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

Medica Hospitalia

Journal of Clinical Medicine

Med Hosp 2025 Vol 12 (1) March 2025 www.medicahospitalia.rskariadi.co.id

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Published by
Medica Hospitalia – Dr. Kariadi Hospital

Medica Hospitalia

Journal of Clinical Medicine

Med Hosp 2025; Vol 12 (1)

March 2025

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

Editorial Address

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

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2025; Vol 12 (1)
March 2025

Original Articles

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2025; vol 12 (1) : 1–8

OPEN ACCESS

Original Article

The Association Vitamin D and Left Ventricular Hypertrophy in Metabolic Syndrome Patients

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v12i1.1196

Accepted: September 30th, 2024
Approved: February 20th, 2025

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Abstract

Background : Vitamin D deficiency is common, especially in people with metabolic syndrome. This condition increases the risk of cardiovascular problems, including left ventricular hypertrophy (LVH). While the connection between metabolic syndrome and LVH is well-documented, it is still unclear whether vitamin D deficiency alone contributes to the development of LVH in these patients. The aims of this study was to the association between vitamin D levels and LVH in patients with metabolic syndrome.
Methods : A cross-sectional study was conducted with 38 patients diagnosed with metabolic syndrome in Kariadi Hospital, Semarang. Serum vitamin D levels were measured using the ELISA method, and LVH was diagnosed via echocardiography. Patients were categorized into normal and LVH groups. Vitamin D levels were classified as sufficient, insufficient, or deficient. The relationship between vitamin D levels, metabolic syndrome components, and LVH was analyzed.
Results : Our findings revealed no significant difference in vitamin D levels between patients with LVH and those without it (mean 19.98 ± 5.59 ng/mL for the LVH group vs. 20.91 ± 6.56 ng/mL for the normal group, p=0.65). However, patients with LVH had a significantly higher number of metabolic syndrome components compared to those without LVH (p=0.044).
Conclusion : While no direct association was found between vitamin D levels and LVH, the cumulative burden of metabolic syndrome components plays a significant role in the development of LVH. Future research should explore larger populations to investigate the therapeutic potential of vitamin D in cardiovascular outcomes.

Keywords : Cardiovascular Disease, Left Ventricular Hypertrophy, Metabolic Syndrome, Vitamin D

INTRODUCTION

Vitamin D deficiency has become a major health problem worldwide, as studies reveal high prevalence rates,[1,2] commonly in conditions where sun exposure and nutritional supplies of vitamin D are repeatedly low.[3] This deficiency is especially pronounced in individuals with metabolic syndrome, a cluster of interrelated disorders characterized by central obesity, insulin resistance, dyslipidemia, and hypertension, who exhibit lower circulating vitamin D levels[4] and impaired vitamin D synthesis.[5–7]

Metabolic syndrome is a well-known contributor to the development of cardiovascular diseases, particularly left ventricular hypertrophy (LVH), a structural cardiac abnormality that significantly increases the risk of heart failure.[8–10] While vitamin D deficiency has been linked to the progression of LVH in hypertensive patients,[11–12] its specific role in metabolic syndrome remains unclear. Addressing this knowledge gap is essential for understanding the interplay between metabolic syndrome, vitamin D status, and LVH.

Based on these considerations, we hypothesize that lower levels of vitamin D in patients with metabolic syndrome may be associated with an increased risk of LVH. This study aims to explore the relationship between vitamin D deficiency and the incidence of LVH in patients with metabolic syndrome. We thereby can examine how vitamin D might influence mechanisms of cardiovascular remodeling and thus perhaps provide new perspectives on therapeutic approaches aimed at alleviating left ventricular hypertrophy in this vulnerable demographic.

METHODS

This observational study utilized a cross-sectional design to examine 38 patients with metabolic syndrome, consisting of 19 patients with left ventricular hypertrophy (LVH) and 19 patients with normal cardiac function, selected through purposive sampling from the inpatient and outpatient wards of Kariadi Hospital Semarang on July and October 2022. Inclusion criteria include (1) being ≥18 years old; (2) having fulfilled the criteria for Metabolic Syndrome based on National Cholesterol Education Program Expert Panel and Adult Treatment Panel III (NCEP ATP III)[13] and (3) being willing to take part in this research. Exclusion criteria included : (1) pregnancy, (2) patients receiving vitamin D therapy, (3) patients with severe infection or sepsis, (4) malabsorption syndrome, (5) patients receiving phenytoin or phenobarbital therapy, (6) chronic liver disease, (7) patients who had undergone total thyroidectomy, (8) chronic renal failure, and (9) malignancies. The level of vitamin D in the serum was assessed using the ELISA method from blood samples provided by the patients. Vitamin D is categorized as sufficient for more than 30 ng/ml, insufficient at 20 to 30 ng/mL, and deficient if less than 20 ng/m. The left ventricular geometry profile was classified as normal or left ventricular hypertrophy (LVH). LVH was defined as Increased left ventricle mass (LVMI) >115 g/m^2 for males and >95 g/m^2 for females as described by the American society of Echocardiography.[14]

The metabolic syndrome status of each patient was evaluated by six components modified from NCEP ATP III[11] (1) Waist circumference > 102 cm for male or > 88 cm for female, (2) serum triglyceride >150 mg/dL, (3) HDL <40 mg/dL for males and < 50 mg/dL for females, (4) blood pressure > 130 / 85 mmHg, (5) fasting glucose > 110 mg/dL and additional (6) obesity. Obesity was taken to be present if BMI exceeded 25 kg/m^2. For each patient, anthropometric measurements, vitamin D levels, and other laboratory tests were collected after the subjects were categorized as having either normal or left ventricular hypertrophy (LVH).

This research has been getting informed consent from patients and the Ethical Clearance of Health Research Ethics Committee of the Faculty of Medicine Diponegoro University and has received permission from the Director of the Kariadi Hospital. The number of ethical approvals was 1193/EC/KEPK-RKDK/2022. To reduce selection biases, information biases, and confounding, inclusion and exclusion were strictly imposed for each subject by at least two examiners. All echocardiographic measurements were done by an internal medicine specialist and cardiovascular consultant, blinded to the results of the other tests.

RESULTS

The characteristics of the patient data we collected from the outpatient ward of Kariadi Hospital from July to October 2022 are presented in Table 1. We observed a trend of decreasing vitamin D levels in patients with LVH, with average level of 20.91 ± 6.56 ng/mL in those with normal LV function and 19.98 ± 5.59 ng/mL in those with LVH, although this difference was not statistically significant (Fig. 1A). A comparison of the observed frequencies of vitamin D deficiency among patients with and without LVH revealed no significant deviation from the expected frequencies (Fig. 1B).

We investigated whether vitamin D influences the occurrence of metabolic syndrome. Our data showed that the level of vitamin D varies between group of metabolic syndromes, 22.10 ± 0.50 ng/mL in patients with two components, 19.30 ± 2.67 ng/mL with three components, 21.76 ± 8.57 ng/mL with four components, 19.97 ± 5.23 ng/mL with five components, and 18.03 ± 4.67 ng/mL with six components. However, these differences were not statistically significant either within or between groups (Fig 1C). Additionally, the observed frequencies of vitamin D deficiency among patients with metabolic syndrome did not differ significantly (Fig 1D).

Our analysis showed a statistically significant association between the number of metabolic syndrome components and the presence of LVH (Fig. 2A) (Mann Whitney, $p = 0.044$). Patients with LVH showed a similar median number of metabolic syndrome components compared to those normal (median = four components in both normal and the LVH group. However, the distribution of metabolic syndrome components skewed from two to five metabolic syndrome components in normal group toward higher values of three to six metabolic syndrome components in the LVH group.

To evaluate the contribution of individual metabolic syndrome factors to the occurrence of LVH, we analyzed six components of metabolic syndrome. Our

TABLE 1
Characteristics of Experimental Subject

Patient characteristics	N	Frequency (%)	Mean ± SD / Median (min-max)
Age			54.42 ± 10.41
<60 years	28	73.68	
>60 years	10	26.32	
Gender			
Male	30	78.95	
Female	8	21.05	
Vitamin D levels			20.44 ± 6.19
Normal	1	2.63	
Insufficiency	17	44.74	
Deficiency	20	52.63	
Left ventricle hypertrophy status			
Normal	19	50.00	
LVH	19	50.00	
BMI			28.5 (18–52)
Waist circumference			99.53 ± 14.53
HDL			34.50 (11–120)
Triglyceride			168.50 (72–677)
Obesity status			
BMI < 25	10	26.32	
BMI ≥ 25	28	73.68	
Waist circumference status			
< 102 cm (male) or < 88 cm (female)	18	47.34	
≥ 102 cm (male) or ≥ 88 cm (female)	20	52.63	
Diabetes status			
No	16	42.11	
Yes	22	57.89	
Hypertension status			
No	6	15.79	
Yes	32	84.21	

TABLE 1
Continued....

