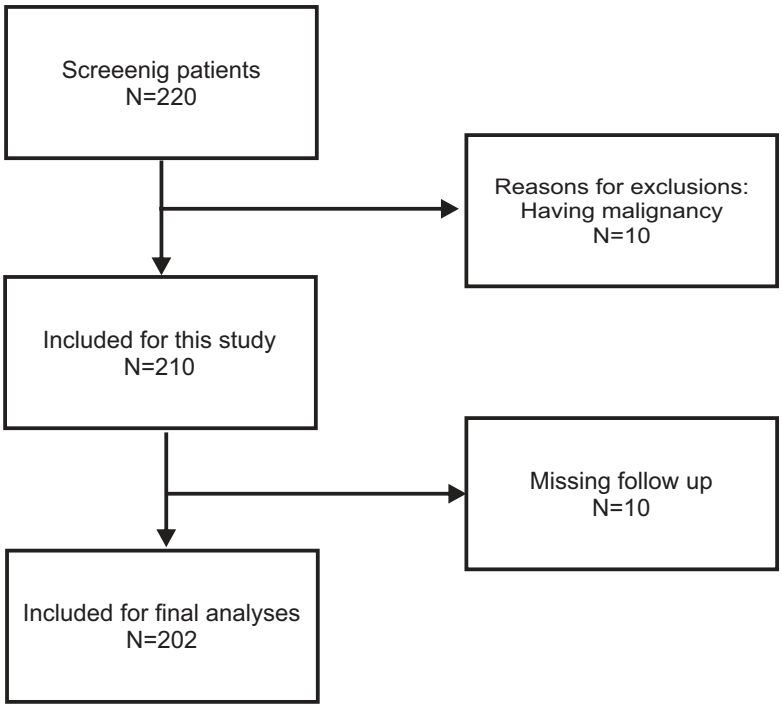


Figure 1. Flowchart of Patients Selection.

tests were carried out in the Clinical Pathology Laboratory of Prof R. D. Kandou Hospital.This study was approved by the Ethics Committee of Prof. Dr. R. D. Kandou Hospital Manado (Reference Number 152/EC/KEPK-KANDOU/IX/2021).

Statistical Analysis

We analyzed the collected data using Statistical Package for Social Sciences (SPSS) program Version 25.0. To determine the association between albumin and hemoglobin levels with hospitalization, we used Chi-square test. If one of the cells had an expected count value less than 5, the *Fisher exact* test was used. The p-value less than 0.05 was considered statistically significant. We also measured the effect size, presented as a relative risk and its corresponding 95% confidence interval.

RESULTS

We enrolled 202 patients with stage 5 CKD who underwent routine hemodialysis. The mean age in this study was 60.2±9.3 years, with 61.8% of total participants were men and 38.2% were women samples. In this study, the mean hemoglobin was 9.43±1.75 g/dl, while the mean albumin was 3.29±0.63 g/dl. Most patients aged 60 years or younger who were hospitalized had hypoalbuminemia and did not have anemia. The **Table 1** presented the baseline characteristics of the study participants.

Table 1. The baseline characteristics of the study participants.

Characteristics	
Men , n (%)	125 (61.8)
Age, mean±SD	60.21±9.32
Age >60 years old, n (%)	96 (47.5)
Hospitalized patients, n (%)	120 (59.4)
Length of hospitalization stay, mean±SD (days)	6.97±18.15
Anemia n(%)	91 (45)
Hypoalbuminemia, n (%)	127 (62.9)
Hemoglobin, mean±SD	9.43±1.75
Albumin, mean±SD	3.29±0.63

There were 120 participants who had been hospitalized within 6 months follow up period. **Table 2** showed the associations as well as the effect sizes between anemia, hypoalbuminemia, and hospitalization in patients with CKD stage 5 on hemodialysis. We found statistically significant association between both anemia and hypoalbuminemia with hospitalization, with p-values 0.007 and 0.001, respectively. The relative risk for being hospitalized over 6 months follow up period in patients having

anemia was 2.32 (95% CI 1.29-4.17), and for hypoalbuminemia was 2.77 (95% CI 1.54-4.99).

Table 2. The associations and effect size measurements between anemia and hypoalbuminemia with 6-months hospitalization in stage 5 CKD patients undergoing hemodialysis.

Variables		Hospitalization		RR (95%CI)*
		Yes	No	
Anemia	Yes	64	27	2.328 (1.299-4.174)
	No	56	55	
Hypo-albuminemia	Yes	87	40	2.768 (1.535-4.994)
	No	33	42	

* Pearson Chi-Square

DISCUSSION

The mean age of the subjects in this study was 60.2 years. Data from the Indonesian Renal Registry shows that CKD occurs most often between the age of 60-70 years old. In addition, CKD patients who undergo hemodialysis are usually aged 45-54 years. This shows that CKD patients undergoing hemodialysis have varied age ranges. This is related to the decline in nephron function, which is physiologically starting at this age (45-54 years). This study found that in CKD patients undergoing hemodialysis, the majority (61.8%) were men. This is congruent with the data from the Indonesian Renal Registry in 2018, showing more male HD patients than female patients. Based on IRR data, out of 30,831 new patients undergoing HD in Indonesia, 17,133 (56%) were men, and the remaining 13,698 (44%) were women. Several factors are associated with increased CKD progression in men compared to women, such as a higher risk of causing diabetic nephropathy, hypertension, hyperglycemia, albuminuria, dyslipidemia, an increased body mass index, lifestyle factors, kidney structure, and sex hormones.[11]

This study's hospitalization incidence was 59.4% in patients undergoing routine HD. Arif et al. revealed that 48,621 patients started hemodialysis, of whom 22,338 (46%) performed routine hemodialysis as inpatients. The length of stay of patients starting hemodialysis was 10 (7-17 days). Hemodialysis was initiated at a median of 3 (2-7 days) after hospital admission, and patients were discharged from the hospital 6 (3-10 days) after the first hemodialysis. Based on a national retrospective cohort in the US, older inpatients can be found to have congestive heart failure and dementia. In addition, they experienced longer hospitalizations during hemodialysis.[12] Medical indications for hospitalization for hemodialysis include patients with congestive heart failure who experience fluid overload or older patients who experience severe consequences of uremia. Li et al investigated the cause of CKD patients who were already on hemodialysis 1-2 years after their hemodialysis initiation. They found that infectious diseases such as pneumonia and urinary tract infection were s the most common indications for admission. Comorbidities also played significant roles in increasing hospitalization risk with cardiovascular diseases being the most significant.[13] Tanmoy et al. analyzed the data of patients on maintenance hemodialysis who were hospitalized in India. They found that the mean length of stay was 10.31±6.07 days, which was longer than our finding. They also found that the most common cause of admission was left ventricular failure (59.18%) and respiratory tract infection (14.29%).[14] We found in our study that anemia increased the risk of hospitalization by 2.3 times ($p = 0.007$). A systematic review by Palaka et al. found that significant association between anemia and hospitalization in CKD stage 5 patients undergoing hemodialysis. They found that hospitalization risk among CKD 5 patients undergoing HD was inversely correlated with hemoglobin level. They found that the hazard ratio of hospitalization in patients on dialysis with Hb 10–12 g/dL was 1.09 (1.07-1.11) and >12 g/dL was 0.91 (0.87–0.96).[15]

Li et al. also found that in their study, the mean hemoglobin level on admission of hospitalized patients with maintenance HD was 7.72±1.82. This finding also showed anemia to be prevalent in CKD patients that were admitted.[13] Anemia is one of the important clinical conditions of dialysis patients. The guideline for treating anemia in Indonesia is to use a limit of 10 g/dL to get supportive therapy. In general, patients with CKD on hemodialysis have Hb levels <10 g/dl, with a percentage of 65.9-100%. This is in accordance with national data, where only 22% of HD patients achieve Hb

≥ 10 g/dl. Meanwhile, the other 78% have Hb < 10 g/dl. Anemia occurs because the kidneys are the main source of erythropoietin. It is one part of the progression of kidney failure. It is independently related to the occurrence of cardiovascular disease in chronic kidney failure. Every decrease in the average hemoglobin of 1 g/dl will increase the risk of heart failure by 25%. More strikingly, the risk of death increases by up to 14%. Signs of anemia appear when GFR falls to 50 ml/minute. The average hemoglobin concentration is 2.3 g/dL. It might be lower in patients with a GFR of 50-25 ml/min compared to those with a GFR >50 ml/min.[16]

In patients with CKD, anemia is an independent predictor of death.[17] In patients with CKD who are not on dialysis, the risk of cardiovascular events, including stroke, is greatly increased when anemia is present.[18] A study in the United States investigated patients with CKD during the predialysis period. The study compared anemic CKD patients who did not use EPO to those who regularly used EPO. The results indicated that the regular use of EPO led to an increase in Hb levels.[19] This is associated with a decrease in hospitalizations, including hospitalizations for CVD. Mortality, morbidity, and CVD were also lower when these EPO-treated patients were eventually on dialysis. In patients already on dialysis, the higher the Hb level, up to 12 g/dL, the lower the patient's mortality and hospitalization rate.[17,20] Correction of anemia with subcutaneous erythropoietin and intravenous iron often results in improved or at least stable renal function. In addition, the patient's quality of life and exercise capacity also improve with anemia correction. In CKD patients, anemia can also play an important role in increasing the risk of death, coronary heart disease, stroke, and developing end-stage kidney disease. Erythropoietin may have direct positive effects on the heart and brain, unrelated to the correction of anemia, by reducing cell apoptosis and increasing neovascularization. Both of which may prevent tissue damage.[21]

We found a significant relationship between albumin and hospitalization in CKD 5 patients who underwent HD by 2.7 times (p = 0.001). Antunes et al. conducted a study to investigate the impact of hypoalbuminemia on the clinical outcome of patients with chronic HD. They observed the patients for 13 months. They found that hypoalbuminemic patients had a significantly higher hospitalization rate and shorter hospitalization free period (p=0.008).[22] Hypoalbuminemia is a poor predictor of worse prognosis for dialysis patients. Many recent studies have shown that serial measurement of serum albumin can even predict chronic inflammation and prognosis well. Based on the results of several studies, it is clear that hypoalbuminemia is associated with mortality in cardio-cerebrovascular and CKD stage 5 patients undergoing hemodialysis. In several studies, the relationship between hypoalbuminemia and cardio-cerebrovascular diseases is a reflection of inflammation-induced malnutrition. The underlying mechanisms behind this are appetite suppression and increased catabolism by inflammatory cytokines. Serum albumin is a potential barrier to free radicals. A decrease in serum albumin levels will lead to a decrease in antioxidant capacity and contribute to the harmful effects of oxidative stress on various tissues, including the arterial walls. These data suggested that hypoalbuminemia can more accurately be viewed as a composite marker reflecting malnutrition and increased acute phase inflammation, given that albumin is also a negative acute phase reactant.[23, 24]

Based on our study, hypoalbuminemia and anemia may play a significant role in increasing the hospitalization risk. However, in this study we did not analyze other hospitalization risk factors as confounding variables, such as the patients' comorbidities. Future studies are also needed to assess the effectivity of hemoglobin and albumin correction in reducing hospitalization incidence among patients with chronic hemodialysis.

CONCLUSION

In conclusion, we found a significant association between anemia and hypoalbuminemiaemia with hospitalization within 6 months of follow up in patients with stage 5 chronic kidney disease who undergo chronic hemodialysis. Optimizing anemia and hypoalbuminemia conditions are required to

reduce the risk of hospitalization over the next 6 months.

ACKNOWLEDGMENTS

We would like to thank the Department of Internal Medicine, Sam Ratulangi University, and Prof. Dr. R. D. Kandou Hospital for supporting this study.

COMPETING INTEREST

The authors declare no conflict of interest.

FUNDING

This research received no external funding.

REFERENCES

1. Kidney Disease Improving Global Outcomes (KDIGO). Clinical practice guideline for the evaluation and management of chronic kidney disease. Journal of The International Society of Nephrology. 2013;3(1):5.
2. Kalantar-Zadeh K, Li PKT. Strategies to prevent kidney disease and its progression. Nat Rev Nephrol. 2020;16(3):129-30.
3. Kemenkes RI. Hasil Riset Kesehatan Dasar Tahun 2018. Kementrian Kesehatan RI. 2018;53(9):1689-99.
4. Nistala R, Savin V. Diabetes, hypertension, and chronic kidney disease progression: role of DPP4. Am J Physiol Renal Physiol. 2017;312(4):F661-70.
5. Ruiz-Ortega M, Rayego-Mateos S, Lamas S, et al. Targeting the progression of chronic kidney disease. Nat Rev Nephrol. 2020;16(5):269-88.
6. Alisa F, Wulandari C. Faktor-faktor yang berhubungan dengan kepatuhan pasien penyakit ginjal kronik (PGK) yang menjalani hemodialisa di RSUP Dr. M. Djamil Padang. Jurnal Kesehatan Mercusuar. 2019;2(2).
7. Watanabe R. Hyperkalemia in chronic kidney disease. Rev Assoc Med Bras. 2020;66:s31-6.
8. Tangri N, Inker LA, Hiebert B, et al. A dynamic predictive model for progression of CKD. Am J Kid Dis. 2017;69(4):514-20.
9. Hounkpatin HO, Fraser SDS, Honney R, et al. Ethnic minority disparities in progression and mortality of pre-dialysis chronic kidney disease: a systematic scoping review. BMC Nephrol. 2020;21(1):1-14.
10. Lim GJ, Liu YL, Low S, et al. Medical costs associated with severity of chronic kidney disease in type 2 diabetes mellitus in Singapore. Ann Acad Med Singap. 2020;49(10):731-41.
11. Major RW, Cheng MRI, Grant RA, et al. Cardiovascular disease risk factors in chronic kidney disease: A systematic review and meta-analysis. PLoS One. 2018;13(3).
12. Arif FM, Sumida K, Molnar MZ, et al. Early mortality associated with inpatient versus outpatient hemodialysis initiation in a large cohort of US veterans with incident end-stage renal disease. Nephron. 2017;137(1):15-22.
13. Li HL, Tai PH, Hwang YT, Lin SW, et al. Causes of hospitalization among end-stage kidney disease cohort before and after hemodialysis. Int J Environ Res Public Health. 2022;19(16):10253.
14. Chattopadhyay T, Banerjee A, Mondal H. Causes of hospitalization in patients on maintenance hemodialysis with arteriovenous fistula 1in a tertiary care hospital in West Bengal, India. Saudi J Kidney Dis Transpl. 2021;32(5):1418-23.
15. Palaka E, Grandy S, van Haalen H, et al. The impact of CKD anaemia on patients: incidence, risk factors, and clinical outcomes-a systematic literature review. Int J Nephrol. 2020;2020:7692376.
16. Levin A. Anemia and left ventricular hypertrophy in chronic kidney disease populations: A review of the current state of knowledge. Kidney Int Suppl. 2002;61(Suppl 80):S35–8.
17. Levin A, Djurdjev O, Duncan J, et al. Haemoglobin at time of referral prior to dialysis predicts survival: an association of haemoglobin with long-term outcomes. Nephrol Dial Transplant. 2006;21(2):370-7.
18. Jurkovitz CT, Abramson JL, Vaccarino LV, et al. Association of high serum creatinine and anemia increases the risk of coronary events: results from the prospective community-based atherosclerosis risk in communities (ARIC) study. J Am Soc Nephrol. 2003;14(11):2919-25.
19. Abramson JL, Jurkovitz CT, Vaccarino V, et al. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC Study. Kidney Int. 2003;64(2):610-5.
20. Vida C, Oliva C, Yuste C, et al. Oxidative stress in patients with advanced CKD and renal replacement therapy: the key role of peripheral blood leukocytes. Antioxidants (Basel). 2021;10(7).
21. Murphy ST, Parfrey PS. The impact of anemia correction on cardiovascular disease in end-stage renal disease. Semin Nephrol. 2000;20(4):350-5.
22. Antunes A, Eugenia C, Campas F, et al. Hypoalbuminemiaemia seems to be associated with a higher rate of hospitalization in hemodialysis patients. J. Bras. Nefrol. 2016;38(1):70-5.
23. Danielski M, Ikizler TA, McMonagle E, et al. Linkage of hypoalbuminemiaemia, inflammation, and oxidative stress in patients receiving maintenance hemodialysis therapy. American Journal of Kidney Diseases. 2003;42(2):286-94.
24. Belinskaia DA, Voronina PA, Shmurak VI, et al. Serum albumin in health and disease: esterase, antioxidant, transporting and signaling properties. Int J Mol Sci. 2021;22(19).

The Iodine Status of Women of Childbearing Age in an Iodine-repleted Area: An Epidemiological Study in Sengi Village on Merapi Mountain Area

Heri Nugroho[1*], Tjokorda Gde Dalem Pemayun[1], Darmono[1], Banundari Rachmawati[2]

[1]Division of Endocrine-Metabolism, Department of Internal Medicine, Faculty of Medicine Diponegoro University - Kariadi General Hospital, Semarang, Indonesia.
[2]Department of Clinical Pathology, Faculty of Medicine Diponegoro University - Kariadi General Hospital, Semarang, Indonesia.

Corresponding Author:
Heri Nugroho, MD., PhD. Division of Endocrine-Metabolism, Department of Internal Medicine, Faculty of Medicine Diponegoro University - Kariadi General Hospital. Jl. Prof Mr. Sunario, Tembalang, Semarang 50275, Indonesia. Email: khris_heri@yahoo.com.

ABSTRACT

Background: *The low iodine content of daily water sources and repeated volcanic eruptions are expected to affect the iodine status and thyroid hormone profile of women of childbearing age in the Magelang regency. This study aimed to determine the iodine and thyroid profile among women of childbearing age.* ***Methods****: We used a cross-sectional descriptive study to learn about 140 women of reproductive age living in Sengi village from October 2017 to January 2018. We assessed the iodine level, dietary intake, and goitrogenic food consumption using food frequency questionnaire (FFQ), urinary iodine concentration (UIC), thyroid stimulating hormone (TSH) and free thyroxine (fT4), and total goiter rate (TGR).* ***Results****: The median UIC was 199.5 (126.0 – 264.0) µg/L. The TGR was 10.7% on palpation and 7.8% on ultrasound. The proportion of UIC levels below 100µg/L was 18.5%. The mean water iodine content was 2.03 ± 4.74 µg/L. The mean salt iodine level was 28.6±13.7ppm. There were only 35% who consumed salt with adequate iodine contents, and only 19.29% consumed >150µg iodine from daily dietary intake based on FFQ. The median TSH and FT4 levels were 1.72 and 1.51mIU/L.* ***Conclusion****: Women of childbearing age in Sengi Village generally had adequate iodine profiles and normal thyroid hormone levels but a considerable proportion of TGR and low UIC. The iodine contents within the freshwater source, table salt, and daily dietary intake were low. There are no significant association between Iodine status, daily goitrogen intake, daily iodine intake and salt iodine concentration*

Keywords*: Iodine profile, Thyroid, Women of childbearing age.*

INTRODUCTION

Iodine deficiency has been one of the major public health problems around the globe.[1,2] In Indonesia, the national Iodine Deficiency Disorders (IDD) survey showed that 8,2% were severely endemic to IDD.[3] In Central Java, the prevalence of iodine deficiency was 24.9%, in which the Magelang Regency accounts for 14.3% of the total cases.[3] The spectrum of IDD may affect any age, and the impacts include miscarriage, stillbirth, increased perinatal morbidity and mortality, goiter, and hypothyroidism.[4] Children, pregnant women, and lactating women are the most vulnerable groups.[4] Undiagnosed IDD among women of childbearing age might increase the risk of developing IDD

and/ or its devastating consequences later during pregnancy and lactating period.[4,5]

The World Health Organization (WHO) and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) have propagated the use of household iodized salt to manage IDD.[6] In 2020, 124 countries or around 88% of the world's population have put in place regulations about mandatory salt iodination.[7] In Indonesia, the widely used household iodized salt is potassium iodate (KIO_3), with a minimum concentration of 30-80 ppm KIO_3.[3] The national household coverage of adequately iodized salt in Indonesia is 55.1%, with higher coverage in the urban population (59.3%) than in the rural counterpart (51.4%).[8]

Geographical conditions, such as climate, topography, and land material, greatly affect the iodine availability in the area.[9] People living in the mountain area usually have a higher risk of developing IDD compared to those who live in the lowland areas.[10] In 2007, the soil in areas surrounding Merapi mountain in Central Java, Indonesia, was reported to possess low iodine content. Sengi Village is one of the villages with moderate danger; a previous study showed that the prevalence of congenital hypothyroidism was 6%, categorizing the area endemic for IDD.[11]

Women of childbearing age are one of the most vulnerable groups to suffer from IDD[4,5]. Studies from several developed and developing countries have shown that in this population, there are still areas that are iodine deficient.[12–15] Considering IDD's irreversible and significant maternofetal, neonatal, and offspring impact, it is essential to assess the iodine status in this population.[16] Therefore, this study aims to assess the iodine profile of women of childbearing age in the Sengi village from 2017 to 2018.

METHODS

We conducted this cross-sectional study in Magelang from October 2017 to January 2018. The population was women aged 18-45 years. The inclusion criteria were women living in the area for a minimum of 1 year who are willing to provide written informed consent to participate in this study. The exclusion criteria were pregnancy, severe sickness, having received iodine supplementation in the past year, or inability to complete the entire study.

The primary outcomes were urine iodine concentration (UIC), iodine concentration within the table salt consumed by the subjects, iodine concentration within the freshwater source for daily use, estimation of daily iodine intake from diet, total goiter rate (TGR), and thyroid hormones concentration including thyroid stimulating hormone (TSH) and free thyroxine (FT_4).

The number of samples needed to estimate the UIC parameter was 140 subjects. All data were compiled, edited, tabulated, then analyzed using descriptive analysis on SPSS. This study protocol was approved by the ethical committee of the Faculty of Medicine Diponegoro University and Kariadi General Hospital (No.676/EC/FK-RSDK/XI/2017).

RESULTS

There were 140 subjects included in this study, of which 97.8% were native residents who had been living there for more than 24 years. The subjects' mean age was 33 years old. The subjects' socioeconomic status was

Table 1. Characteristics of study population.

Variables	N	%	Mean ± SD
Age (years)			33 ± 8
≤ 20	6	4.3	
21-30	54	38.6	
31-40	49	35	
>40	31	22.1	
Subvillage			
Sengi	38	27.1	
Ngampel	24	17.1	
Candi Duwur	24	17.1	
Gowok Pos	19	13.6	
Gowok Sabrang	13	9.3	
Gowok Ringin	11	7.9	
Candi Tengah	6	4.3	
Candi Pos	5	3.6	
Education Level			
Uneducated	1	0.7	
Elementary school	56	40	
Junior high school	48	34.3	
Senior high school	34	24.3	
University	1	0.7	
Occupation			
Farmer	102	72.9	

Housewife	20	14.3	
Blue collar worker	10	7.1	
Merchant	4	2.9	
Teacher	2	1.4	
Private employee	2	1.4	
Monthly income			Rp814.286 ± 657.36
< IDR 500,000 (USD34.90)	34	24.3	
IDR 500,000 (USD34.90 - IDR 1,000,000 (USD69.81)	87	62.1	
IDR 1,000,001 (USD34.90) – IDR 2,000,000 (USD139.62)	15	10.7	
> IDR 2,000,000 (USD139.62)	4	2.9	
Duration of stay			24 ± 13
< 5 years	10	7.1	
5-10 years	25	17.9	
>10 years	105	75	

mainly lower to middle income, with an average monthly income of IDR 814,000 (USD 56.91). The baseline characteristics of the study subjects are presented in **Table 1**.

The mean Body Mass Index (BMI) is 23.67±4.82 kg/m^2. Most subjects (89.3%) did not have enlarged thyroid glands. From the thyroid ultrasound examination, the mean thyroid volume was 12.22±13.43 cc. The TGR at Sengi Village was 7.8%. Among 140 subjects, 37 (25.7%) had thyroid nodule(s). The median UIC was 199.5 µg/L. The complete data are presented in **Table 2**.

The mean KIO_3 concentration within the household salt consumed by the subjects was 28.6±13.7 ppm. Eighty-nine (63,6%) salt samples had lower KIO_3 concentration than the recommended level, and two samples (1.4%) had higher KIO_3 concentration than the recommended level. Based on the salt type, the salt block is the most common salt used (78.6%), followed by regular grains table salt (21.4%). The freshwater iodine content based on the altitude of the water source is illustrated in **Figure 1**.

Daily dietary iodine intake among the subjects was categorized as inadequate in 80.17% of subjects. The iodine profile of the freshwater source, table salt consumption, and daily iodine intake from the diet can be seen in **Table 3**. The most commonly consumed iodine-rich source was eggs (60.7%). They consumed eggs more than three times a week. The most common goitrogenic food consumed by the respondents was cabbage (37.1%). They ate it more than thrice a week. The respondents' dietary patterns are described in **Table 4**.

The median TSH and FT4 levels were 1.72 mIU/L and 1.51 mIU/L. As many as 135 subjects (97.0%) had normal TSH levels, while three subjects (2.0%) had high TSH levels, and two subjects (1.0%) had low TSH levels. All subjects had normal FT4 levels. Almost all (96,5%) of the subjects were euthyroid. The remaining three (2,1%) subjects had subclinical hypothyroidism, and two (1,4%) subjects had subclinical hyperthyroidism.

UIC is the gold standard to define iodine deficiency for a population in a region[17]. WHO

Table 2. The total goiter rate and urine iodine concentration among childbearing-age women in Sengi village.

Variables	N	%
Thyroid gland grade by palpation		
No palpable or visible goiter	125	89.29
Palpable goiter	9	6.43
Visible goiter	6	4.29
Thyroid gland volume by ultrasound examination		
≤18.6 cc	129	92.2
>18.6 cc	11	7.8
UIC (µg/L)		
<20 (severe iodine deficiency)	1	0.7
20-49 (moderate iodine deficiency)	10	7.1
50-99 (mild iodine deficiency)	15	10.7
100-199 (adequate iodine intake)	45	32.1
200-299 (excessive iodine intake)	53	37.9
>300 (iodine-induced hyperthyroidism. thyroid autoimmune)	16	11.4

Table 3. Iodine profile and daily iodine and goitrogenic intake of childbearing women in Sengi village.

Variable	Value
Urinary iodine concentration (mcg/L)	199.5 (126.0 – 264.0[a]
Thyroid volume (cc)	9.1 (3.5-128.3)[b]
Iodine concentration in salt (ppm)	26.5 (5.3-100.5)[b]
Daily salt consumption (gr)	2.5 (0.5-13.3)[b]
Daily iodine intake from salt (mcg/L)	74.0 (74.0-394.6)[b]
Daily iodine intake from food (mcg/L)	12.8 (0.0-100.1)[b]
Daily total iodine intake (mcgg)	91.7 (14.3-456.8)[b]
Daily goitrogen intake (mg)	1.1 (0.0-8.3)[b]

Note: [a]Median (interquartile range), [b]Median (minimum - maximum

Table 4. Dietary pattern of iodine-rich and goitrogenic foods of childbearing-age women in Sengi village in the last 1 month.

Type of Food	Frequency					
	≥ 3 times/ week		< 3 times/ week		Never	
	n	%	n	%	n	%
Iodine-rich foods						
Pindang	7	5	105	75	28	20
Salted fish	5	3.6	83	59.3	52	37.1
Saltwater fish	2	1.4	39	27.9	99	70.7
Shrimp	0	0	4	2.2	136	97.1
Oyster	0	0	1	0.7	139	99.3
Egg	85	60.7	48	34.3	7	5
Milk	20	14.3	19	13.6	101	72.1
Beef liver	0	0	3	2.1	137	97.9
Spinach	24	17.1	64	45.7	52	37.1
Jelly	8	5.7	88	62.9	44	31.4
Goitrogenic foods						
Cassava	30	21.4	99	70.7	11	7.9
Sweet potato	29	20.7	91	65	20	14.3
Mustard greens	52	37.1	70	50	18	12.9
Cabbage	23	16.4	71	50.7	46	32.9
Cassava leaf	21	15	79	56.4	40	28.6

cut-off for IDD in the adult population is when the median UIC of the population is less than 100 mcg/L, and >50% of the population has UIC of less than 100 µg/L or <20% of the population has UIC of less than 50 mcg/L. Among the women of childbearing age in Sengi village, the median UIC was 199.5, with 81.4% of subjects having a UIC value of > 100 mcg/L. Therefore, considering the UIC parameter, the women of childbearing age in Sengi village had adequate iodine status. As many as 10% of subjects had UIC levels of 50.1 - 99,9 mcg/L, and 8.8% of other subjects had UIC levels of <50 mcg/L. Based on palpation and thyroid ultrasound, the IDD prevalence from the TGR parameter was 10.7% and 7.8%. Goiter prevalence in this study was 7.8% by thyroid ultrasound examination. No evaluation of either de novo/residual goiter or thyroiditis goiter was performed in this study; hence the TGR value of this study may not truly represent the IDD problem in the region. Therefore, based on the UIC parameter, women of childbearing age in Sengi village were still considered to possess adequate iodine levels.

Table 5 demonstrates the relationship between iodine intake from the daily consumed table salt and the UIC. This study showed that those with normal UIC mostly consumed salt with >40 ppm of KIO_3. As many as 88.9% of subjects with normal UIC consumed salt with 10-40 ppm of KIO_3, and 8.9% consumed salt with >40 ppm of KIO_3.

The study shows that despite the difference in iodine status based on IUC levels, there are no

Table 5. The distribution of salt iodine concentration consumed by childbearing-age women in sengi village based on their urine iodine concentration level.

Urine Iodine Concentration (µg/L)	Salt Iodine Concentration					
	<10 ppm	10-20 ppm	20.1-30 ppm	30.1-40 ppm	>40 ppm	N
<100	0	26.9	50	11.5	11.5	26
100-199	2.2	22.2	46.7	20	8.9	45
>199	2.9	18.8	31.9	23.2	23.2	69

Table 6. Association between iodine status, daily goitrogen intake, daily iodine intake and salt iodine concentration.

Iodine Status	Daily Goitrogen intake[a] (mg)	p-value	Daily Iodine Intake[a] (µg)	p-value	Salt Iodine Concentration[a] (ppm)	p-value
Deficient	1.09 (0.01-7.95)		87.46 (22.85-276.80)		23.25 (10.6-47.6)	
Adequate	1.05 (0.08-8.11)		86.93 (143-253.93)		26.5 (5.3-63.5)	
Excessive	1.09 (0-8.33)	0.981[b]	93.50 (16.60-456.77)	0.499[b]	28.6 (7.4-106.5	0.109[b]

Note: [a]Median (minimum - maximum), [b]Kruskal-Wallis test

significant association between daily goitrogen intake, daily iodine intake and salt iodine concentration (**Table 6**).

DISCUSSION

The TGR based on the USG examination was 8.6%. It declined significantly from 20% in 2015. Using the WHO epidemiological criteria, Dukun Subdistrict had been categorized as moderately endemic for IDD in 2015 and became mildly deficient of iodine in 2017-2018.[18] The median UIC among women of reproductive age in Indonesia was 189.0 mcg/L in 2013. In Central Java, the value was higher; 240 mcg/L. The higher provincial median UIC was possibly due to several coastal regions where daily water sources contain a much higher level of iodine; hence higher UICs.[18]

Another large-scale survey involving 106,825 pregnant women in Central Java in 2011 showed that the median UIC was 156 mcg/L, and the percentage of pregnant women with UIC lower than 100 mcg/L was 33.87%. There were four districts with mild iodine deficiency found in the study mentioned above. That study further assessed that 18 neonates (0.03%) were suspected of having cretinism, and 174 (0.18%) had TGR degrees of 1 – 2.[17]

Kusrini's study showed that the mean UIC reached 221±88 mcg/L among pregnant women in Magelang. But in the general population in Magelang, it was 244 ± 92 mcg/L.[15] This marked difference was caused by the difference in urine samples used. Kusrini's study measured both spot urine and three days 24-hour urine samples for the mean UIC measurement. In our study, only spot urine samples were used. WHO stated that spot urine is already a reliable representation of an individual's iodine status.[19] Therefore, it is conclusive that the iodine status of both women of reproductive age and pregnant women of Magelang regency, including Sengi village is adequate.

The iodine status of this study was determined by UIC instead of TGR. Total goiter rate (TGR) was a reliable predictor of moderate-to-severe iodine insufficiency when endemic goiter caused by iodine shortage was common. A significant drawback of the usage of TGR is that goiter resolution takes a long time to occur after iodine intake improves. In adults, TGR may represent past IDDs rather than current ones. A change in the TGR may not correctly reflect the possible contribution of IDDs to a decline in intelligence quotient (IQ) and cognitive impairment[20]. The WHO goiter rate criteria were meant to be applied to school-age children[18] . There were other causes that contributes to TGR, such as residual goiters or goiters due to autoimmune thyroiditis. Thus, the TGR data had to be interpreted carefully.

The median TSH and FT_4 levels were within the normal range (median TSH 1.72 mIU/L and median FT_4 1.51 mIU/L), and almost all subjects in this study were categorized as euthyroid (96.5%). Kusrini's study showed an increasing trend of median TSH along with an increase in gestational age. The median TSH level for all subjects from the rural area was 1.30 mIU/L. The median FT_4 level in that study was 1.27 mIU/L among all the subjects.[15] This difference might be caused by the increased maternal thyroid hormone production during pregnancy; hence there were higher subclinical hyperthyroidism cases in that study. Another cohort study reported that lower TSH and greater FT_3 and FT_4 concentrations were linked to lower iodine availability throughout pregnancy and postpartum. The thyroid function improves after iodine supplementation before pregnancy and throughout pregnancy[21].

WHO recommended the minimum daily iodine intake for non-pregnant women of reproductive age to be 150 µg. Iodine can be obtained from salt, foods, and drinks. The mean iodine intake in this study was lower than the recommendation (108.4 mcg/day).[1] The women of childbearing age in this study are at risk of developing IDD. The average iodine concentration of household table salt in all studied samples was 28.6±13.7 ppm, and only 35% of the subjects consumed salt with adequate iodine content. It was significantly lower than Kusrini's study, in which the mean salt iodine content across both areas (rural and urban) was 40.5±20.6 ppm.[22]

There were seven salt brands used by the subjects; each brand displays its iodine content, except for one brand. Each brand stated that the iodine content was within the recommended range (30-80 ppm). This suggested a possible reduction of iodine content in salt during packaging, storing, and/or transportation. The WHO reported that the iodine content in salt is reduced by 50% by the time it reaches consumers due to poor iodine quality, mishandling during packaging, poor storage conditions (high humidity and temperature), and long storage time[6]. Iodized salt is best stored in closed storage to keep the salt dry.[1,6]

The mean salt consumption among respondents was only 3.3 g/day, much lower than the WHO recommendation.[1,6] It might be caused by the food cooking method. The people of Sengi Village usually cook once daily in the morning, and the food will be eaten throughout the day. The food was cooked long before consumption, leading to several episodes of reheating before consumption, lowering the iodine content. Moreover, some participants were cautious of salt usage due to the risk of developing hypertension from consuming too much salt. Other than salt, iodine also can be obtained from food. From the Food Frequency Questionnaire (FFQ), the documented mean iodine consumption was 16.1 µg/ day. Egg was the most frequent iodine-rich food consumed by the respondents because it is affordable and readily available at all times. Saltwater fish, shrimp, and oysters are also rich in iodine, but the respondents rarely consumed them due to their high price and low availability. Almost all respondents did not consume shrimp and oysters during the one-month observation.

Based on the FFQ, the most frequent goitrogenic foods consumed by the respondents were cassava, sweet potato, mustard green, cabbage, and cassava leaf. In this study, the mean cyanide intake among respondents was 1.9 mg/ day, significantly lower than the 10 mg/ day limit set by the FAO/WHO. This goitrogenic food often contains cyanide derivates (thiocyanate and isothiocyanate) that inhibit thyroid hormone synthesis.[19] Exceeding the daily cyanide intake limit might cause health complications, such as acute intoxication, chronic toxicity, neurological disorders, growth retardation, and goiter.[23] Although cassava and sweet potato, which contain a high level of cyanide, are frequently consumed in the sample population, the cyanide intakes of the respondents are within the standard limit. The processing method might also modify the cyanide content in goitrogenic foods. Steaming and boiling cassavas, the most common processing method in Sengi Village were known ways to reduce the cyanide content.[24] Therefore, this might lower the actual cyanide consumption among respondents than predicted.

No significant associations were observed between iodine status, as determined by IUC levels, and daily iodine intake, daily goitrogen intake, and salt iodine concentration in our research. These findings imply that additional factors likely play a role in influencing iodine status within this specific region. The average iodine concentration in the water of Sengi Village was measured at 2.03 mcg/L. Nearly all participants (98.6%) consumed water with insufficient iodine content, indicating a potential heightened risk for inadequate iodine intake and the subsequent development of ID) among residents in the area.The mean water iodine concentration in Sengi Village was 2.03 mcg/L. Almost all respondents (98.6%) consumed water with poor iodine content. Hypothetically, respondents had a high chance of not getting enough iodine and eventually acquiring IDD.

There are several limitations of this study. This study did not employ three days of 24-hour

urine collection for a more precise measurement of UIC. No further laboratory examination, including thyroid peroxidase (anti-TPO), was conducted for possible autoimmune causes in the presence of goiter for any subjects examined. The non-randomized sampling method employed in this study might lead to a selection bias.

CONCLUSION

In summary, women of childbearing age living in the Sengi Village possess adequate iodine status and normal thyroid hormones. Nevertheless, the iodine content within the freshwater sources, the household table salt, and daily dietary iodine intake were still deficient. Accordingly, strenuous public health intervention is required to overcome and supervise the low iodine concentration of the daily consumed salt and low dietary iodine intake.[25] The lack of association between dietary iodine intake, goitrogen intake, iodine salt concentration and iodine status may suggest that other factors such as water iodine content may play a significant role. Despite adequate iodine status in the population, there is a substantial TGR, which may indicates residual goiter from previous severe endemic IDD, or the presence of autoimmune thyroiditis. Further evaluations are needed for the exact cause of high TGR.

Continuous monitoring and public health intervention to optimize iodine intake from household salt and daily dietary intake are essential for eradicating IDD in Sengi village and Magelang regency, especially for women of reproductive age.[25] Further studies are required to re-evaluate the potential cause of high TGR in this area. The implementation of universal hypothyroid newborn screening in several urban areas in Indonesia must be extended to areas previously or currently endemic for IDD to detect, treat and prevent further disabilities.

ACKNOWLEDGMENTS

The authors are thankful for the technical support provided by Farida from GAKY Laboratory. The authors acknowledge Kevin Gracia Pratama, who provided support in editing, formatting, and translating the manuscript.

REFERENCES

1. World Health Organisation. VMNIS | Vitamin and Mineral Nutrition Information System Goitre as a determinant of the prevalence and severity of iodine deficiency disorders in populations Background. 2014;
2. Biban BG, Lichiardopol C. Iodine deficiency, still a global problem? Curr Health Sci J [Internet]. 2017 [cited 2023 Jan 20];43(2):103. Available from: /pmc/articles/PMC6284174/
3. Badan Penelitian dan Pengembangan Kesehatan Kementrian Kesehatan RI. Riset Kesehatan Dasar 2013 [Internet]. 2013 [cited 2023 Jan 20]. Available from: http://labdata.litbang.kemkes.go.id/images/download/laporan/RKD/2013/Laporan_riskesdas_2013_final.pdf
4. Eastman CJ, Zimmermann MB. The iodine deficiency disorders. 2018 Feb 6 [cited 2023 Jan 20]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK285556/
5. Niwattisaiwong S, Burman KD, Li-Ng M. Iodine deficiency: Clinical implications. Cleve Clin J Med [Internet]. 2017 Mar 1 [cited 2023 Jan 20];84(3):236–44. Available from: https://www.ccjm.org/content/84/3/236
6. World Health Organization. Salt reduction and iodine fortification strategies in public health: report of a joint technical meeting convened by the World Health Organization and The George Institute for Global Health in collaboration with the International Council for the Control of Iodine Deficiency Disorders Global Network. 2014 [cited 2023 Jan 20]; Available from: www.who.int
7. Zimmermann MB, Andersson M. GLOBAL ENDOCRINOLOGY: Global perspectives in endocrinology: coverage of iodized salt programs and iodine status in 2020. Eur J Endocrinol [Internet]. 2021 Jul 1 [cited 2023 Jan 26];185(1):R13–21. Available from: https://academic.oup.com/ejendo/article/185/1/R13/6654349
8. Knowles JM, Garrett GS, Gorstein J, et al. Household coverage with adequately iodized salt varies greatly between countries and by residence type and socioeconomic status within countries: Results from 10 national coverage surveys. J Nutr [Internet]. 2017 May 1 [cited 2023 Jan 26];147(5):1004S-1014S. Available from: https://academic.oup.com/jn/article/147/5/1004S/4669673
9. Giulia S, Lea BF, Carol ZC, Lisa M, Harper SL, Elizabeth CJ. The effect of climatic factors on nutrients in foods: evidence from a systematic map. Environmental Research Letters [Internet]. 2020 Nov 26 [cited 2023 Jan 20];15(11):113002. Available from: https://iopscience.iop.org/article/10.1088/1748-9326/abafd4
10. Haap M, Roth HJ, Huber T, Dittmann H, Wahl R. Urinary iodine: comparison of a simple method for its determination in microplates with measurement by inductively-coupled plasma mass spectrometry. Sci Rep [Internet]. 2017 Jan 3 [cited 2023 Jan 20];7.