Patient characteristics	N	Frequency (%)	Mean ± SD / Median (min-max)
HDL status			
≥ 40 mg/dL (male) or ≥ 50 mg/dL (female)	9	23.68	
< 40 mg/dL (male) or < 50 mg/dL (female)	29	76.32	
Triglyceride status			
< 150 mg/dl	13	34.21	
≥ 150 mg/dl	25	65.79	

Normally distributed data is shown as Mean ± SD, while Median (min–max) is used for data with abnormal distribution.

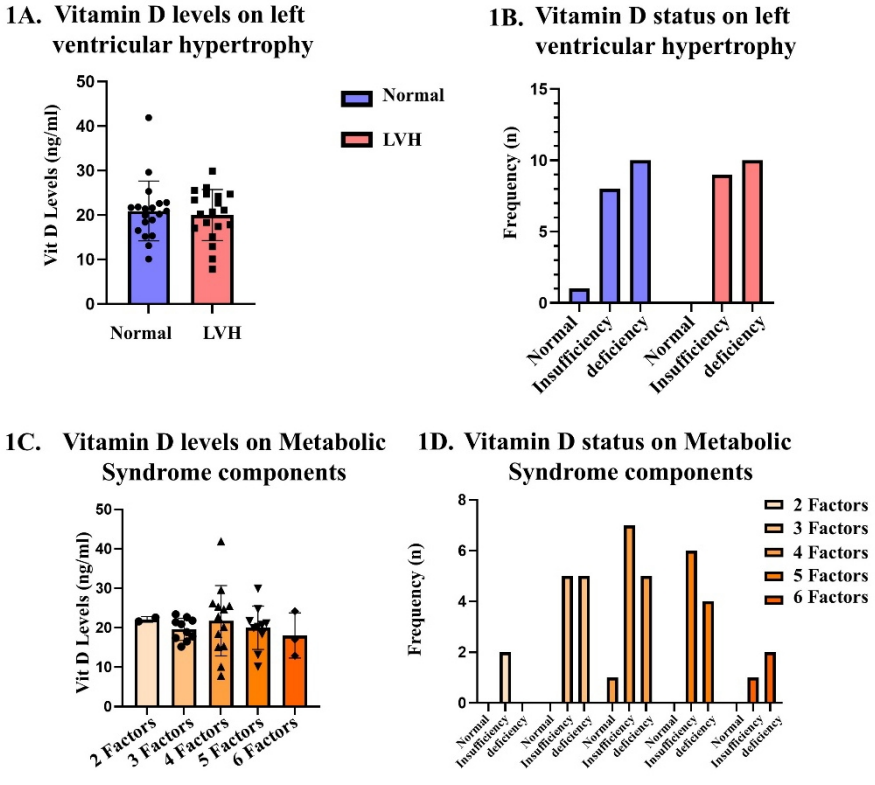

Figure 1. Influence of Vitamin D Levels and Status on Left Ventricular Hypertrophy. **(1A)** Comparison between serum vitamin D levels between individuals with normal left ventricular structure and those with left ventricular hypertrophy (LVH). The data are presented as the mean values with error bars indicating the standard error of the mean. The analysis shows no significant difference (ns) in vitamin D levels between the two groups (independent t-test, p= 0.65). **(1B)** Chi square frequency data of different vitamin D status categories (Normal, Insufficiency, Deficiency) in individuals with normal heart structure (blue bars) and those with LVH (red bars) shows non-significant result (chi square, p=0.58). **(1C)** Comparison between serum vitamin D levels between individuals with the number of metabolic syndromes. The analysis shows no significant difference in vitamin D levels between the two groups (one way ANOVA, p= 0.85) **(1D)** Chi square frequency data of different vitamin D status categories (Normal, Insufficiency, Deficiency) in individuals with metabolic syndrome shows non-significant result (chi square, p=0.81).

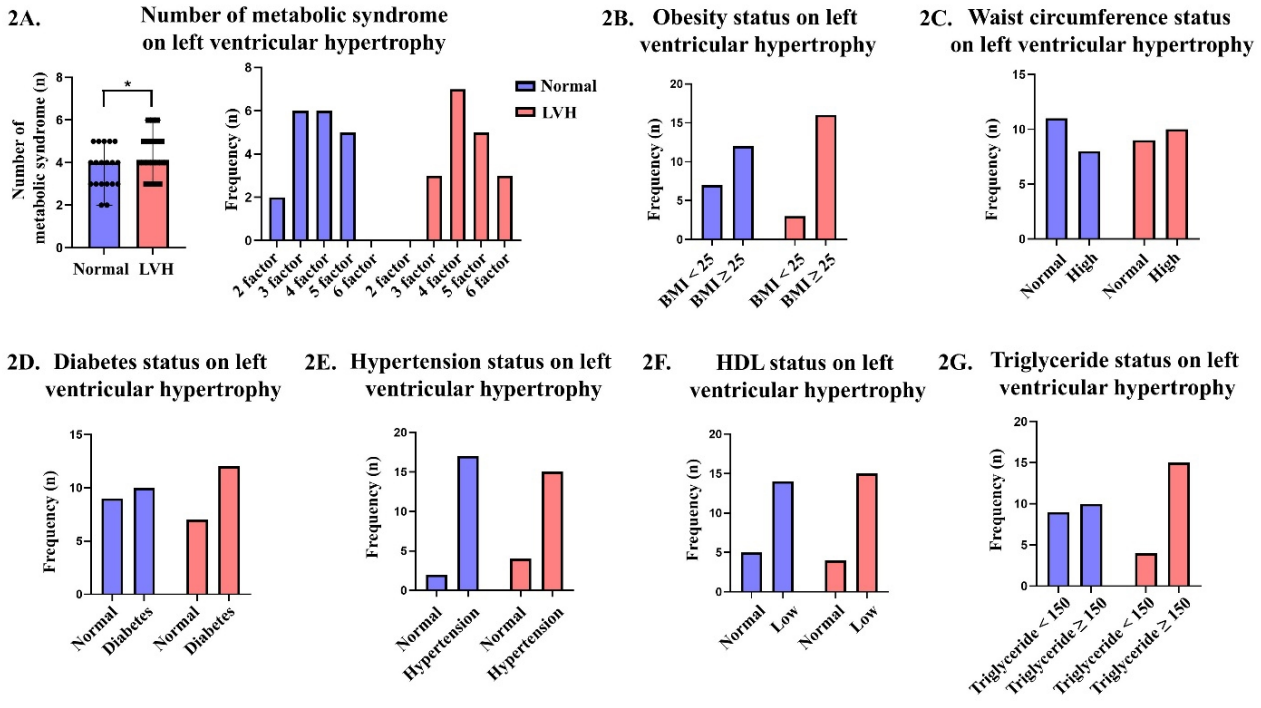

Figure 2. Influence of Metabolic Syndrome Components on Left Ventricular Hypertrophy. **(2A)** Left panel compares the number of metabolic syndrome components between individuals with normal heart structure and those with LVH. The data are shown as the median number of factors with error bars representing max – min value. (Mann Whitney, $p = 0.04$ for 1-tailed, $p = 0.09$ for 2-tailed). The right panel further breaks down the distribution, showing how many people have 2, 3, 4, 5, or 6 factors of metabolic syndrome in both groups. Frequency of individuals with **(2B)** normal BMI and obesity group with BMI ≥25 (chi square, $p = 0.14$), **(2C)** normal and high waist circumferences (> 102 cm for males or > 88 cm for females) (chi square, $p = 0.52$), **(2D)** diabetes status (chi square, $p = 0.51$), **(2E)** hypertension status (chi square, $p = 0.37$), **(2F)** Normal versus low HDL status (< 40 mg/dL for males and < 50 mg/dL for females) (chi square, $p = 0.70$), and **(2G)** Triglyceride status (chi square, $p = 0.09$) in both normal and LVH group.

data showed an increased proportion of patients with a BMI ≥ 25 kg/m² in the LVH group, whereas individuals with a BMI < 25 kg/m² were more prevalent in the normal ventricular function group (Fig. 2B). A similar trend was observed for waist circumference. Patients with a normal waist circumference were more commonly found in the normal group, while those with a high waist circumference (> 102 cm for males or > 88 cm for females) were more frequent in the LVH group (Fig. 2C).

Additionally, diabetes was observed at a higher frequency in the LVH group compared to the normal group (Fig. 2D). However, we didn't find any differences in hypertension status between normal and LVH groups (Fig. 2E). Similarly, HDL levels (Low if < 40 mg/dL for males and < 50 mg/dL for females) did not differ between normal or LVH group (Fig. 2F) Conversely, patients with triglyceride levels ≥ 150 mg/dL were more prevalent in the LVH group (Fig. 2G). Despite these trends, none of the individual metabolic syndrome factors were statistically significantly associated with LVH.

DISCUSSION

Vitamin D deficiency is a prevalent health concern, particularly among individuals with metabolic syndrome. In our study, we hypothesized that lower vitamin D levels in patients with metabolic syndrome might be associated with an increased risk of LVH. However, our findings indicate that low vitamin D levels do not significantly contribute to the development of LVH in these patients. Additionally, vitamin D levels were not associated with the number of positive metabolic syndrome components. Notably, our data revealed that an increased number of metabolic syndrome components is a significant risk factor for LVH, emphasizing the critical role of metabolic syndrome severity in cardiac remodeling.

Although our initial hypothesis suggested a potential link between low vitamin D levels and the incidence of LVH, our results did not show a statistically significant association between the two. The mean serum vitamin D level in patients with LVH was not significantly different from those without LVH.

Moreover, our data indicates that low vitamin D doesn't have any effect on causing metabolic syndrome. Indicating that there is no association of vitamin D levels with LVH or metabolic syndrome. This aligns with several previous studies where vitamin D deficiency alone did not directly correlate with structural cardiac despite its known role in cardiovascular health.[15,16] Our study reveals that nearly all patients with metabolic syndrome exhibited vitamin D levels below the sufficient threshold. This finding is consistent with prior studies that associate metabolic syndrome with reduced vitamin D levels due to factors such as obesity, insulin resistance, and inflammation, all of which are prevalent in this population.[4,17,18]

Vitamin D has been postulated to influence LVH through several mechanisms, including the regulation of calcium homeostasis, modulation of the reninangiotensinaldosterone system (RAAS), and direct effects on cardiomyocytes. Experimental studies have demonstrated that vitamin D metabolites can act on cardiomyocytes, endothelial cells, and smooth vascular muscle cells, suggesting a role in cardiovascular health.[19] Specifically, vitamin D deficiency has been associated with increased activity of the RAAS, leading to hypertension and subsequent cardiac hypertrophy.[20] Moreover, the presence of vitamin D receptors in left ventricular cardiomyocytes indicates that vitamin D may directly affect cardiac structure and function.[21] Despite these theoretical mechanisms, our study did not find a significant association between vitamin D levels and LVH, suggesting that vitamin D's role in cardiac remodeling may be more complex or indirect than previously thought.

The relationship between metabolic syndrome and LVH is well-supported by the literature,[8,9,22–24] and our findings reinforce the understanding that an increased number of metabolic syndrome components elevates the risk of LVH. Obesity, as a key component, plays a significant role in this process through both mechanical and metabolic mechanisms.[8,10,22] Additionally, adipose tissue in obesity is known to secrete pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), contributing to systemic inflammation and oxidative stress.[25] Although our data doesn't show direct evaluation of lipid and inflammatory markers, our study indicates that obesity increases the trend of LVH.

Another metabolic syndrome component, an increase of waist circumference, is closely associated with central obesity, insulin resistance and dyslipidemia, which contribute to LVH.[22,26–29] The presence of high triglyceride levels promotes oxidative stress, which can further damage the vascular endothelium,[30,31] thereby increasing vascular resistance and elevating cardiac afterload. As a result, the heart undergoes hypertrophic changes to cope with the increased workload. Although our study did not show statistically significant differences in triglyceride status between LVH and non-LVH patients, the observed trend aligns with the established understanding that hypertriglyceridemia is a contributor to adverse cardiovascular outcomes including LVH.[30–33] Although our data didn't show the association of individual factors of metabolic syndrome to LVH, we could show that combination of these factors is associated with LVH.

A key limitation of our study is its cross-sectional design, which prevents us from establishing causal relationships between vitamin D deficiency, metabolic syndrome components, and LVH. Additionally, we did not include detailed inflammatory markers, lipid profiles, or oxidative stress parameters, which could provide deeper insights. The single-center population limits the generalizability of our findings, and the lack of longitudinal data prevents us from assessing how changes in vitamin D levels or metabolic syndrome severity influence LVH over time. Future studies with diverse cohorts and longitudinal designs are needed to address these gaps.

Given the scope of metabolic syndrome and its profound impact on cardiovascular health, future research should aim to explore the role of vitamin D in larger sample, multi-center study. Investigating vitamin D supplementation as an intervention in metabolic syndrome populations, particularly in those with established cardiovascular disease, could yield insights into its therapeutic potential for preventing or mitigating LVH progression. Additionally, controlling potential confounders and exploring other biochemical markers associated with metabolic syndrome might offer a more comprehensive understanding of its relationship with cardiovascular outcomes.

CONCLUSION

In conclusion, while our study did not find a direct association between vitamin D levels and LVH, we demonstrated that the cumulative burden of metabolic syndrome components plays a significant role in the development of LVH. This highlights the importance of addressing metabolic syndrome holistically in managing cardiovascular risk.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2025; vol 12 (1) : 9–22

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Original Article

Serum Protein D Surfactant Level Based on Length of Exposure in Workers at the Supit Urang Waste Disposal Site, Malang

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Abstract

Background : Waste collectors are at risk of developing lung disease due to exposure to bioaerosols from organic and inorganic materials. The function of surfactant protein D (SP-D) is as innate immunity that protects the lungs. Exposure to bioaerosols in landfills causes inflammatory reactions which can increase the permeability of the blood-lung barrier. As a result, SP-D will leak into the plasma. This study aims to analyze serum SP-D levels in relation to length of exposure in waste collectors.
Methods : This analytical, cross-sectional study was done in a Supit Urang waste disposal site, Malang, Indonesia. Samples for serum SP-D analysis were taken from peripheral blood samples and analyzed with ELISA technique.
Results : There were 68 subjects, consisting of 24 subjects with exposure duration of 5 years, 14 subjects of 5–10 years, and 30 subjects with exposure of 10 years. The number of smokers and non-smokers were 36 and 32 subjects respectively. Significant differences in SP-D serum levels were found between different exposure durations, particularly with exposure of more than 5years. A significant positive correlation was obtained between serum SP-D levels and exposure duration (r = 0.585; p = 0.000). Meanwhile, there was no significant difference in serum Sp-D levels based on smoking status (p=0.112).
Conclusion : Length of exposure significantly affected SP-D serum levels in waste workers, especially with exposure of more than 5 years.

Keywords : Plasma Protein D Surfactant, waste workers, long exposure, high risk.

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v12i1.1218

Accepted: October 7th, 2024
Approved: February 25th, 2025

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INTRODUCTION

Environmental pollution due to waste management is a global problem. This problem includes environmental contamination, causing social problems and affecting economic conditions.[1–3] Waste workers have a heavy workload and exposure to various bioaerosols, both non-organic and organic. Therefore, waste workers are included in a vulnerable group that has higher risk for health problems and work accidents compared to other jobs. Waste workers also have a risk for work-related lung disease, especially due to exposure to bioaerosols from handling organic materials which include the process of collection, separation, and processing of waste. Infection or injury to the lungs will stimulate the production of surfactant protein-D (SP-D) which is a group of collectins.[1–5]

Globally, waste production is estimated to increase to 3.40 billion tons by 2050. Waste production will continue to increase in both developed and developing countries. As a consequence, there is an increased risk of occupational diseases in low-income developing countries because waste management is still not well controlled. Based on previous researches, significant concentrations of pollutants were found in several final waste disposal sites in developing countries including Asia, Africa and Latin America.[5–8]

Waste workers may have a risk of having those waste particles to enter the respiratory tract. Particles measuring 1 μm or smaller can enter the alveolar surface and will interact with surfactant proteins and alveolar macrophages. The main role of surfactants is as an innate immune response. Surfactant protein-D (SP-D) is a group of collectins (collagen-lectins) with a subgroup of the type C lectin superfamily. SP-D is produced and secreted in type 2 pneumocyte cells in the alveolar. Epithelial duct cells are also responsible for the production of this surfactant. Mucosal cells and grandular/ductal epithelial cells in the gastrointestinal cells also produce small amounts of SP-D in response to inflammation caused by bacteria, viruses, fungi, or other harmful or irritating substances. On the basis of this description, it is important to understand its clinical role. [9,10]