Available from: /pmc/articles/PMC5206638/
11. Djokomoeljanto R. Gangguan akibat kekurangan yodium (GAKI) dan kelebihan yodium (EKSES). Semarang: Badan Penerbit Universitas Diponegoro; 2007. p. 377–424.
12. Azzeh F, Refaat B. Iodine adequacy in reproductive age and pregnant women living in the Western region of Saudi Arabia. BMC Pregnancy Childbirth [Internet]. 2020 Jun 22 [cited 2023 Jan 26];20(1):1–12. Available from: https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-020-03057-w
13. Burns K, Yap C, Mina A, Gunton JE. Iodine deficiency in women of childbearing age: not bread alone? Asia Pac J Clin Nutr [Internet]. 2018 Jul 1 [cited 2023 Jan 26];27(4):853–9. Available from: https://pubmed.ncbi.nlm.nih.gov/30045431/
14. Lucchetta RC, Rodriguez Gini AL, de Andrade Cavicchioli S, et al. Iodine deficiency in women of childbearing age in Brazil: systematic review and meta-analysis. Vitae [Internet]. 2021 May 18 [cited 2023 Jan 26];28(2). Available from: http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0121-40042021000200006&lng=en&nrm=iso&tlng=en
15. Panth P, Guerin G, DiMarco NM. A review of iodine status of women of reproductive age in the USA. Biol Trace Elem Res [Internet]. 2019 Mar 15 [cited 2023 Jan 26];188(1):208–20. Available from: https://link.springer.com/article/10.1007/s12011-018-1606-5
16. Toloza FJK, Motahari H, Maraka S. Consequences of severe iodine deficiency in pregnancy: evidence in humans. Front Endocrinol (Lausanne). 2020;11:409.
17. Hussain H, Selamat R, Kuay LK, et al. Urinary iodine: biomarker for population iodine nutrition. Biochemical Testing - Clinical Correlation and Diagnosis [Internet]. 2019 Apr 17 [cited 2023 Jan 20]; Available from: https://www.intechopen.com/state.item.id
18. World Health Organization. Goitre as a determinant of the prevalence and severity of iodine deficiency disorders in populations [Internet]. 2014 [cited 2023 Jan 20]. Available from: https://apps.who.int/iris/handle/10665/133706
19. World Health Organization. Urinary iodine concentrations for determining iodine status in populations [Internet]. 2013 [cited 2023 Jan 20]. Available from: https://apps.who.int/iris/handle/10665/85972
20. Gorstein JL, Bagriansky J, Pearce EN, Kupka R, Zimmermann MB. Estimating the health and economic benefits of universal salt iodization programs to correct iodine deficiency disorders. Thyroid [Internet]. 2020 Dec 1 [cited 2023 Jan 26];30(12):1802. Available from: /pmc/articles/PMC7757618/
21. Næss S, Markhus MW, Strand TA, et al. Iodine nutrition and iodine supplement initiation in association with thyroid function in mildly-to-moderately iodine-deficient pregnant and postpartum women. J Nutr [Internet]. 2021 Oct 1 [cited 2023 Jan 26];151(10):3187–96. Available from: https://academic.oup.com/jn/article/151/10/3187/6320055
22. Kusrini I, Farebrother J, Mulyantoro DK. Adequately iodized salt is an important strategy to prevent iodine insufficiency in pregnant women living in Central Java, Indonesia. PLoS One [Internet]. 2020 Nov 1 [cited 2023 Jan 20];15(11):e0242575. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0242575
23. Nyirenda KK, Nyirenda KK. Toxicity potential of cyanogenic glycosides in edible plants. Med Toxicol [Internet]. 2020 Mar 20 [cited 2023 Jan 20]; Available from: https://www.intechopen.com/state.item.id
24. Zhong Y, Xu T, Wu X, et al. Dietary exposure and risk assessment of cyanide via cassava consumption in Chinese population. Food Chem. 2021;354:129405.
25. Hatch-McChesney A, Lieberman HR. Iodine and iodine deficiency: a comprehensive review of a re-emerging issue. Nutrients 2022;14:3474 [Internet]. 2022 Aug 24 [cited 2023 Jan 26];14(17):3474. Available from: https://www.mdpi.com/2072-6643/14/17/3474/htm

Prevalence and Factors Related to Hypovitaminosis D in Type 2 Diabetes Mellitus Patients with Depression

Rudi Putranto[1,2*], Siti Setiati[2], Martina W. Nasrun[3], Fiastuti Witjaksono[4], Suzanna Immanuel[5], Imam Subekti[2], Kuntjoro Harimurti[2], Agus Siswanto[6], Hamzah Shatri[2], Suhendro Suwarto[2]

[1]Doctoral Program in Medical Sciences, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.
[2]Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3]Department of Psychiatry, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[4]Department of Clinical Nutrition, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[5]Department of Clinical Pathology, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[6]Department of Internal Medicine, Faculty of Medicine Universitas Gadjah Mada – Sardjito Hospital, Yogyakarta, Indonesia.

Corresponding Author :
Rudi Putranto, MD, MPH. Department of Internal Medicine, Faculty of Medicine Universitas Indonesia. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: putranto.rudi09@gmail.com.

ABSTRACT

Background: *The prevalence of hypovitaminosis D (hypoD) in patients with type 2 diabetes mellitus (T2DM) and depression has not been documented. In addition, the risk factors are unknown. This study aimed to identify the prevalence of and risk factors for hypoD in patients with T2DM who also have depression.* ***Methods:*** *118 patients with T2DM who visited the outpatient endocrinology clinics at Cipto Mangunkusumo National Hospital between December 2019-September 2022 provided the clinical and demographic data for this cross- sectional study, including body mass index, blood pressure, glycosylated haemoglobin (HbA1c), lipid profiles, therapy, gender, age, marital status, and educational background. We used The Beck Depression Inventory II (BDI-II) to evaluate depression. We used enzyme-linked immunosorbent assay kit to assess the dependent variable: serum vitamin D. We characterized serum vitamin D levels into three groups (normal, 30 ng/mL; insufficient, 20-29 ng/mL; deficient, 20 ng/mL). We also used analyses of variance to examine the anthropometric, clinical, and biochemical factors between the three groups.* ***Results:*** *118 subjects with T2DM. Their median age was 56 years old (48, 75-60 years old), with a BDI-II score of 17 (15-19), and a serum concentration of vitamin D. The D level was 18.3 ng/mL (9.17–29.46 ng/mL). Only 21.8% of patients with T2DM and depression had sufficient levels of vitamin D. We used multivariable analysis of variance model to examine the associations between age, BDI-II score, HbA1c, and systolic and diastolic blood pressure with vitamin D level. Age and BDI-II score both had a statistically significant effect on vitamin D levels.* ***Conclusion:*** *This cross-sectional study discovered that patients with T2DM and depression had a high prevalence (77.7%) of hypoD. Age and BDI-II score both affected differences in vitamin D levels with statistical significance.*

Keywords: *hypovitaminosis D, type 2 diabetes mellitus, depression.*

INTRODUCTION

As a global public health issue, hypovitaminosis D (hypoD) affects people of all ages.[1] Some findings suggest that vitamin D has a significant role in the health of the brain, nervous system, and depression, in addition to its effects on calcium metabolism, bone, proliferation, differentiation, and immunological modulation.[2] Vitamin D deficiency was associated with an 8-14% increase in the prevalence of depression.[3] According to cross-sectional studies,[4,5] serum 25-hydroxyvitamin D or 25(OH)D concentrations and depressive symptoms have an inverse relationship. Vitamin D regulates serotonin levels and vitamin D deficiency causes lower amounts of serotonin.[6] Low serotonin levels may contribute to the development of clinical depression.[7]

Strong evidence has emerged recently linking hypoD to the development of insulin resistance and abnormalities in insulin secretion potentially interfering with type 2 diabetes mellitus (DM).[8] Patients with diabetes and prediabetes were found to have lower serum levels of 25(OH)D than people with normal glucose tolerance.[9,10] Low serum 25(OH)D levels have been associated with an increased risk of metabolic syndrome and type 2 diabetes in epidemiologic research, which may be partially explained by a rise in fat mass.[11] Long-term complications of diabetes include micro- and macrovascular disease. According to a recent systematic review and meta-analysis, depression is connected to an increased risk of incident macro- and microvascular issues, and diabetic complications are linked to an increased chance of developing depression in the future.[12]

A change in vitamin D homeostasis may contribute to the emergence of type 2 diabetes and hypoD is directly related to depression.[13,14] Many studies have examined the effect of abnormal vitamin D levels and depression[5,7,11,14,15] and the effect of hypoD in DM.[8,10,11,16,17] However, the prevalence of hypoD in patients with type 2 DM and depression, and its contributing variables are still poorly understood.

Until now, no study has looked at factors related to hypoD in patients with type 2 DM and depression. The goal of this study was to determine the prevalence of vitamin D insufficiency and deficiency in patients with type 2 DM and depression. We also investigated the factors linked to low vitamin D plasma levels. Our hypotheses for age, gender, BDI-II score, body mass index (BMI), glycosylated haemoglobin (HbA1c), systolic blood pressure (SBP), diastolic blood pressure (DBP), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG) were related to low vitamin D levels in patients with type 2 DM and depression.

METHODS

Study Design and Setting

This cross-sectional study used a convenience sampling technique to obtain data from patients in outpatient endocrinology clinics at the Cipto Mangunkusumo National Hospital, Jakarta, from December 2019–September 2022. Patients with type 2 DM aged over 18 years were included in the study cohort. Individuals with pre-existing diseases affecting vitamin D and/or calcium metabolism, such as liver or kidney disease, psychosis, skin disease, or use of high- dose steroids or immunomodulators, were excluded. However, women who were nursing or pregnant were not excluded. The cohort included only participants who provided their signed informed consent. The sample size was calculated using the finding that the prevalence rate of depressive symptoms in patients with type 2 DM in Jogjakarta, Indonesia, was 37.9%. The level of significance was set at 0.05, the allowable error was set at 10%, the invalid questionnaire rate was set at 10%, and the minimum number of samples was 91.

All study procedures and protocols were approved by the institutional ethical review board at Universitas Indonesia Ethics Committee (LB.02.01/2.6.1/0452/2022). Written informed consent was obtained from all participants.

Data Collection Procedure

Patients with type 2 DM were identified using World Health Organisation/American Diabetes Association criteria.[18] Their anthropometric parameters were measured according to standard protocols and their BMI was calculated. HbA1c percentages were measured in whole blood using the immunoturbidometric method.

Serum vitamin D levels were measured using an ELISA kit and categorized into three groups (i.e. normal, 30 ng/mL; insufficient, 20-29 ng/mL; deficient, 20 ng/mL).[19] SBP and DBP were measured using a standard sphygmomanometer while the patients were sitting. LDL, HDL, and triglyceride (TG) levels were determined with an autoanalyzer. Depression was evaluated using the Beck Depression Inventory II (BDI-II). Each item on the scale is scored on a 4-point (0-3) Likert scale, and the total result for the BDI-II is the sum of all 21 items. The BDI-II was analyzed using the following algorithm: depression ranges from mild (score, 14-19), moderate (20-28), to serious (29-63).[20]

Statistical Analysis

The Kolmogorov–Smirnov test was performed to determine the normality of the parameters. Descriptive statistics were used to provide a summary of the demographic characteristics. The arithmetic mean and standard deviation (SD) were used for continuous variables and the count and percentage for categorical variables. We used univariate analyses to compare anthropometric, clinical, and biochemical variables between the two groups (independent *t*-test for quantitative data and chi-square test for categorical data). For the BDI-II score, BMI, HbA1c, SBP, DBP, LDL, HDL, and TG vales were categorized into three groups (i.e. sufficient vitamin D, vitamin D insufficiency, and vitamin D deficiency) using an analysis of variance (ANOVA) test. A p-value of < 0.05 was considered statistically significant in all analyses. To find a potential set of variables that will go into the multivariable (linear regression) model, we used the statistical methodology for variable selection using $p < 0.25$ in the univariable (bivariate) analysis as a threshold.

RESULTS

From December 2019 to September 2022, we performed screening of 170 patients with type2 DM to obtain 118 patients with type 2 DM and depression. We then checked their vitamin D levels (**Figure 1**).

The patients' characteristics are indicated in **Table 1**. The median age was 56 years (48, 75-60 years) with a median BDI-II score of 17 (15-19), while the mean serum 25(OH)D level was 18.3 ng/mL (9.17-29.46 ng/mL).

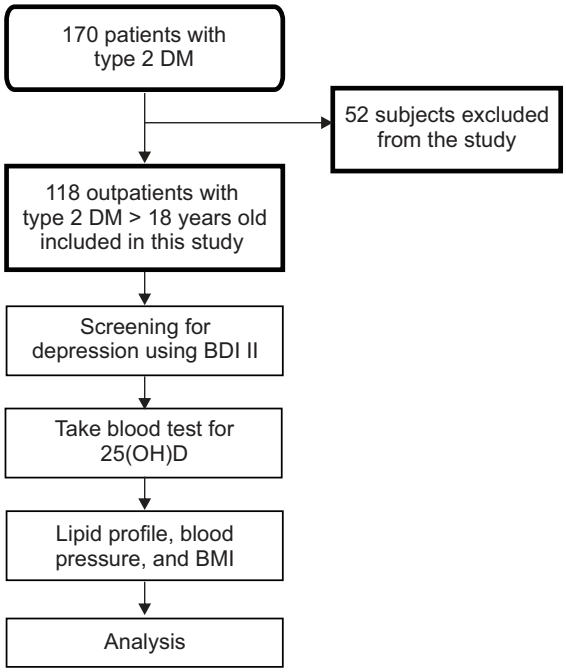


Figure 1. Study recruitment and sampling diagram.

Table 1. Subject characteristics.

Variables	(n = 118)
Age (years), median (IQR)	56 (48.75-60)
Gender, n (%):	
Male	33 (28)
Female	85 (72)
Educational level, N (%)	
Uneducated	2 (1.7)
Primary school	7 (5.9)
Junior high school	10 (8.5)
Senior high school	64 (64.2)
University/college	35 (29.7)
Marital status, n (%)	
Married	94 (79.7)
Unmarried	8 (6.8)
Divorced	16 (13.6)
Religion, n (%)	
Muslim	80 (67.8)
Catholic	4 (3.4)
Christian	32 (27.1)
Buddhist	2 (1.7)
Treatment, n (%)	
Oral antidiabetic drugs (OAD) only	55 (46.6)

Insulin only	14 (11.9)
Combination (OAD + Insulin)	49 (41.5)
Duration of type 2 diabetes mellitus	
< 5 years	77 (65.3%)
> 5 years	41 (34.7%)
With other comorbidities	
Hypertension	59 (50%)
Coronary artery disease	17 (14.4%)
Chronic kidney disease	30 (25.4%)
Stroke ischaemic	7 (5.9%)
Dyslipidemia	78 (66.1%)
Diabetic retinopathy	7 (5.9%)
Diabetic neuropathy	30 (25.4%)
Diabetic ulcer	6 (5.1%)
BDI-II score, median (IQR)	17 (15-19)
BMI (kg/m2), median (IQR)	25.6 (23.4-28.93)
Serum 25(OH)D (ng/mL), mean (SD)	18.3 (9.17-29.46)
HbA1c (%), median (IQR)	7.7 (6,7-9.27)
SBP (mmHg), median (IQR)	135 (117-144.25)
DBP (mmHg), mean (SD)	74.19 (10.32)
LDL-cholesterol, median (IQR)	115.5 (96-138)
HDL-cholesterol, median (IQR)	47.5 (41-55)
TG, median (IQR	140 (97.75-184.5)

Figure 2 shows that among 118 patients, only 22% (n = 26) have a normal/sufficient vitamin D level, with 51.7% having insufficient vitamin D and 26.3% with deficient vitamin D levels.

We compared the age, gender, and metabolic profiles between patients with a normal vitamin D level and those with hypoD (**Table 2**). There was a significant difference in mean HbA1c (p-value = 0.015) and DBP differed between groups (p-value 0.057). and no significant difference in mean of the BDI-II score, BMI, HDL, LDL, and TG. Compared with other variables, HbA1c levels differed between the sufficient/normal, insufficient, and deficient groups with p = 0.015 (**Table 3**).

Table 4 shows that age and HbA1c have a relationship with low vitamin D levels.

Variables with p < 0.25 in the bivariate analysis (i.e. age, BDI-II score, HbA1c, and LDL-cholesterol) were examined further using a multivariate analysis to identify their associations with vitamin D levels. Other factors were not included in this model because they did not show a significant bivariate relationship with vitamin D level. There was a statistically significant difference in vitamin D level based on age and HbA1c. However, the BDI-II score, and SBP and DBP levels did not show statistically significant differences (**Table 5**).

DISCUSSION

Our study found that 77.7% of patients with type 2 DM and depression had hypoD. The

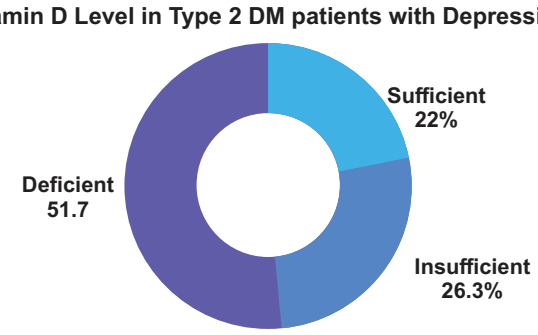


Figure 2. Vitamin D level in type 2 DM with depression.

Table 2. Comparing age and gender with vitamin D grades.

Variable	Sufficient (n = 26)	Insufficient and deficient (n = 92)	p-value
Age in years, median (IQR)	58.5 (55-63.5)	55 (47-60)	0.014*
Gender, N			
Male	8 (24.2)	25 (75.8)	0.910**
Female	18 (21.2)	67 (78.8)	

*Mann–Whitney *U* test; **Chi-square test.

Table 3. Characteristics of patients with sufficient versus Insufficient and deficient vitamin D levels.

Variables	Sufficient (n = 26)	Insufficient (n = 61)	Deficient (n = 31)	p-value
BDI II score, median (IQR)	17 (15-19.2)	17 (14-19)	18 (15-21)	0.072***
BMI (kg/m^2), median (IQR)	25.2 (23.6-28.9)	25.6 (22.9-28.9)	26.9 (23.6-29)	0.834***
HbA1c (%), median (IQR)	6.9 (6.6-7.8)	8 (6.5-9.55)	8.7 (7.5-9.8)	0.015***
SBP (mmHg), median (IQR)	135 (115.5-145)	133 (116.5-143)	138 (118-146)	0.709***
DBP (mmHg), mean	74.65 (9.3)	72.25 (10.01)	77.65 (11.04)	0.057****
LDL-cholesterol, mean	117.35 (25.3)	119.02 (33.6)	112 (30.13)	0.591****
HDL-cholesterol, median (IQR)	49 (41-64.2)	46 (40.5-52.5)	48 (41-53)	0.682***
TG, median (IQR)	130.5 (92.2-178)	125 (106-180.5)	165 (98-201)	0.399***

BDI II, Beck Depression Inventory II; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides.
***Kruskal–Wallis test, ****One-way ANOVA.

Table 4. Relationship between of variables with vitamin D.

Variable	R^2	p-value
Age (years)	0.289	0.002*
Gender		
Male	13.73 (6.58-29.67)	0.283**
Female	20.59 (10.45-29.20)	
BDI II score	−0.153	0.098*
BMI (kg/m$^{2)}$	0.000	0.998*
HbA1c	−0.267	0.004*
SBP	0.018	0.846*
DBP	−0.057	0.539*
LDL-cholesterol	0.108	0.243*
HDL-cholesterol	−0.013	0.891*
TG	−0.105	0.259*

*Spearman rho; **Mann–Whitney *U* test.

Table 5. Linear regression analysis of vitamin D status in DM type 2 patients with depression.

Variable	Unstandardized B	Coef. SE	p-value
(Constant)	1.317	10.954	0.905
Age in years	0.567	0.165	0.001*
BDI II score	−0.665	0.326	0.043*

*p-value < 0.05

median age of the group with insufficient and deficient vitamin D levels was younger than that of the patients with normal vitamin D levels. This result was similar to a previous study by Al Quaiz et al. that showed younger adults had a higher prevalence of vitamin D deficiency compared with older participants,[21] which may be because younger patients spend more time indoors and work inside the office, where they do not get enough sunshine, while older patients often have more free time outdoors. This finding may also be due to the use of calcium and vitamin D supplements for osteoporosis among older age groups.[22]

Our study showed no significant difference in vitamin D levels between genders. Yu et al. found that men had higher serum 25(OH)D levels than women,[23] while another study found that men had a higher prevalence of vitamin D deficiency.[21] Lower vitamin D levels in women may be attributed to their clothing style, spending less time outside, and engaging in less physical activity than men.[22]

There were significant differences in age and BDI-II scores, but no differences in HbA1c, SBP, DBP, or TG levels between patients with normal and abnormal vitamin D levels. In various clinical settings, low serum 25(OH)D levels have been linked to depressive symptoms in adults.[24–26] Our patients with deficient vitamin D levels have a slightly higher BDI-II score than other patients, although this was not statistically significant. Lee et al. showed that there was

an inverse association between 25(OH)D levels and depression.[27] Similarly, Khan et al. also showed that depression was more common in individuals with vitamin D deficiency.[25]

Zhao et al. showed that vitamin D deficiency was related to high HbA1c levels.[28] Buhary et al. also showed that HbA1c was inversely related to serum vitamin D levels and vitamin D supplementation will result in better blood glucose control.[29] In our study, the HbA1c levels were slightly higher in the deficient group than the other groups and the findings were statistically significant and supported the results

of previous studies.

Vitamin D deficiency was recently considered a new risk factor for causing hypertension.[30,31] A systematic review and meta-analysis by He and Hao showed that there was no significant difference in SBP and DBP between the control and vitamin D deficiency groups.[32] Vitamin D supplementation also did not lower blood pressure in a study by Zhang et al.[33]

Low serum vitamin D levels have been associated with an atherogenic lipid profile.[34] Chaudhuri et al. showed that vitamin D deficiency was associated with dyslipidemia in Indian subjects.[35] In a retrospective observational study,[36] vitamin D deficiency was associated with higher LDL and lower HDL levels. However, the results of our study showed no significant difference in lipid profiles between groups.

Interestingly, this study found a correlation between age and lack of vitamin D in patients with type 2 DM and depression. According to a study of male and female respondents aged 50 years, Oliveira et al. linked low serum 25(OH)D levels to an increased chance of depressive symptoms, especially in women. Age, economic circumstances, health, habits, bodily and mental abilities, and cognitive abilities all have an impact on depressive symptoms.[37] William et al. reported vitamin D deficiency in 27.8% of children aged 5 to 9 years, 35.4% of children aged 10 to 14 years, and 50.9% of children aged 15 years or older. Vitamin D deficiency was significantly associated with older age, African American ethnicity, winter/spring seasons, a higher insulin level, the total number of comorbidities, and polycystic ovary syndrome (in girls).[37] A study from Qatar found that subjects aged over 60 years have a 61.3% chance of depression and type 2 DM.[38]

A systematic review and meta-analysis showed that vitamin D supplementation may improve depression in patients with type 2 DM.[39] In a recent study of prediabetic patients, the researchers found that new-onset diabetes occurred in 22.7% of adults who received vitamin D and 25% of those who received a placebo over a 3-year period, resulting in a 15% relative risk reduction. Extrapolating their results to the more than 374 million prediabetic adults worldwide indicates that low-cost vitamin D supplementation could prevent the onset of diabetes in more than 10 million individuals.[40]

Limitation the Study

There are a few limitations to our research findings. This cross-sectional study means that any associations may not necessarily indicate causation. We were unable to determine whether our patients' vitamin D status varied from that of the general community because we did not include healthy controls. Our findings might not be very generalizable in regions with different sun exposure patterns.

CONCLUSION

This study showed that patients with type 2 DM and depression had a high prevalence of hypoD (i.e. 77.7%). In addition, age and BDI-II score were associated with low vitamin D levels.

ACKNOWLEDGMENTS

We are grateful for support from Dr Stevanie and Ms Utami Susilawaty for editing and statistical analyses. Finally, we are thankful to all the participants in this study.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no competing interests or conflicts of interest.

REFFERENCES

1. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol. 2014;144 Pt A:138–45.
2. DeLuca G, Kimball S, Kolasinski J, Ramagopalan S, Ebers G. the role of vitamin D in nervous system health and disease. Neuropathology and Applied Neurobiology. 2013;39(5):458–84.
3. Hoang MT, Defina LF, Willis BL, Leonard DS, Weiner MF, Brown ES. Association between low serum 25-hydroxyvitamin D and depression in a large sample of healthy adults: the Cooper Center longitudinal study. Mayo Clin Proc. 2011;86(11):1050–5.
4. Armstrong DJ, Meenagh GK, Bickle I, Lee ASH, Curran ES, Finch MB. Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. Clin Rheumatol. 2007;26(4):551–4.
5. Hoogendijk WJG, Lips P, Dik MG, Deeg DJH, Beekman ATF, Penninx BWJH. Depression is associated with decreased 25-hydroxyvitamin D and

increased parathyroid hormone levels in older adults. Arch Gen Psychiatry. 2008;65(5):508–12.
6. Patrick RP, Ames BN. Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar disorder, schizophrenia, and impulsive behavior. FASEB J. 2015;29(6):2207–22.
7. Pittampalli S, Mekala HM, Upadhyayula S, Lippmann S. Does vitamin D deficiency cause depression? Prim Care Companion CNS Disord. 2018;20(5):17l02263.
8. Mezza T, Muscogiuri G, Sorice GP, et al. Vitamin D deficiency: A new risk factor for type 2 diabetes. Annals of Nutrition and Metabolism. 2012;61(4):337–48.
9. Fondjo LA, Sakyi SA, Owiredu WK, et al. Evaluating vitamin D status in pre-and postmenopausal type 2 diabetics and its association with glucose homeostasis. BioMed research international. 2018;2018.
10. Gao Y, Zheng T, Ran X, et al. Vitamin D and incidence of prediabetes or type 2 diabetes: a four-year follow-up community-based study. Disease Markers. 2018;2018.
11. Lips P, Eekhoff M, van Schoor N, et al. Vitamin D and type 2 diabetes. J Steroid Biochem Mol Biol. 2017;173:280–5.
12. Nouwen A, Adriaanse MC, van Dam K, et al. Longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis. Diabetic Medicine. 2019;36(12):1562–72.
13. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. The Journal of Clinical Endocrinology & Metabolism. 2007;92(6):2017–29.
14. Menon V, Kar SK, Suthar N, Nebhinani N. Vitamin D and depression: a critical appraisal of the evidence and future directions. Indian Journal of Psychological Medicine. 2020;42:11–21.
15. Penckofer S, Kouba J, Byrn M, Estwing Ferrans C. Vitamin D and depression: where is all the sunshine? Issues Ment Health Nurs. 2010;31(6):385–93.
16. Rafiq S, Jeppesen PB. Is hypovitaminosis D related to incidence of type 2 diabetes and high fasting glucose level in healthy subjects: A systematic review and meta- analysis of observational studies. Nutrients. 2018;10(1).
17. Heath AK, Williamson EJ, Hodge AM, et al. Vitamin D status and the risk of type 2 diabetes: The Melbourne Collaborative Cohort Study. Diabetes Research and Clinical Practice. 2019;149:179–87.
18. Standards of Medical Care in Diabetes-2022. A bridged for primary care providers. Clin Diabetes. 2022;40(1):10–38.
19. Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. BMJ. 2010;340.
20. Upton J. Beck depression inventory (BDI). Encyclopedia of behavioral medicine. 2020;202–3.
21. AlQuaiz AM, Kazi A, Fouda M, Alyousefi N. Age and gender differences in the prevalence and correlates of vitamin D deficiency. Archives of Osteoporosis. 2018;13(1):49.
22. Yildiz Z, Hürmeydan Ö, Madenci ÖÇ, Orçun A, Yücel N. Age, gender and season dependent 25(OH)D levels in children and adults living in Istanbul. Turkish Journal of Biochemistry. 2020;45(5):533–41.
23. Yu HJ, Kwon MJ, Woo HY, Park H. Analysis of 25-hydroxyvitamin D status according to age, gender, and seasonal variation. J Clin Lab Anal. 2016;30(6):905–11.
24. Thurayya Albolushi, Manal Bouhaimed, Thurayya Albolushi, Manal Bouhaimed, Jeremey Spencer. Lower blood vitamin D levels are associated with depressive symptoms in a population of older adults in Kuwait: A cross-sectional study. Nutrients. 2022;14:1548.
25. khan B, Shafiq H, Abbas S, et al. Vitamin D status and its correlation to depression. Annals of General Psychiatry. 2022;21(1):32.
26. Yao Y, Fu S, Zhang H, et al. The prevalence of depressive symptoms in Chinese longevous persons and its correlation with vitamin D status. BMC Geriatrics. 2018;18(1):198.
27. Lee DM, Vanderschueren D, Boonen S, et al. Association of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and parathyroid hormone with mortality among middle-aged and older European men. Age and ageing. 2014;43(4):528–35.
28. Zhao H , Zhen Y, Wang Z, Qi L, Li Y, Ren L, Chen S. The relationship between vitamin d deficiency and glycated hemoglobin levels in patients with type 2 diabetes mellitus. Diabetes Metabolic Syndrome Obesity. 2020;13.
29. Buhary BM, Almohareb O, Aljohani N, et al. Association of glycosylated hemoglobin levels with vitamin D status. J Clin MedRes. 2017;9(12):1013–8.
30. Mehta V, Agarwal S. Does vitamin D deficiency lead to hypertension? Cureus. 2017;9(2):e1038.
31. Vaidya A, Forman JP. Vitamin D and hypertension. Hypertension. 2010;56(5):774–9.
32. He S, Hao X. The effect of vitamin D3 on blood pressure in people with vitamin D deficiency: A system review and meta-analysis. Medicine. 2019;98:e15284.
33. Zhang D, Cheng C, Wang Y, et al. Effect of vitamin D on blood pressure and hypertension in the general population: An update meta-analysis of cohort studies and randomized controlled trials. Prev Chronic Dis. 2020;17:E03.
34. Wang Y, Si S, Liu J, et al. The associations of serum lipids with vitamin D status. PLoS One. 2016;11(10):e0165157.
35. Jaydip Ray Chaudhuri, K Rukmini Mridula, Alluri Anamika, et al. Deficiency of 25- hydroxyvitamin D and dyslipidemia in Indian subjects. Journal of Lipids. 2013 Dec 18.
36. Anantharamakrishnan B, Benansia J. Association between vitamin D level and serum lipid parameters among indian adults working in it sector: a retrospective observational study. medRxiv [Internet]. 2020;

Available from: https://www.medrxiv.org/content/early/2020/10/21/2020.10.20.20215624
37. de Oliveira C, Hirani V, Biddulph JP. Associations between vitamin D levels and depressive symptoms in later life: evidence from the English Longitudinal Study of Ageing (ELSA). The Journals of Gerontology: Series A. 2018;73(10):1377–82.
38. Ismail M, Seif MH, Metwally N, et al. Prevalence and determinants of depression among patients with Type 2 diabetes mellitus attending family medicine clinics in Qatar. American Journal of Medicine Open. 2022;100014.
39. Putranto R, Harimurti K, Setiati S, et al. The effect of vitamin D supplementation on symptoms of depression in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Acta Med Indones. 2022;54(4):574–84.
40. Pittas AG, Kawahara T, Jorde R, et al. Vitamin D and risk for type 2 diabetes in people with prediabetes: a systematic review and meta-analysis of individual participant data from 3 randomized clinical trials. Annals of Internal Medicine. 2023;176(3):355–63.

Mental Health Status and Its Associated Factors Related to Pulmonary Tuberculosis Patients in Primary Health Care Centre in Surabaya, Indonesia

Ni Njoman Juliasih[1,2], Ni Made Mertaniasih[1,3], Cholichul Hadi[4], Soedarsono[1,5,6], Reny Mareta Sari[7], Ilham Nur Alfian[8], Tiffany Tiara Pakasi[9]*

[1]Laboratory of Tuberculosis, Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Public Health, Faculty of Medicine, Universitas Ciputra, Surabaya, Indonesia
[3]Department of Medical Microbiology, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia.
[4]Department of Industrial and Organizational Psychology, Faculty of Psychology Universitas Airlangga, Surabaya, Indonesia.
[5]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Airlangga, Surabaya, East Java, Indonesia.
[6]Sub-Pulmonology Department of Internal Medicine, Faculty of Medicine Hang Tuah University, Surabaya, Indonesia.
[7]Department of Public Health, Institute of Health Sciences STRADA Indonesia, Kediri, Indonesia.
[8]Department of Personality and Social Psychology, Faculty of Psychology Universitas Airlangga, Surabaya, Indonesia.
[9]National TB Program, Directorate of Communicable Disease Prevention and Control, Ministry of Health Indonesia, Jakarta, Indonesia.

Corresponding Author:
Ni Made Mertaniasih, MD. Department of Medical Microbiology, Faculty of Medicine Universitas Airlangga. Jl. Mayjen Prof. Dr. Moestopo No.47, Surabaya 60132, Indonesia. E-mail: nmademertaniasih@gmail.com.

ABSTRACT

Background: *Mental disorders in TB patients are due to long-term treatment, drug side effects, and relapse. This study aimed to analyse the mental health status among TB patients and its associated factors.* ***Methods:*** *The study was carried out on 107 Pulmonary TB patients from 5 Primary Healthcare centres in Surabaya, Indonesia. Furthermore, Mental Health Inventory (MHI-18) was used to measure the mental health status. The MHI-18 has four subscales including, anxiety, depression, behaviour control, and positive affection. In addition, the score range of MHI and its subscales is 0-100, where the higher score showed a better mental health status.* ***Results:*** *The results showed no difference in the score of mental health status, anxiety, depression, and positive affect in all factors. However, behaviour control depicted a significant difference between sex and marital status. In conclusion, mental health problems can occur in all TB patients irrespective of their characteristics.* ***Conclusion:*** *Screening is required for the prevention of severe disease in the early treatment phase and various factors related to mental health should be considered during the implementation of TB management to optimize treatment outcomes.*

Keywords: *mental health status, tuberculosis, anxiety, depression, positive affect, behaviour control.*

INTRODUCTION

WHO (2021) reported that about 10 million people were infected by *Mycobacterium tuberculosis* globally in 2020,[1] including Indonesia due to its large population and high prevalence.[2] The disease is curable and preventable, and a 90% treatment success rate and 85% cure rate are achieved if the TB program is performed well.[1,3]

Depression and anxiety are common mental disorders of global public concerns and TB patients are prone to psychiatric morbidities.[4,5] There is a strong relationship between depression and anxiety and tuberculosis, where one increases the risk of the other. Furthermore, poverty is a risk factor for TB and common mental disorders. Several studies show that anxiety, depression, and mental distress are related to worsening health status, such as progressive symptoms, experiencing symptoms more often, increased use of health services, non-compliance to treatment, and prolonged duration of treatment.[6,7]

Mental disorders in TB patients may be due to long-term treatment, drug side effects, and relapse,[8–10] and the common psychiatric disorder include depression, psychosis, anxiety, and trauma-related disorder.[11] In addition, anxiety and depression are co-occurring in TB patients and are strongly related to non-compliance.[9,12]

The number of mental health problem was high among women, younger age, people with lower income, and lower education.[13] Malnutrition also common cause of both TB and mental health problem.[14] Eventhough TB and mental health problem share cause, mental health problems are neglected in TB patients.[15] because health programs focus on TB. Therefore, screening for a mental health condition and its associated factors are required for prevention and early treatment to prevent further psychiatric disability.[7,16] By knowing what is the major cause of the mental health among TB patients, the prevention and treatment can be applied effectively. This study aimed to analyse the mental health status among TB patients and its associated factors.

METHODS

The study was conducted on 107 pulmonary TB patients from 5 primary healthcare centres in Surabaya, Indonesia, from 2020 to 2021. Furthermore, the respondents were selected randomly based on the data from the primary healthcare centre. This study was approved by the Ethics Committee in Health Research of Dr. Soetomo Hospital with ethical clearance number 103/EC/KEPK/FKUA/2021. The study was non-interventional and the data were obtained by interviewing TB patients as respondents.

Mental health status was measured using the Mental Health Inventory (MHI-18) which consists of four subscales including anxiety, depression, behaviour control, and positive affection. The score range of MHI and its subscales is 0-100, where the higher score depicted a better mental health status.[17,18]

The independent variables include sex, age, level of education, working status, marital status, body mass index, and comorbidities. The age was classified based on the Ministry of Health in Indonesia for descriptive analysis: teenager, young adult, late adult, early elderly, middle elderly, and late elderly. For statistical analysis, age was defined as teenager and young adult, late adult and early elderly, and middle and late elderly.

BMI was classified as underweight which is divided into severely and light underweight, normal, and overweight separated into light and severely overweight. The comorbidities were defined as TB patients with other illnesses or not. Also, we analyzed the data using the T-test and ANOVA with α set at 0.05 to analyse the different mental health between independent variables.

RESULTS

The characteristics of pulmonary TB patients in Surabaya, Indonesia is shown on **Table 1**. **Table 2** showed the characteristic of the respondents, including sex, age, level of education, working status, marital status, body mass index, and

Table 1. Subject's characteristic.

Characteristic	Category	n	%
Sex	Male	51	47.7
	Female	56	52.3
	Total	**107**	**100**
Age	Teenagers (15-25 y)	22	20.6
	Young adult (26-35 y)	20	18.7
	Late adult (36-45 y)	25	23.4
	Early elderly (46-55 y)	14	13.1
	Middle elderly (56-65 y)	23	21.5
	Late elderly (>65 y)	3	2.8
	Total	**107**	**100**
Level of education	Lower educational level	41	38.3
	Higher educational level	66	61.7
	Total	**107**	**100**
Working status	Working	47	43.9
	Not working	60	56.1
	Total	**107**	**100**
Marriage status	Married	39	36.4
	Not married	68	63.6
	Total	**107**	**100**
Body Mass Index	Severe underweight	22	20.6
	Underweight	14	11.2
	Normal	61	57.0
	Overweight	5	4.7
	Severe Overweight	5	4.7
	Total	**107**	**100**
Comorbidity	Yes	39	36.4
	No	68	63.6
	Total	107	**100**

comorbidity. About 56% were female, while 23.4% were late adults. Furthermore, 61% of the respondents had higher education and 43% had a job. The majority had normal body mass index without comorbidity.

Table 2 showed that mental health status and its subscales had a low mean score, indicating that the mental health of respondents was not good except for the positive affect which had a higher average mean.

Table 3 showed no difference in the score of mental health status, anxiety, depression, and positive affect in all factors. However, there was a significantly different in the score of behavioural control between females and males and married and not married.

Table 2. Mental health status of tuberculosis patients.

Variable	Min	Max	Mean	SD
Mental Health	6.67	76.67	41.85	12.55
Anxiety	0	80.00	33.12	18.95
Depression	0	84.00	33.53	16.97
Behaviour control	0	100.00	41.03	18.47
Positive affect	0	100.00	63.97	24.84

Table 3. P-value of factors affecting pulmonary tb patients.

Factors	p-value				
	Mental Health	Anxiety	Depression	Behaviour control	Positive affect
Sex	0.12	0.95	0.77	0.01*	0.16
Age	0.85	0.30	0.68	0.23	0.55
Level of education	0.60	0.95	0.45	0.65	0.79
Working status	0.39	0.28	0.93	0.69	0.58
Marriage status	0.14	0.84	0.39	0.01*	0.72
BMI	0.93	0.66	0.89	0.72	0.52
Co-morbidity	0.55	0.99	0.24	0.36	0.75

*Significantly different

DISCUSSION

Depression increases the risk of worsening the health status, such as comorbidities, disability, suffering, and health-related cost in TB patients. However, the relationship between comorbid TB and depression is not understood.[8,19,20] The patient's psychosocial condition can be worsened by depression, which affects the treatment outcomes. In addition, TB patients with depressive symptoms reduce social relationships, especially at the stage of coughing blood which leads to low self-esteem and hopelessness.[21]

Although their scores are low, the study analysis showed a difference in the score of mental health status, anxiety, depression, and positive affect. This shows that patients with pulmonary TB may experience mental health problems regardless of their demographic variables and whether they have comorbidities.[22]

Mental health affects the ability to handle stress and make a decision, and this varies between men and women. Women are busier than men because they have more responsibilities such as domestic work and jobs. Although there is no difference in mental distress between men and women,[23] there is a variation in behaviour control. Men and women have different values, attitudes, and behaviour due to gender roles, stereotypes, and fundamental genetic and physiological differences.[24,25]

Mental health problems occur in all age groups, with the young being at high risk of mental health challenges and they receive less attention.[26] The younger people establish independence and take responsibility for their actions.[16] However, older people experience a decline in physical condition and health, hence they experience many limitations. TB exacerbates older people's physical health, making it a risk factor for mental health problems in older population.[27]

Generally, education is closely related to health because higher education improves health status due to healthy behaviour.[28] The people with higher education have better health status because education is strongly related to job and income, which play a role in health behaviour, human relationship, family, and community well-being.[29,30]

People with higher education have access to information, which can be harmful if not managed properly. The imprecise knowledge makes TB patients afraid and worried. Furthermore, information overload makes a person feel overwhelmed, confused, powerless, and mentally exhausted, leading to difficulty in making decisions which causes information avoidance.[31]

Those with lower education have difficulty understanding some information[32] which impacts their ability to overcome problems, such as being diagnosed with TB, hence they are prone to mental health problems. Also, they are at risk of unreliable information due to limited knowledge to manage it.

People are susceptible to mental distress, regardless of their employment status. The TB patients were responsible for their job, study, or household activity and they need to continue their responsibilities while receiving treatment simultaneously.[33] Meanwhile, patients who are not working are housewives and students. Due to exposure to responsibilities and workload, tuberculosis may harm patients' mental health and this may worsen in housewives.[23] Students were at high risk for mental health problems due to the pressure from teachers, parents, and several factors such as demanding academic content, study workload, tight schedules, lack of break, conflict with friends, and stigma toward TB.[34–36] The high-level stress, TB symptoms, and the treatment's side effect experienced by students affect their daily life.[34] Additionally, stressful situations due to TB negatively affect workability,[37] hence TB can worsen the patients' responsibility and workload, as well as mental health.

TB patients experience mental distress whether they have comorbid conditions or not because they feel traumatized after the diagnosis. In addition, the duration of treatment and drug side effects impact the psychological condition, such as depression and anxiety.[4] Patients with longer illness duration are prone to depression and anxiety, and being diagnosed of tuberculosis can cause psychological trauma.[38]

Marital status showed a significant result in behaviour control because the spouse monitors and attempts to control the healthy behaviours,

hence it is of better advantage to men than women.[39] Also, lack of support increases psychological distress, especially for the spouse.[40] Generally, TB patients may experience mental distress if their families are not supportive. Several patients experienced excessive worry or mental anguish and did not tell their spouses about the illness due to extreme rejection.[41]

The analysis results show that TB patients are at risk of experiencing mental health problems, so the management of the TB program needs to be integrated with the mental health program. Depression, as one of the mental health problems, poses a substantial risk to achieving the WHO End TB Strategy goals. Integrating TB and mental health programs can reduce costs, improve quality of service and patients quality of life, mortality prevention, reduce symptoms of depression and anxiety, and increase adherence to treatment in TB patients.[42,43]

CONCLUSION

Mental health problems can occur in TB patients regardless of their characteristics. The study results showed no difference in the score of mental health and its subscale except for behavioural control. Furthermore, the behavioural control score was significantly different between married and unmarried people and males and females. Therefore, mental health problems can occur in all patients irrespective of their demographic variables and whether they have comorbidity. Screening for a mental health condition is required to prevent severe disease in the early treatment phase. The implementation of TB management needs to consider various factors related to mental health to optimize treatment outcomes.

DATA AVAILABILITY

The data used to support the findings of this study are included within the article.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

FUNDING STATEMENT

This research was supported by Research Group Funding Program, Universitas Airlangga [345/UN3.14/PT/2020]

ACKNOWLEDGMENTS

We gratefully acknowledge the research funding from Universitas Airlangga and the data support from TB officer in primary health care in Surabaya (Manukan Kulon, Medokan Ayu, Gunung Anyar, Dupak, Rangkah). We also thank Mr. Lantip and Mr. Danny for their technical support and all of students who helped to collect the data used in this study.

REFERENCES

1. WHO. Global Tuberculosis Report 2021. 2021.
2. Mahendradhata Y, Trisnantoro L, Listyadewi S, et al. The Republic of Indonesia health system review. 2017;7:1.
3. Izudi J, Tamwesigire IK, Bajunirwe F. Treatment success and mortality among adults with tuberculosis in rural eastern Uganda: A retrospective cohort study. BMC Public Health. 2020;20(1):1–10.
4. Wang XB, Li XL, Zhang Q, et al. A survey of anxiety and depressive symptoms in pulmonary tuberculosis patients with and without tracheobronchial tuberculosis. Front Psychiatry. 2018;9:1–10.
5. Hayward SE, Deal A, Rustage K, et al. The relationship between mental health and risk of active tuberculosis: a systematic review. BMJ Open. 2022;12(1):e048945.
6. Rao A, Rizvi N. Frequency of depression and anxiety among Tuberculosis patients. J Tuberc Res. 2016;04(04):183–90.
7. Lara-Espinosa J V., Hernández-Pando R. Psychiatric problems in pulmonary tuberculosis: Depression and anxiety. J Tuberc Res. 2021;09(01):31–50.
8. Basu G, Chatterjee C, Singh R, Biswas S. Depression and its correlates among Tuberculosis patients: experience from a DOTS clinic of a sub divisional hospital of West Bengal. Indian J Res Reports Med Sci [Internet]. 2012;2(4):14–7. Available from: www.ijrrms.com
9. Duko B, Gebeyehu A, Ayano G. Prevalence and correlates of depression and anxiety among patients with tuberculosis at WolaitaSodo University Hospital and Sodo Health Center, WolaitaSodo, South Ethiopia, Cross sectional study. BMC Psychiatry [Internet]. 2015;15(1):1–7. Available from: http://dx.doi.org/10.1186/s12888-015-0598-3
10. Husain MO, Dearman SP, Chaudhry IB, Rizvi N, Waheed W. The relationship between anxiety, depression and illness perception in tuberculosis patients in Pakistan. Clin Pract Epidemiol Ment Heal.

2008;4:1–5.
11. Sweetland AC, Galea J, Shin SS, et al. Integrating tuberculosis and mental health services: global receptivity of national tuberculosis program directors. Physiol Behav. 2019;176(3):139–48.
12. Ige OM, Lasebikan VO. Prevalence of depression in tuberculosis patients in comparison with non-tuberculosis family contacts visiting the DOTS clinic in a Nigerian tertiary care hospital and its correlation with disease pattern. Ment Health Fam Med. 2011;8(4):235–41.
13. Reile R, Sisask M. Socio-economic and demographic patterns of mental health complaints among the employed adults in Estonia. Sarker MNI, editor. PLoS One [Internet]. 2021;16(10):e0258827. Available from: https://dx.plos.org/10.1371/journal.pone.0258827
14. Qader G, Seddiq MK, Rashidi KM, et al. Prevalence of tuberculosis among mentally ill patients in conflict-stricken Afghanistan: A cross-sectional study. Int J Infect Dis [Internet]. 2019;89:45–50. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1201971219303467
15. Shyamala KK, Naveen RS, Khatri B. Depression: A neglected comorbidity in patients with Tuberculosis. J Assoc Physicians India. 2018;66(12):18–21.
16. Jurewicz I. Mental health in young adults and adolescents - Supporting general physicians to provide holistic care. Clin Med J R Coll Physicians London. 2015;15(2):151–4.
17. Ritvo PG, Fischer JS, Miller DM, Andrews H, Paty DW, LaRocca NG. MSQLI multiple sclerosis quality of life inventory: a user's manual the consortium of multiple sclerosis centers health services research subcommittee. 1997;30-31,47-50.
18. Yuvaraj, B.Y; Poornima, S; Rashmi S. Screening for overall mental health status using mental health inventory amongst medical students of a government medical college in North Karnataka, India. Int J Community Med Public Heal. 2016;3(12):3308–12.
19. Koyanagi A, Vancampfort D, Carvalho AF, et al. Depression comorbid with tuberculosis and its impact on health status: Cross-sectional analysis of community-based data from 48 low- and middle-income countries. BMC Med. 2017;15(1):1–10.
20. Shrestha P, Subba UK, Brouwer M, Sweetland AC. Depression among TB patients and associated factors in Kathmandu Valley, Nepal. Glob Ment Heal. 2020;7.
21. Dasa TT, Roba AA, Weldegebreal F, et al. Prevalence and associated factors of depression among tuberculosis patients in Eastern Ethiopia. BMC Psychiatry. 2019;19(1):1–7.
22. Peretomode O. Work and stress among academic administrators of higher education. 2012;8(13).
23. Tyagi P. Mental health among married women students. Int J Indian Psychol. 2017;5(1).
24. Wizemann M, Pardue ML. Does sex matter? Cambridge Law Journal. 2002;61:1–52.
25. Van Hooft EAJ, Taris TW, Born MP, Van Der Flier H. Ethnic and gender differences in applicants' decision-making processes: An application of the theory of reasoned action. Int J Sel Assess. 2006;14(2):156–66.
26. Addy ND, Agbozo F, Runge-Ranzinger S, Grys P. Mental health difficulties, coping mechanisms and support systems among school-going adolescents in Ghana: A mixed-methods study. PLoS One [Internet]. 2021;16(4 April 2021):1–19. Available from: http://dx.doi.org/10.1371/journal.pone.0250424
27. Seidel D, Brayne C, Jagger C. Limitations in physical functioning among older people as a predictor of subsequent disability in instrumental activities of daily living. Age Ageing. 2011;40(4):463–9.
28. Jürges H, Reinhold S, Salm M. Does schooling affect health behavior? Evidence from the educational expansion in Western Germany. Econ Educ Rev. 2011;30(5):862–72.
29. Alsulami H. The effect of education and experience on wages: The case study of Saudi Arabia. Am J Ind Bus Manag. 2018;08(01):129–42.
30. Raghupathi V, Raghupathi W. The influence of education on health: an empirical assessment of OECD countries for the period 1995-2015. Arch Public Health. 2020;78(1):20.
31. Soroya, Saira Hanif, Farooq Ali, et al. From information seeking to information avoidance: Understanding the health information behavior during a global health crisis. 2021;(January).
32. Juliasih NN, Mertaniasih NM, Hadi C, Soedarsono, Sari RM, Alfian IN. Factors affecting tuberculosis patients' quality of life in Surabaya, Indonesia. J Multidiscip Healthc. 2020;13:1475–80.
33. Skinner D, Claassens M. It's complicated: Why do tuberculosis patients not initiate or stay adherent to treatment? A qualitative study from South Africa. BMC Infect Dis [Internet]. 2016;16(1):1–9. Available from: http://dx.doi.org/10.1186/s12879-016-2054-5
34. Blazer C. Student stress. Information Capsule. Volume 1006. Res Serv Miami-Dade Cty Public Sch [Internet]. 2010;1006(October):18. Available from: http://131.211.208.19/login?auth=eng&url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=eric3&AN=ED536513;%5Cnhttp://sfx.library.uu.nl/utrecht?sid=OVID:ericdb&id=pmid:&id=doi:&issn=&isbn=&volume=&issue=&spage=&pages=&date=2010&title=
35. Mboya IB, John B, Kibopile ES, Mhando L, George J, Ngocho JS. Factors associated with mental distress among undergraduate students in northern Tanzania. BMC Psychiatry. 2020;20(1):1–7.
36. Nieuwoudt JE. Psychological distress among students in enabling education: An exploratory study. Aust J Adult Learn. 2021;61(1):6–25.
37. Pachi A, Bratis D, Moussas G, Tselebis A. Psychiatric morbidity and other factors affecting treatment adherence in pulmonary tuberculosis patients. Tuberc

Res Treat. 2013;2013:1–37.
38. Singh L, Pardal P, Prakash J. Psychiatric morbidity in patients of pulmonary tuberculosis-an observational study. Ind Psychiatry J. 2015;24(2):168.
39. Umberson D. Gender, marital status and the social control of health behavior. Soc Sci Med. 1992;34(8):907–17.
40. Ayana TM, Roba KT, Mabalhin MO. Prevalence of psychological distress and associated factors among adult tuberculosis patients attending public health institutions in Dire Dawa and Harar cities, Eastern Ethiopia. BMC Public Health. 2019;19(1):1–9.
41. Central TB Division. National framework for a gender-responsive approach to TB in India [Internet]. 2019. Available from: https://tbcindia.gov.in/WriteReadData/l892s/388838054811 NTEP Gender Responsive Framework_311219.pdf
42. Sweetland AC, Jaramillo E, Wainberg ML, et al. Tuberculosis: an opportunity to integrate mental health services in primary care in low-resource settings. The Lancet Psychiatry [Internet]. 2018;5(12):952–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S221503661830347X
43. Pasha A, Siddiqui H, Ali S, Brooks MB, Maqbool NR, Khan AJ. Impact of integrating mental health services within existing tuberculosis treatment facilities. Med Access @ Point Care [Internet]. 2021 Jan 27;5:239920262110113. Available from: http://journals.sagepub.com/doi/10.1177/23992026211011314

Validity and Reliability Studies of the Indonesian Version of Arrhythmia-Specific Questionnaire in Tachycardia and Arrhythmia (ASTA)

Muhammad Yamin[1]*, Simon Salim[1], Siti Setiati[2], Angga Pramudita Pudianto[1], Putri Zulmiyusrini[3], Alexander Edo Tondas[4], Dono Antono[1], Eka Ginanjar[1], Arif Mansjoer[1], M. Syahrir Azizi[1], Annisa Puspitasari Nachrowi[1], Rubiana Sukardi[5], Idrus Alwi[1]

[1]Division of Cardiology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Division of Geriatric, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3]Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[4]Department of Cardiology and Vascular Medicine, Mohammad Hoesin General Hospital, Palembang, Indonesia.
[5]Integrated Cardiac Centre – Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Corresponding Author:
Muhammad Yamin, MD. Division of Cardiology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: muhyam511@gmail.com.

ABSTRACT

Background: *The Arrhythmia-Specific Questionnaire in Tachycardia and Arrhythmia (ASTA) was developed in Sweden using English which may pose cultural and language barriers for Indonesian patients. As such, we aimed to translate the original ASTA into Indonesian, then assess its validity and reliability.* ***Methods:*** *Translation of the ASTA from English to Indonesian was done using forward and backward translation. The final version was then validated with the Short Form-36 (SF-36) questionnaire. Test-retest reliability study was done in a 7-14-day interval.* ***Results:*** *The Indonesian version of ASTA was deemed acceptable by a panel of researchers with Cronbach's α of 0.816 and Intraclass Correlation Coefficient (ICC) ranging from 0.856-0.983. In a comparison to the SF-36, the medication utilization domain was poorly correlated with role limitations due to physical health (r:0.384; p<0.01) and pain (r:-0.317; p<0.05). The arrhythmia-specific symptoms domain was poorly correlated with role limitations due to emotional problems (r:0.271; p<0.05). In addition, the health-related quality of life (HRQOL) domain was poorly correlated with role limitations due to physical health (r:0.359; p<0.01) and emotional problems (r:0.348; p<0.01), also total SF-36 score (r:-0.367; p<0.01). The ASTA total score was poorly correlated with role limitations due to physical health (r:0.37; p<0.01), and emotional problems (r:0.376; p<0.01), also total SF-36 score (r:-0.331; p<0.01).* ***Conclusion:*** *The Indonesian version of ASTA has good internal and external validity as well as good reliability. Both the physical and mental domains of ASTA are correlated with role limitations due to emotional problems and SF-36 total score.*

Keywords**:** *Atrial fibrillation, reliability, validity, quality of life.*

INTRODUCTION

The most common form of tachyarrhythmia is atrial fibrillation (AF), which is found in 2-4% of the world's population. The prevalence increases with age.[1] Morillo et al. reported that AF is the most common type of arrhythmia found in clinical practice, as well as a significant global burden, closely followed by comorbidities which increase disability and mortality rates. As a chronic condition, AF leads to healthcare and medication utilization which increases the economic burden on individuals, as well as nations. The burden of AF is also related to complications, such as stroke, in which one- third of cases have AF.[2]

Taheri et al. reported a gradual decrease in AF patients QOL due to psychosocial distress and hemodynamic instability, which induces dyspnea, palpitations, and fatigue. Increased risk of heart failure, myocardial infarction, venous thromboembolism, and stroke, as well as increased hospitalization length of stay also play a role in QOL reduction.[3,4] Jones et al. reported that patients with AF experienced major lifestyle changes after diagnosis, including role limitations and need for health services, which may decrease QOL in the family or caregivers.[4] Vintila et al. reported that QOL is lower in permanent AF compared to persistent and paroxysmal AF.[5]

QOL evaluations can be used to determine management strategy and treatment success in clinical practice.[6] In addition to objective parameters such as ECG and echocardiography, Patient-Reported Outcomes (PROs) should be considered in order to assess patient welfare. However, the majority of PROs questionnaires for the arrhythmia population were designed exclusively for AF.[7] The Arrhythmia-Specific Questionnaire in Tachycardia and Arrhythmia (ASTA) was the first questionnaire developed to evaluate arrhythmia-specific symptoms and QOL in patients with different types of arrhythmia, including AF.[1] ASTA was first introduced in Sweden in the English language, which may pose language and cultural barriers to Indonesians.[7] As such, we aimed to translate ASTA into Indonesian and analyze the reliability and validity of this Indonesian version of ASTA.

METHODS

We conducted this cross-sectional study in March - April 2022. The inclusion criteria of this study were patients diagnosed with AF according to their medical records, aged ≥18 years, and fluent in the Indonesian language. Patients with a history of cardiac

surgery or hospitalization due to acute or severe chronic conditions within the previous 30 days, physical handicap, or mental or psychiatric disorders were excluded.

The European Heart Rhythm Association (EHRA) score and duration of AF was recorded during history taking. Other general characteristics (gender, age, highest education level attained, and marital status) and clinical characteristics (ejection fraction/EF in the previous 3 months, as well as AF etiology and type) were taken from medical records.

The ASTA and Short Form-36 (SF-36) questionnaires were filled independently in two stages, as the test and retest, respectively. The retest was taken 7-14 days after the test. This study was approved by the Health Research Ethics Committee, Faculty of Medicine Universitas Indonesia, Cipto Mangunkusomo Hospital, with approval number KET-/054/UN2. F1/ETIK/PPM.00.02/2021.

Translation

We conducted this study in two phases. The first phase was translation and cultural adaptation of ASTA from the original English to Indonesian. The translation process was conducted after obtaining permission from Walfridsson et al., the original authors of ASTA. The second phase was assessment of the reliability and validity of the Indonesian version of ASTA. The translation and cultural adaptation of ASTA was done in several steps. First, forward translation from English to Indonesian was conducted by 2 translators: one medical and one non-medical translator. Both translators were certified and experienced in translation and interpretation. After the translation process, they discussed and combined their translations into the Indonesian Synthesis Translation. This version then underwent backward translation (Indonesian to English) performed by two native English speakers

who both had nearly ten years of experience in interpreting and translating between English and Indonesian. Both backward translations were compared to the original version of ASTA. Any differences were reviewed by the research team before the pre- final questionnaire was distributed to participants. This questionnaire was first pre-tested by 30 participants, then edited based on patient feedback, forming the final questionnaire. The final questionnaire was then used for the second phase.

Questionnaire

The ASTA consists of 3 parts: the medication utilization domain consisting of 2 questions, the arrhythmia-specific symptoms consisting of 8 questions, and HRQOL

consisting of 13 questions. The first part evaluates the most recent episode of symptoms and medication utilization. The second part evaluates symptom burden, including the average duration, longest duration, frequency, symptoms, precipitating factors, and severity scale of arrhythmia. The scale has a 4-point range from 0 (not relevant) to 3 (yes, a lot). A lower score indicates milder symptoms of arrhythmia. The third part of ASTA (HRQOL) consists of 7 questions referring to the physical domain and 6 questions referring to the mental domain. Each HRQOL question also has a 4-point scale, from 0 (not relevant) to 3 (yes, a lot). A lower score indicates better QOL related to tachyarrhythmia.[8]

Data Analysis

We analyzed the data using SPSS Statistics 26.0 software and are presented in tables. General and clinical characteristics are presented as frequency and percentage. We performed normality test using Kolmogorov-Smirnov test (n>50). Normally distributed data (p>0.05) were analyzed by Pearson's test, while non-normally distributed data (p<0.05) were analyzed by Spearman's test. The ASTA score was first converted to a 0-100 scale and reversed as needed to balance the scores between questions.

We assessed the reliability using test-retest reliability analysis, resulting in Cronbach's α and Intraclass Correlation Coefficient (ICC) between the first test and the retest. Cronbach's α values were interpreted as low (<0.6), acceptable (0.6-0.8), or very good internal consistency (>0.8).[9] ICC values were considered to have poor (<0.5), moderate (0.5-<0.75), good (0.75-<0.9), or excellent (>0.9) reliability.[10] The validity test was conducted using bivariate correlation analysis of the inter-item correlation and total score.

Analyses of each domain in ASTA and SF-36, as well as clinical parameters were done to evaluate the concordance between the two questionnaires. The degrees of correlation were defined as very low (r:0.00-0.199), low (r:0.20-0.399), moderate (r:0.40- 0.599), high (r:0.60-0.799), and very high (r:0.80-1.00).

RESULTS

General and Clinical Characteristics

In the second phase, 60 participants were recruited. Most participants were elderly (31.67%), male (53.33%), and had EF ≥50% (76.67%), as shown in **Table 1**. The prevalence of AF increased with age. The almost half of participants (40%) were not

troubled by AF symptoms. More than half (53.33%) of our subjects were diagnosed with valvular disease based on echocardiography.

Table 1. General and Clinical Characteristics.

Characteristics	(N=60)	%
Gender		
Male	32	53.33
Female	28	46.67
Age group in years		
≤40	5	8.33
41-50	8	13.33
51-60	17	28.33
61-70	19	31.67
>70	11	18.33
Education		
Primary or less	6	10.00
Junior high	6	10.00
Senior high	22	36.67
University	26	43.33
Marital Status		
Single	6	10.00
Married	50	83.33
Widow/widower	4	6.67
EHRA		
I	4	6.67
IIa	24	40.00
IIb	18	30.00
III	12	20.00
IV	2	3.33

Ejection fraction (%)		
<40	5	8.33
40-49	9	15.00
>50	46	76.67
Duration of diagnosis		
<1 year	2	3.33
1-5 years	50	83.33
>5 years	8	13.33
AF etiology		
Valvular	32	53.33
Non-valvular	28	46.67
AF type		
Paroxysmal	11	18.33
Persistent	9	15.00
Longstanding persistent	2	3.33
Permanent	36	60.00

Reliability and Validity of the Indonesian Version of ASTA

Indonesian version of ASTA had a very good internal consistency as suggested by Cronbach's α of 0.816 (**Table 2**). The ICC values for each domain were more than 0.33 (r: 0.856-0.983; p<0.01). The medication utilization domain, arrhythmia-specific symptoms domain, and HRQOL domain were all reliable, based on Cronbach's α values (0.629-0.789; p<0.01). Based on total score correlation, our version of ASTA was considered to be valid (p<0.01).

The medication utilization domain had a low correlation with total ASTA score (r: 0.378; p<0.01). The arrhythmia-specific symptoms domain was moderately correlated with total HRQOL domain (r: 0.491; p<0.01) and highly correlated with total ASTA score (r: 0.721; p<0.01). The HRQOL domain was very highly correlated with total ASTA score (r: 0.934; p<0.01).

Correlation between the Indonesian Version of ASTA and SF-36

The analysis of our version of ASTA and SF-36 as the gold standard is shown in **Table 3**. The medication utilization domain was poorly correlated with role limitations due to physical

Table 2. Reliability and Validity of Indonesia Version of ASTA.

	Correlations					
Variables	**Medication Utilization**	**Arrythmia-Specific Symptoms Domain**	**HRQOL Domain**	**Total Score**	**ICC D1 and D8-14**	**Cronbach's α**
Total Medication Utilization Domain	1	0.039	0.232	0.378**	0.949**	0.789**
SI_1	0.982**	0.022	0.245	0.378**	0.942**	
SI_2	0.558**	0.092	0.124	0.342**	0.953**	
Total Arrythmia-Specific Symptoms Domain	0.039	1	0.491**	0.721**	0.944**	0.629**
SII_1	-0.11	0.146	-0.441*	-0.389**	0.901**	
SII_2	-0.044	0.093	-0.388**	-0.349**	0.915**	
SII_3	-0.662**	0.047	-0.431**	-0.420**	0.929**	
SII_5	-0.043	0.412**	0.128	0.332**	0.951**	
SII_6a	0.116	0.383**	0.422**	0.462**	0.955**	
SII_6b	-0.025	0.485**	0.631**	0.619**	0.871**	
SII_6c	0.241	0.699**	0.381**	0.573**	0.977**	
SII_6d	0.225	0.466**	0.556**	0.609**	0.966**	
SII_6e	0.378**	0.514**	0.604**	0.691**	0.872**	
SII_6f	0.418**	0.451**	0.529**	0.623**	0.868**	
SII_6g	0.046	0.607**	0.466**	0.561**	0.962**	
SII_6h	0.085	0.609**	0.418**	0.535**	0.910**	
SII_6i	0.216	0.501**	0.542**	0.610**	0.970**	
SII_7	0.095	-0.09	-0.482**	-0.384**	0.956**	
SII_8	0.01	0.451**	-0.016	0.346**	0.913**	
Total HRQOL	0.232	0.491**	1	0.934**	0.973**	0.766**

* Significant correlation in α = 0.05 (2-tailed)
** Significant correlation in α = 0.01 (2-tailed)

Table 3. Analysis of the Indonesian Version of ASTA and SF-36.

Domain Variables	Medication Utilization Domain	Arrythmia- Specific Symptoms Domain	HRQOL Domain	Total score
Physical functioning	0.056	0.114	0.146	0.156
Role limitations due to physical health	0.384**	0.113	0.359**	0.370**
Role limitattions due to emotional problems	0.225	0.271*	0.348**	0.376**
Energy/fatigue	0.065	-0.081	0.040	0.012
Emotional well-being	0.183	-0.031	0.024	0.042
Social functioning	0.108	0.112	-0.003	0.060
Pain	-0.317*	-0.199	-0.167	-0.254
General health	0.097	-0.098	-0.020	-0.031
Total score	-0.188	-0.043	-0.367**	-0.331**

All data were analyzed using Pearson's test
* Significant correlation in α = 0.05 (2-tailed)
** Significant correlation in α = 0.01 (2-tailed)

health (r: 0.384; p<0.01) and pain (r: -0.317; p<0.05). Arrhythmia-specific symptoms domain was poorly correlated with role limitations due to emotional problems (r: 0.271; p<0.05). HRQOL domain was poorly correlated with role limitations due to physical health (r: 0.359; p<0.01), role limitations due to emotional problems (r: 0.348; p<0.01), and total SF-36 score (r: -0.367; p<0.01). The total score of the Indonesian version of ASTA was poorly correlated with role limitations due to physical health (r: 0.37; p<0.01), role limitations due to emotional problems (r: 0.376; p<0.01), and total SF- 36 score (r: -0.331; p<0.01). The lower total score of the HRQOL domain and total ASTA (better QOL) was correlated with higher SF-36 score.

The physical HRQOL domain was poorly correlated with role limitations due to emotional problems (r: 0.342; p<0.01) and moderately correlated with total SF-36 score (r: -0.456; p<0.01). While mental HRQOL domain was moderately correlated with role limitations due to emotional problems (r: 0.492; p<0.01) and total score (r: -0.512; p<0.01) as shown in **Table 4**. This poor correlation indicates that these domains are useful for assessing different aspects of a patient's life, such as the physical or emotional, with little overlap, as they were devised to do.

Table 4. Analysis of the HRQOL domain of the Indonesian Version of ASTA and SF-36.

Domain Variables	HRQOL Domain (Physical)	HRQOL Domain (Mental)
Physical functioning	0.229	0.006
Role limitations due to physical health	0.202	0.080
Role limitations due to emotional problems	0.342**	0.492**
Energy/fatigue	0.031	0.044
Emotional well-being	0.023	0.021
Social functioning	0.076	-0.097
Pain	-0.129	-0.184
General health	0.000	-0.041
Total score	-0.456**	-0.512**

All data were analyzed using Pearson's test
* Significant correlation in α = 0.05 (2-tailed)
** Significant correlation in α = 0.01 (2-tailed)

Correlation between the Indonesian Version of ASTA, Ejection Fraction and EHRA

There were no correlations between medication utilization domain, arrhythmia-specific symptoms domain, HRQOL domain, or ASTA total score and other clinical parameters such as EF and EHRA in our study.

DISCUSSION

AF symptoms are the main reason for hospital admission, although Rienstra et al. reported that 15-30% of AF is asymptomatic. AF may present as palpitations, chest discomfort, and reduced exercise capacity. Approximately two-thirds of AF patients who visit the emergency department end up hospitalized.[11]

The Cronbach's α of our Indonesian version of ASTA was slightly lower (0.816) than the Brazilian version (0.88) or the Swedish version (0.91). The Cronbach's α in the physical domain was lower in our study than in the Swedish version (0.87 vs. 0.89, respectively), while the Cronbach's α in the mental domain was higher in our study (0.86 vs 0.79, respectively). The difference may have been due to our smaller sample size (60 participants) compared to the Brazilian (172 participants) and Swedish (185 participants) versions.[1,8]

Our ICC ranged from 0.856 to 0.983, which was considered to be good or excellent reliability. Between the test and retest of 7-14 days, there were no major changes in AF patient symptoms. This finding was supported by Lindberg et al., who stated that AF is a chronic lifelong condition which requires regular medical control. Prevention of complications, such as stroke, and routine medical treatment demand regular clinic visits, diet and alcohol restriction, and regular evaluation of bleeding or drug interactions.[12]

In our study, higher SF-36 score (better QOL) was poorly correlated with lower ASTA total score (r: -0.331; $p<0.01$) and moderately correlated with the physical HRQOL domain (r: -0.456; $p<0.01$). Higher HRQOL domain score was also significantly correlated with inability to perform daily activities due to both physical health (r:0.359; $p<0.01$) and emotional problems (r: 0.348; $p<0.01$). Barbaglia et al. stated that disability has become an important component of disease burden, with cardiovascular disease contributing to one of nine disability-causing health conditions.[13] These limitations might be caused by AF symptoms such as lack of energy (92%), dyspnea (76%), and palpitations (70%) due to lack of atrial contraction and irregular diastole leading to decreased stroke volume, cardiac output, and blood pressure.[14,15] Concomitant diseases such as coronary artery disease (35.6%), heart failure (12.7%), and thyroid disease (7.6%) may contribute to both physical and emotional limitations.[14]

Rienstra et al. reported that more than half of AF patients present with reduced exercise capacity, with shortness of breath as the main complaint. Rapid ventricular rate and atrioventricular dyssynchrony impair diastolic filling, which may result in cardiac output reduction. Diastolic dysfunction also increases left ventricular pressure, which may predispose patients to development of subclinical pulmonary edema. Rapid atrial rate and changes in cardiac pressure give rise to structural changes, which lead to worsening AF symptoms and reduced physical capacity.[11] However, there was no correlation between any ASTA domains and EF in our study, which might have been due to the small sample size.

Psychological complications of AF may be exacerbated by lack of social understanding, feeling isolated, and inadequate social support, which result in frustration and a feeling of helplessness.[16] In our study, the arrhythmia-specific symptoms domain (r:0.271; $p<0.05$) and HRQOL domain (r:0.348; $p<0.01$) were poorly correlated with role limitations due to emotional problems. Kupper et al. reported an elevation of anxiety (35%) and depression (20%) prevalence in AF patients in relation to chronic use of medication, drug side effects, fear of worsening symptoms, symptom emergence during activity, and planned intervention to control symptoms.[14] Gayman et al. reported that pain, physical limitations, chronic stress, and daily social discriminations were all correlated with daily activity limitation.[17] Ironically, Lampert et al. also reported that anger and stress increased the risk of AF due to sympathetic nerve system activation.[18]

EF and EHRA score were not significantly correlated with any ASTA domain. These parameters were correlated with physical functioning and exercise tolerance. Both physical and mental domains affect total ASTA score in our study. However, mental domain has a stronger affects the total score.[19] The limitation of this study was the small sample size, which may have affected the degree of statistical significance.

CONCLUSION

The Indonesian version of ASTA has good internal and external validity as well as good reliability to evaluate the QOL of individuals with AF. The Indonesian version of ASTA can be used to assess QOL changes over time, as severity and treatment evaluations. Both the physical and mental domains of ASTA are correlated with role limitations due to emotional problems and SF-36 total score.

REFERENCES

1. Cannavan PMS, Cannavan FPS, Walfridsson U, Lopes MHBM. Translation and validation of the arrhythmia-specific questionnaire in tachycardia and arrhythmia (ASTA) to the Brazilian context: An instrument focusing on arrhythmia symptoms. Cardiol Res Pract. 2020;2020:1–7.
2. Morillo CA, Banerjee A, Perel P, Wood D, Jouven X. Atrial fibrillation: The current epidemic. J Geriatr Cardiol. 2017;14(3):195–203.
3. Taheri L, Poorgholami F, Zare A, Jahromi MK. Quality of life in patients with atrial fibrillation: An intervention. Nurs Crit Care. 2020;15(6):7–11.
4. Jones J, Stanbury M, Haynes S, et al. Importance and assessment of quality of life in symptomatic permanent atrial fibrillation: Patient focus groups from the RATE-AF trial. Cardiol. 2020;145(10):666–75.
5. Vintila A, Stanciu A, Horumba M, Vintila V, Lupusoru M, Gurghean A. Impact of atrial fibrillation on quality of life. J Hypertens. 2019;37(June):2019.
6. Kotecha D, Ahmed A, Calvert M, Lencioni M, Terwee CB, Lane DA. Patient- reported outcomes for quality of life assessment in atrial fibrillation: A systematic review of measurement properties. PLoS One. 2016;11(11):1–13.
7. Walfridsson U, Arestedt K, Stromberg A. Development and validation of a new Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia (ASTA) with focus on symptom burden. Health Qual Life Outcomes. 2012;10:1–10.
8. Walfridsson U, Stromberg A, Arestedt K. Development and validation of an arrhythmia-specific scale in tachycardia and arrhythmia with focus on health- related quality of life. J Cardiovasc Nurs. 2015;30(2):98–108.
9. Daud KAM, Khidzir NZ, Ismail AR, Abdullah FA. Validity and reliability of instrument to measure social media skills among small and medium entrepreneurs at Pengkalan Datu River. Int J Dev Sustain. 2018;7(3):1026–37.
10. Han X. On statistical measures for data quality evaluation. J Geogr Inf Syst. 2020;12(03):178–87.
11. Rienstra M, Lubitz SA, Mahida S, et al. Symptoms and functional status of patients with atrial fibrillation: State of the art and future research opportunities. Circulation. 2012;125(23):2933–43.
12. Lindberg T, Sanmartin Berglund J, Elmståhl S, Bohman DM. Older individuals' need for knowledge and follow-up about their chronic atrial fibrillation, lifelong medical treatment and medical controls. Scand J Caring Sci. 2017;31(4):1022–30.
13. Barbaglia G, Adroher ND, Vilagut G, et al. Health conditions and role limitation in three European Regions: a public-health perspective. Gac Sanit. SESPAS; 2017;31(1):2–10.
14. Kupper N, van den Broek KC, Widdershoven J, Denollet J. Subjectively reported symptoms in patients with persistent atrial fibrillation and emotional distress. Front Psychol. 2013;4(April):1–9.
15. Carlisle MA, Fudim M, DeVore AD, Piccini JP. Heart failure and atrial fibrillation, like fire and fury. JACC Hear Fail. 2019;7(6):447–56.
16. Hilow H, Whibley D, L.Kratz A, Ghanbar H. A focus group study to inform design of a symptom management intervention for adults with atrial fibrillation Author links open overlay panel. Cardiovasc Digit Heal J. 2021;2(5):246–55.
17. Gayman MD, Turner RJ, Cui M. Physical limitations and depressive symptoms: Exploring the nature of the association. Journals Gerontol - Ser B Psychol Sci Soc Sci. 2008;63(4):219–28.
18. Lampert R, Burg MM, Jamner LD, Dziura J, Brandt C, Li F. Effect of beta-blockers on triggering of symptomatic atrial fibrillation by anger or stress. Heart Rhythm. 2019;16(8):1167–73.
19. Bekfani T, Nisser J, Derlien S, et al. Psychosocial factors, mental health, and coordination capacity in patients with heart failure with preserved ejection fraction compared with heart failure with reduced ejection fraction. ESC Hear Fail. 2021;8(4):3268–78.

Vitamin D Levels in Pre-frail Older Adults and Its Correlation with Hand Grip Strength

Noto Dwimartutie[1,2]*, Siti Setiati[1], Tirza Z. Tamin[3], Ani Retno Prijanti[4], Alida R. Harahap[2], Dyah Purnamasari[5], Kuntjoro Harimurti[1], I Dewa Putu Pramantara[6]

[1]Division of Geriatric, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Doctoral Program in Medical Sciences, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.
[3]Division of Musculoskeletal Rehabilitation, Department of Physical Medicine and Rehabilitation, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[4]Department of Biochemistry and Molecular Biology, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.
[5]Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[6] Division of Geriatric, Department of Internal Medicine, Faculty of Medicine, Publich Health and Nursing, Universitas Gadjah Mada, Sardjito Hospital, Yogyakarta, Indonesia.

Coresponding author:
Noto Dwimartutie, MD. Division of Geriatric, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: noto.dwimartutie@ui.ac.id.

ABSTRACT

Background: *Vitamin D deficiency is frequent in older adults and associated with poor musculoskeletal function. The prevalence of pre-frailty is also high in older persons, who may proceed to a frail state. This study aimed to determine the vitamin D levels in pre-frail older adults and its correlation with hand grip strength.* ***Methods:*** *A cross-sectional study was conducted on older adults (age ≥ 60 years) with a pre-frail condition who were visiting the outpatient geriatric clinic at Cipto Mangunkusumo Hospital in Jakarta, Indonesia. Serum levels of vitamin D, measured as 25(OH)D, were determined by enzyme-linked immunosorbent assay (ELISA), and hand grip strength was measured using a Jamar hydraulic dynamometer. Correlations between vitamin D levels and hand grip strength were evaluated by Spearman's rank correlation coefficient. Multiple linear regression analysis was carried out to assess contribution of variables that influence hand grip strength.* ***Results:*** *Of 95 pre-frail older adults (mean age 70.08 ± 5.35 years), 67.4% were female, and the median vitamin D level was 17.91 (interquartile range/IQR 13.68–26.36) ng/mL. Overall, 11.6% of the participants had normal vitamin D levels, whereas 34.7% and 53.7% had insufficient and deficient levels, respectively. Females were more likely to have inadequacy of vitamin D than males. Those with vitamin D deficiency tended to have a higher body mass index (BMI) and lower vitamin D intake than normal levels. A significant correlation between serum vitamin D levels and hand grip strength was observed (r = 0.283; P = 0.006). After adjusting for age, comorbidities, nutritional status, functional status, BMI, protein intake, and sun exposure score, regression analysis between hand grip strength and vitamin D levels gave standard coefficient beta = 0.255 (P = 0.013).* ***Conclusion:*** *In this study, pre-frail older adults had a high proportion of deficient and insufficient vitamin D levels, and a significant correlation was found between serum vitamin D levels and hand grip strength.*

Keywords**:** *Hand grip strength, older adults, pre-frail, vitamin D level.*

INTRODUCTION

Vitamin D is a hormone that plays an important role in various organ systems, including the musculoskeletal system. Vitamin D affects muscle mass by stimulating muscle cell proliferation and muscle function by exerting both genomic and non-genomic effects. Vitamin D deficiency is known to cause muscle weakness.[1] In older populations, many people have been found to have vitamin D deficiency. Although Indonesia is a tropical country with abundant sunshine, the prevalence or proportion of vitamin D deficiency in older adults is quite high.[2,3]

Frailty is a geriatric syndrome characterized by a decrease in various organ functions that make individuals more vulnerable to stressors. Decreased hand grip strength and walking speed, weight loss, fatigue, and low physical activity are phenotypes of frailty.[4] Older adults with a frail condition easily fall into disability conditions, require hospital care, have low quality of life and high mortality.[5] Vitamin D deficiency is considered to be one of the causes of sarcopenia and frailty.[6,7] Studies found that pre-frail conditions are more common than frail conditions in older adults.[8] Pre-frail seniors with vitamin D deficiency are at increased risk of frailty and mortality compared with those who are not[9], which highlights the importance of maintaining good vitamin D status in pre-frail older adults to prevent deterioration into a frail condition.

However, studies on the relationship between vitamin D levels and hand grip strength have reported inconsistent results. While several studies have reported an association[10-14], others have found no relationship.[15-19] As far as the researcher is concerned, until now, there has been no research on the vitamin D level and its correlation with hand grip strength in pre-frail older adults. Therefore, this study aimed to determine vitamin D levels in older adults with a pre-frail condition and its correlation with hand grip strength.

METHODS

This cross-sectional study consecutively recruited older adults aged ≥ 60 years who were visiting the outpatient geriatric clinic at Cipto Mangunkusumo Hospital in Jakarta, Indonesia from June to August 2021. The inclusion criteria were pre-frail older adults as defined by the Cardiovascular Health Study[4], and who could understand and follow instructions. We excluded older adults who had acute medical conditions or exacerbation of previous medical conditions, who had conditions that could affect the assessment of muscle performance, such as paresis, who had cognitive impairment (abbreviated mental test score < 8), and mental status disorder/depression (Geriatric Depression Scale score > 10), or who refused to participate. All participants provided written informed consent before the study began. Ethical approval was obtained from Ethical Committee of the Faculty of Medicine Universitas Indonesia.

The comorbidity index of each participant was evaluated using the Cumulative Illness Rating Scale (CIRS)[20], nutritional status was evaluated based on the Mini Nutritional Assessment[21] which classified into normal (≥24), risk of malnutrition (17-23.5) and malnutrition (<17); functional status was evaluated based on Barthel's Activity of Daily Living (ADL) Index[22] which classified into totally dependent (0–4), severely dependent (5–8), moderately dependent (9–11), mildly dependent (12–19), and independent (20); sarcopenia was evaluated using the SARC-F[23] which classified into score ≥ 4 (at risk of sarcopenia) and score <4; nutritional intake was evaluated using a 3-day food recall (2 working days and 1 holiday), and body mass index (BMI) was evaluated based on Asia-Pacific criteria.[24] Sun exposure was evaluated using questionnaire to assess time in sun and skin exposure[25], and divided into 2 categories low (≤18) and moderate-high (19-56) exposure.[26] All data were collected from the patient's medical history and medical record.

Hand grip strength was measured three times in the dominant hand using a Jamar hydraulic dynamometer and the average was taken. Serum vitamin D levels (measured as 25(OH) D) were determined using the enzyme-linked immunosorbent assay technique with commercial 25-OH Vitamin D reagent (Euroimmun). Serum vitamin D was classified into three levels: normal (≥ 30 ng/mL), insufficient (20–<30 ng/mL), and

deficient (< 20 ng/mL).

The data were analysed using SPSS statistical package software. Descriptive data were presented in the form of text and tables. Subjects characteristics presented in number and percentages, mean and standard deviation if the distribution was normal, or median and interquartile range (IQR) if the distribution was not normal. Pearson's test was used for the correlation between vitamin D levels and hand grip strength if the distribution was normal, and the Spearman correlation test if the distribution was not normal. Multiple linear regression analysis was performed to evaluate the influence of other variables which were considered to affect hand grip strength. Values of $P < 0.05$ were considered statistically significant.

RESULTS

Of the 95 subjects who fulfilled the selection criteria, the mean age was 70.08 ± 5.35 years. Most subjects were female (67.4%). The median overall vitamin D level was 17.91 (IQR 13.68–26.36) ng/mL. Overall, 11.6% of the pre-frail older adults had a normal vitamin D level, whereas most of the others had an insufficient (34.7%) or deficient (53.7%) level. Most of the participants had normal nutritional status, independent functional status, obesity and no sarcopenia. Subjects in the vitamin D deficient group tended to have a higher BMI and lower vitamin D intake than did those in the normal groups. Hand grip strength in the subjects with normal vitamin D levels was higher than in subjects with insufficiency and deficiency. Female subjects had lower serum vitamin D level [median 17.6 ng/ml (IQR 12.66-24.83)] than male [median 23.95 ng/ml (IQR 16.63-29.59)]. Obesity had lowest vitamin D level [16.2 ng/ml (IQR 12.95-24.4)] followed by overweight [20.59 ng/ml (IQR 15.82-28.01)], normal [23.28 ng/ml (IQR 15.08-29.93)] and underweight subjects (29.59 ng/ml). General characteristics of subjects and characteristic based on vitamin D status showed in **Table 1** and **Table 2**.

A significant positive correlation was found between vitamin D levels and hand grip strength ($r = 0.283$, $P = 0.006$) (**Figure 1**).

Table 1. Characteristics of the study subjects.

Characteristics	Total (N=95)
Age, mean (SD)	70.08 (5.04)
Age group, n (%)	
- 60-69 years	40 (42.1)
- 70-79 years	50 (52.6)
- ≥ 80 years	5 (5.3)
Sex, n (%)	
- Male	31 (32.6)
- Female	64 (67.4)
Body Mass Index/ BMI (kg/m^2), mean (SD)	
- Male	24.9 (3.86)
- Female	25.8 (3.65)
BMI category, n (%)	
- Underweight	1 (1.1)
- Normal	25 (26.3)
- Overweight	20 (21.1)
- Obesity	49 (51.6)
Comorbidities, n (%)	
- Diabetes melitus	43 (45.3)
- Hypertension	76 (80)
- Dyslipidemia	61 (64.2)
- Osteoarthritis	42 (44.2)
- Coronary heart disease	20 (21.1)
- Congestive heart disease	14 (14.7)
- Chronic Obstructive Pulmonary Disease	3 (3.2)
- Osteoporosis	3 (3.2)
- Benign Prostatic Hyperplasia	18 (18.9)
- Peripheral arterial disease	3 (3.2)
CIRS score, n (%)	
- ≤ 5	24 (25.3)
- >5	71 (74.7)
Number of drugs, n (%)	
- 0-4	19 (20)
- 5-10	64 (67.4)
- >10	11 (11.6)
Vitamin D supplementation, n (%)	
- Yes	29 (30.5)
- No	66 (69.5)
Sun exposure score, median (IQR)	21 (14-28)
Sun exposure, n (%)	
- Low exposure	40 (42.1)
- Moderate - high exposure	55 (57.9)
MNA score, n (%)	
- Normal (≥24)	91 (95.8)
- Risk of malnutrition (17-23.5)	4 (4.2)

Barthel ADL score, n (%)	
- Independent	86 (90.5)
- Mild dependent	9 (9.5)
Nutritional intake, median (IQR)	
- Protein (gram)	55.6 (44.4-63.9)
- Vitamin D (mcg)	1.6 (0.6-5.8)
Handgrip strength (kg), mean (SD)	23.53 (5.04)
SARC-F Score, n (%)	
- < 4	77 (81.1)
- ≥ 4 (risk of Sarcopenia)	18 (18.9)
25(OH)D (ng/ml), median (IQR)	17.91 (13.68-26.36)

Using linear regression analysis, after adjusting for variables age, BMI, comorbidities, protein intake, nutritional status, functional status, and sun exposure score, vitamin D levels remained significantly correlated with standard coefficient beta = 0.255 (P = 0.013).