Some waste workers also have a smoking habit. Nicotine, acroline, and substances contained in cigarettes reduce alveolar SP-D levels and increase alveolar epithelial damage, characterized by increased serum SP-D and decreased SP-D in bronchoalveolar lavage.[11] Study that compared smokers and ex-smokers reported that serum SP-D was higher in smokers compared to non-smokers and ex-smokers. Subjects without lung function problems had lower baseline SP-D than the group with decreased lung function. Thus, SP-D was significantly associated with decreased lung function during follow-up but only in the smoker group. In a study which examined smokers and COPD group, serum SP-D was examined in healthy smokers and the COPD group, serum SP-D was similar between the two groups.[11–13]

Loss of air blood barrier integrity due to toxic exposure causes intravascular leakage of lung proteins. Thus, the increase of concentration gradient of SP-D allows SP-D synthesized in the respiratory tract to leak into the bloodstream. In some circumstances, including acute cigarette smoke exposure, SP-D can be decreased in bronchial lavage (BAL) while serum SP-D will be increased. Smoking status is a strong predictor of this translocation. Several other conditions that can cause SP-D extravasation are found in COPD, asthma, and cystic fibrosis. Several studies in rabbits and humans have provided evidence that protein clearance is dependent on molecular size from the airspace in the lung. Different things were conveyed by Herbein and Wright who reported that the amount of SP-D from BAL fluid was lower compared to control lungs, due to increased SP-D uptake in tissue neutrophils, so that clearance causes a decrease in alveolar SP-D levels.[12,14–16]

However, there has been no research on serum SP-D levels based on exposure duration in waste workers based on smoking status. Therefore, based on this background, further research is needed to examine serum SP-D levels based on exposure duration and smoking status in waste workers, which aims to determine the risk of lung disease.

METHODS

The research design was a cross-sectional study. Subjects were workers exposed to garbage in the Supit Urang waste disposal site, Malang, East Java, Indonesia. The inclusion criteria were age of 17–80 years, more than 6 months of work with working hours more than 8 hours a day. The exclusion criteria in this study were workers who had been diagnosed with lung malignancy, extrapulmonary cancer, pneumonia and pulmonary TB with or without treatment based on clinical data and treatment history found during the history taking and physical examination.

This research was conducted at the Supit Urang waste disposal site, Microbiology and Biomedical Laboratory, Central General Hospital of Saiful Anwar East Java on August December 2023. The ethics committee has approved the study and procedures of Medical Faculty of Brawijaya University Malang. Subjects who took part within the study had signed informed consent. The subjects underwent anamnesis, physical analysis and examination, and serum SP-D levels using quantitative sandwich ELISA.

As much as 3 ml blood specimens from workers exposed to inhalation at the Supit Urang waste disposal site met the inclusion criteria. The enzyme-linked immunosorbent assay (ELISA) Kit (Elabscience) measured SP-D serum levels.

Processing and data analysis using SPSS software version 26. Serum SP-D levels and other variables in workers were analyzed using the Shapiro-Wilk test to assess the normality of the data distribution. To assess the correlation between variables, the Spearman test was used and to assess the effect, the independent T-test and ANOVA test were used if the data were normally distributed or the Mann-Whitney test or the Kruskal-Wallis test if the data were not normally distributed, with 95% confidence degree, α=0.05. Value means if p<0,05.

Data normality test using Shapiro Wilk to assess serum SP-D based on age groups showed an abnormal data distribution. Therefore, we continued the comparison test using the Kruskal Wallis test. Then from the results of the Kruskal Wallis Test, a p value of 0.000 (p <0.05) was obtained, so it can be concluded that there is a significant difference in SP-D based on age group. Therefore, we continue with pairwise comparisons testing with the Dunn Test to test the comparison of SP-D between age groups wich can be seen in Figure 1.

RESULTS

There was 68 subjects who met the inclusion criteria. Characteristics data and supporting clinical data are described in Tables 1. The range age of subjects were between 17 and 78 years old with the mean age of 44,7±17,31 years. The number of male subjects were twice the female. Education level of the subjects were varied, with the highest proportion of them were uneducated. Almost all subjects had normal BMI values. The subjects' work type consisted of 32 scavenger, 17 waste sorter, 8 waste processor, and 2 garbage truck drivers. The majority of study subjects had exposure time of more than 10 years (30%). Comparison of smoking status was balanced between smokers (52.9%) and non-smokers (47.1%). Of the total 36 smokers, 26 subjects were included in the mild Brinkman index group, and 10 subjects were included in the moderate group. Fifty-six subjects did not have comorbidities from anamnesis. While the remaining had various comorbidities such as hypertension, diabetes mellitus, asthma, and chronic pulmonary obstructive disease.

Almost all subjects did not have respiratory complaints (80.9%), while those who had complaints consisted of 7 subjects with shortness of breath and 6 subjects with frequent coughing. Waste workers were grouped using complete personal protective equipment when using masks, gloves, and boots based on recommendations from the CDC (Center for Disease Control and Prevention). However, only 13 subjects (19%) used complete PPE, and 31 (45.6%) subjects used masks. All subjects underwent CO exhalation examination and it was found that the majority of subjects were in the non-smoker category (73.5%). In the CO exhalation data, the average was 5.12 ppm, with the non-smoker group having an average of 2.3 ppm. Meanwhile, the SP-D level value had an average of 109.64ng/mL.

The pairwise comparisons test using Dunn Test for the comparison of SP-D in the 17–25 age group, it was significantly different from the SPD in the 36-45 age group, 46–55 age group, 56-65 age group, and the age group >65 years. The comparison of SPD in the 26–35 age group was significantly different from the SP-D in the 56–65 age group, and the age group >65 years.

Based on the test results shown in Figure 1, it is

TABLE 1
Subject's Characteristics

Demography Characteristic	n	%
Age (year)		
Mean±SD	44.7±17.31	
Min–max	17–78	
17–25	11	16.2
26–35	16	23.5
36–45	7	10.3
46–55	11	16.2
56–65	12	17.6
>65	11	16.2
Gender		
Male	46	67.6
Female	22	32.4

TABLE 1. Continued.

Demography Characteristic	n	%
Education		
Uneducated	21	30.9
Elementary School	13	19.1
Junior High School	5	7.4
Senior High School	21	30.9
Bachelor	8	11.8
BMI Classification		
Underweight	12	17.6
Normal	25	36.8
Overweight	15	22.1
Obesity grade I	12	17.6
Obesity grade II	4	5.9
Work type		
Scavenger	41	60.3
Waste sorter	17	25.0
Waste processor	8	11.8
Garbage truck drivers	2	2.9
Exposure Time (year)		
< 5	24	35.3
5–10	14	20.6
>10	30	44.1
Smoking Status		
Smoker	36	52.9
Non-Smoker	32	47.1
Indeks Brinkman (Smoker)		
Mild	26	72.2
Moderate	10	27.8
Severe	0	0
Comorbid		
Hypertension	4	**5.9**
Diabetes Mellitus	2	2.9
Asthma	3	4.4
Chronic Obstruction Pulmonary Disease	3	4.4
Respiratory Symptom		
No Symptom	55	80.9
Symptom		

TABLE 1. Continued.

Demography Characteristic	n	%
Shortness of breath	7	10.3
Cough	6	8.8
Personal Protective Equipment		
Mask	31	45.6
Gloves	34	50.0
Boots	28	41.2
Complete Personal Protective Equipment		
Complete	13	19.1
Not Complete	55	80.9
CO Exhalation		
Non-smoker	50	73.5
Borderline	7	10.3
Smoker low addicted	6	8.8
Smoker moderately addicted	4	5.9
Smoker heavily addicted	1	1.5
		Mean±SD
Sistolik Blood Pressure (mmHg)		133.0 ± 20.1
Diastolic Blood Pressure (mmHg)		86.3 ± 12.7
Body Weight (kg)		59.6 ± 13.5
Body Height (cm)		161.7 ± 7.7
Body Mass Index (kg/m^2)		22.7 ± 4.6
CO Exhalation (ppm)		
Non-smoker		2.3 ± 1.59
Borderline		8.1 ± 0.7
Smoker low addicted		11.5 ± 1.05
Smoker moderately addicted		19.0 ± 3.16
Smoker heavily addicted		31.0 ± 0
SP-D (ng/mL)		109.6 ± 66.6

concluded that the age group of 36 years to over 65 years has a high average SP-D and is not significantly different. Thus, the age group of 36 years to over 65 years is classified as an age group at high risk of being exposed to waste with a high average of SP-D.