DISCUSSION

The results of this study showed that in pre-frail older adults, only 11.6% had a normal vitamin D level; most had an insufficient or deficient level. This result is in line with studies

Table 2. Subject characteristics based on vitamin D status.

Characteristics	Normal (≥ 30 ng/ml) (N=11)	Insufficiency (20-<30 ng/mL) (N=33)	Deficiency (<20 ng/mL) (N=51)
Age, mean (SD)	69.64 (5.35)	70.64 (5.49)	69.82 (4.75)
Age group, n (%)			
- 60-69 years	5 (12.5)	13 (32.5)	22 (55)
- 70-79 years	5 (10)	17(34)	28 (56)
- ≥ 80 years	1 (20)	3 (60)	1 (20)
Sex, n (%)			
- Male	7 (22.6)	13 (41.9)	11 (35.5)
- Female	4 (6.3)	20 (31.3)	40 (62.5)
BMI (kg/m2), mean (SD)			
- Male	23.04 (2.88)	24.98 (3.86)	25.99 (4.28)
- Female	23.3 (4.79)	25.34 (3.64)	26.21 (3.52)
BMI category, n (%)			
- Underweight	0	1 (100)	0
- Normal	6 (24)	9 (36)	10 (40)
- Overweight	3 (15)	8 (40)	9 (45)
- Obesity	2 (4.1)	15 (30.6)	32 (65.3)
CIRS score, n(%)			
- ≤ 5	0	9 (37.5)	15 (62.5)
- >5	11 (15.5)	24 (33.8)	36 (50.7)
Number of drugs, n (%)			
- 0-4	2 (10.5)	7 (36.8)	10 (52.6)
- 5-10	5 (7.8)	23 (35.9)	36 (56.3)
- >10	4 (36.4)	2 (18.2)	5 (45.5)
Vit D supplementation, n (%)			
- Yes	4 (13.8)	12 (41.4)	13 (44.8)
- No	7 (10.6)	21 (31.8)	38 (57.6)
Sun exposure, n (%)			
- Low exposure	5 (12.5)	15 (37.5)	20 (50)
- Moderate-high exposure	6 (10.9)	18 (32.7)	31 (56.4)
Sun exposure score, median (IQR)	21 (9-30)	20 (12-27.5)	22 (15-28)
MNA score, n (%)			
- Normal (≥24)	10 (11)	31 (34.1)	50 (54.9)
- Risk of malnutrition (17-23.5)	1 (25)	2 (50)	1 (25)

Barthel ADL score, n (%)			
- Independent	11 (12.8)	31 (36)	44 (51.2)
- Mild dependent	0	2 (22.2)	7 (77.8)
Handgrip strength (kg), mean (SD)	26.87 (4.12)	24.29 (5.44)	22.31 (4.59)
Nutritional intake, median (IQR)			
- Protein (gram)	55.7 (44.1-65.3)	57.9 (44.6-72.5)	51.1 (44.4-62.1)
- Vitamin D (mcg)	3.86 (1.2-6.5)	1.2 (0.5-9.95)	1.6 (0.6-5.1)
SARC-F score, n (%)			
- < 4	9 (11.7)	29 (37.7)	39 (50.6)
- ≥ 4 (risk of Sarcopenia)	2 (11.1)	4 (22.2)	12 (66.7)
25(OH)D (ng/ml), median(IQR)	31.33 (30.86-34.32)	25.23 (23.48-27.8)	14.04 (11.83-16.63)

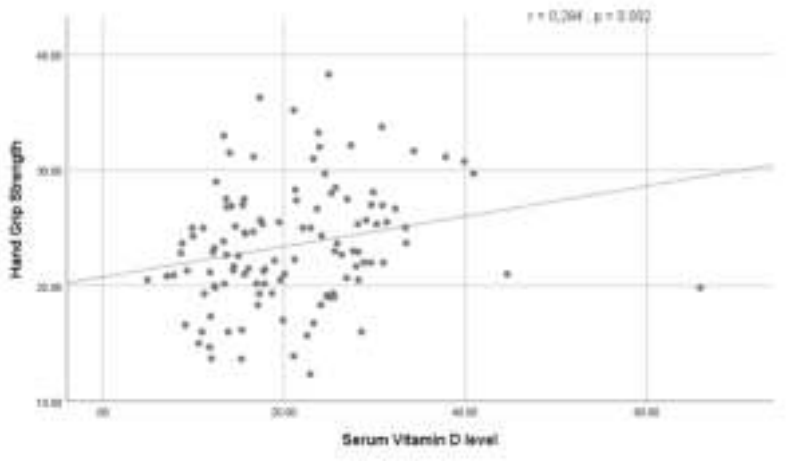


Figure 1. Correlation between serum vitamin D levels and hand grip strength

in other tropical countries such as Singapore, where 14.2% of older adults in a rehabilitation unit were found to have normal vitamin D levels.[27] In Indonesia, studies have shown that older adults are more likely to have inadequate vitamin D levels. A study of older adults in the PUSAKA Jakarta community by Sudarma et al.[28] found that the proportion of individuals with vitamin D deficiency was 80.2%, followed by insufficiency, at 15.9%; normal vitamin D levels were found in only 4%. Biben et al.[3] conducted a study in West Java and implemented a higher hypovitaminosis D cut-off value of < 36 ng/mL (compared with the laboratory reference cut-off of ≤29.9 ng/mL) as determined based on parathyroid hormone suppression, and found that this cut-off point increased the proportion of individuals with vitamin D deficiency from 90.9% to 94.3%. Our study found a higher percentage of older persons with vitamin D deficiency compared to the study by Setiati et al.[2] in nursing home, which found a 35% deficiency prevalence. This could be owing to variations in the settings, as our study was conducted in older persons at an outpatient clinic, who have various comorbidities that can be linked to low vitamin D levels.

Several factors are known to contribute to vitamin D deficiency in seniors, such as decreased vitamin D intake, increased body fat, decreased synthesis of vitamin D in the skin, a lack of outdoor activity and exposure to sunlight, and decreased kidney function1.[29,30] Based on the nutritional adequacy rate of older adults in Indonesia[31], vitamin D intake in the subjects in our study was low, even though the majority of the subjects had a good nutritional status. In our study, the majority of subjects had a low daily intake of vitamin D, in line with the findings of a systematic review on the older population in Indonesia, which showed a high prevalence of low vitamin D intake.[32] A lack of understanding

about balanced nutrition and inadequate income for consuming foods high in vitamin D may also lead to insufficient vitamin D intake.

The higher percentage of overweight and obesity found in this study may also be contributing factors to vitamin D deficiency and/or insufficiency. Previous studies have reported an association between low vitamin D levels and high BMI and body fat percentage in older adults.[33] Hypothesized mechanisms underlying the association between obesity and low vitamin D levels include differences in the lifestyle of individuals with obesity, such as eating habits, sedentary lifestyle, clothing used, the presence of vitamin D storage in adipose tissue, and impaired hydroxylation in the liver.[34,35] A meta-analysis found that the prevalence of vitamin D deficiency was 35% higher in obese than in eutrophic subjects (prevalence ratio 1.35; 95% confidence interval [CI], 1.21–1.5) and 24% higher in overweight subjects (prevalence ratio 1.24; 95% CI 1.14–1.34).[36]

According to our findings, vitamin D deficiency/insufficiency was more common in females than in males. This might be due to larger body mass index in female than male. Studies reported that females tend to have lower levels of vitamin D than males.[37,38] This sex difference occurs mainly because of the female behaviour of protecting themselves from sun exposure for reasons of beauty, the need for using sunscreen, and more closed dress style, especially in Muslim women.[38]

Although this study discovered that sun exposure scores were generally higher in subjects with vitamin D deficiency compared to those with normal vitamin D levels, the proportion of older adults who were vitamin D deficient remained higher than that of individuals with normal/insufficient vitamin D. This could be related to the lower vitamin D intake in the deficient group. Even though subjects in this study seemed to follow Indonesian Ministry of Health recommendation for older adults to keep sunbathing during the COVID-19 pandemic,[39] the possibility of ineffective vitamin D synthesis in older adults cannot be ruled out as a cause of vitamin D deficiency.[40] Sunlight promotes vitamin D synthesis in the skin and sun exposure is known to increase vitamin D levels. It is estimated that nearly 90% of the body's vitamin D comes from sunlight activation through skin synthesis.[40] After exposure to UVB sunlight (wavelength 290–315 nm), photolysis of 7-dehydrocholesterol (provitamin D3) in the skin transforms into pre-vitamin D3, which is then isomerized to vitamin D3.[41] Setiati et al.[42] reported that older adults in nursing homes who were exposed to sunlight for 25 minutes at 09:00, three times a week for 6 weeks, showed an increase in vitamin D levels from 59 to 84 nmol/L.

Based on a meta-analysis, frailty is associated with low vitamin D levels, where the lower the vitamin D level, the more severe the frailty status.[6,43] Several studies have linked vitamin D levels to a frailty component, whereas weakness, low physical activity, fatigue, and low gait speed are all associated with low vitamin D levels.[44,45] Individuals with these conditions tend to be physically inactive, which disturbs the balance of protein metabolism in the muscles. Older populations are at risk of adverse effects due to vitamin D deficiency. Inadequacy of vitamin D levels are also associated with a number of chronic diseases in addition to frailty[46], but this condition can be improved.

The results of the present study revealed a significant positive correlation between serum vitamin D levels and hand grip strength in older adults with a pre-frail condition. This is in line with studies on older women in the community by Caniago et al.[13], older outpatients by Bachry et al.[14], older males by Kocak et al.10, and patients with hip fracture by Dhanwal et al.[11] However, our results differ from a population study that included Korean men aged ≥ 50 years and postmenopausal women[16] and a Taiwanese study of participants aged ≥ 55 years[18], which reported finding no relationship between vitamin D and hand grip strength or between vitamin D and performance on the Short Physical Performance Battery (SPPB). Vitamin D is known to influence skeletal muscle through both genomic and non-genomic effects. Through genomic effects, vitamin D binds to the vitamin D receptor (VDR) in the cell nucleus, inducing gene transcription in myoblasts, thereby resulting in the proliferation and differentiation

of muscle cells. Through non-genomic effects, via regulatory pathways, the calcium messenger system affects signal transduction and affects skeletal muscle contraction.[1,47]

To the best of our knowledge, our study is the first to evaluate the vitamin D level and its relationship with hand grip strength in older adults with a pre-frail condition in Indonesia. However, because this was an observational study, no causal relationship could be investigated. Further research is needed to evaluate whether vitamin D supplementation can improve physical performance in pre-frail older adults and help prevent frailty.

CONCLUSION

In older adults with a pre-frail condition, proportion of vitamin D deficiency and insufficiency were high. There was positive correlation between serum vitamin D levels and hand grip strength in pre-frail older adults.

ACKNOWLEDGMENTS

The authors would like to thank all participants and nurses at geriatric clinic Cipto Mangunkusumo Hospital.

CONFLICT OF INTEREST

All authors have no conflict of interest.

REFERENCES

1. Halfon M, Phan O, Teta D. Vitamin D: a review on its effects on muscle strength, the risk of fall, and frailty. Biomed Res Int. 2015;2015.
2. Setiati S. Vitamin D status among Indonesian elderly women living in institutionalized care units. Acta Med Indones. 2008;40(2):78-83.
3. Biben V, Defi I, Nugraha G, Setiabudiawan B. Vitamin D status and its impact on body composition in elderly community-dwelling individuals in Bandung and Sumedang, West Java Province, Indonesia. Asian J Epidemiology. 2017;10:63-9.
4. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.
5. Bernabei R, Martone AM, Vetrano DL, Calvani R, Landi F, Marzetti E. Frailty, physical frailty, sarcopenia: A new conceptual model. Stud Health Technol Inform. 2014;203:78-84.
6. Marcos-Perez D, Sanchez-Flores M, Proietti S, et al. Low vitamin d levels and frailty status in older adults: A systematic review and meta-analysis. Nutrients. 2020;12(8):1-20.
7. Visser M, Deeg DJ, Lips P, Longitudinal Aging Study A. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab. 2003;88(12):5766-72.
8. O'Caoimh R, Sezgin D, O'Donovan MR, et al. Prevalence of frailty in 62 countries across the world: a systematic review and meta-analysis of population-level studies. Age Ageing. 2021;50(1):96-104.
9. Shardell M, D'Adamo C, Alley DE, et al. Serum 25-hydroxyvitamin D, transitions between frailty states, and mortality in older adults: the Invecchiare in Chianti Study. J Am Geriatr Soc. 2012;60(2):256-64.
10. Kocak MZ, Aktas G, Atak B, et al. The association between vitamin D levels and handgrip strength in elderly men. Acta Endocrinol (Buchar). 2020;16(2):263-6.
11. Dhanwal DK, Dharmshaktu P, Gautam VK, Gupta N, Saxena A. Hand grip strength and its correlation with vitamin D in Indian patients with hip fracture. Arch Osteoporos. 2013;8:158.
12. Mendes J, Santos A, Borges N, et al. Vitamin D status and functional parameters: A cross-sectional study in an older population. PloS one. 2018;13(8):e0201840.
13. Caniago MR, Ngestiningsih D, Fulyani F. Hubungan antara kadar vitamin D dengan kekuatan genggam tangan lansia. Jurnal Kedokteran Diponegoro (Diponegoro Medical Journal). 2019;8(1):300-12.
14. Bachry NC, Riviati N, Kusnadi Y, Bahar E. Correlation of vitamin D serum levels with muscle mass, muscle strength, and physical performance in the elderly community in Mohammad Hoesin General Hospital Palembang. Bioscientia Medicina: Journal of Biomedicine & Translational Research. 2021;5 (3):307-19.
15. Mathei C, Van Pottelbergh G, Vaes B, Adriaensen W, Gruson D, Degryse JM. No relation between vitamin D status and physical performance in the oldest old: results from the Belfrail study. Age Ageing. 2013;42(2):186-90.
16. Kim BJ, Kwak MK, Lee SH, Koh JM. Lack of association between vitamin D and hand grip strength in Asians: A nationwide population-based study. Calcif Tissue Int. 2019;104(2):152-9.
17. Annweiler C, Beauchet O, Berrut G, et al. Is there an association between serum 25-hydroxyvitamin D concentration and muscle strength among older women? Results from baseline assessment of the EPIDOS study. J Nutr Health Aging. 2009;13(2):90-5.
18. Chuang SC, Chen HL, Tseng WT, et al. Circulating 25-hydroxyvitamin D and physical performance in older adults: a nationwide study in Taiwan. Am J Clin Nutr. 2016;104(5):1334-44.
19. Vaes AMM, Brouwer-Brolsma EM, Toussaint N, et

al. The association between 25-hydroxyvitamin D concentration, physical performance and frailty status in older adults. Eur J Nutr. 2019;58(3):1173-81.
20. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. 1968;16(5):622-6.
21. Vellas B, Guigoz Y, Garry PJ, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition (Burbank, Los Angeles County, Calif). 1999;15(2):116-22.
22. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL index: a reliability study. International disability studies. 1988;10(2):61-3.
23. Malmstrom TK, Morley JE. SARC-F: a simple questionnaire to rapidly diagnose sarcopenia. J Am Med Dir Assoc. 2013;14(8):531-2.
24. World Health Organization. Regional Office for the Western P. The Asia-Pacific perspective: redefining obesity and its treatment: Sydney: Health Communications Australia; 2000.
25. Hanwell HE, Vieth R, Cole DE, et al. Sun exposure questionnaire predicts circulating 25-hydroxyvitamin D concentrations in Caucasian hospital workers in southern Italy. J Steroid Biochem Mol Biol. 2010;121(1-2):334-7.
26. Olmedo-Martín RV, González-Molero I, Olveira G, Amo-Trillo V, Jiménez-Pérez M. Sunlight exposure in inflammatory bowel disease outpatients: Predictive factors and correlation with serum vitaminD. Gastroenterologia y hepatologia. 2019;42(10):604-13.
27. Neo JJ, Kong KH. Prevalence of vitamin D deficiency in elderly patients admitted to an inpatient rehabilitation unit in Tropical Singapore. Rehabil Res Pract. 2016;2016:9689760.
28. Sudarma V HL. High skeletal muscle mass is associated with increased serum 25(OH)D levels in elderly. Univ Med. 2017;36:236-42.
29. Meehan M, Penckofer S. The Role of Vitamin D in the Aging Adult. J Aging Gerontol. 2014;2(2):60-71.
30. de Jongh RT, van Schoor NM, Lips P. Changes in vitamin D endocrinology during aging in adults. Mol Cell Endocrinol. 2017;453:144-50.
31. Peraturan Menteri Kesehatan Nomor 28 Tahun 2019 Tentang Angka Kecukupan Gizi yang Dianjurkan untuk Masyarakat Indonesia. Jakarta. 2019.
32. Dewiasty E, Agustina R, Saldi SRF, et al. Malnutrition prevalence and nutrient intakes of Indonesian community-dwelling older adults: A systematic review of observational studies. Front Nutr. 2022;9:780003.
33. Oliai Araghi S, van Dijk SC, Ham AC, et al. BMI and body fat mass is inversely associated with vitamin D levels in older individuals. J Nutr Health Aging. 2015;19(10):980-5.
34. Bennour I, Haroun N, Sicard F, Mounien L, Landrier JF. Vitamin D and obesity/adiposity-A brief overview of recent studies. Nutrients. 2022;14(10).
35. Vranic L, Mikolasevic I, Milic S. Vitamin D deficiency: Consequence or cause of obesity? Medicina (Kaunas). 2019;55(9).
36. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev. 2015;16(4):341-9.
37. Kim SH, Oh JE, Song DW, et al. The factors associated with Vitamin D deficiency in community dwelling elderly in Korea. Nutr Res Pract. 2018;12(5):387-95.
38. Nimitphong H, Holick MF. Vitamin D status and sun exposure in southeast Asia. Dermatoendocrinol. 2013;5(1):34-7.
39. Direktorat Jenderal Kesehatan Masyarakat. Panduan Pelayanan Kesehatan Lanjut Usia Pada Era Pandemi Covid-19. Jakarta: Kementerian Kesehatan Republik Indonesia; 2020.
40. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr. 2004;80(6 Suppl):1678S-88S.
41. Wacker M, Holick MF. Sunlight and Vitamin D: A global perspective for health. Dermatoendocrinol. 2013;5(1):51-108.
42. Setiati S. Pengaruh pajanan sinar ultraviolet B bersumber dari sinar matahari terhadap konsentrasi vitamin D (25(OH)D) dan hormon paratiroit pada perempuan usia lanjut Indonesia. Kesmas National Public Health Journal 2008;2 (4):147-53.
43. Zhou J, Huang P, Liu P, et al. Association of vitamin D deficiency and frailty: A systematic review and meta-analysis. Maturitas. 2016;94:70-6.
44. Vogt S, Decke S, de Las Heras Gala T, et al. Prospective association of vitamin D with frailty status and all-cause mortality in older adults: Results from the KORA-Age Study. Prev Med. 2015;73:40-6.
45. Shardell M, Hicks GE, Miller RR, et al. Association of low vitamin D levels with the frailty syndrome in men and women. J Gerontol A Biol Sci Med Sci. 2009;64(1):69-75.
46. Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. Mayo Clin Proc. 2013;88(7):720-55.
47. Christakos S, Hewison M, Gardner DG, et al. Vitamin D: beyond bone. Ann N Y Acad Sci. 2013;1287:45-58.

The Characteristic of Recurrent Malaria Episode: An Observational Study in Timika Papua

Novyan Lusiyana, Anggia Fitria Agustin*

Department of Parasitology, Faculty of Medicine Universitas Islam Indonesia- Yogyakarta, Indonesia.

Corresponding Author:
Novyan Lusiyana, MD., M.Sc. Department of Parasitology, Faculty of Medicine Universitas Islam Indonesia, Yogyakarta, Indonesia. Email: 107110411@gmail.com.

ABSTRACT

Background*: People living in malaria endemic areas are at risk of suffering from the recurrent malaria episodes. The recurrent episode of malaria can be determined by various factors and will bring some serious impacts on all life aspects. This study aims to identify malaria demographics and factors associated with the recurrent episodes of malaria in Timika, Papua.* ***Methods****: This observational study used medical record data from the Naena Muktipura Sub-District Health Center, Timika Papua in 2020. Plasmodium infection was identified based upon microscopic examination. Subjects were then categorized into positive and negative malaria followed by the determination of the positivity rate. Each case of malaria was traced regarding frequency, time, and type of Plasmodium. The recurrent episodes of malaria were defined as Plasmodium infections occurred more than once in a year. Demographic data including age, sex, and ethnicity were then analyzed using Chi square.* ***Results****: The incidence of recurrent malaria in Timika Papua was 16% with the highest positivity rate occurred in June. The most recurrent episodes of malaria were 2 episodes (77.2%) in which men were more at risk (OR 2.512). Meanwhile, ethnicity and age were not associated with recurrent episodes. Most of recurrent episodes of malaria are caused by the similar plasmodium species, particularly Plasmodium falciparum (82.25%) with the shortest interval between episodes of 14 days.* ***Conclusion****: Malaria is mostly experienced by men, of productive age and Javanese ethnicity. Men were found more at risk of experiencing recurrent episodes of malaria. The identification of these demographic factors is important to issue the policies on malaria elimination and malaria transmission termination in Timika, Papua.*

Keywords: *Malaria, epidemiological characteristic, recurrent episode, Timika Papua.*

INTRODUCTION

Malaria still becomes a global health issue as proven by the 87 countries with malaria endemic status. Southeast Asia Region is one of the regions with the highest number of malaria cases in the world in which Indonesia becomes the country with the highest number of cases in that region.[1] The high morbidity of malaria leads to the increasing health cost both for treatment and for prevention.[2] One of the malaria endemic areas in Indonesia is Timika Regency, Papua Province.[3] Timika consists of forests, beaches, swamps and has high rainfall throughout the year.[4] Regional characteristics and sociodemographic factors of the community have caused the local transmission of malaria to occur continuously; as a consequence, the residents in endemic areas are at risk of being infected with Plasmodium more than one episode.[5-7]

The prevalence of recurrent episodes of malaria reaches 16%, in which the average within 5 years can reach 5-16 episodes.[8,7] Recurrent episodes are determined by age, sex, ethnicity, occupation and history of malaria in the family.[7]

Previous study stated that the episode of malaria is not associated with an inadequate immune system, but more associated with recurrent Plasmodium infection.[8] This condition is mainly experienced by children and then decreases along with aging.[9] Children are the potential reservoir in malaria transmission.[10] In which the parasitemia of children is higher than that of adult.[11] It has been suggested that epidemiological characteristic could lead to caused recurrent of malaria episode, but there are yet no published data.

The recurrent malaria episode can be caused by failure of malaria treatment that caused recrudescence, reinfection from mosquito bite, or reactivation of hypnozoite stadium in liver called relaps.[3] This recurrent malaria can impose severe burdens not only for the people but also governments. The impact on malaria patients also varies, such as decreases work productivity and cognitive decline in school children. Far, little is known about the condition of recurrent malaria episode especially in Timika as a high endemic area in Indonesia.[3] Identifying factors associated with recurrent episode of malaria, which is core indicator of this study, can give valuable information. All these factors need to be studied in depth to formulate the policies on malaria prevention efficiently.

METHODS

This observational study used medical record data at the Sub-District Health Center of Naena Muktipura, Timika, Papua. It has received approval from the health research ethics committee of the Faculty of Medicine, Islamic University of Indonesia with number 2/Ka.Kom. Et/70/KE/VI/2021.

Data Collection

Malaria cases were found by tracing malaria examination data carried out by officers during 2020 that met the inclusion and exclusion criteria. All malaria cases between 1 January 2020 and 31 December 2020 in sub-district health center of Naena Muktipura, were enrolled (**Figure 1**). Totality sampling is used to determine the sample size. Based on observational sample size, only 246 samples were needed, while the sample on this study was 386. The research was conducted in Naena Muktipura Village. This village is one of the high endemic villages for malaria and there is a sub-district health center to facilitate the residents to have medical treatment Malaria cases in the sub-health center were obtained through passive case detection (PCD). Malaria negative and RDT examination for diagnosis malaria, incomplete medical record was also excluded. Patients who examined with RDTs

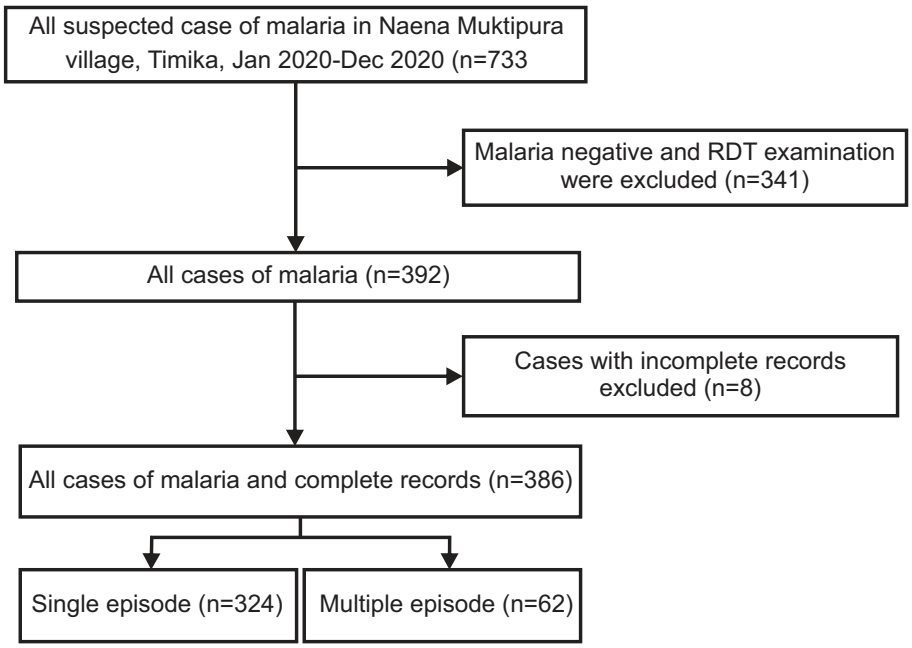


Figure 1. Flowchart of patients included and excluded.

were excluded, so bias could result from it. The diagnosis by RDT was not analyzed because the type of RDTs that used could not identify the plasmodium species.

Research Variables

The subjects of this study were all villagers showing symptoms related to malaria and were examined for malaria at the Naena Muktipura Sub-District Health Center. The diagnosis of malaria was done when *Plasmodium sp.* was found on microscopic examination as a gold standard for diagnose malaria. From the results of microscopic examination, Plasmodium species (*Plasmodium falciparum* and *Plasmodium vivax*) can be identified. The number of malaria incidents in the same person during 2020 was defined as the recurrent episode of malaria. The incidence of malaria in one month was also recorded to calculate the positivity rate.

Each malaria case was continued by recording demographic data including age, sex, ethnicity, Plasmodium type, and number of malaria episodes. The recurrent episodes of malaria were defined as *Plasmodium* infections occurred more than once throughout 2020. Each incident of recurrent episodes of malaria was recorded in the form of the month of infection, type of *Plasmodium* and the distance between episodes. The interval between episodes was defined as the average number of days between recurrent episodes.

Statistical Analysis

We analyzed the data using SPSS and the demographic characteristics of the subject were presented in a descriptive form. The positivity rate for malaria was obtained by adding up the malaria cases in one month divided by all malaria examinations within one month in percent units.[12] The correlation of the demographic characteristics of the subjects and recurrent episodes of malaria was analyzed using the Chi Square test.

RESULTS

Patients' Characteristic and Positivity Rate of Malaria in Naena Muktipura Village

In 2020 Naena Muktipura Village was populated by1492 people. During this year, a total of 733 people were examined related to malaria and 386 (52.66%) of them confirmed malaria. The incidence of malaria in Naena Muktipura Village in 2020 reached 25.87%. As shown in **Table 1**, malaria in Naena Muktipura Village was dominated by men (60.88%), in the range of 15-64 years old (64.25%) and were those as the ethnic Javanese (42.49%). The highest positivity rate occurred in June, i.e., 65 cases (60.18%) and the lowest one occurred in May with 13 cases (38.23%) (**Table 2**).

Table 1. Characteristics of malaria demography in Naena Muktipura Village.

Variables	Total
Gender, n (%)	
Male	235 (60.88)
Female	151 (39.12)
Age (years), n (%)	
0-11	4 (1.03)
1-4	31 (8.03)
5-9	36 (9.33)
10-14	55 (14.25)
15-64	248 (64.25)
>64	12 (3.11)
Ethnic, n (%)	
Timika	65 (16.84)
Java	164 (42.49)
East Nusa	123 (31.86)
Papua	9 (2.33)
Sulawesi	23 (5.95)
Sumatra	2 (0.53)

Table 2. Positivity Rate Malaria in pada 2020.

Month	Malaria Examination, n (%)		Total
	Positive	Negative	
January	39 (52)	36 (48)	75
February	9 (47.4)	10 (52.6)	19
March	6 (54.54)	5 (45.45)	11
April	17 (42.5)	23 (57.5)	40
Mei	13 (38.23)	21 (61.77)	34
June	65 (60.18)	43 (39.82)	108
July	54 (64.28)	30 (35.72)	84
August	56 (64.36)	31 (35.64)	87
September	48 (46.6)	55 (53.39)	103
October	30 (46.15)	35 (53.85)	65
November	23 (40.35)	34 (59.65)	57
December	26 (52)	24 (48)	50
Total	386 (52.66)	347 (47.34)	733

Correlation of Risk Factor and Recurrent Malaria in Timika

Episodes of malaria in 2020 were dominated by single episodes of malaria by 324/386 people (83.93%), while 62 people (16.06%) experienced

the recurrent episodes of malaria dominated by men (12.43%), aged 15-64 years (66.1%), and Javanese ethnic (17.7%). As shown in **Table 3**, the recurrent episodes of malaria in sequence from the highest number included 2-episodes (48 people; 77.42%), 3-episodes (12 people; 19.35%) and 4-episodes (2 people; 3.23%). A total of 48 people experienced 2 recurrent episodes, and the most recurrent episodes were 4 episodes within one year. A total of 21/62 children (33.87%) were children ≤15 years old, and one of them experienced 4-episodes within one year. The results of the Chi Square test showed that age and ethnicity were not associated with malaria episodes (p>0.05), while sex was associated with malaria episodes (p=0.004). The proportion of recurrent episodes of malaria in males was 2.51 times higher than that of females.

Plasmodium Type in Multiple Episode

Subsequently, it was continued to analyze the types of plasmodium and multiple malaria. The Plasmodium species identified in Naena Muktipura Village were *Plasmodium falciparum* and *Plasmodium vivax*. *Plasmodium falciparum* was the most common type (82.25%; n=51/62) (**Table 4**). Recurrent infections caused by the similar Plasmodium species were experienced by 50% of people, most of which were caused by *P. falciparum* (32.26%; n=20/62), followed by *P. vivax* (17.74%; n=11/62), while 31/62 people (50 %) experienced recurrent infections by 2 Plasmodium species. The mean time between the nearest malaria episodes was from episode 2 to episode 3 (72 days) and the shortest distance between episodes was 14 days (**Table 4**).

Table 3. Correlation of risk factors and recurrent malaria in Timika.

Characteristic	Single Episode	Multiple Episode			Total	p
		2nd	3th	4th		
Sex, n (%)						
Male	187 (48.45)	34 (54.84)	12 (19.35)	2 (3.22)	235 (60.88)	0.004*; OR 2.512 (1.331-4.739)
Female	137 (35.5)	14 (22.58)	0	0	151 (39.12)	
Age (year), n (%)						
0-0,11	3 (0.9)	0	0	0	4 (1.03)	0.763
1-4	26 (8)	5 (8.06)	0	1 (1.62)	31 (8.03)	
5-9	30 (9.3)	5 (8.06)	1 (1.62)	0	36 (9.33)	
10-14	46 (14.2)	5 (8.06)	4 (6.45)	0	55 (14.25)	
15-64	207 (63.9)	33 (53.23)	7 (11.29)	1 (1.62)	248 (64.25)	
>64	12 (3.7)	0	0	0	12 (3.11)	
Ethnic, n (%)						
Timika	55 (84.6)	8 (12.9)	1 (1.62)	1 (1.62)	65 (16.84)	0.287
Java	135 (82.3)	21 (33.87)	7 (11.29)	0	164 (42.49)	
Nusa Tenggara	102 (82.9)	19 (30.65)	3 (4.84)	1 (1.62)	123 (31.86)	
Papua	9 (100)	0	0	0	9 (2.33)	
Sulawesi	22 (95.7)	0	0	0	23 (5.95)	
Sumatra	1 (50)	0	1 (1.62)	0	2 (0.53)	

Table 4. Plasmodium types and distance in malaria episodes.

Characteristics of malaria episode	Number
Type of *Plasmodium*	
P.f - P.f	18 (29.03)
P.f - P.f - P.f	2 (3.23)
P.v - P.v	7 (11.29)
P.v - P.v - P.v	4 (6.45)
Mix	31 (50)
Time transition of malaria episodes (day)	
Episode 1 to 2	94±64,46 (14-328)
Episode 2 to 3	72.14±56.19 (14-214)
Episode 3 to 4	96.5±101.11 (25-168)

Plasmodium falciparum (*P. f*); *Plasmodium vivax* (*P. v*); mix (*P.f* + *P.v*)

DISCUSSION

The results of this study indicated that more males suffered from recurrent episodes of malaria compared to females. Men were more at risk of suffering from malaria i.e. 2.51 times compared to women, as also shown in other studies.[7,12,13] This might be caused by the occupation of males as a farmer in which this occupation became one of predisposition factors of the malaria incidence.[14] Working as a farmer has made them to work outside leading them to be more potential to have a contact with the malaria vector (*Anopheles sp*),[15] as the due to *Anopheles sp*. activity was outdoor in nature, and exophagic feeding.[16,17] This is supported with information showing that malaria transmission occurs outdoors more.[16]

In Timika, malaria was dominated by those at productive age (64.25%) and this finding was found the same with other studies.[12] Most of the productive age population in endemic areas work as farmers. Agricultural land in malaria endemic area is new land resulted from the forest clearing.[4] The work located near forests and living near forests are one of the risks of malaria.[7,18] This phenomenon was similar to what has occurred in the border of Myanmar-Thailand where land clearing and staying in huts near fields can increase the risk of Plasmodium infection.[18]

Interestingly, the recurrent episodes of malaria were mostly experienced by people with ethnic Javanese living in Timika (42.49%). The results of this study are similar to those of previous studies stating that malaria was found in the immigrants more compared to the natives of Iran and Uganda.[19,20] This might be due to the fact that most of ethnics of the immigrants have been living in Timika for so long, thus they have been acculturated with the local environment and culture in Timika. The population of Timika consists of the natives of Timika and the migrants. The indigenous Timika tribe consists of Kamoro and Amume tribes, while the immigrant are mostly those coming from various regions in Indonesia, one of which is Javanese tribe.[21-24]

The prevalence of recurrent episodes of malaria in this study was found similar to a study in Thailand where 16% of malaria cases were the recurrent episodes of malaria.[7] 33.87% of cases of the recurrent episodes of malaria in this study occurred in children. The results of this study are in line with other studies showing that children aged ≤ 10 years are at risk of experiencing the recurrent episodes of malaria. The risk of recurrent episodes of malaria in children will decrease along with the aging.[25] This risk will recur until the 4th year after birth, while other studies mentioned at the age of 7 years.[25,26] The recurrent episodes of malaria in children might be related to the modifications of the immune system, where children who often experience recurrent malaria are more at risk of again experiencing the episodes of malaria.[26,27]

In this study, the distance between malaria episodes was in the range of 72 to 94 days and it was more related to the type of infecting *Plasmodium* and repeated exposure to *Plasmodium sp.* - not caused by the failure of immune system.[7,8] In endemic areas, the recurrent episode of malaria might be associated with the relapse, recrudescent and reinfection condition of *Plasmodium* sp.[28] Also, in endemic areas might occur up to 16 episodes, and the average episode per person per year might reach 5 episodes.[29]

Plasmodium species identified in this study included *P. falciparum* and *P. vivax*. 32% of cases of recurrent episodes of malaria were caused by *Plasmodium falciparum*. These findings were similar to those as reported by previous studies where recurrent infection of *P. falciparum* occurred in 64.51% cases. Meanwhile, other studies have shown that recurrent episodes of malaria can also be caused by different *Plasmodium*.[7,25,30] The results of this study revealed that 50% of cases were the mixed infections that might be associated with the incidence of cerebral malaria, although in mixed infections the proportion of organ failure will be more apparent.[31,32]

In Timika, Malaria cases can be found throughout the year, but an increase in cases occurs from June to September. The increasing cases was accompanied by an increase in rainfall from June to September with the highest rainfall of 819 mm3 in June.[21] High rainfall will cause areas dominated by swamps, sago forests

and shallow ponds inundated by rainwater. These characteristics are consistent with the characteristics of the Papua region where there are many stagnant waters in swamps, sago forests, shallow pools exposed to direct sunlight.[4] This location is a breeding place for mosquito *Anopheles sp*.[22,23] Also the existence of breeding place of *Anopheles sp.* near forests and agricultural land, and the activity of *Anopheles* mosquitoes, which are more active at night to suck the blood, makes malaria transmission continual.[24]

This research, nevertheless, also has some weaknesses. First, in this study there was no information regarding clinical manifestations of malaria cases due to limited information in medical records. This study also did not look at parasitemia as the examination carried out at the sub-district health center of Naena Muktipura only looked at *Plasmodium* species followed by calculating parasitemia. Patients diagnosed with malaria were also not subjected to re-evaluation of post-treatment microscopic examination. As a consequence, its relation to recurrent episodes and treatment success could not be evaluated. Further research also needs to identify the conditions of submicroscopic malaria and the incidence of recurrent episodes of malaria in Timika, Papua. This is necessary to be able to develop malaria control policies in Timika, Papua. This is in line with the endeavor to break the chain of malaria transmission to reduce the morbidity will decrease and to realize the malaria elimination immediately.

CONCLUSION

Men are more at risk of suffering from the recurrent episodes of malaria. Moreover, the incidence of recurrent malaria was more found in productive age and migrants, particularly those from Javanese ethnic. These results can be of particular concern to related agencies considering that the residents suffering from the recurrent episodes might become a reservoir of malaria transmission. Also, it is necessary to evaluate malaria examination to ensure the *Plasmodium* elimination in the patient's blood to prevent recurrence and break the chain of malaria transmission, especially in endemic areas.

ACKNOWLEDGMENTS

We thank all parties that contributed to the accomplishment of this research. We also express our gratitude to all staff of the sub-district health center of Naena Muktipura Village.

CONFLICT OF INTEREST

The researcher declared that there will be no conflict of interest in this research

FUNDING

This research has been funded by the Research Grant of Medical Faculty, Universitas Islam Indonesia.

REFERENCES

1. WHO. World Malaria Report 2021; 2021.
2. Monroe A, Williams NA, Ogoma S, et al. Reflections on the 2021 World Malaria Report and the future of malaria control. Malar J. 2022;21(1):1-6.
3. Kemenkes RI. Situasi terkini perkembangan program pengendalian malaria di Indonesia tahun 2018; 2018.
4. BPS. Kabupaten Mimika dalam angka 2020; 2020.
5. Hasyim H, Dale P, Groneberg DA, et al. Social determinants of malaria in an endemic area of Indonesia. Malar J. 2019;18(1):1-11.
6. Arwati H, Yotopranoto S, Rohmah EA, et al. Submicroscopic malaria cases play role in local transmission in Trenggalek district, East Java Province, Indonesia. Malar J. 2018;17(2):1-6.
7. Lawpoolsri S, Sattabongkot J, Sirichaisinthop J, et al. Epidemiological profiles of recurrent malaria episodes in an endemic area along the Thailand - Myanmar border: a prospective cohort study. Malar J. 2019;18(124):1-11.
8. Rono J, Färnert A, Murungi L, et al. Multiple clinical episodes of *Plasmodium falciparum* malaria in a low transmission intensity setting: Exposure versus immunity. BMC Med. 2015;13(1):1-11.
9. Eldh M, Hammar U, Arnot D, et al. Multiplicity of asymptomatic *Plasmodium falciparum* infections and risk of clinical malaria: A systematic review and pooled analysis of individual participant data. J Infect Dis. 2020;221(5):775-785.
10. Walldorf JA, Cohee LM, Coalson JE, et al. School-age children are a reservoir of malaria infection in Malawi. PLoS One. 2015;10(7):1-13.
11. Gonçalves BP, Kapulu MC, Sawa P, et al. Examining the human infectious reservoir for *Plasmodium falciparum* malaria in areas of differing transmission intensity. Nat Commun. 2017;8(1).
12. Kassam NA, Kaaya RD, Damian DJ, et al. Ten years of monitoring malaria trend and factors associated with malaria test positivity rates in Lower Moshi. Malar J. 2021;20(1):1-9.

13. Meireles BM, De Souza Sampaio V, Monteiro WM, et al. Factors associated with malaria in indigenous populations: A retrospective study from 2007 to 2016. PLoS One. 2020;15(10 October):1-14.
14. Nlinwe NO, Ateh TAE. Assessment of malaria predisposing factors among crop production farmers attending the ndop district hospital, northwest region of cameroon. J Parasitol Res. 2020;2020:9-12.
15. Bamou R, Rono M, Degefa T, et al. Entomological and anthropological factors contributing to persistent malaria transmission in Kenya, Ethiopia, and Cameroon. J Infect Dis. 2021;223(2):S155-S170.
16. Keïta M, Doumbia S, Sissoko I, et al. Indoor and outdoor malaria transmission in two ecological settings in rural Mali: implications for vector control. Malar J. 2021;20(1):1-11.
17. Martin JA, Hendershot AL, Saá Portilla IA, et al. Anopheline and human drivers of malaria risk in northern coastal, Ecuador: A pilot study. Malar J. 2020;19(1):1-11.
18. Edwards HM, Sriwichai P, Kirabittir K, et al. Transmission risk beyond the village: Entomological and human factors contributing to residual malaria transmission in an area approaching malaria elimination on the Thailand-Myanmar border. Malar J. 2019;18(1):1-20.
19. Amirshekari MB, Nateghpour M, Raeisi A, et al. Determination of asymptomatic malaria among Afghani and Pakistani immigrants and native population in south of Kerman province, Iran. Iran J Parasitol. 2016;11(2):247-252.
20. Donnelly B, Ford LB, Labbé J, et al. Plasmodium falciparum malaria parasitaemia among indigenous Batwa and non - indigenous communities of Kanungu district, Uganda. Malar J. Published online 2016.
21. BMKG. Jumlah curah hujan dan hari hujan menurut bulan di Kabuapten Mimika; 2019.
22. Setiyaningsih R, Yanti S AO, Lasmiati L, et al. Keanekaragaman Anopheles dalam ekosistem hutan dan resiko terjadinya penularan malaria di beberapa provinsi di Indonesia. Media Penelit dan Pengemb Kesehat. 2019;29(3):243-254.
23. Bariyah K, Utomo B, Sulistiawati, et al. Different types of Anopheles breeding place in low and high malaria case areas. J Kesehat Masy. 2018;14(2):178-185.
24. Sandy S. Bionomi vektor malaria kelompok Anopheles punctulatus (*Anopheles farauti, Anopheles koliensis, Anopheles punctulatus*) di Provinsi Papua. Balaba. 2014;10(01):47-52.
25. Seyoum D, Kifle YG, Rondeau V, et al. Identification of different malaria patterns due to *Plasmodium falciparum* and *Plasmodium vivax* in Ethiopian children: A prospective cohort study. Malar J. 2016;15(1):1-11.
26. Valletta JJ, Addy JWG, Reid AJ, et al. Individual-level variations in malaria susceptibility and acquisition of clinical protection. Wellcome Open Res. 2021;6:22.
27. Bediako Y, Adams R, Reid AJ, et al. Repeated clinical malaria episodes are associated with modification of the immune system in children. BMC Med. 2019;17(1):1-14.
28. White NJ. Determinants of relapse periodicity in Plasmodium vivax malaria. Malar J. 2011;10(1):297.
29. Jagannathan P, Muhindo MK, Kakuru A, et al. Increasing incidence of malaria in children despite insecticide-treated bed nets and prompt anti-malarial therapy in Tororo, Uganda. Malar J. 2012;11(1):1.
30. Camargo M, Soto-De León SC, Del Río-Ospina L, et al. Micro-epidemiology of mixed-species malaria infections in a rural population living in the Colombian Amazon region. Sci Rep. 2018;8(1):1-14.
31. Genton B, D'Acremont V, Rare L, et al. Plasmodium vivax and mixed infections are associated with severe malaria in children: A prospective cohort study from Papua New Guinea. PLoS Med. 2008;5(6):0881-0889.
32. Kotepui M, Kotepui KU, De Jesus Milanez G, et al. Plasmodium spp. mixed infection leading to severe malaria: a systematic review and meta-analysis. Sci Rep. 2020;10(1):1-12.

Factors Affecting the Quality of Life of Patients After Kidney Transplantation: A Cross-Sectional Study

Maruhum Bonar H. Marbun[1], Dories Septiana[2], Hamzah Shatri[3,4], Ikhwan Rinaldi[4]*

[1]Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo National Hospital, Jakarta, Indonesia
[2]Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo National Hospital, Jakarta, Indonesia
[3]Division of Psychosomatic and Palliative, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo National Hospital, Jakarta, Indonesia
[4]Clinical Epidemiology Unit, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo National Hospital, Jakarta, Indonesia

Corresponding Author:
Hamzah Shatri, MD., PhD. Division of Psychosomatic and Palliative, Departement of Internal Medicine Universitas Indonesia-Cipto Mangunkusumo National Hospital. Jl. Diponegoro No. 71, Jakarta 10430, Indonesia. E-mail: hshatri@yahoo.com.

ABSTRACT

Background: *Kidney transplantation is currently the best choice for renal replacement therapy, due to its effect in reducing mortality and improving the quality of life (QoL) of patients with end-stage renal disease. This study aimed to identify factors affecting QoL after kidney transplantation.* ***Methods:*** *We conducted a cross sectional study by recruiting patients who had kidney transplantation at Cipto Mangunkusumo General Hospital, Jakarta, Indonesia, from 2018 – 2020. QoL was assessed using the 36-item Short Form Health Survey (SF-36) questionnaire. We evaluated age, sex, body mass index, hemoglobin level, estimated glomerular filtration rate, duration of dialysis before transplantation, history of diabetes, depression, and performance status as factors associated with QoL score.* ***Results:*** *We involved 107 subjects in our study. Depression, hemoglobin level, ECOG performance status, and duration of dialysis were factors affecting the physical component score (R^2=0.21). Depression and hemoglobin level were factors affecting the mental component score (R^2=0.34). Depression, hemoglobin level, and ECOG performance status were factors contributed to the total QoL score (R^2=0.41).* ***Conclusion:*** *Factors that contributed to QoL status were depression, ECOG performance status, and hemoglobin levels. This study supported the need for assessment of QoL on regular basis, psychological aspects including depression, as well as other factors that can affect QoL such as performance status and hemoglobin level in patients before and after kidney transplantations.*

Keywords*: Kidney transplantation, mental aspect, physical aspect, quality of life, transplant recipient.*

INTRODUCTION

Chronic kidney disease (CKD) is often associated with high morbidity and mortality rate. According to a Global Burden Disease (GBD) study (2019),[1] CKD ranked in the top ten leading causes of death in the age groups 50-74 and ≥75. In the Indonesian Registry 2018, there were around 130,000 patients on hemodialysis therapy, with around 60,000 new patients compared to those in 2017.[2] Indeed, CKD could reduce the QoL and impose high cost burden for patients due to its progressive

course.[3,4] Complications that arise from CKD, such as cardiovascular and pulmonary diseases, electrolyte imbalance, and bone diseases, may also limit physical activities and social interactions.[5,6] Other factors, including age, hemoglobin, albumin, and duration of dialysis, were reported to be significantly associated to the QoL of patients with CKD.[7] Even adding to the burden, about 5-9% women and 2-3% men with CKD tend to have depression.[8–10]

Kidney transplantation is currently the best choice for renal replacement therapy, especially for patients with end-stage renal disease. It has attracted increasing interest in recent decades as it aims to increase the quality of life (QoL) and reduce disease burden,[11–13] especially by improving physical health and psychosocial functions.[12,14] A prospective study comparing the QoL status of patients with CKD before and after kidney transplantation using the Kidney Disease Quality of Life Short Form (KDQOL-SF) instrument found that QoL status was improving in 14 out of 19 (74%) dimensions. Meanwhile, by using a 36-item Short Form Health Survey (SF-36) questionnaire, a significant improvement was found in the domains of physical, emotional, and vitality limitations.[14]

QoL is currently attracting lots of attention due to its impact on morbidity and mortality rate.[15,16] In this study we aimed to identify factors affecting QoL in patients after kidney transplantation.

METHODS

This study was a cross-sectional study, reported as part of a large retrospective cohort study entitled "Overview of recipient and donor characteristics of kidney transplantation at Dr. Cipto Mangunkusumo Hospital 2011-2020".[17] Sample size was calculated using a numerical predictive multivariate formula.[18] The research subjects were all patients aged ≥18 years with CKD who had kidney transplantation at Cipto Mangunkusumo General Hospital for more than 6 months in the last 3 years. Subjects who had a history of other organ transplantation or had undergone dialysis programs in acute condition and were unable to communicate were excluded from the study.

QoL was assessed using the SF-36 questionnaire,[19] which consisted of 8 domains: physical functioning, physical role, body pain, general health, vitality, social functioning, emotional role, and mental health. Each domain scores 0-100, with higher scores indicating better QoL.

We also recorded factors affecting QoL, namely age, sex, body mass index (BMI), hemoglobin level, eGFR, duration of dialysis before transplantation, history of diabetes, depression (assessed by Hospital Anxiety and Depression Scale (HADS)[20]), and performance status (assessed by Eastern Cooperative Oncology Group (ECOG) performance status[21]).

We classified the age groups as <60 years old and ≥60 years old based on the definition of elderly by the National Health Ministry of Indonesia.[22] BMI was classified in accordance to the World Health Organization (WHO) BMI classification for Asian populations.[23] Depression score was classified as normal if the subject scored 0-7, borderline if the subject scored 8-10, and abnormal if the subject scored 11-21. ECOG performance status was classified as 0 if the subject had no limitation in their activity, 1 if the subject could not conduct heavy physical activity, 2 if the subject could do basic daily activity but not moderate physical activity, 3 if the subject could only move from bed to chair, 4 if the subject was bedridden, and 5 if the subject died.

Ethical Clearance

This study has been approved by the Ethical Committee Board, Faculty of Medicine, Universitas Indonesia (KET – 498/UN2.F1 / ETIK/ PPM.00.02/2021).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software (version 26.0).[24] Descriptive data were reported as mean, median, or frequency. Comparisons of factors were performed using bivariate analysis. All factors with a *p*-value <0.25 were included in the multivariate analysis using a linear regression model.

RESULTS

There were 187 patients who had kidney transplantation at Cipto Mangunkusumo General Hospital from January 2018 to December 2020. During the recruitment process, 8 subjects aged <18 years old, 7 subjects were on dialysis, and 65 subjects were not willing to be interviewed. Therefore, a total of 107 subjects were included in our study, are shown in **Figure 1**.

The subjects were mostly male (67.3%). Mean age was 43 ± 12.51 years. Most of our subjects were highly educated (75.7%) and were working (81.3%). The most common comorbidities were obesity and hypertension. Subjects' characteristics are shown in **Table 1**.

Using SF-36 the questionnaire (**Table 2**), we found out that among the 8 domains, emotional role had the highest score. When those 8 domains were classified to either physical or mental component, the physical component summary (PCS) score was higher than the mental component summary (MCS) score (93 vs 79, respectively).

Bivariate analysis showed that hemoglobin level (p=0.023), ECOG performance status (p<0.001), and depression (p=0.004) were significantly related to PCS score, whilst eGFR (p=0.042) and depression (p<0.001) were significantly related to MCS score. Overall, hemoglobin (p=0.014), ECOG performance

Table 1. The characteristics of post-transplant patients enrolled as participants in the study.

Characteristics	N = 107
Age < 60 years, n (%)	96 (89.7)
n Male, n (%)	72 (67.3)
Level of education, n (%)	
High school	26 (24.3)
Bachelor	81 (75.7)
Currently working, n (%)	87 (81.3)
BMI (kg/m^2), mean (SD)	24.68 (4.25)
BMI categories, n (%)	
Underweight (<18.5 kg/m^2)	8 (7.5)
Normal (18.5 – 22.9 kg/m^2)	30 (28.0)
Overweight (23.0 – 24.9 kg/m^2)	20 (18.7)
Obese (>25 kg/m^2)	40 (45.7)
Diabetes mellitus, n (%)	23 (21.5)
Hypertension, n (%)	66 (61.7)
Duration of dialysis (months), median (IQR)	12 (6-24)
Type of dialysis, n (%)	
CAPD	6 (5.6)
HD	95 (88.8)
HD and CAPD	4 (3.7)
No dialysis	2 (1.9)
Hemoglobin level (g/dL), mean (SD)	13.71 (2.31)
eGFR (ml/min/1.73 m^3), mean (SD)	61.55 (18.45)
Total depression score, median (IQR)	4 (3-5)
Depression categories, n (%)	
Normal	99 (92.5)
Borderline	7 (6.5)
Abnormal	1 (0.9)
ECOG performance status, n (%)	
0	62 (57.9)
1	44 (41.1)
2	1 (0.9)

CAPD: continuous ambulatory peritoneal dialysis, ECOG: Eastern Cooperative Oncology Group, eGFR: estimated glomerular

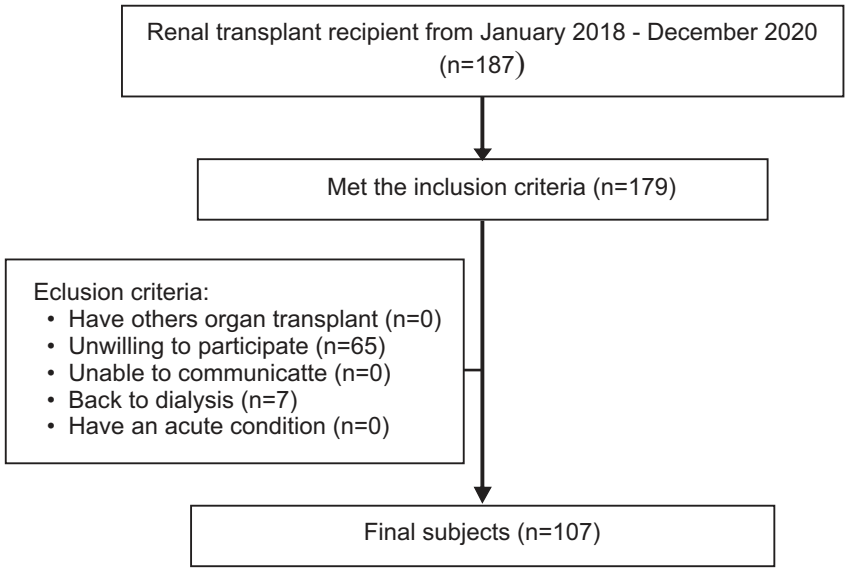


Figure 1. Flowchart for selecting research subjects.

Table 2. The scores of 36-items short form health survey scale inpatients after kidney transplantation.

SF-36	Median (IQR)
Physical function	90 (80-100)
Role of physical	100 (75-100)
Bodily pain	90 (78-100)
General health	74 (62-78)
Vitality	75 (65-85)
Social function	88 (88-100)
Role of emotional	100 (100-100)
Mental health	92 (80-96)
PCS	93 (79-97)
MCS	79 (72-84)
Total SF-36	83 (76-80)

IQR: inter quartil rank, MCS: mental component summary, PCS: physical component summary, SF-36: 36-item Short Form Health Survey

status (p<0.001), and depression (p=0.001) were significantly related to the total SF-36 score.

We continued to multivariate analysisby including hemoglobin level, duration of dialysis, ECOG performance status, and depression to linear regression against PCS score; hemoglobin level and depression against MCS score; and hemoglobin level, ECOG performance status, and depression against the total SF-36 score. Multivariate analysis showed that depression, hemoglobin level, ECOG performance status, and duration of dialysis were factors affecting the PCS score; depression and hemoglobin level were factors affecting the MCS score; while depression, hemoglobin level, and ECOG performance status were factors affecting the total SF-36 score (**Table 3**).

DISCUSSION

We identified factors affecting the QoL, which were depression, higher hemoglobin level, and lower ECOG performance status which had lower QoL.

Baseline characteristics showed that the most of subjects were male aged <60 years. This finding was similar to that of other studies,[16,25] probably because most patients eligible for receiving kidney transplant were <65 years old.[26] The main comorbidities were hypertension (61.7%), obesity (45.7%), and diabetes (21.5%). This finding was in accordance with that of other studies,[27,28] in which hypertension and diabetes are the two most common causes of end-stage renal disease. Previous studies suggest that those comorbidities are associated with greater functional impairment and weakness, affecting QoL after transplantation.[28]

WHO defines health not merely as the absence of disease, but as a state of physical health, mental well-being, and social well-being.[29] Meanwhile, a good QoL is defined as having a good, high QoL by having aspects including physical, psychological, social, family, and environmental aspects.[30,31] One important thing to pay attention to is that QoL covers a very broad multidimensional concept, which includes how individuals perceive their lives and their expected goals according to their society culture.[30,31]

We found in this study that the total SF-36 score was generally much higher than that

Table 3. Final regression models for QoL of patients after kidney transplantation.

Dimensions	Variables	β coefficient (95%CI)	p-value
PCS	Intercept	46.27 (22.44; 70.10)	<0.001
N = 107	Duration of dialysis	-0.11 (-0.22; - 0.006)	0.038
R^2 = 0.21	Hemoglobin level	1.40 (0.46; 2.36)	0.004
	ECOG PS	-5.90 (-10.39; -1.43)	0.01
	Depression	7.47 (2.81; 12.13)	0.002
MCS	Intercept	28.11 (14.00; 42.27)	<0.001
N = 107	Hemoglobin level	1.04 (0.33; 1.76)	0.005
R^2 = 0.34	Depression	12.07 (8.61; 15.53)	<0.001
Total SF-36	Intercept	42.79 (30.45; 55.13)	<0.001
N = 107	Hemoglobin level	1.12 (0.51; 1.66)	<0.001
R^2 = 0.41	Depression	9.21 (6.197; 12.23)	<0.001
	ECOG PS	-5.30 (-8.20; -2.39)	<0.001

CI: confidence interval, ECOG PS: Eastern Cooperative Oncology Group performance status, MCS: mental component summary, PCS: physical component summary, SF-36: 36-item Short Form Health Survey

of other studie indicating that our subjects perceived their QoL much better than those in other studies.[32,33] A recent study reported that Indonesian people's concept of health is mainly based on limitations to perform daily activities.[34] Hence, although our subjects had end-stage renal disease and comorbidities, as long as they still could conduct their routine activities, they tended to regard themselves as having good QoL.

According to the physical and mental component, we found that MCS score was much lower than PCS score. This result was different from the study by Gentile et al (2013) which reported that MCS score was higher than PCS score.[32] Another study by Griva et al (2011) observed that MCS score was quite similar to PCS score.[33] This showed that our subjects perceived more psychological problems rather than physical ones. Similar to our previous hypothesis, we suspect that this is due to the fact that Indonesian people tend to neglect physical symptoms as long as they can still perform their work.[34] However, psychological distress tend to impose a greater force in reducing QoL,[35] that even slight psychological symptoms are enough to disturb daily routine.

According to our multivariate analysis, subjects with depression, higher hemoglobin level, lower ECOG performance status, and longer duration of dialysis had lower PCS score. A higher ECOG performance status reflected more limitations in conducting physical activities; therefore, logically, it reflected lower PCS score. Depression, on the other hand, proved that psychological distress might also affect physical capabilities,[35] although the hemoglobin level was higher in subjects with lower PCS score. Interestingly, ECOG performance status was not a significant factor affecting MCS score. This denoted that while psychological factor affected the physical performance in our subjects, the opposite did not apply.

Overall, subjects with depression and lower ECOG performance status had lower QoL. This finding was quite similar to the study by Hwang et al (2021) in which perceived health status is the most essential factor affecting QoL.[25] However, our study showed that socio-demographic factors, such as age and sex, and clinical characteristics did not affect QoL as in other studies.[16] This supports the fact that restricted daily routines play a more essential role in the QoL of Indonesian population.[34] Meanwhile, in previous studies, the role of mental health is not as powerful.[25,32] We suspect that this is due to the high social support and awareness toward mental health in the Western-based population studies; whilst Indonesian population tend to neglect this aspect because psychological distress is often regarded as taboo.[34] Adherence to psychological assistance has also been reported low.[34] Depression in transplant recipients is associated with higher risk of mortality and graft failure.[36] There is no explanation about the R^2 of the variables in this study.

There were several factors which had significant impact on QoL (41%), which remained 59% were explained by another factors that has not studied, such as monthly income, infectious condition, use of immunosuppresant agent, and length of stay in the hospital,[16,32] However, the end of the result of QoL in this study was good but it will be better if the significant factors get more attention.

CONCLUSION

Depression, hemoglobin level, and ECOG performance status are factors contributing to the QoL of patients receiving kidney transplantation. Based on the results of this study, we recommend the need for assessment of QoL on regular basis, psychological aspects including depression, as well as other factors that can affect QoL such as performance status and hemoglobin level in patients before and after kidney transplantations.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTION

MB, DS, HS, IR contributed to the development of the study concept and design. MB contributed to acquisition of data and responsible to patient treatment after kidney transplantation. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by HIBAH PUTI Universitas Indonesia 2022 (grant number: PENG-003/UN2.RST/PPM.00.00/2022).

REFERENCES

1. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204–22.
2. PERNEFRI. 11th report of Indonesian renal registry 2018. Indones Ren Regist. 2018;1–46.
3. Couser WG, Remuzzi G, Mendis S, et al. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. Kidney Int. 2011;80(12):1258–70.
4. Anjarwati A. Health related-quality of life in CKD and dialysis patients in Asian countries: A systematic review. ARKESMAS (Arsip Kesehat Masyarakat). 2018;3(2):50–5.
5. Dimova R, Keskinova D, Tzekov V, et al. Health-related quality of life in end-stage renal disease patients, using the missoula-vitas quality of life index: A multicenter study. Med Pharm Reports. 2019;92(4):374–81.
6. Chen SS, Al Mawed S, Unruh M. Health-related quality of life in end-stage renal disease patients: How often should we ask and what do we do with the answer? Blood Purif. 2016;41(1–3):218–24.
7. Yang F, Griva K, Lau T, et al. Health-related quality of life of Asian patients with end-stage renal disease (ESRD) in Singapore. Qual Life Res. 2015;24(9):2163–71.
8. De Mendonca AEO, Torres GDV, Salvetti MDG, et al. Changes in quality of life after kidney transplantation and related factors. Acta Paul Enferm. 2014;27(3):287–92.
9. Shirazian S, Grant CD, Aina O, et al. Depression in chronic kidney disease and end-stage renal disease: Similarities and differences in diagnosis, epidemiology, and management. Kidney Int Reports. 2017;2(1):94–107.
10. Cohen SD, Norris L, Acquaviva K, et al. Special feature: Primary care issues for the nephrologist screening, diagnosis, and treatment of depression in patients with end-stage renal disease. Am Soc Nephrol. 2007;10(15):1332–42.
11. Dąbrowska-Bender M, Dykowska G, Żuk W, et al. The impact on quality of life of dialysis patients with renal insufficiency. Dovepress. 2018;12:577–83.
12. Chan-on C, Sarwal MM. A comprehensive analysis of the current status and unmet needs in kidney transplantation in Southeast Asia. Front Med. 2017;4:1–14.
13. Kaballo MA, Canney M, O'Kelly P, et al. A comparative analysis of survival of patients on dialysis and after kidney transplantation. Clin Kidney J. 2018;11(3):389–93.
14. Kostro JZ, Hellmann A, Kobiela J, et al. Quality of life after kidney transplantation: A prospective study. Transplant Proc. 2016;48(1):50–4.
15. Finkelstein FO, Wuerth D, Finkelstein SH. Health related quality of life and the CKD patient: challenges for the nephrology community. Kidney Int. 2009;76(9):946–52.
16. Mouelhi Y, Jouve E, Alessandrini M, et al. Factors associated with health-related quality of life in kidney transplant recipients in France. BMC Nephrol. 2018;1–12.
17. Marbun MBH, Susalit E, Susilowati U, et al. Long-term outcomes and prognostic factors in kidney transplant recipients in Jakarta, Indonesia: a cohort study. BMJ Open. 2022;12(5):e059631.
18. Riley RD, Snell KIE, Ensor J, et al. Minimum sample size for developing a multivariable prediction model: Part I - Continuous outcomes. Stat Med. 2019;38(7):1262–75.
19. Saris-Baglama RN, Dewey CJ, Chisholm GB, et al. QualityMetric health outcomes™ scoring software 4.0: installation guide. Lincoln, RI: QualityMetric Incorporated; 2010. p. 138.
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361–70.
21. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649–55.
22. National Health Ministry of Indonesia. Situasi lanjut usia di Indonesia. Jakarta; 2016.
23. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157–63.
24. IBM Corp. IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp; 2011.
25. Hwang Y, Kim M, Min K. Factors associated with health-related quality of life in kidney transplant recipients in Korea. PLoS One. 2021;16(3 March):1–13.
26. Matas AJ, Smith JM, Skeans MA, et al. OPTN/SRTR 2013 annual data report: Kidney. Am J Transplant. 2015;15:1–34.
27. Supit T, Nugroho EA, Santosa A, et al. Kidney transplantation in Indonesia: An update. Asian J Urol. 2019;6(4):305–11.
28. Shetty AA, Wertheim JA, Butt Z. Health-related quality of life outcomes after kidney transplantation. Kidney Transplantation, Bioeng Regen. 2017;699–708.
29. World Health Organization (WHO). Constitution of the World Health Organization. In: World Health Organization (WHO), editor. World Health Organization: Basic documents. 45th ed. Geneva:

World Health Organization (WHO); 2005.
30. González-blanch C, Hernández-de-hita F, Muñoz-navarro R, et al. The association between different domains of quality of life and symptoms in primary care patients with emotional disorders. 2018;(June):1–10.
31. Theofilou P. Quality of life: Definition and measurement. Eur J Psychol. 2013;9(1):150–62.
32. Gentile S, Beauger D, Speyer E, et al. Factors associated with health-related quality of life in renal transplant recipients: results of a national survey in France. Health Qual Life Outcomes. 2013;11(1):88.
33. Griva K, Stygall J, Ng JH, et al. Prospective changes in health-related quality of life and emotional outcomes in kidney transplantation over 6 years. J Transplant. 2011;2011:1–12.
34. Widayanti AW, Green JA, Heydon S, et al. Health-seeking behavior of people in Indonesia: A narrative review. J Epidemiol Glob Health. 2020;10(1):6.
35. Huang I-C, Lee JL, Ketheeswaran P, et al. Does personality affect health-related quality of life? A systematic review. PLoS One. 2017;12(3):e0173806.
36. Cho S, Park S, Kim JE, et al. Incidence of depression in kidney transplant recipients in South Korea: a long-term population-based study. Sci Rep. 2022;12(1):17603.

The Challenges of Diagnosis and Management of Wegener's Granulomatosis with Negative ANCA

Lia Sasmithae[1*]

[1]Department of Internal Medicine - Faculty of Medicine, University of Palangkaraya, Indonesia.

Coressponding Author:
Lia sasmithae, MD. Department of Internal Medicine - Faculty of Medicine, University of Palangkaraya. Jl. Hendrik Timang, Kampus Tanjung Nyaho. Palangka Raya 73112, Indonesia. Email: lia@med.upr.ac.id.

ABSTRACT

Wegener's granulomatosis is an autoimmune disease that affects the walls of small and medium-sized blood vessels due to an immune complex reaction. Meanwhile, at present, the etiology of the disease is unknown with certainty. One of the diagnoses is the detection of cytoplasmic antineutrophilic cytoplasmic antibody (c-ANCA), but a negative ANCA examination is very rare. Therefore, this is a case report of a 33-year-old man that complained of sores on both legs, which were difficult to heal. The patient also experienced joint pain, fever at night, weight loss, hair loss as well as recurrent nosebleeds with an unknown cause. Furthermore, the physical examination found a saddle nose and black spots from the right and left groin to the back of the legs. Multiple irregular ulcers with different sizes were also discovered in the region cruris and dorsum pedis. The laboratory examination results showed Hb of 8.7 g/dl, 130 mm/hour ESR. Based on peripheral blood smear, the patient was suspected to have hypochromic-microcytic anemia, which caused chronic process along with bleeding. The IF pattern was also speckled with a titer of 1:320, and the ANCA test was negative (-). Meanwhile, the results of routine urine examination found blood +4 macroscopically and observed leukocyturia 2-10 LPB and 8-21 LPB erythrocyturia microsopically. The Doppler ultrasound of the left inferior extremity revealed the swelling of the left pedis soft tissue with peripheral arteritis in the cutis lesion area. The Anatomical Pathology examination showed non-specific chronic inflammation in the cruris and pedis region. Subsequently, the patient was administered with wound debridement by a surgeon, packed red cell (PRC) transfusion, metylprednisolone mg, azathioprine, and cefixime. After the treatment, the nosebleed was no longer felt, the joint pain reduced, and the fever improved.

Keywords*: Wegener's granulomatosis, Autoimmune vasculitis, negative ANCA.*

INTRODUCTION

Wegener's granulomatosis is a vasculitis that affects small and medium-sized blood vessels, thereby leading to changes in their walls. Furthermore, it is often found in patients within the age range of 40-50 years, especially in men, and the main symptoms include vasculitis, glomerulonephritis, and respiratory tract involvement.[1-2] Moreover, wegner's granulomatosis can be classified into 2 forms, namely the general and rare/limited forms. The general form is characterized by a triad of symptoms, including vasculitis, glomerulonephritis, and respiratory tract involvement, while the rare/limited form only affects the respiratory tract and does not involve the kidneys.[2,3]

At present, its etiology is not known with certainty, and some hypotheses stated that it is an autoimmune disease caused by an immune complex reaction on the walls of blood vessels, which leads to damage.[4,5] The

disease can be diagnosed through the detection of cytoplasmic antineutrophilic cytoplasmic antibody (c-ANCA). However, a negative ANCA examination is very rare because it is often caused by a localized form of the disease. There are also few studies or case reports on the Wegener's granulomatosis with ANCA-negative, hence, it is necessary to carry out a study to add information on its diagnosis.

CASE ILLUSTRATION

A 33-year-old man complained of sores on both legs that were difficult to heal. The wound had occurred since December 1, 2020, and has been treated by a surgical specialist, but it reappeared again. At first, it was a red spot that gradually turned black with pain when pressed. The wound then started to peel off, ooze fluid/pus, and bleeds easily. Furthermore, the patient also complained of high fever and sweating, especially at night, which did not improve despite being given fever-reducing medication, and in April 2021, a large number of nosebleeds occurred. The complaints that were felt came in waves and were accompanied by headaches and pain throughout the body, especially from the waist to the soles of the feet. An ENT specialist was then consulted, and bone damage was observed in the nasal cavity. The patient also experienced a significant weight loss in the last 1 year as well as hair loss, watery eyes, and forgetfulness.

The conjunctiva was pale, the nose was snub, which appeared as a saddle nose, and there were black spots from the right and left groin to the back of the legs. In the cruris and dorsum pedis regions, multiple irregular ulcers were also found, which varied in size, well-demarcated, accompanied by livedo reticularis, pus (+), and crust (+). Otolaryngological examination using nasendoscopy showed perforation of the nasal septum, which was then diagnosed as suspected Lethal Midline Granuloma (LMG). Physical examination s are shown in **Figure 1 and Figure 2**.

Laboratory test results suggested hemoglobin level of 8.7 g/dl, MCV 73.5 fl, MCH 22.4 pg, and erythrocyte sedimentation rate of 130 mm/hour. The results of the peripheral blood smear showed the appearance of erythrocytes, namely hypochromic, microcytic, anisocytosis, normocytes, ovalocytes, anulocytes, the appearance of teardrop cells and the presence of erythroblast cells. The leukocyte population was within normal limits and no blast cells were found. The picture of platelets found in normal numbers and evenly distributed, found the existence of giant platelets. Based on the result of the tests, the patient was suspected to have hypochromic-microcytic anemia, which caused chronic process along with the bleeding process.

The ANA-IF pattern was speckled with a titer of 1:320,l and negative ANCA test result. Routine urine examination macroscopically found positive blood 4, while microscopic observation found leukocyturia 2-10 LP.40X and erythrocyturia 8-21 LP.40X.

The Thorax PA examination results were within normal limits (**Figure 3**), while the Doppler ultrasound examination in the left lower extremity showed swelling of the left pedis soft tissue with peripheral arteritis in the cutis lesion area **(Figure 4).**

The histopathological examination of a skin biopsy revealed the presence of tissues that were partially lined with stratified squamous epithelium and keratin cell nuclei that are within normal limits (**A**). The Subepithelial had visible fibrocollagenous connective tissue with massive inflammation of lymphocytes, PMNs, histiocytes, and dilated blood vessels (**B-D**). Furthermore, no malignant tumor cells were found, hence, the patient was diagnosed with a non-specific chronic inflammation of the cruris and pedis region (**Figure 5).**

Based on the aforementioned findings, the patient was diagnosed with a suspected autoimmune disease caused by Wegener's granulomatosis. The patient also had microcytic hypochromic anemia, epistaxis, and hematuria. Subsequently, wound debridement by a surgeon, packed red cell (PRC) transfusion, methylprednisolone 16 mg t.i.d., azathioprine 50 mg b.i.d., and cefixime 200 mg b.i.d. were administered. After treatment for approximately 2 weeks, the complaints improved, the fever was gone, the joint pain was reduced, the nosebleeding ceased, and the wounds on the legs were healing gradually.

Figure 1. The nasal bone shows a saddle nose, and eyebrow hair loss.

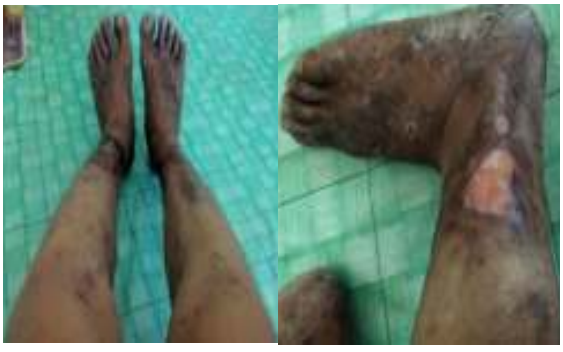


Figure 2. Black spots, varied shapes, multiple ulcers of varying sizes, pus (+), irregular, livedo reticularis (+), crustae (+)

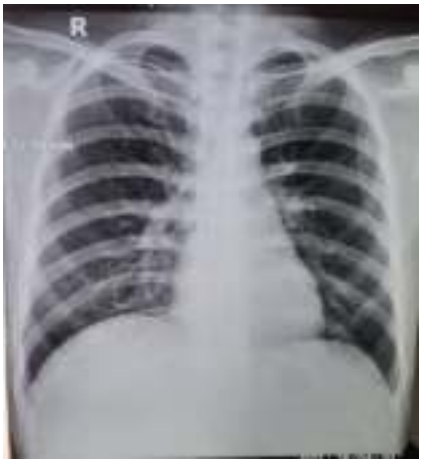


Figure 3. Thorax Postero Anterior showing the heart and lungs within normal limits.

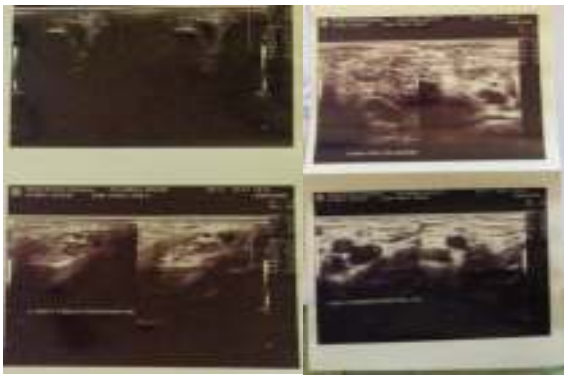


Figure 4. Doppler ultrasound showing left pedis soft tissue swelling with peripheral arteritis in the cutaneous lesion area

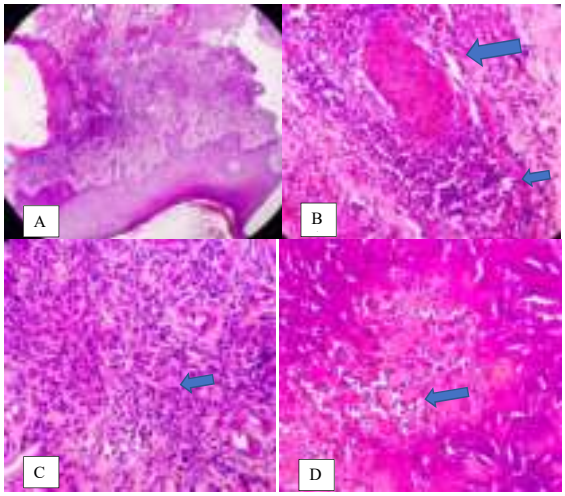


Figure 5. The histopathological examination of a skin biopsy

Microscopic skin biopsy showed tissue fragments that are partially lined with stratified squamous epithelium, keratinized with normal cell nuclei (10X magnification);

Subepithelial visible fibrocollagenous connective tissue massively strewn with inflammatory cells of lymphocytes, PMNs, histiocytes, and dilated blood vessels (100X magnification);

Fibrocollagenous tissue with lymphocyte and PMN inflammatory cells (100X magnification); PMN and histiocyte infiltration with granulomatous inflammation (100X magnification).

DISCUSSION

Wegener's granulomatosis is an autoimmune disease that attacks small and medium-sized blood vessels. The manifestations of the disease include symptoms in the respiratory tract, kidneys, and lungs.[6-9] The disease can also be classified into 2 groups, namely the generalized and limited form. The generalized form is characterized by 3 classic granulomatosis symptoms, including glomerulonephritis, vasculitis, and airway involvement, while the limited form only affects the respiratory tract without the involvement of the kidneys.[3,10]

Furthermore, constitutional symptoms in the early stages of the disease include weight loss, fever, and weakness. The patient can also experience manifestations in the upper respiratory tract, such as nasal congestion, rhinitis, pain in the nose, epistaxis, brown crusts mixed with blood, and septal perforation, which causes a saddle-shaped nose.[11] Until now, the etiology of Wegener's granulomatosis is not known with certainty. The diagnosis of the disease can be established with the criteria issued by the American College of Rheumatology in 1990 along with further examinations, namely cytoplasmic Anti-Neutrophil Cytoplasmic Antibodies (cANCA), complete blood count, chest X-ray examination, urinalysis, presence of mouth ulcers or nasal secretions, and histological observation to check for the presence of granulomatous inflammation.[12]

In this case report, the patient experienced constitutional symptoms of fever, weakness, and weight loss. Manifestations in the respiratory tract were in the form of nose pain, recurrent epistaxis, which occurred sometimes in large quantities. Meanwhile, the results of the ENT-KL specialist examination using nasendoscopy showed a perforation of the nasal septum, which was diagnosed as a suspected lethal midline granuloma (LMG). The ENT-KL doctor did not perform a biopsy on this patient because of the limited examinations that could be carried out at our hospital, and also the patient at that time refused to be referred for further examination due to cost constraints and the referral hospital was far away.

The histopathological ulcers biopsy in the cruris region revealed the presence of tissues that were partially lined with stratified squamous epithelium and keratinized cells within normal limits. The Subepithelial examination showed fibrocollagenous connective tissue with massive inflammation of lymphocytes, PMNs, and histiocytes as well as dilated blood vessels. Furthermore, no malignant tumor cells were found along with the granulomatous inflammation. Based on the tests and examinations, the patient was concluded to have a non-specific chronic inflammation in the cruris and pedis region as well as a granulomatous inflammation.

Subsequently, the diagnosis was made based on the criteria of the American College of Rheumatology in 1990, namely abnormalities in urine sediment, the presence of nasal secretions, and histopathological results showing a granulomatous inflammation. The diagnosis of the disease can also be made when 2 or more ACR criteria are met.[13,14] This case belongs to the general form because the patient had glomerulonephritis, vasculitis with airway involvement. The disease can still be confirmed even though the cANCA test results was negative. However, the diagnosis cannot be made quickly because the patient should be referred to a hospital for a more complete investigation and the initial symptoms shown were not typical of Wegener's Granulomatosis. cANCA is one of the tests that support the diagnosis of the disease, but in 10-20% of cases, ANCA is negative.[15-17]

Other criteria that can be used to establish Wegener's diagnosis Granulomatosis can be

Iran's criteria, and the latest criteria were the 2017 ACR/EMA criteria. The Iran's criteria consist of manifestations in the ear, nose and throat (ENT) (3 points), pulmonary (2 points), kidney (1 point), ANCA (2 points), and biopsy (3 points).[18] Iran's criteria are met if there are 4 out of 11 points. In this patient, ENT and kidney criteria were met, namely 4 points. ACR/EMA 2017 criteria, these criteria are used when no biopsy is performed. The parameters consist of manifestations in the lower respiratory tract based on chest X ray, ear, nose and throat (ENT) manifestations, glomerulonephritis, and positive ANCA.[18] Based on the 2017 ACR / EMA criteria, this patient was found to have manifestations in nose area. Glomerulonephritis is still possible because it is found presence of hematuria +4. In this patient, no renal biopsy was performed to support the manifestation of glomerulonephritis because the patient still does not agree and also Renal biopsy examination at our hospital cannot be done.

In addition to using the three criteria above, the diagnosis of Wegener's granulomatosis can also be supplemented by using several supporting examinations such as histopathological biopsy examination, ANCA examination of proteinase 3 (PR3) and myeloperoxidase (MPO) and radiological examination.[18] The histopathologic features of Wegener's granulomatosis are varied and non-specific. Some of these features include acute and chronic inflammation, granulomatous foci, collagen deposition, necrosis, plasma cells and eosinophil infiltrates, lymphocytes and histiocytes that form a granulomatous reaction with multinucleated giant cells.[19-21] The patient in this case showed a histopathological picture from the skin biopsy according to the theory (**Figure 5**).

The cANCA results can also be used to describe the disease's activity, and in patients with limited clinical manifestations or mild symptoms, cANCA results were negative in more than 40% of cases.[11,13] due to early stages of the disease. A negative cANCA made it difficult for clinicians to make a diagnosis because the initial symptoms were atypical, hence, the therapy given was asymptomatic.[13]

Possibility, which occurs when the titer is not sufficient or it does occur, Wegener's granulomatosis in this case is still in early onset. Wegener's patient granulomatosis with upper respiratory manifestations generally has ANCA negative, and 83% of negative ANCA cases involve disorders of the central nervous system brightly.[11,17,22]

A negative cANCA test result does not exclude Wegener's diagnosis of granulomatosis because the results of the cANCA examination did not meet one of the criteria diagnosis. However, the cANCA results are still used to support Wegener's diagnosis granulomatosis (ACR 1990 criteria) due to a positive cANCA result in 80-90% of Wegener's granulomatosis patients in the general form and 55-56% in patients with the limited form.[11,23] However, after the patient's condition was evaluated and reviewed through the history, physical examination, and positive ANA test results with negative cANCA, Wegener's granulomatosis was confirmed.

Wegener's granulomatosis therapy consists of 2 phases, namely an initial phase for 3-6 months to achieve remission and a maintenance phase for 12-24 months to prevent recurrence. The gold standard therapy for Wegener's granulomatosis is a combination of corticosteroids and immunosuppressants, but one can also be given. Administration of cyclophosphamide and corticosteroids is an effective therapy for active Wegener's granulomatosis.[25] Maintenance therapy of Wegener's granulomatosis is by combining oral corticosteroids with azathioprine or methotrexate.[26]

The patient then received wound debridement therapy, antibiotics, azathioprine, and methylprednisolone. The gold standard in the management of the disease is a combination of corticosteroids and immunosuppressants. Therapy can be given until remission occurs, and this can take up to 3-6 months.[11] Meanwhile, the administration of the immunosuppressant azathioprine was based on the availability of drugs at the hospital as well as the cost constraints and the distance of the patient's home.

The diagnosis in this report had limitations because the clinical symptoms that appeared were atypical and not all gold standard examinations

were carried out due to cost constraints as well as the long-distance to the hospital where supporting examinations can be carried out. These constraints affected the choice of therapy and the disease's prognosis.[27]

CONCLUSION

Wegener's granulomatosis is a rare disease, and its diagnosis requires history taking, physical examination, ANCA, and cytology, but under certain conditions, a negative cANCA examination may be found. However, a negative cANCA test result does not rule out the diagnosis of the disease. Treatment can be carried out when the history, physical examination, and further examinations confirm the disease. Therefore, prompt diagnosis and appropriate treatment are needed to accelerate remission and prevent the worsening of the disease.

ACKNOWLEDGMENTS

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The author declares that there is no conflict of interest.