Based on Table 2, it shows that there are 27 samples aged between 17 and 35 years who are classified as having a low risk of being exposed to waste, and 41 samples aged between 36 and >65 years who are classified as having a high risk of being exposed to waste. This has been explained in detail in Figure 1. This is related to the younger age group (17–35 years) who tend to have a low risk of being exposed to waste, while the older age group (36–>65 years) tend to have a high risk of being exposed to waste.

For the influence between gender and the risk of exposure to waste, a p-value of 0.048 (p<0.05) was obtained, so it can be concluded that male gender has a significantly lower influence on the risk of exposure to waste.

In the variable based on the last education group, in the group classified as low risk, more people had a high

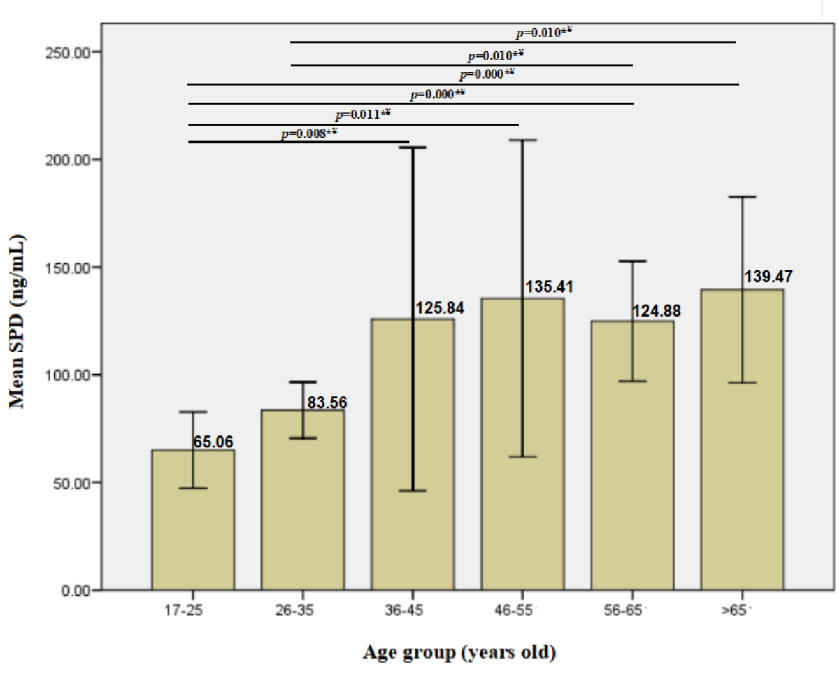

Figure 1. Comparison graph of plasma serum SP-D levels between age group.
Description: *Significant ($p < 0.05$); ¥ Dunn test comparison

TABLE 2
Demography Characteristics That Influence Waste Exposure Based on Serum SP-D

Variable	Waste Exposure Group				*p*
	Low Risk		High Risk		
	n	%	n	%	
Age (years)					0.000*¶
17–25	11	40.7%	0	0.0%	
26–35	16	59.3%	0	0.0%	
36–45	0	0.0%	7	17.1%	
46–55	0	0.0%	11	26.8%	
56–65	0	0.0%	12	29.3%	
>65	0	0.0%	11	26.8%	
Gender					0.048*¶
Male	22	81.5%	24	58.5%	
Female	5	18.5%	17	41.5%	
Education					0.000*¶
Uneducated	2	7.4%	19	46.3%	
Elementary School	2	7.4%	11	26.8%	
Junior High School	1	3.7%	4	9.8%	
Senior High School	15	55.6%	6	14.6%	
Bachelor	7	25.9%	1	2.4%	

TABLE 2. Continued.

Variable	Waste Exposure Group				*p*
	Low Risk		High Risk		
	n	%	n	%	
BMI Classification					0.021*¶
Underweight	2	7.4%	10	24.4%	
Normal	10	37.0%	15	36.6%	
Overweight	4	14.8%	11	26.8%	
Obesity grade I	7	25.9%	5	12.2%	
Obesity grade II	4	14.8%	0	0.0%	
Work Type					0.000*¶
Scavenger	5	18.5%	36	87.8%	
Waste sorter	17	63.0%	0	0.0%	
Waste processor	3	11.1%	5	12.2%	
Garbage truck drivers	2	7.4%	0	0.0%	
Comorbid					
Hypertension	1	3.7%	3	7.3%	0.536
Diabetes Mellitus	0	0.0%	2	4.9%	0.244
Asthma	0	0.0%	3	7.3%	0.151
Chronic Obstruction Pulmonary Disease	0	0.0%	3	7.3%	0.151
Respiratory Symptom					
Shortness of breath	1	3.7%	6	14.6%	0.147
Cough	1	3.7%	5	12.2%	0.227
Personal Protective Equipment					
Mask	18	66.7%	13	31.7%	0.005*¶
Gloves	16	59.3%	18	43.9%	0.215
Boots	10	37.0%	18	43.9%	0.031*¶
Complete Personal Protective Equipment					0.247
Complete	20	74.1%	35	85.4%	
Not Complete	7	25.9%	6	14.6%	

Description: *Significant ($p < 0.05$); ¶ Chi square

school education (55.6%), while in the group classified as high risk, more people did not attend school (46.3%). For the influence between the last education and the risk of being exposed to waste, a *p* value of 0.000 was obtained, so it can be concluded that education has a significant influence on the risk of being exposed to waste. This is correlated with the use of personal protective equipment.

Based on BMI classification, in the low-risk group, there were more normal patients (37.0%), while in the high-risk group, there were also more normal patients (36.6%), where out of 68 samples, the largest number of patients were normal (36.8%). For the influence between BMI classification and the risk of waste exposure, a *p* value of 0.021 was obtained ($p<0.05$), it can be concluded that BMI classification has a significant influence on the risk of waste exposure (low or high risk).

In the type of work variable, in the low-risk group, more people work as waste sorters (63.0%), while in the high-risk group, more people work as scavengers (87.8%). For the influence between the type of work and the risk of exposure to waste, a *p* value of 0.000 was obtained, so it can be concluded that the type of work has

TABLE 3
Demography Characteristics in Relation with Exposure Time

Variable	Exposure Time (years)						*p*
	< 5		5–10		>10		
	n	%	n	%	n	%	
Age (years)							0.000*¶
17–25	10	41.7%	1	7.1%	0	0.0%	
26–35	11	45.8%	4	28.7%	1	3.3%	
36–45	1	8.3%	3	21.4%	2	6.7%	
46–55	1	4.2%	1	7.1%	9	30.0%	
56–65	0	0.0%	3	21.4%	9	30.0%	
>65	0	0.0%	2	14.3%	9	30.0%	
Gender							0.007*¶
Male	22	91.7%	7	50.0%	17	56.7%	
Female	2	8.3%	7	50.0%	13	43.3%	
Education							0.003*¶
Uneducated	3	12.5%	4	28.6%	14	46.7%	
Elementary School	1	4.2%	3	21.4%	9	30.0%	
Junior High School	2	8.3%	1	7.1%	2	6.7%	
Senior High School	11	45.8%	5	35.7%	5	16.7%	
Bachelor	7	29.2%	1	7.1%	0	0.0%	
BMI Classification							0.000*¶
Underweight	2	8.3%	1	7.1%	9	30.0%	
Normal	7	29.2%	11	78.6%	7	23.3%	
Overweight	4	16.7%	0	0.0%	11	36.7%	
Obesity grade I	7	29.2%	2	14.3%	3	10.0%	
Obesity grade II	4	16.7%	0	0.0%	0	0.0%	
Work Type							0.000*¶
Scavenger	7	29.2%	8	57.1%	26	86.7%	
Waste sorter	13	54.2%	3	21.4%	1	3.3%	
Waste processor	2	8.3%	3	21.4%	3	10.0%	
Garbage truck drivers	2	8.3%	0	0.0%	0	0.0%	
Comorbid							
Hypertension	1	4.2%	0	0.0%	3	10.0%	0.383
Diabetes Mellitus	0	0.0%	0	0.0%	2	6.7%	0.271
Asthma	0	0.0%	1	7.1%	2	6.7%	0.424
Chronic Obstruction Pulmonary Disease	1	4.2%	0	0.0%	2	6.7%	0.603
Respiratory Symptom							
Shortness of breath	2	8.3%	0	0.0%	5	16.7%	0.220

TABLE 3. Continued.