REFERENCES

1. Rudita BAA, Werdiningsih Y, Nurudhin A, et al. 38 years old man with anca negatif Wegener's granulomatosis vasculitis with type 2 diabetes mellitus and electrolyte imbalance: A case report. Ina J Rheum. 2020:12(2):309-4.
2. Almouhawis HA, Leao JC, Fedele S, Porter SR. W egener's granulomatosis: a review of clinical features and an update in diagnosis and treatment. J Oral Pathol Med. 2013;42(7):507-16.
3. Sudibyo TKAP, Mulya DP, Budiono E, et al. Meningoensefalitis manifestation in Wegener's granulomatosis with anca negative: Case report. JPDI. 2019;6(3):150-5.
4. Erickson VR, Hwang PH. Wegener's granulomatosis: Current trends in diagnosis and management. Curr Opin Otolaryngol Head Neck Surg. 2007;15:170-17.
5. Nolle B, Specks U, Ludemann J, Rohrbach MS, DeRemee RA, Gross WL. Autoantibodi antisitoplasma: nilai imunodiagnostiknya pada granulomatosis Wegener. Ann Intern Med. 1989;111:28-40.
6. Petkovic TR, Radovic M, Pejcic T, Rancic M, Borovac DN, Djordjevic I. Wegener's granulomatosis - case report. Acta Medica Medianae. 2008;47(3):78-81.
7. Mubashir M, Eisha MD, Ahmed, et al. Granulomatosis Wegener: A case report and update. South Med J. 2006;99(9):977-988.
8. Sharma P, Sharma S, Baltaro R, Hurley J. Systemic vasculitis. Am Fam Physician. 2011;83:556-65.
9. Marisca S, Tanurahardja B. Aspek klinikopatologik vaskulitis. Departemen Patologi Anatomik Fakultas Kedokteran Universitas Indonesia. Pratista Patologi. 2015;4(1):1-10.
10. Duggal L, Jain N. Limited Wegener's granulomatosis. J Indian Acad of Clin Med. 2004:5(2):186-7.
11. McCarthy E, Mustafa M, Watts M. ANCA-negative granulomatosis with polyangiitis: a difficult diagnosis. EJCRIM 2017;4: doi:10.12890/2017_000625
12. Afsha K, Catherine AL, Mark AQ, et al. Case report: Successful treatment of ANCA-negative Wegener's granulomatosis with Rituximab. Int J Rheumatol. 2010;2: doi:10.1155/2010/84606
13. Hiz F, Cinar M, Karagol T, Bozkurt D, Ozcan RK. Wegener's granulomatosis: Case report. J Neurol. 2007;6(1):1-5.
14. Chaturvedi J, Shobha V, Rout P, Alexander B, Nayar RC. Diagnostic dilemma of a midline destructive disease - a case report. Int J Oto Laryngol. 2010;12(1).
15. Greco P, Palmisano A, Vaglio A, et al. Meningeal involvement in apparently ANCA-negative Wegener's granulomatosis: a role for PR3 capture-ELISA? Rheumatology. 2007:46:1375–6.
16. Salahi-Abari I. 2017 ACR/EMA revised criteria fot too early diagnosis of granulomatosis with polyangitis (GPA). Autoimmune Dis and Ther Approaches. 2016;3(2):1-9.
17. Thiel G, Shakeel M, Ah-See K.. ANCA-negative Wegener's granulomatosis with Wegener's granulomatosis presenting as meningitis. J Laryngol Otol. 2012;126(2):207-9.
18. Muller K, Lin JH. Orbital granulomatosis with polyangiitis (Wegener granulomatosis): clinical and pathologic findings. Arch Pathol Lab Med. 2014;138(8):1110-4.
19. Sarsat VW and Thieblemont N. Granulomatosis with polyangiitis (Wegener granulomatosis): a proteinase-3 driven disease? Joint Bone Spine. 2018;85(2):185-9.
20. Guevara DL, Cerda F, Carreno MA, Piottante A, Bitar P. Update in the study of granulomatosis with polyangiitis (Wegener's granulomatosis). Rev Chil Radiol. 2019;25(1):26-34.
21. Isa H, Lightman S, Luthert PJ, Rose GE, Verity DH, Taylor SRJ. Histopathological features predictive of a clinical diagnosis of ophthalmic granulomatosis with polyangiitis (GPA). Int J Clin Exp Pathol. 2012;5(7):684-9.
22. Graves N. Wegener granulomatosis. Proc (Bayl Univ Med Cent). 2006;19(4):342–4.
23. LanguageF, Cinar M, Karagol T, Bozkurt D, Ozcan RK. Wegener's granulomatosis: case report. J Neurol. 2007;6(1):1-5.
24. Jokar M, Amir Feizi Z. Granulomatosis with polyangiitis (Wegener's granulomatosis): An analysis

of 59 patients. Rheum Resc. 2017;2(4):115-8.
25. Kesel N, Kohler D, Herich L, et al. Cartilage destruction in granulomatosis with polyangiitis (Wegener's granulomatosis) is mediated by human fibroblasts after transplantation into immunodeficient mice. Am J Pathol. 2012;180(5):2144-55.
26. Comarmond C, Cacoub P. Granulomatosis with polyangiitis (Wegener): clinical aspects and treatment. Autoimmun Rev. 2014;13(11):1121-5.
27. Sangle S, Karim MY, Hughes GRV, D'Cruz DP. Sulphamethoxazole-trimethoprim in the treatment of limited paranasal Wegener's granulomatosis. Rheumatol. 2002;41:589-90.

A Case Report of Profuse Bleeding in the Lower Gastrointestinal Tract due to Dieulafoy Lesion in the Rectum

Saskia A. Nursyirwan[1], Roy Soetikno[1,2], Noto Dwimartutie[3], Kaka Renaldi[1]*

[1]Division of Gastroenterology, Pancreatobiliary, and Digestive Endoscopy, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Division of Gastroenterology and Hepatology, San Francisco Veterans Affairs Medical Center, San Francisco, California, USA.
[3]Division of Geriatric, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Saskia A. Nursyirwan, MD. Division of Gastroenterology, Pancreatobiliary, and Digestive Endoscopy, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl Diponegoro no. 71, Jakarta Pusat, Indonesia. email: saskia.aziza@gmail.com.

ABSTRACT

Dieulafoy lesion is a rare condition that usually occurs in cases of gastric bleeding in the upper gastrointestinal tract. However, this condition can also occur in the lower gastrointestinal tract but less frequently. The lesion is an arteriolar malformation that extends to the submucosa, causing erosion and bleeding. Meanwhile, this is a case of a 67-year-old woman presenting with a bright red bloody stool prior to admission, as well as a history of constipation which was relieved by digital stool evacuation two weeks earlier. The medical history of the patient reveals episodes of repeated ischaemic stroke for over seven years and three months, which has led to other conditions such as right-sided paralysis, transcortical motor aphasia, and neurogenic dysphagia. The patient was routinely on antithrombotic medications, which was stopped during hospitalisation where repeated packed cell transfusion was done in order to avoid hematochezia. The patient needed the support of her caregiver most of the time since she was bedridden. Furthermore, the haemostasis and platelet function of the patient were normal. On colonoscopy, there was the discovery of a small lesion of about 3mm in her rectum, protruding into the lumen and pulsated, which was discovered to be Dieulafoy's lesion. Subsequently, this lesion was closed using rubber band ligation, and after a month, there was no recurrence of the lower gastrointestinal bleeding.

Keywords*: Hematochezia, lower gastrointestinal bleeding, Dieulafoy's lesion, ligation.*

INTRODUCTION

Dieulafoy lesion (DL), also known as caliber persistent artery, is a rare cause of gastrointestinal bleeding. This condition accounts for about 6% of gastrointestinal nonvariceal bleeding, and about 1% to 2% of all acute gastrointestinal hemorrhages.[1] The difficulty in making a correct diagnosis makes DL seem like a rare condition. However, it is believed that it occurs more frequently in reality than what is reported. DL can occur in the stomach, duodenum, oesophagus, colon and rectum at 71%, 15%, 8%, 2% and 2%, respectively, as well as the jejunum-ileum and gastric anastomosis at 1% each.[2]

An artery of the GI tract will usually narrow as it gradually passes through the wall of the end organ. A DL is characterized by a vessel with an abnormally large diameter of about 1 to

3 mm, as it follows a tortuous path through the submucosa. This causes a lesion that typically protrudes through the submucosal membrane as a defect, ranging in size from 2 to 5 mm and containing fibrinoid necrosis at its base.[3] The difficulty in diagnosing lesions during endoscopy may be due to the heavy bleeding that occurs at the surrounding, as well as the small size of the lesions. There is no consensus concerning the treatment of DL, which could vary depending on the symptoms presented in the patient, site of the lesion, and the experts available during therapy. Also, the evolution of endoscopic methods of haemostasis has significantly reduced the need for surgery in DL.[2]

CASE ILLUSTRATION

A 67-year-old woman presented with a bright red bloody stool for about two weeks before admission to the hospital, where she denied feeling any pain in her abdomen. The patient had a history of constipation, which was relieved by digital stool evacuation two weeks earlier. Also, the medical history of the patient shows repeated ischemic strokes for over seven years and three months, which progressed to other conditions, such as right-sided paralysis, transcortical motor aphasia, and neurogenic dysphagia. The patient was previously diagnosed with diabetes mellitus and hypertension, and was on antithrombotic medication regularly. The support of a caregiver was required most of the time since the patient was bedridden. During a previous visit to the hospital, the patient underwent a colonoscopy that revealed a giant adenoma polyp in the sigmoid. Subsequently, this was removed through polypectomy, but the patient continued to have recurrent lower gastrointestinal bleeding. However, abdominal CT scan and esophagogastroduodenoscopy revealed no significant findings from previous checkups in the hospital.

The patient was fully alert on physical examination, despite having aphasia as a result of her stroke. The vital signs of the patient, such as the body mass index (BMI), blood pressure and pulse rate were 20 kg/m^2, 120/70 mmHg and 98 beats per minute, respectively. Furthermore, pallor conjunctiva was observed, with the absence of organomegaly, palpable mass, or tenderness in any region of the abdomen, according to the abdominal examination. The patient was completely bedridden due to the right-sided paralysis she experienced. Other examinations conducted were insignificant since her platelets and haemostasis function were both normal.

Also, the patient presented with repeated bloody stool in our ward, with a total of about 200-300cc in each episode of bleeding, and received recurrent packed red cell transfusions when there was a drop in the haemoglobin level after bleeding from about 10 g/dl to 4 g/dl.

On colonoscopy, there was the discovery of a fibrin-based ulcer on the sigmoid without any active bleeding, which confirmed that polypectomy was previously carried out in that area. However, the patient developed hematochezia, which prompted enteroscopy that revealed erosive enteritis without active bleeding. She did not recover from the recurrent haemorrhage despite the discontinuation of antithrombotic therapy from the first onset of bleeding, and the administration of a proton pump inhibitor, as well as other drug analogues, such as rebamipide, and sucralfate. Therefore, another colonoscopy was performed to determine the source of the bleeding. Eventually, a Dieulafoy lesion was found, which was in the form of a pulsated ulcer, with a diameter of 3 mm. Furthermore, it was at about 2 cm from the anocutaneous line, protruding into the lumen. Ligation was then performed on the lesion, and

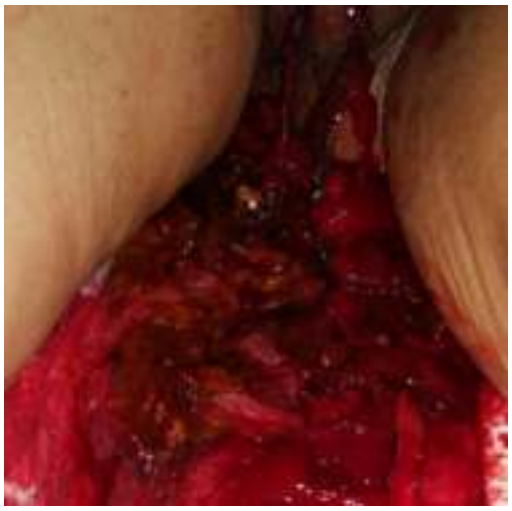


Figure 1. Massive hematochezia on each episode of bleeding.

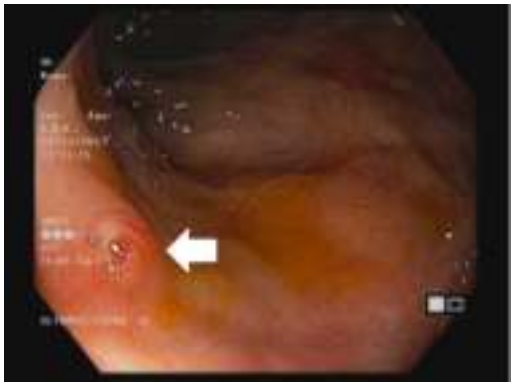


Figure 2. Dieulafoy lesion presented as a 3mm, pulsated lesion in the rectum.

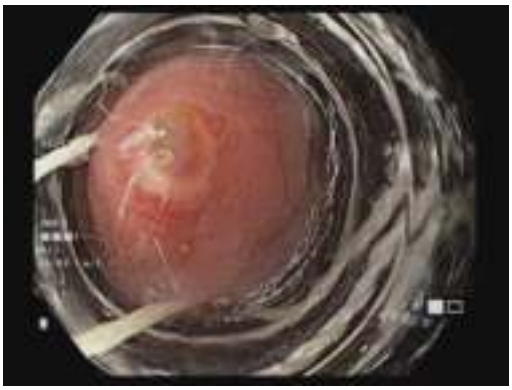


Figure 3. Rubber band ligation of Dieulafoy lesion.

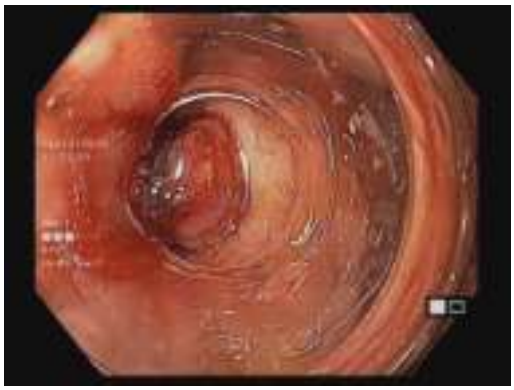


Figure 4. Dieulafoy lesion post rubber band ligation.

after a month, the patient confirmed that she no longer experienced lower gastrointestinal bleeding during the follow-up.

DISCUSSION

Despite its rarity, Dieulafoy's lesion should always be considered as a cause of gastrointestinal bleeding due to its potential to cause massive, life-threatening, and recurring bleeding, as well as its amenability to life-saving endoscopic therapy. DL occurs mostly in the stomach, with only a small percentage of cases occurring in the lower gastrointestinal tract. According to epidemiological data, males are more likely to be affected than females at a proportion of approximately 2:1.[2] Furthermore, this condition can occur within any age group, but the majority of reported cases were older people, particularly those in their sixth or seventh decades. Non-gastrointestinal comorbidities such as cardiovascular disease, hypertension, diabetes, and chronic renal insufficiency are common in affected patients. Patients who are on nonsteroidal anti-inflammatory drugs (NSAIDs) or anticoagulants may also experience bleeding symptoms, which increases the likelihood of bleeding due to Dieulafoy lesions.[4] All of these conditions are consistent with the age and comorbidity of our patient.

Meanwhile, the patient usually presented with sudden, massive gastrointestinal bleeding, which led to a hemodynamically unstable condition that required multiple blood transfusions. Also, the initial gastrointestinal endoscopy is only useful in diagnosing up to 70% of patients. That low rate is due to the small and inconspicuous lesions, which cannot be observed during examination. [5] However, we could use CT angiography if endoscopy fails to locate the source of the bleeding, but its role is limited due to a lack of therapeutic capabilities.

Endoscopic therapy can be classified into three, which include ablation, mechanical therapy and injection involving the use of epinephrine or sclerosing agent. The most effective is mechanical therapy, such as band ligation or endoscopic clips, which has been shown in some studies to stop bleeding by mechanically closing off the bleeding vessel.[6,7] According to studies, band ligation in rectal Dieulafoy is relatively safe and effective in the treatment of active bleeding from colorectal Dieulafoy lesion.[8,9]

Additionally, there are other options aside from endoscopic therapy, which include angiography and embolization, as well as surgical treatment. In cases where endoscopic therapy fails to stop the bleeding, angiography can be used to embolize the active bleeding caused by

the DL. However, embolization increases the risk of bowel ischaemia in the area supplied by the relevant artery.[2] Lastly, surgery is reserved for 5% of the cases that are not amenable to endoscopic or angiographic methods.[3]

CONCLUSION

DL should be considered as a potential cause of profuse gastrointestinal bleeding. Mechanical endoscopic therapy such as band ligation of the rectum is relatively safe and effective in the treatment of active bleeding from colorectal DL.

REFERENCES

1. Jeon HK, Kim GH. Endoscopic management of Dieulafoy's lesion. Clin Endosc. 2015;48(2):112–20.
2. Baxter M, H Aly E. Dieulafoy's lesion. Current Trends Diagnosis and Management. 2010;92:548.
3. Chaer RA, Helton WS. Dieulafoy's disease. J Am Coll Surg. 2003;196(2):290–6.
4. Nojkov B, Cappell MS. Gastrointestinal bleeding from Dieulafoy's lesion: Clinical presentation, endoscopic findings, and endoscopic therapy. World J Gastrointest Endosc. 2015;7(4):295–307.
5. Marangoni G, Cresswell AB, Faraj W, Shaikh H, Bowles MJ. An uncommon cause of life-threatening gastrointestinal bleeding: 2 synchronous Dieulafoy lesions. J Pediatr Surg. 2009;44(2):441–3.
6. Chung I-K, Kim E-J, Lee M-S, et al. Bleeding Dieulafoy's lesions and the choice of endoscopic method: Comparing the hemostatic efficacy of mechanical and injection methods. Gastrointest Endosc. 2000;52(6):721–4.
7. Alis H, Oner OZ, Kalayci MU, et al. Is endoscopic band ligation superior to injection therapy for Dieulafoy lesion? Surg Endosc. 2009;23(7):1465–9.
8. Vandervoort J, Montes H, Soetikno RM, Ukomadu C, Carr-Locke DL. Use of endoscopic band ligation in the treatment of ongoing rectal bleeding. Gastrointest Endosc. 1999;49(3):392–4.
9. Gil Park J, Chul Park J, Hwan Kwon Y, Young Ahn S, Jeon S. Endoscopic management of rectal Dieulafoy's lesion: A case series and optimal treatment. Clin Endosc. 2014;47:362–6.

A Case Report of Hereditary Angioedema: Challenges in Diagnosis and Management

Alvina Widhani, Suzy Maria, Rifky Yulian, Anshari Saifuddin Hasibuan, Sukamto Koesnoe*

Division of Allergy and Clinical Immunology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Alvina Widhani, MD. Division of Allergy and Clinical Immunology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: alvina.widhani@gmail.com.

ABSTRACT

Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder which causes bradykinin mediated angioedema. Although it can be life threatening, HAE may be underdiagnosed due to a lack of awareness of the disease and limited access to laboratory testing. Here, we report a case of HAE which was diagnosed only after the patient was referred for COVID-19 vaccination even though he had been experiencing recurrent angioedema for the past 30 years.

Keywords: *Hereditary, angioedema, diagnosis, management.*

INTRODUCTION

Hereditary angioedema (HAE) is a genetic disorder manifests as intermittent swelling of the skin or mucosal tissue of the upper respiratory and gastrointestinal tracts which can be life-threatening but cannot be predicted. This rare disease has autosomal dominant inheritance.[1] In Indonesia, there are difficulties in the diagnosis and treatment of HAE. Not only is awareness of the disease lacking, but there is also limited access to the laboratory test that can confirm a diagnosis and first line medication for HAE management is unavailable.

CASE ILLUSTRATION

A 48-year-old male was referred to Cipto Mangunkusumo Hospital for evaluation of eligibility for a COVID-19 vaccination. He had a history of recurrent swelling in the face, hands, and feet (**Figure 1**) which had been triggered by fatigue or cold weather ever since he was in senior high school. His symptoms worsen in the first 24 hours of an attack and then disappear within 3-5 days. They do not improve with an antihistamine or oral corticosteroid. During his most severe attack, he felt shortness of breath which brought him to an emergency ward. The attending doctor told him that he had airway swelling. The first attack he ever experienced was as a teenager.

There has never been any urticaria or other skin lesions. The man had no history of taking an angiotensin-converting enzyme (ACE) inhibitor or non-steroidal anti-inflammatory drugs (NSAIDs) and also no history of food or drug allergy. His mother and siblings also had histories of the same attack (**Figure 2**). When the patient came to the outpatient clinic, his physical examination was normal. Laboratory results showed a normal peripheral blood count, C4 level 4 mg/dL (10–40 mg/dL), and C1 inhibitor 4 mg/dL (21-39 mg/dL). The patient

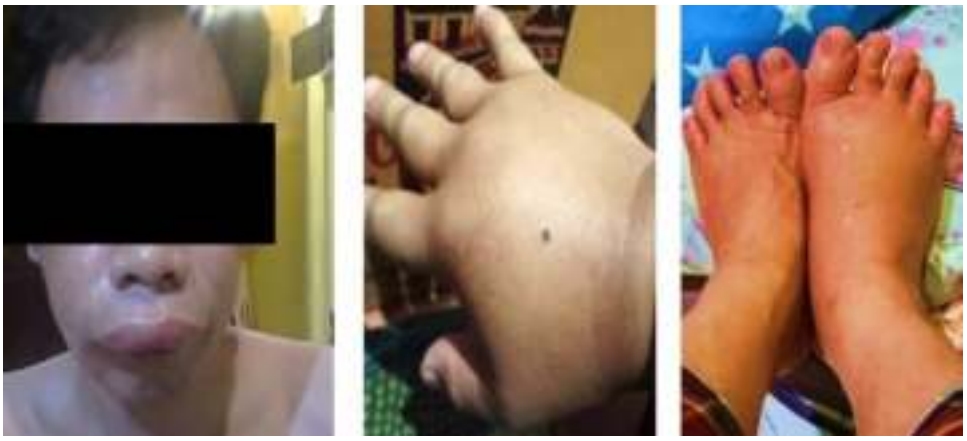


Figure 1. Recurrent angioedema experienced by the patient.

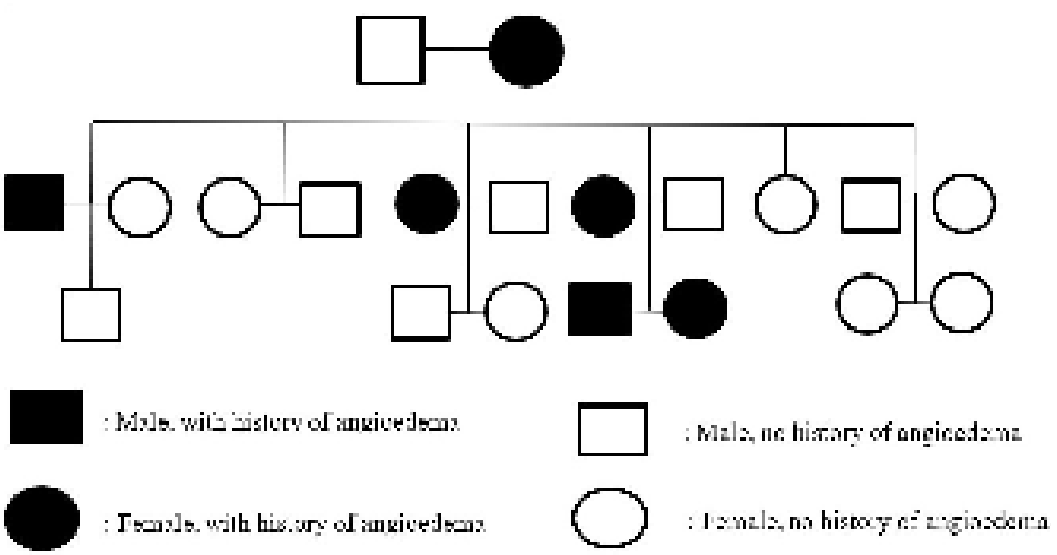


Figure 2. Patient's family tree.

was assisted financially by a foundation to check for C1 inhibitor (INH) as this is not covered by the Indonesia National Insurance because a sample must be sent to a laboratory in the United States by a private laboratory in Indonesia. We diagnosed the patient with type 1 HAE. For long term prophylaxis, we have administered tranexamic acid. After he was given prophylaxis, the patient rarely had angioedema attack (**Figure 3**). The COVID-19 vaccine, Coronavac, was safely administered in this patient without adverse event following vaccination.

Figure 3. After prophylaxis, the patient rarely had angioedema attack.

DISCUSSION

Prevalence of HAE globally is approximately 1 in 10,000 to 1 in 50,000 people.[2] Even though

it is rare, the mortality rate from laryngeal edema is about one death for every 20 patients.[3] Prevalence of the disease in Indonesia is unknown and possibly underdiagnosed. This case shows a patient that had symptoms for a long time before visiting our clinic for diagnostic work up. He also has family members with similar symptoms who have not planned to visit a doctor because they don't consider it a serious problem. Underdiagnosis of the disease is not only due to a lack of awareness, but there are also problems related to diagnostic tests of C1-INH and C1-INH function because samples must be sent to laboratories outside Indonesia.

Hereditary angioedema is one of the bradykinin mediated angioedema. Angioedema - tissue swelling caused by regional increased in the permeability of blood vessels - can be mediated by bradykinin and/or mast cell mediators including histamine.[4] Histamine has important role in angioedema associated with wheals, while bradykinin is the most important mediator in angioedema not associated with wheals.[2]

Bradykinin mediated angioedema can be hereditary or acquired.[4] Acquired bradykinin mediated angioedema might be caused by drugs, such as ACE inhibitors, angiotensin II receptor blockers (ARB), tissue plasminogen activators, neprilysin inhibitors or gliptins.[2,4] ACE inhibitor inhibits degradation of bradykinin. Other acquired causes are lymphoma or autoimmune diseases.[2]

Two types of HAE make up the majority of HAE cases. Type 1 HAE is caused by C1-INH deficiency which lead to decrease of C1-INH level and function. Meanwhile, type 2 HAE has normal or elevated C1-INH level, but low C1-INH function. Type 1 and type 2 HAE are caused by a mutation in gene which code C1-INH (SERPING1). C1-INH is the main inhibitor of mannose binding lectin-associated serine protease, C1s, and C1r (complement proteases). It also inhibits contact-system proteases (coagulation factor XIIa and plasma kallikrein) and plasmin, a protease which dissolves fibrin blood clot.[4] Mutations in SERPING1 gene for type 1 and type 2 HAE are different. In type 1 HAE, C1-INH cannot be secreted because it is misfolded. It is caused by insertion, nonsense, deletion, missense, or frameshift in SERPING1 gene. Low C1-INH function seen in type 2 HAE is caused by mutant C1-INH.[8]

Other types of HAE are the result of known or unknown mutation. They show normal C4 and C1-INH levels and functions. The mutations are mutations of the factor XII gene, angiopoietin-1 gene, plasminogen gene, kininogen 1 gene, myoferlin gene, or heparan sulfate 3-O-sulfotransferase 6 gene. Deficiency or dysfunction of C1-INH cause increase of bradykinin level then it will activate bradykinin B2 receptors. This condition increases vascular permeability which manifests as angioedema.[1,4]

Typical manifestation of HAE is swelling of the lips, hands, feet, eyes, or genitals. HAE attack can also cause life-threatening laryngeal edema and abdominal pain.[2] The attack which can be triggered by procedure, trauma, infection, or stress, lasts for 2-5 days which can resolve without treatment.[8] Clinicians should suspect for type 1 or type 2 HAE when they find angioedema without wheals which do not improve with antihistamine or steroid.[2,4] Another supporting data are onset of manifestations in childhood or adolescence, a positive family history, and prodromal signs or symptoms before swellings. To confirm the diagnosis, measurements of C4 and C1-INH level and function are needed.[4] Our patient had history of swelling in his lips, hands, feet, and upper air way without wheals since adolescence which was not responsive to antihistamines or corticosteroids. This manifestation, with a positive family history and low C4 and C1-INH levels, supports the diagnosis of type 1 HAE in our patient. In one case report, a patient with type 1 HAE can present with atypical manifestation limited to gastrointestinal system (severe abdominal pain with bowel wall oedema and colitis). The patient had a family history for HAE and the laboratory work up showed low C4 level and C1q esterase inhibitor.[5]

Clinicians should know how to manage HAE patients during acute attacks and how to give prophylaxis before procedure or for long term.[2,6] Medications for treatment or prophylaxis that target the pathway in bradykinin mediated

angioedema include C1-INH replacement, inhibition of the bradykinin B2 receptor, and inhibition of kallikrein which decrease bradykinin production (**Figure 4**).[1,2,6,7] Low or dysfunctional C1-INH can be treated with plasma-derived or recombinant C1-INH which has similar target with endogenous C1-INH. Bradykinin-mediated angioedema cannot be treated with antihistamine, steroid, and epinephrine.[1,4]

First line medication for long time prophylaxis is plasma-derived C1-INH. Other choices are lanadelumab and berotralstat. Lanadelumab is a fully human antiactive plasma kallikrein monoclonal antibody which can be given subcutaneously. Meanwhile berotralstat is an oral plasma kallikrein inhibitor. Attenuated androgens (danazol) have also been used for long-term prophylaxis, but there are dose-related side effects related to its androgenic and anabolic effects.[4] The dose of danazol varies between 100 mg every other day and 200 mg three times daily (2.5-10mg/kg/d, max 600mg).[4,6] Due to side effects, danazol more than 200 mg daily is not recommended for long term treatment. Danazol increases C1-INH produced by the liver and C1-INH messenger RNA expression in circulating monocytes. It is not useful for acute attack because danazol takes 1-2 days to have effect.[1] When first-line prophylactic treatment is not available and androgens are contraindicated, antifibrinolytics, such as tranexamic acid, can be used.[4] Antifibrinolytic inhibits plasminogen conversion to plasmin. This condition decrease activation of FXII.[1] Contraindications/ precautions for antifibrinolytics are high thrombotic risk, thrombophilia, or acute thrombosis. Dosage of tranexamic acid is between 30 and 50 mg/kg of body weight daily, which can be divided into two or three doses with a maximum of 6 g per day.[4] In the case of this study, because the first-line medication for long term prophylaxis is not available in Indonesia, we chose to administer tranexamic acid rather than attenuated androgen because of its fewer side effects.

We also educated the patient about the preparations he would need to do if he planned to undergo a procedure involving the upper aerodigestive tract. For preprocedural short-term prophylaxis in procedures related to the upper aerodigestive tract, the first line recommendation is intravenous plasma-derived C1-INH (pdC1-INH). If intravenous pdC1-INH cannot be given, recombinant human C1-INH (rhC1-INH) can be considered. If this medication is also unavailable, fresh frozen plasma (FFP) is an alternative option. Attenuated androgens (eg, danazol) can also be

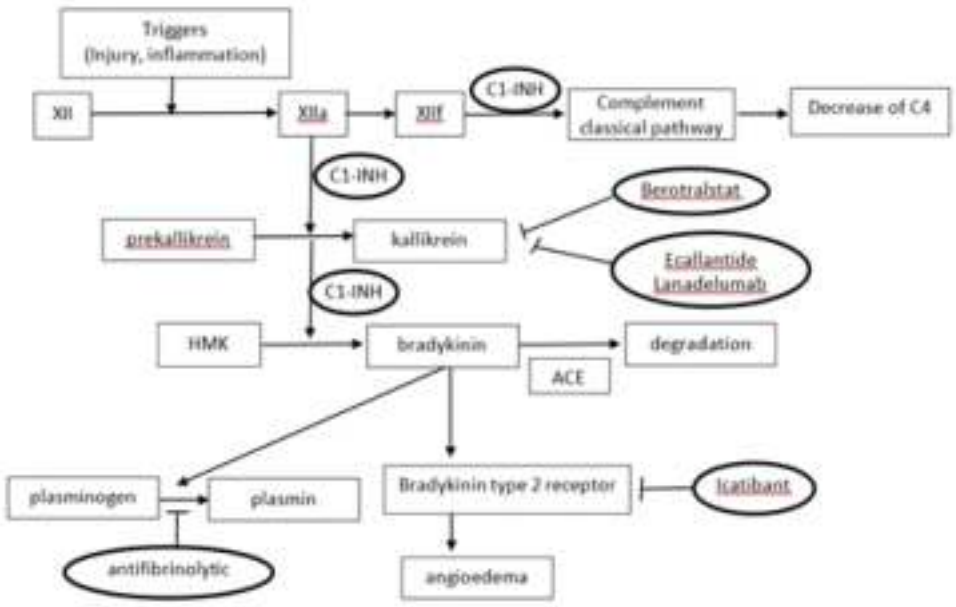


Figure 4. Bradykinin mediated angioedema pathway and treatment modalities in hereditary angioedema. C1-INH: C1 inhibitor; ACE: angiotensin converting enzyme.

used for scheduled preprocedural prophylaxis as it is given 5 days before the procedure and 2–3 days post procedure. In the past, tranexamic acid has been used for preprocedural prophylaxis, however it is not recommended by most guideline experts.[4] Because first line short time prophylaxis is not available in Indonesia, the alternatives are FFP and attenuated androgen.

For acute attack, especially one affecting the upper airway, the treatments of choice are icatibant (bradykinin-receptor antagoninst), ecallantide (kallikrein inhibitor), and intravenous C1- INH. If these first-line options are not available, solvent detergent-treated plasma (SDP) can be given for acute attack. If SDP is also not available, FFP is the alternative.[4] The available treatment option in Indonesia for acute attack is FFP.

Educating patients about HAE is also an important part of HAE management. Although most HAE attacks are unpredictable, the patient should be informed about avoiding triggers and consider long term prophylaxis. HAE attacks can be triggered by trauma, estrogen-containing oral contraceptive agents, estrogen hormone replacement therapy, ACE inhibitors, fatigue, menstrual cycle, febrile illness, and psychological stress. It is also important to educate family members displaying similar symptoms and encourage them to visit a doctor for HAE work up. It is recommended that family members of type 1 and type 2 HAE patients are screened for C4 level and C1-INH level and function because this medical condition has autosomal dominant inheritance.[4]

There is concern that COVID 19 vaccine can trigger angioedema attack because it shows more side effects (fatigue, pain, fever) than other vaccine. Study by Fijen et al.[9] reported that of the 111 doses of COVID 19 vaccine administered, there were 11 angioedema attacks with nine attacks happened after first dose. All attacks were mild or moderate and no hospitalization or laryngeal edema. One attack happened in patient that was already given pre procedural prophylaxis with danazol. Four attacks happened in patient that were taking long term prophylaxis with intravenous C1-INH. Eight attacks were treated with intravenous C1-INH. In this study, COVID 19 vaccine platform given were mRNA-1273 (Moderna), BNT162b2 (Pfizer-BioNTech), ChAdOx1 nCov-19 (AstraZeneca), and Ad26. COV2-S (Janssen). There were 8 attacks from 38 patients who got Pfizer-BioNTech vaccine, 2 attacks from 10 patients with Moderna vaccine, 1 attack from 6 patients with Jansen vaccine, and none from 9 patients with AstraZeneca vaccine. Our patient got Coronavac vaccine, an inactivated COVID 19 vaccine, which has different platform with COVID-19 vaccine given in the study by Fijen et al. Although our patient did not report any adverse event following vaccination, more data is needed to know whether inactivated vaccine is safer than other COVID 19 vaccine platform for patient with HAE.

CONCLUSION

Although HAE is a rare genetic disease, it can be life threatening. To improve its detection and management, awareness and knowledge of physicians needs to be increased. HAE might be underdiagnosed because of limited access to the required laboratory test, which is an issue that should be addressed by health care providers. Until now, first line treatment and prophylaxis for HAE are not available in Indonesia, probably because of unknown demand due to limited detection.

REFERENCES

1. Wilkerson RG, Moellman JJ. Hereditary angioedema. Emerg Med Clin North Am. 2022;40:99–118.
2. Jindal AK, Bishnoi A, Dogra S. Hereditary angioedema: Diagnostic algorithm and current treatment concepts. Indian Dermatol Online J. 2021;12(6):796–804.
3. Minafra FG, Goncalves TR, Alves TM, Pinto JA. The mortality from hereditary angioedema worldwide: A review of the real-world data literature. Clin Rev Allergy Immunol. 2022; 62(1):232-9.
4. The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update. World Allergy Organ J. 2022; 15(3):100627.
5. Soni P, Kumar V, Alliu S, Shetty V. Hereditary angioedema (HAE): a cause for recurrent abdominal pain. BMJ Case Rep. 2016; 2016: bcr2016217196.
6. Zafra H. Hereditary angioedema: a review. WMJ. 2022;121(1):48-53.
7. Kaplan AP, Joseph K. Complement, kinins, and hereditary angioedema: mechanisms of plasma instability when C1 inhibitor is absent. Clinic Rev Allerg Immunol. 2016;51:207–15.

8. Abdulkarim A, Craig TJ. Hereditary angioedema. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.
9. Fijen LM, Levi M, Cohn DM. COVID-19 vaccination and the risk of swellings in patients with hereditary angioedema. J Allergy Clin Immunol Pract 2021;9(11):4156-8.

HIV-Associated Progressive Multifocal Leukoencephalopathy: A Case Study

Elsayed Abed[1], Ahmed Farag El-adawey[1], Mohamed Hamed Rashad[1], Ahmed Essmat[1], Mohammed Ali[1], Ahmed Hassan Elsheshiny[1], Abdel-Ghaffar Fayed[1], Fathy Elbaz[1], Mahmoud Galal Ahmed[1], Zohreh Abna[2], Shaimaa Sayed Khater[3]*

[1]Department of Neurology, Faculty of Medicine, Al-Azhar University, Cairo, 11651, Egypt.
[2]MS Fellowship, Department of Neurology, Tehran University of Medical Sciences, Tehran, Iran.
[3]Department of Neurology, Faculty of Medicine, Ain Shams University, Cairo, 11566, Egypt.

[*] ***Corresponding Author:***
Elsayed Abed, MD. Department of Neurology, Faculty of Medicine, Al-Azhar University, Cairo 11651, Egypt. Email: elsayedabed.226@azhar.edu.eg.

ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is a rare, life-threatening, infectious, lytic, demyelinating disease that results from reactivation of the virulent JC polyomavirus (JCV) "major opportunistic infection" in immunosuppressed individuals. We reported a case of a young girl who presented with new onset focal neurological defect, evaluated, and laboratory and radiological findings in the context of a clinical setting confirmed HIV-related-PML infection. However, remyelination does not occur, the patients may develop complications in the long term including cognitive impairment, sensory deficits, motor deficits, and disturbances in balance. We must increase our knowledge about HIV- related PML in any patient with reduced immunity and who presented with new onset neurological defect.

Keywords: *Progressive multifocal, leukoencephalopathy, JC virus, demyelinating disease.*

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a rare, life-threatening, infectious, lytic, demyelinating disease which affects glial cells in the white matter of the central nervous system.[1,2] Reactivation of the virulent JC polyomavirus (JCV) "major opportunistic infection" in immunosuppressed individuals with human immunodeficiency virus (HIV) infection, post solid organ and bone marrow transplant recipients, and malignancies causes PML disease.[3,4] The only known clinical manifestation results from the reactivation of dormant JC virus is PML. Although the cases associated with HIV account for about 85% of the cases that have been diagnosed with PML, the clinical entity of such presentation is to be suspected in patients who present with seizures, conscious level deterioration, and focal neurologic deficits.[5] Here, we reported a case of PML in an HIV-infected patient.

CASE ILLUSTRATION

A 13-year-old girl with normal perinatal and developmental history was admitted to the emergency department with the sub-acute onset of weakness of her right lower limb and deviation of mouth to the left side for one week. There was no history of seizure, headache, fever, disturbed conscious level, other cranial

nerves involvement, disequilibrium, sensory affection, or bladder disturbances. Her mother reported recurrent oral infection in the previous 6 weeks. She had a history of tonsillectomy at age of three years and left side hip surgery in her first year of life. The patient is right-handed without any history of medical importance. On examination, pulse was 75 beats/min, blood pressure was 110/70 mmHg and respiratory rate was 16/min. She was confused, limited verbal fluency, right lower motor facial nerve affection, right side hemiparesis (upper limb 4/5, and lower limb 3 /5), and extensor planter response bilaterally. The rest of the examination was normal. After admission, an urgent laboratory investigation was requested and showed normal blood pictures, electrolyte levels, blood gases, and biochemistry. Cerebrospinal fluid (CSF) analysis revealed normal biochemistry, cytology, culture, and sensitivity. CSF analysis for the virology panel was negative as well as negative for cryptococcal infection. CSF was also found negative for tubercular antigen by polymerase chain reaction. The patient started supportive treatment (intravenous fluid, vitamin), and brain imaging was requested. Magnetic resonance imaging (MRI) of the brain showed large confluent nonenhanced, infiltrative, ill-defined, subcortical, and cortical mass lesions, involving the left hemisphere, which crosses the midline to involve the right hemisphere via the splenium of the corpus callosum. Hemorrhage

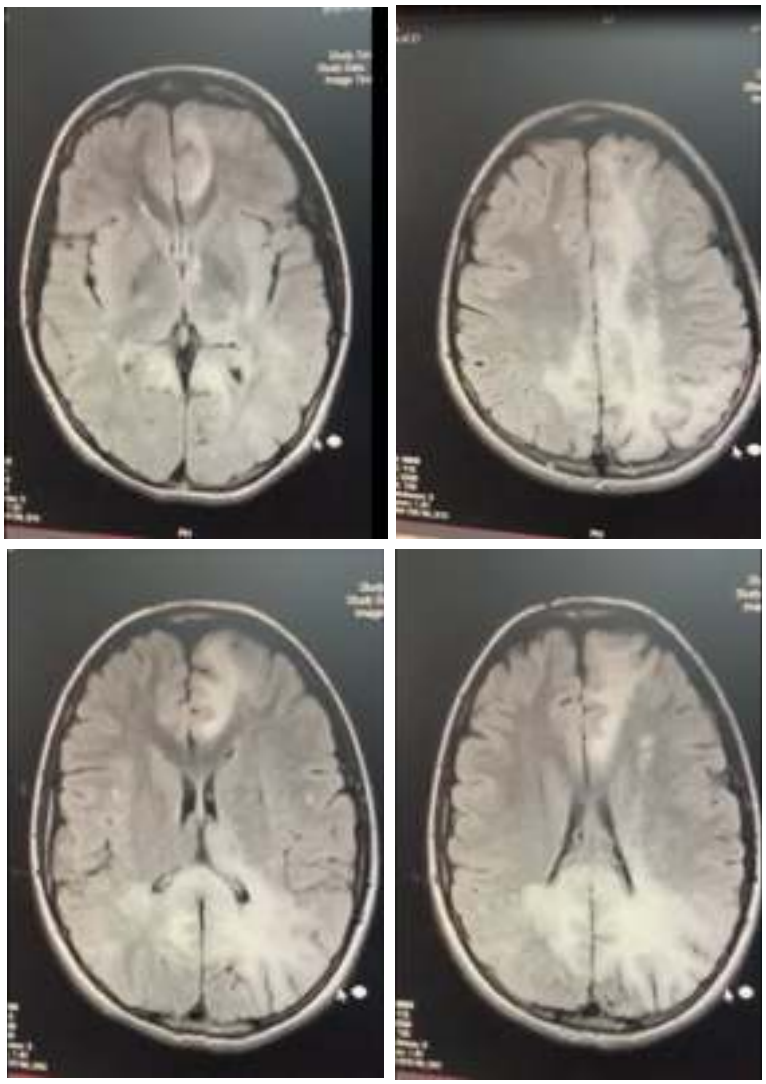


Figure 1. MRI of the patient's brain in the course of the disease shows large confluent non-enhanced, infiltrative, ill-defined, subcortical, and cortical mass lesions, involving the left hemisphere, which crosses the midline to involve the right hemisphere via the splenium of the corpus callosum.

or necrotic region is not detected. Infection of the CNS was suspected, and a blood sample for toxoplasmosis and virology screen was taken. ELISA for HIV-1 was positive. The absolute CD4 count was 120/μL. The possibility of PML was increased and confirmed with positive polymerase chain reaction (PCR) for JC virus in CSF. Given the above clinical features and investigations, the patient was diagnosed to have HIV-related PML. The patient started highly active antiretroviral therapy (HAART) with prophylaxis of opportunistic infections, but she died after 1 month.

DISCUSSION

The incidence of PML has increased significantly since the onset of the AIDS epidemic in 1981 and now HIV-associated cases account for up to 85% of all cases of PML. PML is a rare, life-threatening, demyelinating disease that affects the white matter of the central nervous system caused by the JC virus.[1] JC virus is a DNA virus of the polyomaviridae family that remains dormant in renal tubules and could be activated when the host developed any state of depressed immunity.[6] In a reduced immunity state, reactivation of the latent form of JC virus to cause active disease needs rearrangement of gene sequences in the virus DNA.[7] The natural course of the disease is determined primarily by the cellular immune response of the host particularly the cytotoxic T lymphocytes. In the case of reduced immunity, there was intense perivascular infiltration of immune cells, HIV antigens, and viral proteins resulting in severe, lytic demyelination. However, CSF has a major role in the clearance of the virus; we can depend on an elevated level of cytotoxic T lymphocytes in CSF samples of patients with suspicion of active PML.[8] PML should be considered in the differential diagnosis of any patient presented with a new onset neurological defect particularly when the CD4 count was less than 200. However, the most commonly involved sites include the subcortical white matter, periventricular areas, and cerebellar peduncles, the patients may manifest with variable presentation including cognitive decline, limb or gait ataxia, long tract affection, and aphasia.[7,8] Moreover, the presentation of PML could mimic different CNS infections clinically; toxoplasma encephalitis, primary CNS lymphoma (PCNL), HIV encephalopathy, and CMV encephalitis should be strongly considered in the differential diagnosis. Radiologically, PML is asymmetric, well-demarcated, and non-contrast-enhancing lesion without a mass effect, whereas both Toxoplasma and PCNL present as contrast-enhancing lesions.[8] Routine blood tests, infectious panel, and HIV PCR testing are indicated to identify the cause of the immunosuppressed state or any comorbid condition that led to the reactivation of the JC virus. The evaluation of abnormal neurological findings in immunosuppressed patients, such as those with AIDS, begins with Contrast-enhanced imaging with either CT or MRI to reveal the presence of inflammatory change and mass effect, and could help to differentiate the PML from other mimics.[9] The treatment for the complete cure of PML has not been found and is guided by the efforts made to boost the adaptive immune response of the patient.[10]

CONCLUSION

PML is a fatal, severe, progressive, multifocal, demyelinating disease. The main goal of current therapeutic approaches is directed at prolonging survival rates. However, remyelination does not occur, the patients may develop complications in the long term including cognitive impairment, sensory deficits, motor deficits, and disturbances in balance. We must increase our knowledge about HIV- related PML in any patient with reduced immunity and who presented with new onset neurological defect.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in concordance with declaration of Helsinki and the participant signed a written informed consent before being enrolled in the study. The institutional review board (IRB) approval was obtained from the ethical committee of Faculty of Medicine, Al-Azhar University, Cairo. The ethical code is “Near-Med._71 HIV- associated progressive multifocal leukoencephalopathy; a

case study._000071".

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

FUNDING

This study was self-funded by the authors.

AUTHORS' CONTRIBUTIONS

All authors participated in manuscript writing and editing. All authors have read and approved the manuscript.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to the Department of Neurology, Tehran University of Medical Sciences, Tehran, Iran.

REFERENCES

1. Major EO. Progressive multifocal leukoencephalopathy in patients on immunomodulatory therapies. Annual Review of Medicine. 2010;61:35-47.
2. Wüthrich C, Cheng YM, Joseph JT, et al. Frequent infection of cerebellar granule cell neurons by polyomavirus JC in progressive multifocal leukoencephalopathy. Journal of Neuropathology & Experimental Neurology. 2009;68(1):15-25.
3. Mancall EL. Ricahrdson EPJr. Progressive multifocal leukoencephalopathy: hitherto unrecognized complication of chronic lymphatic leukemia and Hodgkins disease. Brain. 1958;81:93-111.
4. Koralnik IJ. Progressive multifocal leukoencephalopathy revisited: has the disease outgrown its name? Annals of Neurology. 2006;60(2):162-73.
5. Choudhary S, Parashar MK, Parashar N, Ratre S. AIDS-related progressive multifocal leukoencephalopathy-really rare in India: A case report and review of literature. Indian Journal of Sexually Transmitted Diseases and AIDS. 2018;39(1):55.
6. Jensen N, Eugene O, Major P. A classification scheme for human polyomavirus JCV variants based on the nucleotide sequence of the noncoding regulatory region. Journal of Neurovirology. 2001;7(4):280-7.
7. Lima MA, Marzocchetti A, Autissier P, et al. Frequency and phenotype of JC virus-specific CD8+ T lymphocytes in the peripheral blood of patients with progressive multifocal leukoencephalopathy. Journal of Virology. 2007;81(7):3361-8.
8. Gildenberg PL, Gathe Jr, JC, Kim JH. Stereotactic biopsy of cerebral lesions in AIDS. Clinical Infectious Diseases. 2000;30(3):491-9.
9. Miller RF, Hall-Craggs MA, Costa DC, et al. Magnetic resonance imaging, thallium-201 SPET scanning, and laboratory analyses for discrimination of cerebral lymphoma and toxoplasmosis in AIDS. Sexually Transmitted Infections. 1998;74(4):258-64.
10. Clifford DB, Nath A, Cinque P, et al. A study of mefloquine treatment for progressive multifocal leukoencephalopathy: results and exploration of predictors of PML outcomes. Journal of Neurovirology,. 2013;19(4):351-8.

Rare Case: Unilateral Acute Primary Angle-closure Glaucoma After Colonoscopy in Malang, East Java, Indonesia

Supriono[1*], Amalia Nurul Hatinah[2], Mochamad Fachrureza[1], Syifa Mustika[1], Bogi Pratomo Wibowo[1]

[1]Division of Gastroentero-Hepatology, Department of Internal Medicine, Saiful Anwar General Hospital - Faculty of Medicine Universitas Brawijaya, Malang, Indonesia.
[2]Department of Internal Medicine, Saiful Anwar General Hospital, Faculty of Medicine Universitas Brawijaya, Malang, Indonesia.

Corresponding Author:
Supriono, MD. Division of Gastroentero-Hepatology, Department of Internal Medicine, Saiful Anwar Hospital - Faculty of Medicine Universitas Brawijaya. JL. JA. Suprapto No. 2, Malang, Indonesia.
Email: supriono_ipd.fk@ub.ac.id.

ABSTRACT

Glaucoma is a heterogeneous group of optic neuropathies characterized by a progressive loss of retinal ganglion cells (RGCs) with corresponding visual field defects, and one of the main risk factors is elevated intraocular pressure (IOP). Furthermore, colonoscopy procedures require insufflation of the colon lumen with gases which can increase intraabdominal pressure (IAP) and ends with an elevation of IOP. Glaucoma is an infrequent complication due to colonoscopy; in this case, a 63 years-old woman was diagnosed with glaucoma after a colonoscopy procedure. A few hours after the colonoscopy, the patient suffered blurred vision in the left eye, and the physical examination revealed mixed conjunctival and ciliary injection with visual acuity of 1/300. There was an increase in IOP with a value of 40,2 mmHg on Schiotz tonometry. This case presented the pitfalls of the procedure and the importance of taking glaucoma awareness before a colonoscopy.

Keywords: *colonoscopy, glaucoma, intraabdominal pressure, intraocular pressure.*

INTRODUCTION

Glaucoma is a heterogeneous group of optic neuropathies characterized by a progressive loss of retinal ganglion cells (RGCs) with corresponding visual field defects, and one of the main risk factors is elevated intraocular pressure (IOP).[1] Meanwhile, colonoscopy is an endoscopic examination of the large bowel, and the distal part of the small bowel with a fiber optic camera on a flexible tube passed through the rectum.[2] As the colon is insufflated during colonoscopy, facilitating the visualization of the colonic lumen, the dilated bowel loops transmit the pressure and increase intraabdominal pressure (IAP).[3] Intraabdominal hypertension (IAH) might lead to an increase in the IOP.[3,4] Elevated IOP is a risk factor for several ophthalmic pathologies, such as anterior ischemic optic neuropathy, retinal vascular occlusion, and glaucoma.[5,6] Due to the high worldwide prevalence of glaucoma and the wide use of colonoscopy as a screening examination, there is a potential risk for glaucoma in patients undergoing colonoscopies. Therefore, this case report aims to raise awareness of colonoscopy complications in relation to glaucoma to prevent further irreversible morbidity.

CASE ILLUSTRATION

A 63 year-old woman was admitted to the hospital for a colonoscopy after complaining of hematochezia with decreased body weight. The preparation was suboptimal, and the colonoscopy was performed with an air insufflation technique and without sedation, contributing to severe abdominal pain during the scope insertion.

Based on the clinical evaluation, the patient appeared to be in pain with a vas score of 6/10, blood pressure 118/61 mmHg, heart rate of 74 beats/minute, oxygen saturation of 98% in ambient air, and right lower abdominal pain. The colonoscopy also revealed ulcerative proctitis, multiple polyps of the rectosigmoid, and diverticula of the transverse colon, as shown in **Figure 1**.

A few hours after the colonoscopy, the patient suffered blurred vision in the left eye, while ophthalmological examination showed mixed conjunctival and ciliary injection, visual acuity of 1/300, and hardening of the left orbit on palpation with IOP of 40.2 mmHg on Schiotz tonometry. The anterior chamber was shallow, the cornea was edematous, the pupil was mid-dilated with a diameter of 4 mm and unresponsive to light, the iris crypt was unclear, and the lens was hazy. Moreover, the contralateral eye had a shallow anterior chamber with normal pressure and a hazy lens.

In outpatient care, some tests were performed, including gonioscopy which showed narrowing of the anterior chamber angle. Additionally, the ocular computed tomography (OCT) presented thinning of the inferior retinal nerve fiber layer (RNFL), confirming the diagnosis of closure angle glaucoma. The patient was given oral acetazolamide and timolol 0,5% ED to lower the pressure in the eye. After five days, the pain was getting less severe, conjunctival and ciliary injections were decreased, the left eye visual acuity was 6/20, and IOP on Schiotz's tonometry was 14 mmHg (**Figure 3**).

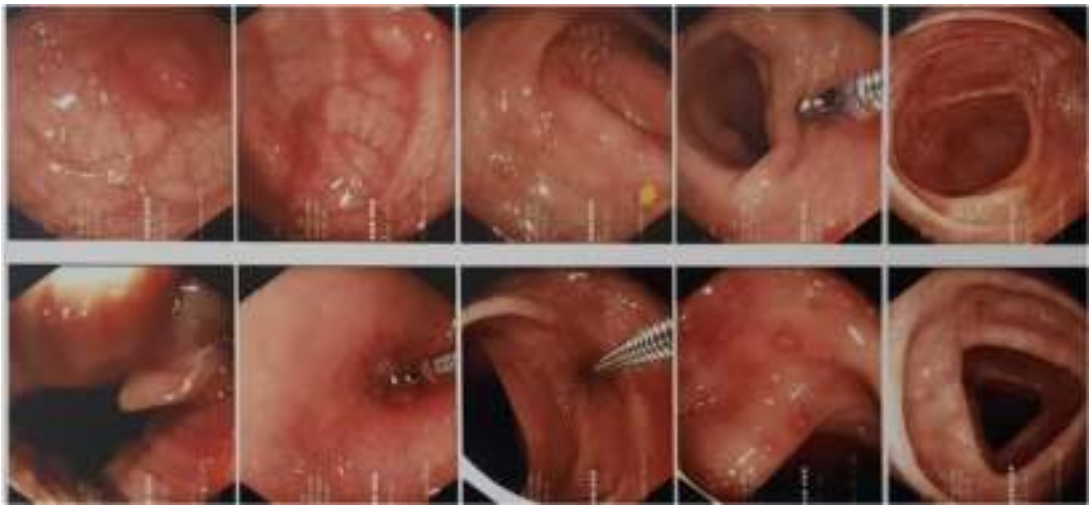


Figure 1. Multiple ulcers and multiple polyps reveal in the rectosigmoid.

Figure 2. Ocular presentation after the colonoscopy procedure.

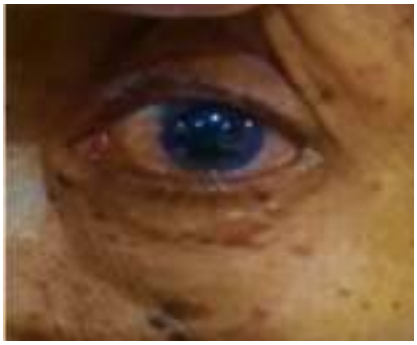


Figure 3. Ocular presentation after treatment of glaucoma.

DISCUSSION

Colonoscopy is one of the most frequently performed interventional endoscopic procedures for screening, diagnosis, and treatment.[7] During the procedures, the elevation in IAP created by air to enhance the image quality can increase IOP and cause undesirable spikes in IOP.[7] Meanwhile, a high IOP above 21 mmHg is one of the most important risk factors for glaucoma.[8] This is an optic neuropathy that leads to structural and functional defects within the eye, particularly optic disc damage, and visual field loss. There are two main forms of illness, namely open-angle, and angle-closure.[8]

Angle-closure glaucoma affects a total of 20 million people worldwide,[9,10] and the number is estimated to increase to 23 million in 2020, as well as 32 million in 2040.[10] It is also known as one of the leading causes of irreversible blindness worldwide, affecting 3.9 million people in 2010.[9] In Indonesia, the prevalence of glaucoma was 4.6 per 1.000 populations in 2007.[11] Furthermore, angle-closure glaucomas is a true ophthalmic emergency that might cause progressive damage to the optic nerve.[12]

Increased IOP is a major risk factor for glaucoma since it causes pressure on the retinal layer, culminating in thinning of RGCs and visual disturbances. IOP is determined by the production and drainage of aqueous humor. Other risk factors of glaucoma that should also be considered are increasing age, family history, and female.[1]

IAP occurs in the abdominal cavity due to the interaction between the abdominal wall and visceral organs. Colonoscopy using air insufflation techniques can cause distension and leads to IAH, which decreases systemic venous return, episcleral vein flow, and drainage of aqueous humor. IAH also increases intracranial pressure (ICP) by reducing drainage of the sagittal sinus. It changes the TLD (translaminar gradient difference) and causes an increase in IOP to return the TLD to its original state.[13,14] Along with pain due to unsedated procedures and suboptimal bowel preparation, IAH can disrupt the balance of production and drainage of aqueous humor as well as increase IOP.

In our gastroenterology department, the operators can carry out a colonoscopy in less than 30 minutes. Hence, the procedure was performed mainly without sedation after considering the benefit and the risk. In this case, the colonoscopy was performed without sedation with procedure took about 20 minutes. The patient experienced pain during the procedure, which caused neurogenic shock. Midazolam is a good option to reduce anxiety and calm the patient because it relaxes the extraocular muscles and lowers IOP during ocular procedures.[7] It must also be noted that the pre-procedural anxiety levels of the patient undergoing colonoscopy might affect this situation, but in this case, the pre-procedural anxiety levels were not questioned.

The standard Trendelenburg tilt position during procedures was associated with a more significant increase in IOP compared to a reverse Trendelenburg tilt, which was associated with a slight reduction in several patients.[15] These changes were reversed in patients when intra-abdominal pressure was below 14 mmHg and operative time was not beyond 90 minutes.[15] In this case, colonoscopy was performed in the lateral decubitus position, which is also known to increase IOP.[16,17] Due to the short-term procedure, which was less than 30 minutes, the effect of different positions during colonoscopy did not significantly increase IOP. Therefore, the reverse Trendelenburg tilt position is recommended when the procedure takes more than 90 minutes.

CONCLUSION

This case report is the first instance of unilateral acute primary angle-closure glaucoma after a colonoscopy procedure in Malang,

Indonesia. This investigation suggested the importance of pre-procedural ophthalmologic examination to patients at risk of developing glaucoma and anxiety before colonoscopy. Additionally, selecting the appropriate sedation drug based on the patient's condition and performing the reverse Trendelenburg tilt position when the procedure is more than 90 minutes can help reduce the risk of glaucoma post-colonoscopy.

REFERENCES

1. Lee SSY, Mackey DA. Glaucoma–risk factors and current challenges in the diagnosis of a leading cause of visual impairment. Maturitas. 2022.
2. Kent I, Geffen N, Stein A, Rudnicki Y, Friehmann A, Avital S. The effect of colonoscopy on intraocular pressure: an observational prospective study. Graefe's Archive for Clinical and Experimental Ophthalmology. 2020;258:607–11.
3. Yoo YC, Shin S, Choi EK, Kim CY, Choi YD, Bai SJ. Increase in intraocular pressure is less with propofol than with sevoflurane during laparoscopic surgery in the steep Trendelenburg position. Canadian Journal of Anesthesia. 2014;61(4):322.
4. Ece I, Vatansev C, Kucukkartallar T, Tekin A, Kartal A, Okka M. The increase of intra-abdominal pressure can affect intraocular pressure. BioMed Research International. 2015;2015.
5. Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol. 2000;130(4):429–40.
6. Drance S, Anderson DR, Schulzer M, Collaborative Normal-Tension Glaucoma Study Group. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. American Journal of Ophthalmology. 2001;131(6):699–708.
7. Bayraktaroglu M, Kurtay A, Horasanli E. Comparison of two sedation protocols on intraocular pressure and hemodynamic responses during colonoscopy. Eur Rev Med Pharmacol Sci. 2022;26(12):4295–302.
8. Quigley HA. Glaukoma. The Lancet. 2011;2011(377):1367–77.
9. Sun X, Dai Y, Chen Y, et al. Primary angle closure glaucoma: what we know and what we don't know. Progress in Retinal and Eye Research. 2017;57:26–45.
10. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014;121(11):2081–90.
11. Kemenkes R. Situasi dan analisis glaukoma. Jakarta Selatan: Pusat Data dan Informasi; 2015.
12. Wetarini K, Dewi NMRP, Mahayani NMW. Acute angle closure glaucoma: management in acute attack setting. Bali Medical Journal. 2020;9(1):386–9.
13. Depauw PR, Groen RJ, Van Loon J, Peul WC, Malbrain ML, De Waele JJ. The significance of intra-abdominal pressure in neurosurgery and neurological diseases: a narrative review and a conceptual proposal. Acta Neurochirurgica. 2019;161:855–64.
14. Ficarrotta KR, Passaglia CL. Intracranial pressure modulates aqueous humour dynamics of the eye. The Journal of Physiology. 2020;598(2):403–13.
15. Adisa AO, Onakpoya OH, Adenekan AT, Awe OO. Intraocular pressure changes with positioning during laparoscopy. JSLS: Journal of the Society of Laparoendoscopic Surgeons. 2016;20(4).
16. Yamada MH, Takazawa T, Iriuchijima N, Horiuchi T, Saito S. Changes in intraocular pressure during surgery in the lateral decubitus position under sevoflurane and propofol anesthesia. Journal of Clinical Monitoring and Computing. 2016;30:869–74.
17. Park J, Joo J, Kwon SG, Jang Y, Hyeon T. Synthesis of monodisperse spherical nanocrystals. Angewandte Chemie International Edition. 2007;46(25):4630–60.

Pulmonary Artery Wedge Pressure Formula Using Echocardiography Finding

Lukman H. Makmun[1], Telly Kamelia[2], Prasandhya Astagiri Yusuf[3]*

[1]Division of Cardioloy, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Division of Respirology and Critical Care Medicine, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3]Department of Medical Physics, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.

***Corresponding Author:**
Telly Kamelia, MD., PhD. Division of Respirology and Critical Care Medicine, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: tellykamelia99@gmail.com.

ABSTRACT

This study aims to introduce a new formula for pulmonary artery wedge pressure (PAWP) derived from the pathophysiology of Velocity A (V_A) waves. The current formula is the the Nagueh formula. Left ventricular (LV) filling is described as a velocity A (VA) wave. The VA wave represents the filling rate of the end-diastolic blood phase from the left atrium (LA) to the LV which can be determined on echocardiography. Left ventricular end diastolic pressure (LVEDP) is equivalent to LA pressure and is also equivalent to PAWP. The gold standard method for obtaining PAWP values is right heart catheterization. By measuring the VA waves in the bloodstream, a new PAWP formula is obtained, and the PAWP examination can be validated in research and can be compared with several other PAWP formulas that are currently the world's standard formula for calculating pulmonary artery wedge pressure (PAWP).

The new PAWP formula is obtained from the conversion of the VA wave. This formula could be validated further in research and used in clinical practice.

Keywords: *Velocity A wave (VA wave), pulmonary artery wedge pressure (PAWP) formula.*

INTRODUCTION

Pulmonary arterial wedge pressure (PAWP) is between 4 to 12 mmHg. It is used to asses for severity of mitral stenosis (MS), to differentiate between cardiogenic and non-cardiogenic pulmonary edema, and to confirm the diagnosis of pulmonary hypertension (PH).[1] PAWP is a critical component of the hemodynamic evaluation, as the sole parameter to define precapillary PH (PCPH) from PH due to left heart disease.[2]

The gold standard method to assess the functionality of the pulmonary circulation is by right heart catheterization (RHC), which measures pulmonary vascular pressures using fluid-filled Swan-Ganz catheter and pulmonary flow thermodilution or the Fick principle. PAWP is acceptable as estimate of left atrial pressure (LAP) or left ventricular end diastolic pressure (LVEDP).[3]

The current formula to calculate PAWP is the Nagueh formula. It uses the measurements of E wave velocity and early diastolic velocity of mitral annulus (E_a) during Doppler tissue imaging. These velocities reflect the shortening and lengthening of the myocardial fibers along a longitudinal plane, with each corner of the annulus being influenced more by the adjacent

left ventricle (LV) wall. It demonstrated that the ratio of the transmitral E velocity to E_a (i.e., the E/E_a ratio) is related significantly with PAWP.[4]

On Doppler echocardiographic examination, LV filling is described as a velocity A (V_A) wave. The V_A wave represents the filling rate of the end-diastolic blood phase from the LA to the LV, and is also equivalent to PAWP. By measuring the V_A waves in the bloodstream, a new PAWP formula is obtained.

CALCULATION OF CONVERSION OF VA VALUE TO PAWP VALUE (PC), EQUIVALENT TO P_{LA}

P_{LA} or pressure on the LA area stereometrically caused by the suppression of the blood volume contained in the LA in the end diastolic phase. The amount of pressure in the LA area is calculated using the formula:

Pressure (P_{LA}) = Force (F) / Area on which the force act (A)

or: $P_{LA} = F / A$……..1).

F = Force ……..in N (Newton).

W (Weight) = m x g; W = or F (N).

W = weight (N); m = mass (kg); g = gravitational field strength = 9,8 m/sec^2

1 N = 1 kg. 1 m/sec^2 = 1 kg.m/sec^2

1 Dn (Dyne) = 1 g cm/sec^2

1 N = 10^3 .g. 10^2 cm/ sec^2 = 10^5 gcm/sec^2

1 N = 10^5 Dn.

By using the formula for kinetic energy:

$E = ½ mv^2$ ……2).

E = Energy; m = mass; v = velocity.

Then combined with this formula:

E = F x d ……3)

E = energy; F = Force; d = distance

Thus becoming:

F x d = $½ mv^2$

$F = ½ mv^2 / d$ ……4)

F = m x g.

Thus: m x g = $½ mv^2 / d$

or $d = v^2 / 2 g$ ……..…5)

Pressure formula:

$P_{LA} = F / A$ ……..1)

= m g / A ……6).

CALCULATION OF LA VOLUME IN THE END DIASTOLIC PHASE:

Referring to the heart on Atlas Netter, mitral cross section > LA Basic Cross Section

h = height from apex, LV peak to LA base

h_1 = distance from apex – mitral cross section

d = distance = distance from LA base – mitral cross section.

R = pseudo "LA basic cross section" radius (look at the image)

r_1 = Mitral cross section radius.

r_2 = "pseudo" cross radius at LA level

Based on the comparison count in the heart image on Atlas of Human Anatomy:

$h_1 = 2/3$ h; d = 1/3 h; $r_1 = 2/3R$; $R = r_1 + 2 r_2$

or: $r_2 = ½ (R – r_1)$

= ½ (R – 2/3R)

= 1/6 R.

Based on the comparison calculation in the heart image on Atlas of Human Anatomy, the shape from basic to apex is more like a tube, so the general volume formula is: $V = \pi R^2 h$

V (volume) LA $= \pi R^2h – \pi r_1^2 h_1 – 2 (\pi r_2^2 d)$

$V = \pi (R^2h – r_1^2 h_1 – 2. r_2^2 d)$

$V = \pi (R^2h – r_1^2. 2/3 h – 2. r_2^2 1/3h)$

$= \pi h (R^2 – 2/3 r_1^2 – 2/3. r_2^2)$

$= \pi h \{R^2 – 2/3(r_1^2+r_2^2)\}$

$= \pi h \{R^2 – 2/3(4/9R^2+ 1/36R^2)\}$

$= \pi h (R^2 – 2/3x17/36R^2)$

$= \pi h. 37/54 R^2$

or $= 37/54 \pi h R^2$ ……7)

Formula: Mass = Volume x Density

m = V x D.

m = mass; V = volume from formula 7);

D = blood density = 1,060 g/cm3.

$m = 37/54 \pi h R^2$ x D.

$= 37/54 \pi h R^2 D$ gram (cgs unit) ……8)

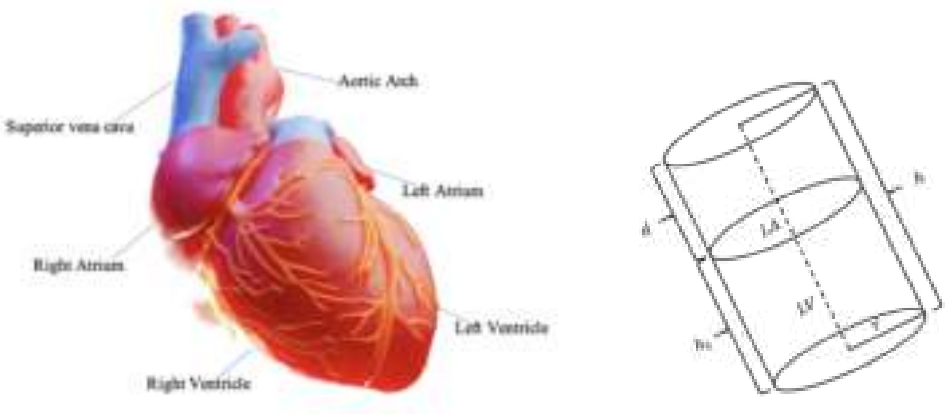


Figure 1. Comparison of anatomical and schematics drawing of a heart.[5]

A = LA space surface area

LA area approximation = the total conical wall area with side length s approximately equal to length h, minus the conical wall area "LV" and minus the area of 2 "pseudo" small cone sections at the base.

Area of 1 full circle with radius = s, is = πs^2

Area of a section with angle α at the center = $\alpha/ 360\ \pi s^2$

R/h = tg ½ α.

Based on the calculation of the ratio of R and h on the heart image in Atlas Netter:

R = 6 cm, h = 10 cm → tg ½ α.= 0,6

tg 30^0 =0,58.

Thus 1/2 α = 30^0 or angle $\boldsymbol{\alpha = 60^0}$

LA half area = ½ A

1/2 A = $\alpha/ 360\ \pi s^2 - \alpha/360\ \pi\ s_1^2 - 2$ x $(1/2\alpha)/360\ \pi\ s_2^2$.

= $\alpha/360\ \pi\ (s^2 - s_1^2 - s_2^2)$; length s approximately = h

= $\alpha/360\ \pi\ (h^2 - h_1^2 - d^2)$

= $\alpha/360\ \pi\ (h^2 - 4/9\ h^2 - 1/9\ h^2)$

= $\pi\ \alpha/360.\ 4/9\ h^2$

The total surface area of LA = A = 2x . 4/9 π $\alpha/360\ h^2$

= $8/9\ \pi\ 60/360\ h^2$

= $4/27\ \pi h^2$ cm^2 ……..……9).

Pressure on LA

P_{LA} = m. g / A from formula 6)

= $37/54\ \pi h\ R^2$ D. g / $4/27\ \pi h^2$ from formula 8) and 9)

= $37/8$ D R^2 . g h / h^2

= $37/8\ (R/h)^2$ D g. 3d ;……..see also formula 5).: h = 3d and d = $v^2/2$ g

= $37/8\ (R/h)^2$ D. g. 3 x $v^2/2$ g

D = 1,060 g/cm^3, g = gravitational field strength

R/h = tg 1/2 α; α= 60^0; 1/2 α = 30^0 → tg 30^0 = 0,58.

P_{LA} = 111/16. $0,58^2$. 1,060 . x v^2.

$\mathbf{P_{LA} = 2,47\ v^2\ g/cm.sec^2}$ **……10)**

1 P_a = 1 N/ 1 m^2. (P_a = Pascal)

= 1 kgm/sec^2 / 1 m^2 =1 kg/m sec^2

= 10 g/cm sec^2

1 mmHg = 133,3 P_a atau 1 P_a = 0.0075 mmHg

$\mathbf{P_{LA} = 2,47\ V_A^2\ g/ cm.sec^2}$

= 0,247. V_A^2 Pa (Pascal)

= 0,247 V_A^2 x 0,0075 mmHg

or: $\mathbf{P_{LA} = 18,525.\ 10^{-4}\ x\ V_A^2}$ mmHg cgs → VA units must be in cm/s

= 18,525. 10^{-4}**.** 10^4 x V_A^2 mmHg V_A value in **m/s**

$\mathbf{P_{LA} = 18,525\ V_A^2\ mmHg}$…….(V_A in **m/s**) …… Formula **11**.

Example: if $V_A = 0,7$ m/s

$P_{LA} = 18,525 \times 0,7^2$ mmHg.

$= 9,1$ mmHg

One of the clinical benefits is in treating acute heart failure, according to the Nohria method with Wet and Cold data, other than cardiac output, PC (Pulmonary Capillary) or PAWP pressure is required.

CONCLUSION

The new PAWP formula has advantages over the Nagueh formula, where the new formula uses blood flow while the Nagueh formula uses tissue imaging. This formula can enrich the knowledge, especially in the field of cardiology. It is recommended that this formula be validated with right heart catheterization using Swan-Ganz catheter, to compare its advantages and disadvantages over the Nagueh formula.

ACKNOWLEDGMENTS

This PAWP formula has been registered to the Indonesian Copyright Service (HAKI) by Lukman H. Makmun (Reg. no.EC00202297063, November 30, 2022).

REFERENCES

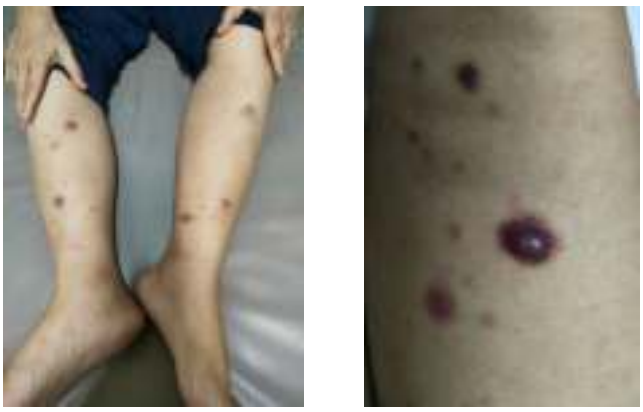
1. Nair R, Lamaa N. Pulmonary capillary wedge pressure. StatPearls [Internet]. 2022 Apr 21; Available from: https://www.ncbi.nlm.nih.gov/books/NBK557748/
2. Viray MC, Bonno EL, Gabrielle ND, et al. Role of pulmonary artery wedge pressure saturation during right heart catheterization: A prospective study. Circ Heart Fail [Internet]. 2020;660–2. Available from: https://www.ahajournals.org/doi/abs/10.1161/CIRCHEARTFAILURE.120.007981
3. Naeije R. Physiology of the pulmonary circulation and the right heart. Curr Hypertens Rep. 2013;15(6):623–31.
4. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol. 1997;30(6):1527–33.
5. Netter FH. Netter atlas of human anatomy. 7th Edition. Philadelphia, PA: Elsevier Health Sciences; 2019.

Generalized Reddish Skin Nodules

Laniyati Hamijoyo[1]*, Dinar F. Yaddin[1], Indra Wijaya[2], Panji Irani Fianza[2], Hermin Aminah Usman[3], Bethy S Hernowo[3], Harjuli Yoy Ceana[1], Miranti Pangastuti[4], Yovita Hartantri[5]

[1] Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine Universitas Padjadjaran - Hasan Sadikin Hospital, Bandung, Indonesia.
[2] Division of Haematology and Oncology, Department of Internal Medicine, Faculty of Medicine Universitas Padjadjaran - Hasan Sadikin Hospital, Bandung, Indonesia.
[3] Department of Pathology Anatomy, Faculty of Medicine Universitas Padjadjaran - Hasan Sadikin Hospital, Bandung, Indonesia.
[4] Department of Dermatology, Faculty of Medicine Universitas Padjadjaran - Hasan Sadikin Hospital, Bandung, Indonesia
[5] Division of Infectious and Tropical Disease, Department of Internal Medicine, Faculty of Medicine Universitas Padjadjaran - Hasan Sadikin Hospital, Bandung, Indonesia.

Corresponding Author:
Laniyati Hamijoyo, MD. Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine Universitas Padjadjaran - Hasan Sadikin Hospital. Jl. Pasteur 38, Bandung, Indonesia. Email: hamijoyo@yahoo.com.



(A) (B)

Figure 1. Skin nodules on both legs (A), the reddish nodule (B).

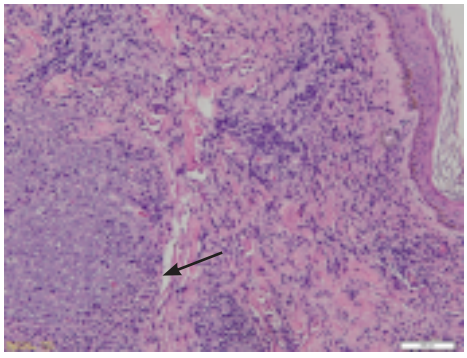


Figure 2. Histopathology H&E stain of the skin biopsy (1:100).

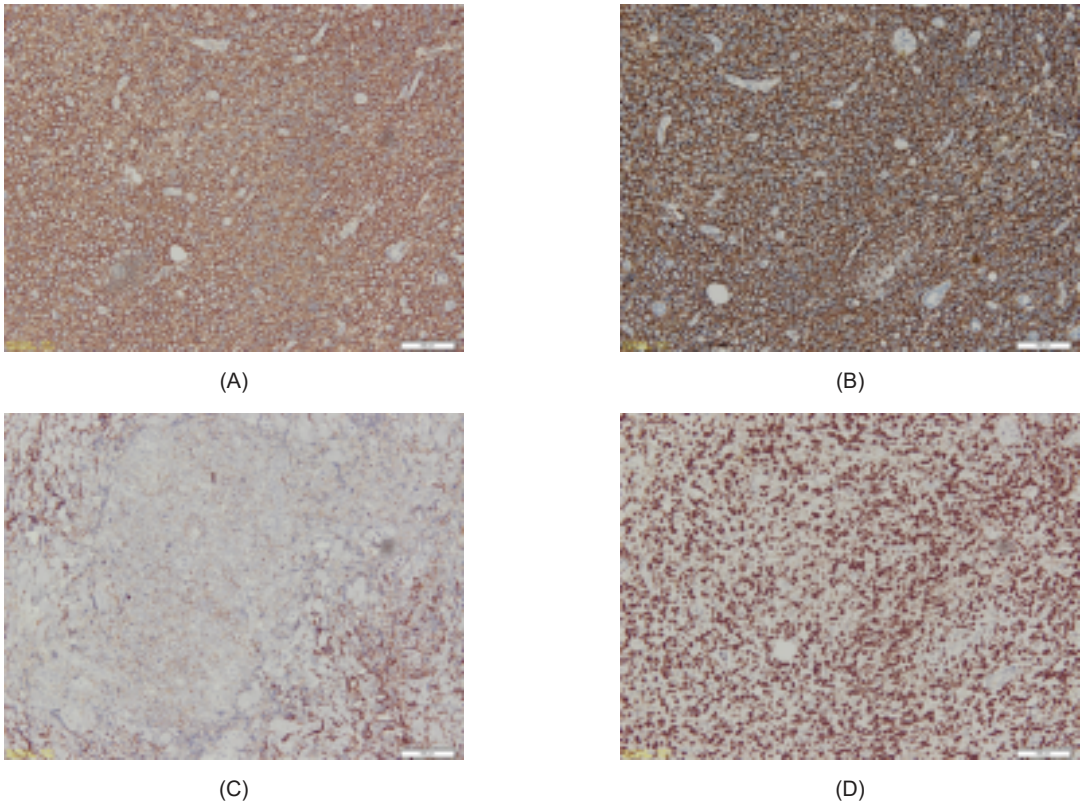


Figure 3. The IHC stain (1:100) of CD45 (A), CD20 (B), CD10 (C) and Ki67 (D).

Diagnosis of nodular skin red lesions is challenging. The differential diagnosis includes dermal nevus, angioma, pyogenic granuloma, amelanotic melanoma, eccrine poroma, Kaposi's sarcoma, skin malignancy or metastasis.[1] Fully work up should be done to find the right diagnosis.

A 60 years old female admitted to our hospital due to generalized reddish skin nodules since one month. She had continuously high grade fever of 39 Celsius accompanied by arthralgia and fatigue since two months prior to admission and she lost 6 kg of weight in 2 months. She had visited a physician, diagnosed as erythema nodosum and was given low dose corticosteroid. On admission, physical examination revealed slight fever, pale conjunctiva, mild hepatosplenomegaly, non-tender reddish skin nodules from 0.3 to 2.0 cm with firm edge on her cheek, abdominal area and both lower extremities (**Figure 1**). No lymph nodes enlargement was noticed. Her laboratory test showed haemoglobin 9.1 g/dl, WBC 3,040/μL, PLT 149,000/μL, SGOT 48 U/L, SGPT 43 U/L, urea 12.5 mg/dL, creatinine 0.67 mg/dL. She was found to be non-reactive for HBsAg, HCV, and HIV antigens. Urine routine and microscopic examination was unremarkable.

Her histopathology of left foot nodule biopsy showed cutaneous lymphoma (**Figure 2** and **3**). It lined by stratified squamous epithelium, nuclei are within normal limit. Subepithelial consists of edematous fibrocollagenous connective tissue with dilatation of large blood vessel and bleeding. Round, oval, medium size tumor cells (arrow) are seen diffusely within stroma and nuclei with coarse chromatin; mitotic figures are noted.

The immunohistochemical (IHC) stain of CD45, CD20, and CD10 were positive, and Ki67 were also positive with >70% tumor cells, while CD3,CD56, CD30, and Granzyme were negative. Her final diagnosed was Cutaneous Diffuse large B cell lymphoma.

Primary cutaneous B-cell lymphoma (PCBCL) is a rare malignancy of primary B-cell lymphocytes in the skin with varied

clinicopathological, immunophenotypic and prognostic features. They may appear on the skin as a reddish rash, lump or nodular lesions.[2] Primary cutaneous lymphomas of B-cells occur less frequently than primary cutaneous T-cells lymphomas.[3] Primary extra-nodal diffuse large B-Cell lymphoma (DLBCL) can be seen in up to 40% of cases. However skin involvement is less common and in a large cohort of DLBCL cases, skin involvement at presentation was seen only in 3.3% of cases.[4] It characterized by few lesions, in general showing nodules or infiltrations of relatively fast growth and have no itching. The diagnosis is made by the immunohistochemical findings, clinicopathological correlation, and molecular pathology.[5] Cutaneous lymphomas have different clinical behaviours despite being identical in morphological appearance. Many types of cutaneous lymphoma start as flat red patches on the skin, which can sometimes be itchy. With darker skin, the patches may appear lighter or darker than the surrounding skin. In the early stages, the skin patches can look like other common conditions such as eczema or psoriasis. PCBCL tend to have lumps on their skin in 1 or 2 areas, rather than affecting all of the body. Local recurrence in PCBCL is up to 68% of the cases and with rare extra-cutaneous dissemination, with an average rate of 5-year survival varying from 89 to 96%.[6] Cutaneous B-cell lymphoma could become one of considered diagnosed of generalized skin reddish nodules even it is rare.

REFERENCES

1. Adone B. A red skin nodule. J Integr Oncol. 2018;7:1. DOI: 10.4172/2329-6771.1000i101
2. Lima M. Cutaneous primary B-cell lymphomas: from diagnosis to treatment. An Bras Dermatol. 2015;90(5):687–706.
3. Kilaru S, Panda SS, Mishra S, et al. Cutaneous involvement in diffuse large B cell lymphoma at presentation: report of two rare cases and literature review. J Egypt Natl Canc Inst. 2021; 33:25. https://doi.org/10.1186/s43046-021-00085-1
4. Castillo JJ, Winer ES, Olszewski AJ. Sites of extranodal involvement are prognostic in patients with diffuse large B-cell lymphoma in the rituximab era: an analysis of the surveillance, epidemiology and end results database. Am J Hematol. 2014;89(3):310–4. https://doi.org/10.1002/ajh.23638.
5. Kerl H, Fink-Puches R, Cerroni L. Diagnostic criteria of primary cutaneous B-cell lymphomas and pseudolymphomas. Keio J Med. 2001;50:269–73.
6. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105:3768–85.

Sleep Problem in Post COVID-19 Patient, Its Impact on Quality of Life and Current Management: An Evidence-based of Case Report

Hamzah Shatri[1,2], Rizka Zainudin[1], Yanuar Ardani[1], Edward Faisal[1], Rudi Putranto[1]

[1] Division of Psychosomatic and Palliative, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo National Hospital, Jakarta, Indonesia.
[2] Clinical Epidemiology Unit, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo National Hospital, Jakarta, Indonesia.