Variable	Exposure Time (years)						*p*
	< 5		5–10		>10		
	n	%	n	%	n	%	
Cough	2	8.3%	0	0.0%	4	13.3%	0.346
Personal Protective Equipment							
Mask	18	75.0%	4	28.6%	9	30.0%	0.002*¶
Gloves	18	75.0%	5	35.7%	11	36.7%	0.010*¶
Boots	10	41.7%	5	35.7%	13	43.3%	0.038*¶
Complete Personal Protective Equipment							0.539
Complete	18	75.0%	11	78.6%	26	86.7%	
Not Complete	6	25.0%	3	21.4%	4	13.3%	

Description: *Significant ($p < 0.05$); ¶ Chi square

TABLE 4
Plasma Serum SP-D Level based on Exposure Time

Exposure Time (years)	Mean±SD SP-D (ng/mL)	*p*
Age (years)		0.000*¥
< 5	70.3 ± 18.44	
5–10	98.4 ± 26.76	
>10	146.4 ± 83.15	

Description: *Significant ($p < 0.05$); ¥ Kruskal-Wallis

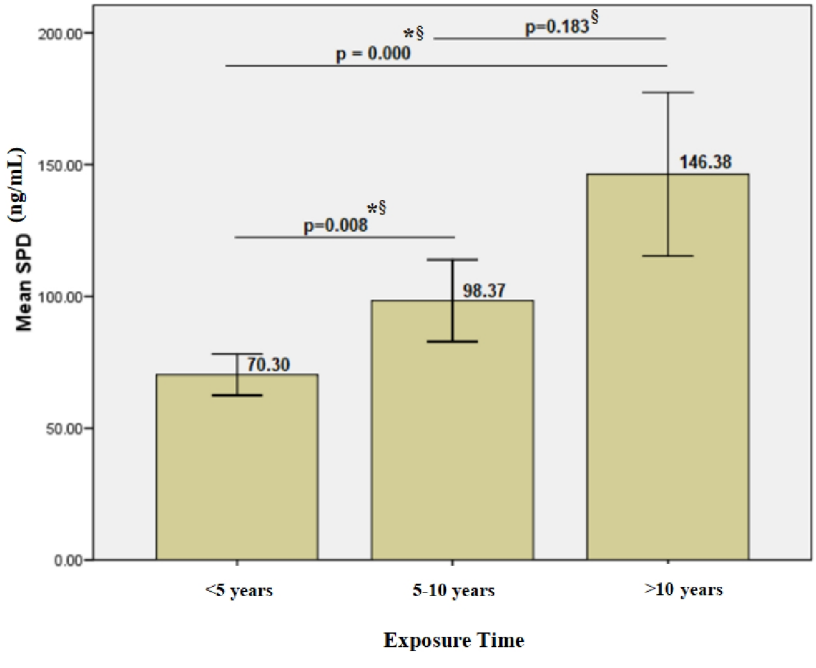

Figure 2. Comparison graph of serum SP-D levels between exposure time; *Significant ($p < 0.05$); § Dunn.

TABLE 5
Correlation of Serum SP-D Levels with Exposure Duration

Exposure Time (years)	SP-D Serum	
	r	*p*
All Subject	0.585	0.000*¶
Smoker	0.492	0.002*¶
Non-Smoker	0.648	0.000*¶

Description: *Significant ($p < 0.05$); ¶ Spearman test

TABLE 6
Serum SP-D Levels base on Smoking Status

Smoking Status	Mean ± SD SP-D (ng/mL)	*p*
		0.112α
Non-Smoker	120.7 ± 74.79	
Smoker	99.9 ± 57.63	
Indeks Brinkman		0.543α
Mild	96.0 ± 56.55	
Moderate	109.6 ± 62.32	
CO Exhalation		0.617¥
Non-smoker	100.1 ± 64.28	
Borderline	121.9 ± 77.56	
Smoker low addicted	87.0 ± 20.30	
Smoker moderately addicted	75.9 ± 18.58	
Smoker heavily addicted	111.0 ± 0	

Description: *Significant ($p< 0.05$); α Mann-Whitney Test; ¥ Kruskal-Wallis

a significant influence on the risk of exposure to waste (low or high risk).

Based on comorbidities, for comorbidities of hypertension, diabetes mellitus, asthma, and COPD each have *p*-values of 0.536, 0.244, 0.151, and 0.151, respectively, so it can be concluded that comorbidities do not have an influence on the high or low risk of exposure to waste.

In the group of subjects with complaints of shortness of breath, the group classified as low risk was 3.7%, while in the group classified as high risk there were 14.6%. Meanwhile, in the group of subjects with complaints of cough, the group classified as low risk was 3.7%, while in the group classified as high risk there were 12.2% who had complaints of cough. For the influence between complaints of shortness of breath and cough with the risk of exposure to waste (low or high risk), the p=0.147 and p=0.227 so that it can be concluded that complaints of shortness of breath and cough do not have a significant effect on the waste risk of exposure.

In the use of masks, in the low-risk group there were 66.7%, while in the high-risk group there were 31.7% who used masks. For the influence between the use of masks and the risk of exposure to waste (low or high risk) a *p* value of 0.005 was obtained, so it can be concluded that the use of masks has a significant effect on the risk of exposure to waste (low or high risk). The same results were obtained in the group using boots, in the low-risk group there were 37.0%, while in the high-risk group there were 43.9% and p=0.031 was obtained. In contrast to the group using gloves, in the low-risk group there were 59.3%, and in the high-risk group there were 43.9% and p=0.215 was obtained, so it can be concluded that the use of gloves has no effect on the risk of exposure to waste. In the Complete Personal Protective Equipment usage group, a *p*-value of 0.247 was obtained, so it can be concluded that Complete Personal Protective Equipment has no influence on the risk of exposure to waste.

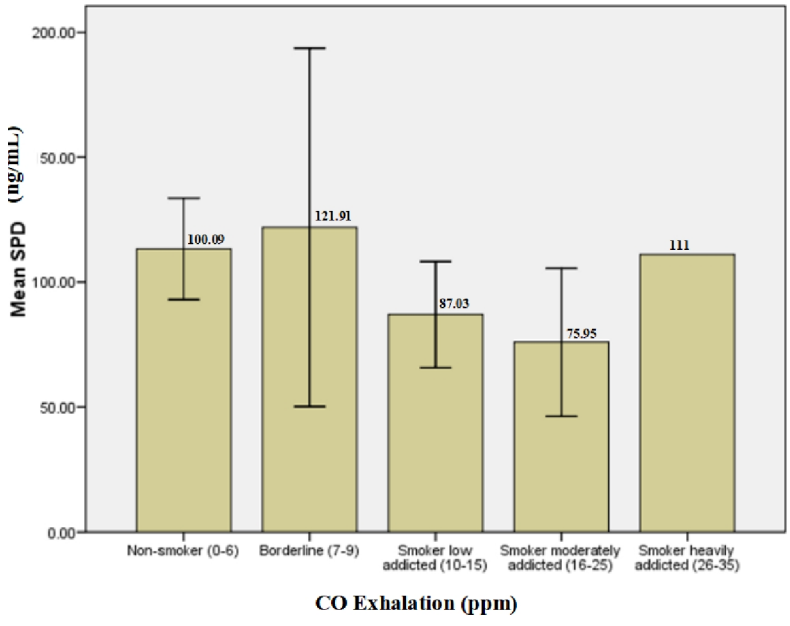

Figure 3. Graph of Serum SP-D Levels based on CO Exhalation (smokelyzer).

Based on Table 3, as many as 24 subjects exposed to waste exposure for <5 years were mostly aged 17–35 years, of the 14 samples exposed to waste exposure for 5–10 years were mostly aged 26 years to >65 years, and of the 30 samples exposed to waste exposure for >10 years were mostly aged 46 years to >65 years. For the influence between age and duration of waste exposure, a *p* value of 0.000 was obtained, so it can be concluded that age group has a significant influence on the duration of waste exposure, where there is a tendency that younger patients tend to have more exposure duration <5 years, while older patients tend to have more >10 years.

Cross tabulation between gender and duration of exposure shows that there are 24 samples exposed to waste exposure for <5 years dominated by men, from 14 samples exposed to waste exposure for 5–10 years shows the number of men and women have the same percentage, and from 30 samples exposed to waste exposure for >10 years slightly more men. For the influence between gender and duration of exposure to waste exposure, with p=0.007 was obtained where there is a tendency that women tend to experience more exposure durations of >10 years, while men tend to experience more <5 years.

There is an influence between the last education and the duration of exposure to waste with a p=0.003 where there is a tendency that patients with higher education tend to have more exposure durations of <5 years, compared to patients with lower education with longer exposure durations. Cross tabulation between BMI classification and duration of exposure shows that the *p* value is 0.003, there is a significant influence between BMI classification and duration of exposure, where there is a tendency that patients who have normal BMI and obesity tend to have more duration of exposure <5 years, compared to patients with a lower BMI classification with a longer duration of exposure.