Corresponding Author:
Hamzah Shatri, MD., PhD. Psychosomatic and Palliative Division, Department of Internal Medicine, Faculty Medicine Universitas Indonesia - Cipto Mangunkusumo National Hospital. Jl Diponegoro No. 71, Jakarta 10430, Indonesia. Email: hshatri@yahoo.com; psikosomatik.paliatif@gmail.com.

ABSTRACT

Background: *COVID-19 is a global health problem that affects both physical and psychological aspect of patients. Sleep problems were experienced by many patients during the acute phase of after COVID-19 recovery. It affects patient's quality of life and required comprehensive management. This evidence-based case report aims to study the effect of sleep disturbance on quality of life and what is the appropriate management in post COVID-19 patients.* ***Methods:*** *searching were conducted in Pubmed, Cohcrane, EBSCO according to clinical questions. Study was selected based on inclusion and exclusion criteria, then it was critically appraised.* ***Results:*** *high score on the insomnia severity index and the Pittsburgh sleep quality index were found to be associated with quality of life. Cognitive Behavioural Therapy is currently the best evidence-based treatment in patient during and after COVID-19.* ***Conclusion****: sleep disturbance is a problem that many post COVID-19 patient face and CBT can improve their quality of life.*

Keywords*: sleep problem, post COVID-19, quality of life, cognitive behavioural therapy.*

INTRODUCTION

COVID-19 pandemic became a worldwide devastating health issue starting in December 2019 in China and then gradually was a global health problem. The World Health Organization (WHO) on March 2020 has declared the novel coronavirus (COVID-19) outbreak a global pandemic and the world should be more aggressive in facing this infection.[1] As of March 2022, globally there have been more than 400 billion confirmed cases of COVID-19, including 6 billion death. In Indonesia there have been more than 5 billion cases and around 150,000 death.[2]

COVID-19 has double weapon on physical and mental domains of health. Along with its high infectivity and fatality rates, COVID-19 has caused universal psychosocial impact by causing mass hysteria, economic burden, and financial losses, social curfew and ambiguity about the future.[3] Furthermore, quarantine leading to emergence of fearful reaction, stressful condition, significant anxiety and sleep disorder among general population.[4] Study showed that mental health problems, such as depression, anxiety, insomnia and post-traumatic stress disorder (PTSD), dramatically increased after COVID-9 pandemic.[4]

Sleep is an important biological mechanism for maintaining homeostasis and quality of life. Sleep problems negatively affected the immune response by their effect on circadian rhythm of the body. PTSD after recovery from COVID-19 have been correlated to sleep problems, high anxiety level and depressive manifestations, also quality of life of front liner workers and patients was extremely burdened during the post recovery period.[4]

CLINICAL QUESTION

A female patient, 40 years old, came to the psychosomatic clinic with complaints of sleeping problem since last month. The patient said that it was difficult to start sleeping and woke up several times during the night. One month ago the patient had a covid-19 infection and was hospitalized because she had oxygen desaturation up to 90% (room air). Since then, the patient was afraid due to her history of shortness of breath and still remembered several times saw other patients died because of COVID-19 when hospitalized. At this time there were no complaints of shortness of breath, cough, and fever. The patient is a housewife and does not have any children. The patient's husband is a bus driver. There was no previous history of psychiatric disorders or sleep disturbances.

METHODS

A comprehensive literature searching was conducted on March 6 th 2022 to answer the question mentioned by exploring several online databases such as Pubmed, Cochrane Library, and EBSCO. The keyword used are "sleep disorder", "sleep problem", insomnia, "post covid", "after covid, and "quality of life" combined with Boolean operator "AND" and "OR" were used. Articles obtained were screened according to predetermined selection criteria.

The articles were selected based on inclusion and exclusion criteria. The inclusion criteria included: (1) Research articles including meta-analyses, systematic reviews, randomized controlled trials, observational studies, quantitative studies, qualitative studies, and mixed method studies evaluating sleep problem or sleep disorder or insomnia ; (2) post COVID-19 or after COVID-19 population; (3) determining quality of life on different domain. The exclusion criteria are case series, case reports, review articles, and other studies which were reported in language other than English and not relevant to PICO.

After meeting the inclusion and exclusion criteria, every article will be assessed for its validity, importance, and applicability by using the critical appraisal worksheet available from Centre of Evidence-Based Medicine (CEEBM) University of Oxford in accordance to the type of article obtained. Level of evidence of each article would be classified according to the Oxford Central for Evidence-Based Medicine Classification.

There were 5 articles obtained after searching through online data base. The queries are described in **Table 1**.

After screening through titles and abstracts, we filtered one article that suited the formulated clinical question and PICO. Screening and reviewing processes based on the inclusion and exclusion criteria were done. After further full-text reading, there were one article found to be matched to answer the clinical question. Flowchart of the searching strategy is presented in **Figure 1**.

Table 1. Queries used to conduct literature searching in journal databases.

Journal database	Keywords	Hits	Screened
PubMed/ MEDLINE	((((("sleep disorder") OR ("sleep problem")) OR (insomnia) AND (y_5[Filter])) AND (("post covid") OR ("after covid") AND (y_5[Filter]))) AND ("quality of life")	5	1
Cochrane Library	sleep disorder OR sleep problem OR insomnia AND post covid OR after covid AND quality of life (Word variations have been searched)	0	0
EBSCO	sleep disorder OR sleep problem OR insomnia AND post covid OR after covid AND quality of life	0	0

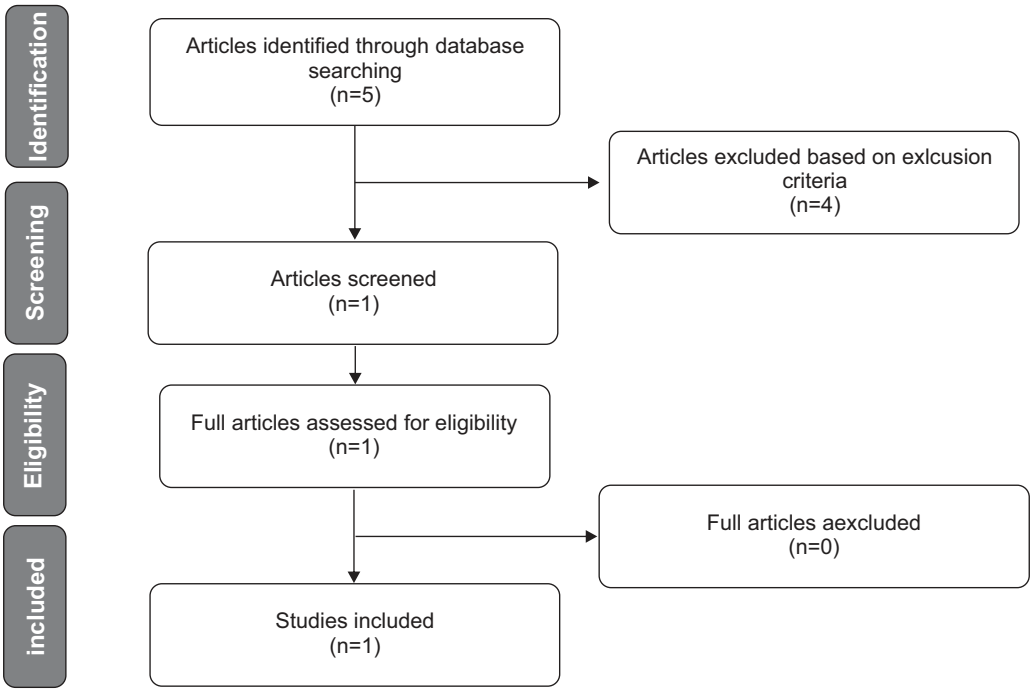


Figure 1. Flow diagram of literature searching.

RESULTS

The study that included to be appraised is a single centre cross sectional observational study by Samir El Sayed et.al.[5] Summary of the article is presented in **Table 2**. Critical appraisal of the study is presented in **Table 3.**

DISCUSSION

Apart from its physical burden, COVID-19 has enormous psychosocial impact. Disease itself multiplied by forced quarantine, "infodemic" spread via different platforms of social media and bad experience in having COVID-19 may cause mental distress such as anxiety, depression, and PTSD.[3,5]

Sleep disorder is one of the psychiatric problems that arise during and post COVID-19 patient[6]. COVID-19 insomnia is manifested by lack of sleep at night, sleepiness during the day and increase needs for naps. It occurs due to disrupted circadian rhythm during isolation and increased cytokine due to infection that interfere both non-REM and REM sleep.[6]

This study found that there were sleep problem in post COVID-19 patient based on ISI and PSQI assessment. Based on ISI, 133 (26%) and 27 (5.4%) subjects had moderate

Table 2. Summary of articles used in this study.

Reference	Study design	Subjects	Determinants	Inclusion criteria	Exclusion criteria	Outcomes	Level of evidence
El Sayed et al.[5]	Cross sectional study	500 subjects	Sleep problem (Insomnia severity index (ISI) And Pittsburgh sleep quality index (PSQI))	(1) age ranged from 18 to 60 years; (2) must have two negative PCR test for COVID 19 within one month after recovery	(1) primary language other than English; (2) patients with well-known psychiatric disorders and under effect of psychotropic medication	Different domains of Quality of Life (QOL)	2c

Table 3. Critical appraisal of cross-sectional study based on criteria by Center of Evidence-Based Medicine.

Article: El Sayed et al.[5]	
1. Did the study address a clearly focused question / issue?	Yes.
2. Is the research method (study design) appropriate for answering the research question?	Yes.
3. Is the method of selection of the subjects (employees, teams, divisions, organizations) clearly described?	Yes.
4. Could the way the sample was obtained introduce (selection) bias?	Yes.
5. Was the sample of subjects representative with regard to the population to which the findings will be referred?	No
6. Was the sample size based on pre-study considerations of statistical power?	Yes
7. Was a satisfactory response rate achieved?	Unclear
8. Are the measurements (questionnaires) likely to be valid and reliable?	Yes
9. Was the statistical significance assessed?	Yes
10. Are confidence intervals given for the main results?	Yes
11. Could there be confounding factors that haven't been accounted for?	Yes
12. Can the results be applied to your organization?	Yes

and severe clinical insomnia. Regarding global PSQI, based on 7 components, sum of this score was 15±4 which indicates a disturbed quality of sleep. Other study also found high score of PSQI in the post COVID-19 patients with persistent anxiety, depressive disorder and sleep quality insufficiency conducted in medical staff. There were also case series that said some patients will have worsening in subjective sleep quality and problems, including sleep latency and daytime function in 85% patient who recovered from COVID-19 and were re-evaluated in 8 weeks after discharge.[4]

There were also association between socio-demographic data and severity of insomnia which there was a significantly positive correlation between age, female gender, single of marital status, days after recovery from COVID 19, Physical functioning, Role limitation due to physical health, Role limitation due to emotional problems, General health and Global PSQI.[4]

This study found a statistically significant positive association between ISI and different domains of QOL scale SF 36 including physical health, role restriction because of physical health, role limitation due to emotional burdens and general wellbeing which in parallel with the result of the study concluded impaired quality of life (QoL) independently related to high anxiety score, severe depressive manifestations, poorer quality of sleep and insomnia problem.[4]

Cognitive Behavioral Therapy is the best evidence-based treatment for patient during and after COVID-19 infection. Medication may be considered for patients with severe depressive or anxiety disorder as well. Multicomponent interventions include a comprehensive history, sleep diary highlighting potential behavioral changes, addressing dysfunctional beliefs, and use of stimulus control, sleep restriction and various relaxation methods based on patient and therapist preference.[7]

The European CBT-I Academy offered to: 1) follow natural sleep rhythm on a set schedule; 2) address worry and stress by using diaries and conversations; 3) use the bed only for sleep (and sex); 4) share feelings via social media; 5) avoid devices in the 1–2 h before bed; 6) engage in safe, enjoyable activities; 6) follow healthy habits such as regular exercise, no eating in the 2–3 h before bed, seek natural light in the morning and then evening dim light; and 7) relax before bedtime, e.g. reading a book, yoga, etc.[7]

However, pharmacological treatment is still preferred and used in non-severe cases because, in some cases, CBT is not effective and not applicable. For acute anxiety in post COVID-19 patients, short acting benzodiazepine could be used. SSRI and SNRI, venlafaxine is the first choice. After remission, the drug should be continued at least several months to prevent relapse. On the other hand, patient post COVID-19 with General Anxiety Disorder (GAD) could use SSRI and SNRIS as the first choice and pregabalin as the second drug choice. Other drug that can be used are buspirone and hydroxyzine.

Benzodiazepine used only for long treatment therapy if the other drugs or CBT were failed.[8,6]

Overall, the use of anti-insomnia drugs in COVID-19 patients must be very careful and need more attention since there were broad spectrum of the symptoms and patient's comorbidity. Caution and close monitoring were needed if anti-insomnia drugs were used together with COVID-19 drugs because of its risk and interaction.[6]

Sleep related strategies of melatonin and sedating psychotropic medications have been suggested as potentially beneficial in infected COVID-19 patients. The use of melatonin in COVID-19 patients is recommended as an adjuvant therapy. Exogenous administration of melatonin up to 10 mg have modestly improved the sleep of ICU patients.[7] Besides its increasing sleep parameters, it also had anti-inflamatory and immunomodulatory effect. The essential role of circadian sleep rhythm in the deterioration of sleep quality during and post COVID-19 and the lack of melatonin on respiratory drive indicate that melatonin has potential effect for sleep disturbance related COVID-19. Melatonin may also increase the efficacy of COVID-19 vaccination. The high safety profile and its anti-SARS-CoV-2 effects make this drugs preferred for treating sleep disturbace in COVID-19 patient.[9]

Benzodiazepine can be used judiciously in anxious patients with COVID-19 to provide symptom relief. The lowest possible dose of alprazolam or lorazepam is recommended up to 4 times daily and should be continued at the lowest daily dose to avoid benzodiazepine withdrawal-induced delirium. Second option include gabapentin, anti-convulsant GABA analogue. With both of these medications, sedation is minimal and there is no major respiratory depression.[10]

CONCLUSION

Management of sleep during and after COVID-19 is challenged and need to be more analyzed to get and effective therapeutic intervention. This EBCR revealed high score of insomnia and sleep disturbances during the recovery period of COVID-19 infection, and these problems have implications in quality of life which must be managed during this critical era of COVID-19.

REFERENCES

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed [Internet]. 2020 [cited 2022 Mar 8];91(1):157–60. Available from: https://pubmed.ncbi.nlm.nih.gov/32191675/
2. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data [Internet]. 2022 [cited 2022 Mar 8]. Available from: https://covid19.who.int/
3. Dubey S, Biswas P, Ghosh R, et al. Psychosocial impact of COVID-19. Diabetes Metab Syndr [Internet]. 2020 Sep 1 [cited 2022 Mar 8];14(5):779–88. Available from: https://pubmed.ncbi.nlm.nih.gov/32526627/
4. El Sayed S, Gomaa S, Shokry D, Kabil A, Eissa A. Sleep in post-COVID-19 recovery period and its impact on different domains of quality of life. Egypt J Neurol psychiatry Neurosurg [Internet]. 2021 Dec 1 [cited 2022 Mar 8];57(1). Available from: https://pubmed.ncbi.nlm.nih.gov/34924750/
5. Choi EPH, Hui BPH, Wan EYF. Depression and anxiety in Hong Kong during COVID-19. Int J Environ Res Public Health [Internet]. 2020 May 5 [cited 2022 Mar 8];17(10). Available from: https://pubmed.ncbi.nlm.nih.gov/32466251/
6. Saputra BD, Levita J, Mustarichie R. Efficacy, Safety, and Drug. Drug interactions for insomnia therapy in COVID-19 patients. J Multidiscip Healthc [Internet]. 2022 Jan 21 [cited 2022 Mar 8];15:137–52. Available from: https://www.dovepress.com/efficacy-safety-and-drugdrug-interactions-for-insomnia-therapy-in-covi-peer-reviewed-fulltext-article-JMDH
7. Becker PM. Overview of sleep management during COVID-19. Sleep Med [Internet]. 2021 [cited 2022 Mar 8]; Available from: /pmc/articles/PMC8106485/
8. Maramis MM. Pandemi COVID-19 dan ansietas. In: Sutrisno, Kalalo RT, Andrianto, editors. COVID-19 dan problematika kesehatan mental. Surabaya: Ikatan Dokter Indonesia Wilayah Jawa Timur; 2021. p. 73–104.
9. Wichniak A, Kania A, Siemiński M, Cubała WJ. Melatonin as a potential adjuvant treatment for COVID-19 beyond sleep disorders. Int J Mol Sci [Internet]. 2021 Aug 2 [cited 2022 Mar 8];22(16). Available from: https://pubmed.ncbi.nlm.nih.gov/34445329/
10. Khawam E, Khouli H, Pozuelo L. Treating acute anxiety in patients with COVID-19. Cleve Clin J Med [Internet]. 2020 May 14 [cited 2022 Mar 8];87(5):1–4. Available from: https://www.ccjm.org/content/early/2020/05/12/ccjm.87a.ccc016.

Current Diagnostic and Treatment Approach of *Clostridioides difficile* Infection

Bella Yunita[1], Achmad Fauzi[2]*

[1] Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2] Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Achmad Fauzi, MD. Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro No. 70. Jakarta 10430, Indonesia. Email: bellaaabellss@gmail.com

ABSTRACT

C. difficile infection is related to wide spectrum of disease, from self-limiting diarrhea to fulminant disease that can cause toxic megacolon or pseudo-membrane colitis. Difficult approach to diagnose this disease is also problem. C. difficile infection is diagnosed when diarrhea occurred in high risk patient with positive result of GDH or NAAT test that was confirmed by positive result of toxin test. Nevertheless, there is limited choice of treatment in Indonesia. Thus, the main priority of C. difficile infection in Indonesia is associated with its prevention, by implementing standard precaution and use of rational antimicrobial.

Keywords*: C. difficile infection, colitis, diagnosis, diarrhea, treatment.*

INTRODUCTION

Clostridioides difficile (*C. difficile)* infection causes wide spectrum of disease; it may cause self-limiting diarrhea to severe and fulminant infection such as pseudo-membrane colitis and toxic megacolon. Several risk factors are reported to contribute for this infection: older age, history of hospitalization, people who lived in healthcare facilities, or history of antimicrobial use.[1] *C. difficile* infection is defined as *C. difficile* colonization that causes diarrhea, with positive result of *C. difficile* toxins or toxigenic *C. difficile* is detected from feces specimen, or pseudo-membrane colitis found by colonoscopy and/or histopathology examination. In the patient with risk factors and experienced diarrhea 3 times/day, this patient should undergo *C. difficile* examination.[2-3] Nevertheless, prevalence of community acquired *C. difficile* infection increased, because it can also occurred in patient without prior history hospitalization.[4]

In the United States, *C. difficile* infection is associated with 15,000-30,000 deaths/year, while in Indonesia, studies related to *C. difficile* infection is limited.[1,4] *C. difficile* infection is often undetected in Indonesia, yet higher use of over the counter (OTC) antimicrobial in Indonesia can lead to higher prevalence of *C. difficile* infection. Study from Collins, et al (2017) that was conducted in hospital located in Central Java reported positive glutamate dehydrogenase (GDH) results in 20.6% patients with detected toxins in 5.6% patients. From culture, toxigenic *C. difficile* was detected in 10.9% and non-toxigenic was detected in 10.6%. Other results from this study: ribotype 017 was detected in 24.3%, non-toxigenic QX 224 in 9.5%, and QX 238 and QX 108 was detected in 8.1%. This

prevalence was higher than in neighbor countries such as Australia (7%), Singapore (7-11%), and Malaysia (13.7%).[1] Because high prevalence of *C. difficile* infection and difficult diagnostic and treatment approach of this disease, this review article intend to explain current diagnostic and treatment approach of *C. difficile* infection.

CLOSTRIDIOIDES DIFFICILE VIROLOGY

C. difficile is gram positive rod, anaerobic bacteria that produces pathogenic spores for gut.[4-6] Transmission of *C. difficile* infection occurred as fecal-oral transmission. Once the *C. difficile* spores infected stomach, this spores can not be disintegrated even when exposed to acid secretion of stomach. The bacteria then enters small gut, and exposed to bile acid that can induce vegetative state of this bacteria. Prior exposure to antimicrobial decreased number of normal flora of the gut, thus induce colonization of *C. difficile* in colon. This colonization then produces *C. difficile* toxins.[5,6] *C. difficile* toxins inhibits polymerization of actin from host cell and then causes cell death. In colon, this bacteria produces spores that will exit with feces. *C. difficile* is reported can withstand heat and ethanol based disinfectant.[5]

There are three types of toxins produced by *C. difficile* bacteria, toxin A, toxin B, and CDT. Toxin A is enterotoxin, while toxin B is cytotoxin, thus both of these toxins play the role to impair gut mucosa and acute inflammation that causes colitis and diarrhea as the main clinical manifestation.[1,4] The third toxin, CDT, which is a binary toxin is rarely detected in host cell, yet it is associated with inflammation and water loss from colon.[1,7] Host immunity to fight the toxin is associated with severity of clinical manifestation and recurrent infection. Risk factors for *C. difficile* consist of history of hospitalization, history of antimicrobial use (clindamycin, cephalosporin, carbapenem, fluoroquinolone, and monobactam), and older age. Study from Smilings, et al.[8] (2014) reported that antimicrobial that is associated with *C. difficile* infection are third generation cephalosporin (OR 3.2; 95% CI 1.8-5.71), clindamycin (OR 2.9; 95% CI 2-4), forth generation cephalosporin (OR 2.14; 95% CI 1.3-3.52), carbapenem (OR 1.8; 95% CI 1.3-2.7), cotrimoxazole (OR 1.8; 95% CI 1.3-2.7), and fluoroquinolone (OR 1.7; 95% CI 1.2-2.4). Other risk factors are *inflammatory bowel disease* (IBD), heart disease, chronic kidney disease, and white race.[3] Table 1 explains clinical characteristic of *C. difficile* infection.[4]

Once *C. difficile* enters the body, it causes innate immune system by four virulence factor, TcdA/TcdB (or toxin A and toxin B), flagellin, protein A (SlpA), and PG fragment. All of this virulence factor then inducing production of nuclear factor κβ (NF-κβ) and AP-1 protein to release chemokine and pro-inflammatory cytokine.[7] *C. difficile* infection is different from *C. difficile* colonization. Toxigenic *C. difficile* always consists of toxin B and usually consists of toxin A. Nontoxigenic *C. difficile* does not cause infection. Nevertheless, toxigenic strain of *C. difficile* can cause colonization in asymptomatic patient. For diagnosing *C. difficile* infection, we need to obsereve diarrhea as clinical manifestation of *C. difficile* infection with positive result of toxin A and/or toxin B from feces specimen.[1]

DIAGNOSTIC APPROACH AND CLASSIFICATION

Active infection of *C. difficile* is marked by new onset of 3 times/day diarrhea with unknown cause. Other clinical manifestation that can occur

Table 1. Clinical characteristic of C. difficile infection.[4]

Characteristic	Hospital-acquired	Community-acquired	Recurrent
Age (median)	72	50-51	56-75
Risk factors	Prior use of antimicrobial, PPI, IBD	Prior use of antimicrobial, heart disease, CKD, IBD	Older age, female, CKD, IBD, prior use of corticosteroid, immunocompromised
Strain	078, 106	Ribotype 002, 020, 014, 015, 027, 078, 106	Ribotype 027
30-day mortality rate	10.6%	3-17%	7.8-9.3%

is fever, nausea and vomiting, and abdominal pain. Every patient with flare of IBD and diarrhea as clinical manifestation is recommended to undergo *C. difficile* examination. Normal result of colonoscopy and histopathology excludes *C. difficile* infection in patient with diarrhea.[3] **Table 1** explains clinical manifestation of *C. difficile* infection.[6]

Patient with clinical manifestation of *C. difficile* infection (diarrhea ≥ 3 times/day) should undergo *C. difficile* examination. *C. difficile* examination consists of GDH or NAAT examination. Negative results excludes *C. difficile* infection, yet if the result is positive it means the patient is recommended to undergo toxin examination. NAAT or GDH examination alone can not distinguish *C. difficile* infection from *C. difficile* colonization. Repeat examination within 7 days in the same diarrhea episode and in asymptomatic patient are not recommended.[2] **Table 3** explains choices for diagnostic examination with each sensitivity and specificity.[3] Picture 1 explains algorithm for diagnosing *C. difficile* infection.[3]

Table 2. Clinical manifestation of C. difficile infection.[6]

Spectrum of disease	Diarrhea	Other symptoms	Physical examination	Colonoscopy and other finding
Asymptomatic carrier	None	None	Normal	Normal
Simple antibiotic associated diarrhea	Mild	Absent	Usually normal	Normal
Early colitis	Profuse	Nausea, anorexia	Low grade fever, with/ without mild abdominal tenderness	Nonspecific patchy erythema
Pseudo-membranous colitis	Profuse	Nausea, malaise, abdominal discomfort	Fever (sometimes high); abdominal distension and tenderness	Pseudo-membrane (raised yellow plaque), leukocytosis (> 50,000/µl) with shift to the left pattern
Fulminant colitis	Usually profuse and sever, may be absent in ileus or toxic megacolon	Nausea, abdominal discomfort	Toxic appearance, high fever, abdominal distension, tenderness and peritoneal sign	Endoscopy is contraindicated in severely ill patient, leukemoid reaction, radiographic may show colonic dilatation, mucosa; thickening or perforation

Table 3. Choices for diagnostic examination of C. difficile infection.[3]

Examination	Sensitivity	Specificity	PPV	NPV	Comment
Toxigenic culture	94	99	-	-	Detect toxigenic strain Not differentiate colonization from active infection
Glutamate dehydrogenase (GDH)	94-96	90-96	34-38	100	Not differentiate toxigenic and non-toxigenic strain Not differentiate colonization from active infection
Cell cytotoxicity neutralization assay (CCNA)	93	98	-	-	Detect free toxin B Differentiate colonization from active infection
Nucleic acid amplification testing (NAAT)	95-96	94-98	46	100	Gene detection for toxin B Not differentiate colonization from active infection
Enzyme immunoassay (EIA) toxin A and toxin B	57-83	99	69-81	99	Detect free toxin Differentiate colonization from active infection

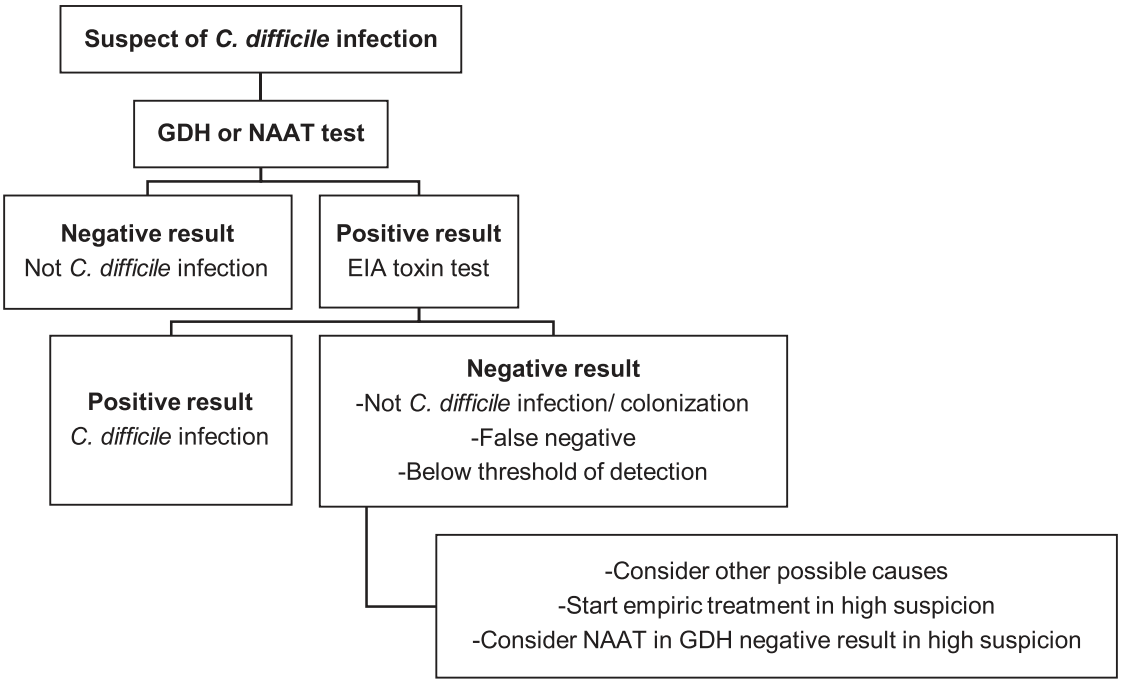


Figure 1. Diagnostic Algorithm for C. difficile Infection.[3]

Classification of *C. difficile* infection consists of severe disease, fulminant disease, and recurrent disease. Severe *C. difficile* infection is characterized by leucocyte ≥ 15,000/µl or SCr > 1.5 mg/dl. From post hoc analysis of RCT study, it was reported that leukocytosis (RR 2.29; 95% CI 1.63-3.21) and renal failure (RR 2.52; 95% CI 1.82-3.5) that occurred in *C. difficile* infection were associated with failure of fidaxomicin and vancomycin therapy.[9] Other definition of severe disease comes from European Society of Clinical Microbiology and Infectious Diseases (ESCMID), which defines severe *C. difficile* infection as infection with fever > 38.5°C, leukocytosis with leucocyte count of > 15,000/µl, and rise in SCr > 50% above baseline.[10] Fulminant *C. difficile* infection is characterized by criteria of severe disease and hypotension or shock or ileus or toxic megacolon. Fulminant disease is associated with needs of colectomy, increased risk of mortality after procedure, or increased risk of death. Other predictor for poor prognosis includes hypoalbuminemia, eosinophilia, fecal calprotectin > 2,000 µg/g, and fever > 38.5°C. Hypoalbuminemia is marker of protein loss in the condition of colopathy and host defense mechanism to bind toxin A or B, thus it promotes proteolytic formation to gut epithelial and avoid cytotoxic effect of infection.[3]

Recurrent infection is characterized as recurrent episode of diarrhea with positive result of confirmation test (NAAT or EIA) within 8-12 weeks after initial treatment of *C. difficile* infection. Outcome of recurrent infection divides into 2 categories: clinical recover (no diarrhea episode and no recurrent diarrhea) and bacteriologic recover (clinical recover and negative result from feces test).[3]

PRIMARY AND SECONDARY PREVENTION

Prevention of *C. difficile* infection includes standard precautions such as use of gloves (handschoen) and gown, wash hands with water and soap and implementation of hand hygiene for health workers, family, or caregiver who treat *C. difficile* infection patients.[2-3] Other primary prevention of *C. difficile* infection includes rational use of antimicrobial.[6] Patient with *C. difficile* infection room and bathroom should be separated with other patient, until 48 hours after diarrhea resolved. Asymptomatic patient is carrier of *C. difficile* infection, yet this group of patient does not have to be isolated from other patient.[2,5] Probiotic (living microorganism

with good effect for health, due to colonization of this microorganism is related to inhibition of pathogenic microorganism, modulation of immune system, and protect gut mucosa integrity) is not recommended as primary and secondary prophylaxis for *C. difficile* infection.[3]

Fecal microbiota transplantation (FMT), a new prevention approach of *C. difficile* infection, is recommended to prevent recurrent infection. Gut has normal flora that can inhibits or as competitor for pathogenic microorganism. In patient with proliferation of *C. difficile*, reduced number of normal gut flora is observed; thus FMT is thought to be a better option to increase number of normal gut flora that comes from healthy person.[11] FMT is administered during colonoscopy procedure or by capsule. Both of this administration of FMT is not different statistically from studies, but if it can not be done other approach is by enema administration. From RCT study, enema administration of FMT is not different statistically with placebo, thus it is better if FMT was administered by capsule or colonoscopy. Enema FMT can be considered in children with *C. difficile* infection. Repeat dose of FMT can be given 8 weeks after the first dose.[3]

Adverse effect of FMT administration is abdominal cramp, bloating, abdominal pain, nausea, diarrhea, constipation, and sub-febrile fever. Risk of other pathogenic infection is also observed with FMT administration. From study, it was reported that bacteremia from extended spectrum beta lactamases (ESBL) *Escherichia coli* can occur in FMT administration. FMT administration can also causes perforation, gastrointestinal bleeding, and sedation complication. Failure of FMT is defined as recurrent diarrhea with positive result of *C. difficile*. Administration of FMT from colonoscopy procedure or antimicrobial can be given in this situation.[3] Donor candidate for FMT should be screened from HIV, hepatitis A, B, and C, viral, bacterial, and parasite infection.[11]

Medical treatment for prevention of *C. difficile* infection consists of antimicrobial use or bezlotoxumab (BEZ). Oral vancomycin with the dose of 125 mg daily can be offered in patient who is not FMT candidate, relapse after FMT administration, or high risk of recurrent *C. difficile* infection. This approach can be offered in older patient (age ≥ 65 years old) or immunocompromised patient.[3] BEZ is monoclonal antibody that can bind with toxin B of *C. difficile* and can inhibit the toxin from attachment to gastrointestinal cell thus it can prevent colon cell damage. BEZ should be considered in older age (age ≥ 65 years old) with other criteria that consists of severe infection, immunocompromised patient, or recurrent infection of *C. difficile* within 6 months. BEZ should be used with caution in patient with heart failure or other heart comorbid. BEZ is administer in the dose of 10 mg/kg/day in 60 minutes, antibody can be detected 3 months after administration.[3,12]

MANAGEMENT

Based on newest guidelines from American College of Gastroenterology (ACG) 2021, management of *C. difficile* infection with antimicrobial consists of

- Initial treatment for non-severe infection: oral vancomycin 125 mg q.d.s. or oral fidaxomicin 200 mg b.i.d. for 10 days
- Initial treatment for low risk and non-severe infection: oral metronidazole 500 mg t.i.d. for 10 days
- Initial treatment for severe infection: oral vancomycin 125 mg q.d. or oral fidaxomicin 200 mg b.i.d. for 10 days
- Fulminant disease: fluid resuscitation followed by oral vancomycin 500 mg q.d.s. within 48-72 hours, or in combination with intravenous metronidazole 500 mg t.i.d.. FMT should be considered in patient that refractory from antimicrobial therapy and poor candidate of surgery procedure
- Ileus patient: enema vancomycin 500 mg q.d.s. IBD patient: oral vancomycin 125 mg q.d.s. for 14 days
- Immunocompromised patient: vancomycin or fidaxomicin as antimicrobial
- Pregnant or lactation: vancomycin as antimicrobial[3]

Table 4 explains antimicrobial recommendation from Infectious Disease Society of America (IDSA) 2021.[12]

Table 4. Antimicrobial recommendation from Infectious Disease Society of America (IDSA) 2021[12]

Clinical manifestation	Recommended treatment	Comments
Initial episode	Preferred: oral fidaxomicin 200 mg b.i.d. for 10 days Alternative: oral vancomycin 125 mg q.d.s. for 10 days Alternative for non-severe disease: oral metronidazole 500 t.i.d. 10-14 days	Non-severe disease: leucocyte < 15,000/µl and SCr < 1.5 mg/dl
First recurrent disease	Preferred: oral fidaxomicin 200 mg b.i.d. for 10 days or 200 mg b.i.d. for 5 days followed by once every other day for 20 days Alternative: oral vancomycin 125 mg q.d.s. for 10 days or in tapered and pulsed regimen Adjunctive: intravenous BEZ 10 mg/kg during antimicrobial administration	If metronidazole is given in the first treatment, consider oral vancomycin Tapered/pulsed vancomycin regimen: 125 mg q.d.s. for 10-14 days, followed by 125 mg b.i.d. for 7 days, 125 mg o.d. for 7 days, then every 2-3 days for 2-8 weeks
Second or subsequent recurrent disease	Oral fidaxomicin 200 mg b.i.d. for 10 days or 200 mg b.i.d. for 5 days followed by once every other day for 20 days Oral vancomycin in tapered and pulsed regimen Oral vancomycin 125 mg q.d.s. for 10 days followed by rifaximin 125 mg t.i.d. for 20 days FMT Adjunctive: intravenous BEZ 10 mg/kg during antimicrobial administration	Antimicrobial should be offered first then FMT
Fulminant infection	Oral or NGT administration of vancomycin 500 mg q.d.s. Combination with intravenous metronidazole 500 mg t.i.d. should be considered in ileus patient Rectal instillation of vancomycin in ileus patient	Fulminant: hypotension or shock, ileus, toxic megacolon

Fidaxomicin is superior to prevent recurrent *C. difficile* infection, followed by vancomycin, and then metronidazole. Low risk patient (younger patient with less comorbid) can be treated with metronidazole; this treatment is also cost-effective in this group of patient. Other antimicrobial that is studied for *C. difficile* infection treatment are teicoplanin, nitazoxanide, surotomycin, cadazolid, and ridinilazole.[3,13,14] Other approach of antibody based therapy that has been studied for treatment of *C. difficile* infection beside BEZ, included intravenous immunoglobulin (IVIG). Yet, current study regarding use of IVIG in *C. difficile* infection is not associated with improve mortality, colectomy, and hospital duration.[13]

Antimotility agent such as loperamide without antimicrobial administration in fulminant disease is not recommended, due to trapped of *C. difficile* toxin can increase risk of toxic megacolon. If the patient is already in antimicrobial therapy, antimotility treatment can be considered. Cholestyramine is not recommended as *C. difficile* infection treatment, moreover in patient with vancomycin administration due to drug interaction between this two drugs. high fiber diet should be considered in *C. difficile* infection, because it can increase gut microbiota and reduce *C. difficile*.[3]

Fulminant *C. difficile* infection should be treated in multidisciplinary approach, involving gastroenterologist, infection specialty, critical care, and surgeon. Supportive treatment with fluid resuscitation is administered with the target of normal urine output (0.5-1 ml/kg/hour) and renal function. Antimicrobial is recommended with option and dose as previously stated. In ileus patient, enema vancomycin is recommended, due to more effective delivery of treatment compared to oral administration of drug. Combination with metronidazole should be considered, because metronidazole has greater delivery to colon in ileus patient compared to oral vancomycin.[3]

Surgery should be done with colectomy and end ileostomy and stapled rectal stump or diverting loop ileostomy with colon lavage and intraluminal vancomycin for 10 days. Surgery is recommended in patient with fulminant disease and followed by toxic megacolon, ischemia, or perforation of the gut. FMT is also recommended in fulminant or severe infection, with colonoscopy approach, especially in pseudo-membrane disease. FMT can be administered 3-5 days until loss of pseudo-membrane. FMT administration is also associated with reduce risk of colectomy and sepsis. Recurrent infection should be treated with different antimicrobial with initial therapy. For patient with vancomycin and metronidazole as initial therapy, for recurrent infection this patient should be treated with fidaxomicin. Metronidazole is not recommended in recurrent infection. Anti-secretory agent such as proton pump inhibitor (PPI) should be continued once it is started.[3]

Patients with IBD exposed to higher risk of *C. difficile* infection due to corticosteroid and biological agent (infliximab, adalimumab) exposure, more comorbid, hospitalization history and repeat visit to hospital to control their disease. *C. difficile* infection in IBD increase risk of colectomy. In patient with IBD, oral vancomycin 4 x 125 mf should be given of minimal 14 days. In flare IBD, immunosuppressive agent should not be stopped, yet if the symptom does not improve after *C. difficile* infection treatment, escalation of immunosuppressive agent should be considered.[3]

In special population such as lactating or pregnant women, vancomycin is antimicrobial of choice, because higher risk of failure with metronidazole therapy. Fidaxomicin should be avoided in lactating or pregnant women, while FMT should be avoided in pregnancy. Vancomycin is not transferred in breast milk, thus it is safe to give to lactating women. Immunocompromised patient can be given vancomycin or fidaxomicin. In immunocompromised patient, *C. difficile* is easier to occur, with high risk of severe and recurrent disease. This risk increased due to history of hospitalization, neutropenia, history of antimicrobial and immunosuppressive agent. Increased risk occurred in HIV patient with CD4 $\leq$ 50 cell/mm^3 and multiple organ transplantation.[3]

CONCLUSION

Due to high spectrum of disease, diagnostic and management approach of *C. difficile* infection should be noticed. For patient with high risk of this infection (older age, history of hospitalization, history of antimicrobial use) that experience diarrhea 3 times/day, GDH or NAAT test should be conducted. Negative result defined negative *C. difficile* infection, while positive result should be confirmed with toxin detection. If the toxin detection is positive, thus the patient is diagnosed with *C. difficile* infection. Antimicrobial agent should be administered based on initial or recurrent disease, severity of disease, with FMT, BEZ as adjunctive treatment to prevent recurrent infection. Unfortunately, choices of treatment is not much in Indonesia, because the only option of antimicrobial that is available is metronidazole. Thus, primary prevention by implementing standard precaution and rational use of antimicrobial should be primary priority in limited resource country.

REFERENCES

1. Collins DA, Gasem MH, Habibie TH, et al. Prevalence and molecular epidemiology of *Clostridium difficile* infection in Indonesia. New Microbe and New Infect. 2017;18:34-7.
2. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society of Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66:e1-48.
3. Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. Am J Gastroenterol. 2021;116:1124-47.
4. Fu Y, Luo Y, Grinspan AM. Epidemiology of community-acquired and recurrent *Clostridioides difficile* infection. Therap Adv Gastroenterol. 2021;14:1-11.
5. Sandhu BK, McBride SM. *Clostridioides difficile*. Trends Microbiol. 2018;26:1049-50.
6. Guh AY, Kutty PK. In the clinic: *Clostridioides difficile* infection. Ann Intern Med. 2018;169:ITC49-64.
7. Liwang F, Sinto R. Pendekatan klinis terkini infeksi *Clostridium difficile* nosocomial. JPDI. 2021;8:104-9.
8. Smilings C, Riley TV. Antibiotics and hospital-

acquired *Clostridium difficile* infection: update of systematic review and meta-analysis. J Antimicrobe Chemother. 2014;69:881-91.
9. Bauer MP, Hensgens MP, Miller MA, et al. Renal failure and leukocytosis are predictors of a complicated course of *Clostridium difficile* infection if measured on day of diagnosis. Clin Infect Dis. 2012;55:S149-53.
10. van Prehn J, Reigadas E, Vogelzang EH, et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on treatment guidance document for *Clostridioides difficile* infection in adults. Clin Microbiol Infect. 2021;27:S1-21.
11. Gupta A, Khanna S. Fecal microbiota transplantation. JAMA. 2017;318:1.
12. Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. Clin Infect Dis. 2021;73: e1029-44.
13. Cho JM, Pardi DS, Khanna S. Update on treatment of *Clostridioides difficile* infection. Mayo Clin Proc. 2020;95:758-69.
14. Guery B, Galperine T, Barbut F. *Clostridioides difficile*: diagnosis and treatments. BMJ. 2019;366:l4609.