There is a significant influence between occupation and duration of exposure with p=0.000, where there is a tendency that patients who work as waste sorters tend to have more exposure duration <5 years, compared to patients with occupation as waste scavengers who have a longer exposure duration. Cross tabulation between comorbidities and duration of exposure showed a *p* value >0.05, so there was no significant influence between any type of comorbidity and duration of exposure. The same thing was also found between respiratory complaints and duration of exposure, showing a *p* value >0.05, so there was no influence between any respiratory complaints and duration of exposure.

For the influence between the use of masks, gloves, or boots with the duration of exposure to waste, *p* value of >0.05 were obtained, so it can be concluded that there are significant influence between the use of masks, gloves, or boots with the duration of exposure, where there is a tendency that subject who use masks tend to have more exposure durations of <5 years, while patients who do not use one of personal protective equipment tend to have more exposure to waste between 5–10 years and >10 years. Meanwhile, there was no significant relationship between the completeness of personal protective equipment and the duration of exposure, with p=0.539.

Based on Table 4, a comparative test between exposure duration groups was obtained with *p* value of 0.000 and continued with a pairwise comparisons test and a significant increase in the average SP-D levels was obtained in the 5–10 and >10 year groups compared to the less than 5 year exposure group (p=0.08 and p=0.000). However, there was no significant increase in the average SP-D levels in the 5–10 year exposure group compared to the >10 year exposure group (p=0.183) although there was a tendency to increase in the exposure period >10 years. The number of subjects who smoked was 36 people (52.9%), and the average serum SP-D levels in the study subjects were found to increase along with the duration of exposure with a *p* value = 0.000. Because there was a significant difference, it was necessary to continue with the Dunn pairwise comparisons test. There was a significant increase in the average SP-D levels in the 5–10 and >10 year groups compared to the less than 5 year exposure group (p= 0.08 and p=0.000). This will be seen more clearly in Figure 2. Based on the Spearman correlation test between the duration of exposure and SP-D in all groups, a positive correlation coefficient value of 0.585 was obtained with p=0.000.

Based on the correlation test between exposure time and SP-D in all subject, there is a significant positive correlation coefficient value of 0.585 (p=0.000). In this study, we also differentiated the correlation test between smoker and non-smoker groups. A significant positive correlation coefficient value of 0.492 (p =0.002) was obtained in the smoker group. Meanwhile, in the non-smoker group obtained a significantly strong positive correlation coefficient value of 0.648 (p <0.000).

Based on Table 6, the average SP-D in non-smoking patients was 120.74 ng/mL, and the average SPD in smoking patients was 99.78 ng/mL, but there was no significant increase (p=0.112) in SP-D levels in the smoking group, and there was actually a tendency for a decrease in the average serum SP-D levels in smokers. The group of subjects with moderate Brinkman index showed a non-significant increase in serum SP-D levels compared to subjects with mild Brinkman index (p=0.543), although there was a tendency for increased serum SP-D levels. Serum SP-D levels based on the CO exhalation group can be seen in Table 6 as well, and there was no significant difference between groups with the Kruskal Wallis test results obtaining a *p* value of 0.617.

In Figure 3, the borderline group had the highest serum SP-D levels, while the moderately addicted smoker group had the lowest serum SP-D levels.

DISCUSSION

The subject characteristics data in this study, were of age between 17 and 78 years old with an average age distribution of 44.71 ± 17.31 years, the majority were 46 male, the 22 female. This is in accordance with another research previously done in Malang bird market. In demographic analysis, the population age structure is divided into three groups, namely (a) young age group, under 15 years; (b) productive age group, aged 15–64 years; and (c) old age group, aged 65 years and over, where the majority of workers are male and entering productive age. Similar to the study previously, there was a significant difference in age category (p=0.07). This is associated with the length of exposure received by the subjects.[17,18]

In terms of education level, the majority of the subjects were high school graduates and did not attend school. In the BMI category, the majority of subjects were in the normal category. While in terms of work type, the most subjects were 41 scavengers, where the rest were waste sorters, waste processors, and 2 others were waste transport drivers. In line with the researches conducted in 2010 and 2011, most of the subjects had normal BMI due to the heavy workload with high physical activity that made the workers continue to move with high metabolism.[19,20] In the education category, there were also the most subjects with high school education because this type of work does not require a high educational classification. However, in contrast to the two studies where the majority of subjects worked as liquid waste workers,[19,20] this study mostly involved scavengers who worked in solid waste as much as 41% of the total subjects.

In contrast to the previous study which divided the subject groups based on the duration of exposure into 4 groups, this study divided the subject groups into 3 groups, consisting of <5 years, 5–10 years, and >10 years with the assumption that the previous 4 groups had significant differences in the <1 year, 2–10 years, and 11–20 years groups. While in the >20 years group it was not significantly significant (p = 0.171).[17]

In this research design, the research subjects were divided into 3 groups based on smoking status according to previous research namely non-smokers, active smokers, and former smokers.[16,17] However, of the 68 subjects in this study, there were no former smokers. So the smoking history category was only divided into 2, smokers and non-smokers. In grouping smoker subjects, in line with previous research in 2021, dividing smoker groups based on objective data and subjective data. Objective data uses grouping based on smokelyzer to measure CO exhalation levels, which divides subject groups into non-smokers, borderlines, low-addicted smokers, moderately addicted smokers, and heavily addicted smokers. While subjective data uses anamnesis of the number of cigarettes per day which is grouped based on the Brinkman index: mild, moderate, and heavy Brinkman index.[21] In this study, data on the smoker group was only on the mild and moderate Brinkman index.

Most of the research subjects had a duration of

exposure >10 years, consist of 30 people (44.1%). The difference in serum SP-D levels in each group was found to be significant and increased with the duration of exposure (p = 0.000). Based on the one sample test of each exposure category, exposure <5 years and 5–10 years were more significant than exposure >10 years. This means that a significant increase was obtained when exposure was >5 years. This should be a special concern for policy makers, namely the local Environmental Service, to be able to start conducting periodic health checks for workers with a service period of more than 5 years. The relationship between duration of exposure and serum SP-D levels showed a significant relationship between duration of exposure and SP-D levels, which had a positive correlation in all groups of research subjects (r = 0.585, p = 0.000), a positive correlation in the smoker group (r = 0.492, p = 0.002), and a positive correlation in the non-smoker group (r = 0.685, p = 0.000).

In line with previous study found an increase in serum SP-D levels in bird market workers according to the duration of exposure. Bioaerosols in landfills can cause inflammatory reactions that can increase the permeability of the blood and lung barriers. So that occupational exposure to bioaerosols can cause increased leakage of surfactant protein D into the bloodstream. Chronic exposure to bioaerosols can cause damage to epithelial secretory cells and reduce the amount and function of lipopolysacharides which can cause subclinical inflammatory reactions, so that lung protein leakage can describe an early sign of bioaerosol exposure from waste workers. A previous study stated that SP-D tended to be higher in groups exposed to waste or garbage compared to groups not exposed (administrative employees). [17,19,20,22]

From 68 research subjects, the numbers of smokers and non-smokers were almost the same, 36 and 32 subjects respectively. The Mann Whitney test obtained a p value of 0.112 (p>0.05), there is no significant difference in serum SP-D levels in SP-D between the smoker and non-smoker groups in terms of subjective data (Brinkman index) and objective data (CO exhaled levels). The same thing was found in previous study,[18] where in the group of workers who smoked in the poultry market the p-value was 0.245. In another study there was also no significant difference in SP-D levels between the group of waste workers with smoking status and type of waste exposure in both the non-smoker group (p=0.2), the smoker group (p=1.0), and the former smoker group (p=0.1). In several studies focusing on smokers, SP-D levels increased in the group of smokers with COPD. In smokers who have not been diagnosed with COPD, in this case smokers do not have complaints with normal function tests, SP-D levels are not different compared to non-smokers. Acrolene contained in cigarettes has the ability to damage the structure of SP-D multimers, so it is estimated to reduce the amount and function of SP-D. Even in a previous study, BAL SP-D levels in the non-smoker group were the highest compared to smokers with or without COPD, associated with good innate immune function. Another possible cause of increased serum SP-D levels in non-smoking status is exposure factors to particle pollutants, antigens, and aerosol agents including debris or organic dust in the waste disposal environment which causes inflammation in the respiratory tract with good innate immunity compared to the smoking group due to the content of substances in cigarettes which can distort the components and function of SP-D.[13,16,17,20,23]

CONCLUSION

Serum SP-D levels in smokers was not higher than non-smokers in waste workers at the Supit Urang landfill. Both Co exhaled levels and Brinkman index were not associated with serum SP-D levels in workers who smoked at the Supit Urang landfill. Meanwhile, exposure duration was positively correlated with serum SP-D levels in waste workers at the Supit Urang landfill, in smokers, non-smokers, and all study subjects. Which means longer the exposure time, the higher the serum SP-D level.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2025; vol 12 (1) : 23–28

OPEN ACCESS

Original Article

The Correlation Between Folic Acid Supplementation and Change in Cognitive Function in Elderly
(A Study of The Effect of Folic Acid Supplementation on Homocysteine Levels)

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v12i1.985

Accepted: July 05th, 2023
Approved: March 17th, 2025

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Abstract

Background : A good cognitive function is one of the things that affect the quality of life of the elderly. Decreased cognitive function in elderly can be caused by physiological or pathological processes. Increased homocysteine is one of risk factors associated with decreased cognitive function. Folic acid supplementation has been shown to reduce homocysteine levels. This study was aimed to know the relationship between folic acid supplementation and change in cognitive function in elderly.
Methods : This research is a quasi-experimental study at Pucang Gading Nursing Home, Semarang. A total of 30 subjects were divided into 2 groups, namely 15 treatment subjects (given folic acid supplementation 1 mg/24 hours) and 15 control group subjects (given placebo), 1 subject dropped out due to death. The study was conducted for 12 weeks, assessment of homocysteine level and cognitive function (with MoCA Ina) was carried out before and after the study.
Results : There was no relationship between folic acid supplementation and changes in homocysteine level (*p* 0.322). There is a relationship between folic acid supplementation with change in cognitive function in elderly (*p* 0.000). There is a relationship between changes in homocysteine level and global change in cognitive function in elederly (*p* 0.018).
Conclusion : There is a significant relationship between folic acid supplementation and change in cognitive function in elderly.

Keywords : Elderly, cognitive function, MoCa Ina, homocysteine, folic acid

INTRODUCTION

Elderly is a group of people aged over 60 years. The better standar of living and health in Indonesia then the number of elderly in Indonesia continue increasing from 7.6% in 2010 to 8.03 % in 2014. Survey Data from the National Socio – Economic Survey (Susenas) on March 2022 shows 10.48% of the population is elderly. The number of elderly keep growing along with the improvement of life expectancy. The number of elderly in Indonesia in 2017 was 23.66 million and predicted to increase more than double on 2035. Globally, by 2030, it is estimated at least 1 in 6 people in the world will age 60 years of older. Currently, the proportion of resident aged over 60 years will increase from 1 billion in 2020 to 1.4 billion. Population resident aged over 60 years in the world will double (2.1 billion) by 2050.

The good cognitive Function is a factor influencing quality life in elderly. As age increases, body experience aging process including brain. The declined brain cell function will cause short term memory loss, reduced ability in decision making and actions, concentration disorder, slowing information processing so that hinder communication process as well as psychic and social life, and physical activities in elderly. [2]

Homocysteine, amino acids containing sulfur, is an intermediate compound formed from methionine metabolism. The high homocysteine level is related to increased risk of heart attack, stroke, Alzheimer's and declined cognitive function. Some studies report improved homocysteine plasma level related to declined cognitive function and cerebral atrophy, as well as to predict the existence of dementia development among middle age and old people with previously normal cognition. [3–5]

The effect of hyperhomocysteinemia on cognitive function may be indirectly caused by previous vascular damage. Imaging examinations show that individuals with hyperhomocysteinemia have silent infarcts, white matter lesions, and brain atrophy associated with decreased cognitive function. Research on nerve cell cultures shows that high homocysteine levels can cause neurotoxicity without previous vascular damage. High homocysteine levels can reduce the availability of methionine with the consequence of affecting the synthesis and degradation of neurotransmitters, both of which are thought to play a role in decreased cognitive function. Folic acid administration has been shown to be able to reduce homocysteine levels, although not consistently in several studies, and in separate studies it has been shown that folic acid administration can improve patient cognitive outcomes. Research conducted by Balk *et al* in America, proved that consumption of folic acid supplements provided better cognitive outcomes. Evaluations were carried out in 5 weeks and 11 weeks after treatment, with significant results in the 11th week in the 1 mg/day folic acid group (control group 0.4 mg/day). Inge Permadhi *et al* found that routine folic acid supplementation of 1 mg/day in the elderly for 6 weeks was able to reduce homocysteine levels by 36.68%. With these data, the study will be conducted for 12 weeks. [6–9]

Montreal Cognitive Assessment Indonesia version (MoCA Ina) is an initial screening of cognitive function, which can be completed in 10 minutes, with 30 points designed to help health professionals detect mild cognitive impairment. The recommended cut-off score for MoCa is 26. MoCA Ina is more appropriate for assessing cognitive function, because it is more sensitive than MMSE in detecting mild cognitive impairment. MoCa Ina can also be completed in less than 10 minutes, thus reducing the influence of fatigue in determining test results. In addition, MoCa more broadly assesses attention, visual-spatial abilities, learning, and executive functions compared to MMSE. [10–13]

Pucang Gading Social Home is a social home managed by the Social Service of the Central Java Provincial Government with elderly people from several regions in Central Java, not only from Semarang area. Thus, it is expected that the elderly in Pucang Gading Social Home have more diverse characteristics and are considered to be able to represent the elderly in Central Java.

METHODS

This study was a quasi-experimental at Pucang Gading Social Home, Semarang. The minimum sample calculation for the experimental design obtained 13 subjects per group, with an estimated dropout of 10%, so that 15 subjects per group were determined. Consecutive sampling was carried out with a total of 30 subjects divided into 2 groups, namely 15 treatment subjects (given 1 mg/24 hours folic acid supplementation) and 15 control group subjects (given placebo), 1 subject dropped out of the control group due to death. Inclusion criteria include being able to read and write and agreeing to participate in the study. Exclusion criteria included elderly people with aphasia, depression, diarrhea, and alcoholism.

The study was conducted for 12 weeks, assessing serum homocysteine levels using the ELISA method and cognitive function (with MoCA Ina) before and after the study. Changes in cognitive function in the elderly based on MoCA Ina were associated with the provision of folic acid supplementation, based on the calculation of the unpaired categorical test statistical method in two groups, and the pre-post-test. Researchers also conducted an analysis to prove the effect of age, gender, education level, body mass index, hypertension, dyslipidemia, diabetes mellitus, on changes in cognitive function in elderly.

TABLE 1
Characteristics of Experimental Subject

Variables	N	%	Control N = 14	Treatment N = 15
Gender				
Man	10	34.48%	6 (43%)	6 (43%)
Woman	19	65.52%	8 (57%)	8 (57%)
Age				
≤ 65 year	7	24.14%	4 (29%)	4 (29%)
> 65 year	22	75.86%	10 (71%)	10 (71%)
Hypertension				
No	19	65.52%	11 (79%)	11 (79%)
Yes	10	34.48%	3 (21%)	3 (21%)
Diabetes Mellitus				
No	22	75.86%	9 (64%)	9 (64%)
Yes	7	24.14%	5 (36%)	5 (36%)
Level Education				
≤ 12 year	19	65.52%	7 (50%)	7 (50%)
> 12 year	10	34.48%	7 (50%)	7 (50%)
Index Mass Body				
Underweight	3	10.34%	1 (7%)	1 (7%)
Normal	23	79.31%	12 (86%)	12 (86%)
Overweight	1	3.45%	1 (7%)	1 (7%)
Obese	2	6.90%	0 (0%)	0 (0%)
Dyslipidemia				
No	19	65.52%	9 (64%)	9 (64%)
Yes	10	34.48%	5 (36%)	5 (36%)

RESULTS

There were 29 subjects who met the inclusion and exclusion criteria during the research period November 2022 – February 2023 with the characteristics listed in Table1.

DISCUSSION

Table 1 describes the demographic and clinical characteristics of the study subjects. All numeric variables have been tested for data normality, and show a normal distribution. All subjects in the treatment group have been recorded, none of whom experienced nausea, vomiting, diarrhea during 12 weeks of folic acid supplementation. In the initial and final homocysteine examinations, pre-study data were obtained with a mean of 6.4 µmol/L (minimum value 0.33 µmol/L – maximum value 28.83 µmol/L) and post-study data with a mean of 7.77 µmol/L (minimum value 0.02 µmol/L – maximum value 18.16 µmol/L). From these data, only 2 subjects in the pre and post-study results experienced hyperhomocysteinemia, so further analysis used numeric and nominal variables (increased or not increased). Table 2 shows the initial, final homocysteine levels, and their differences, between the control and treatment groups. In the initial homocysteine examination, there was a difference between the control and treatment groups based on the unpaired T-test (p 0.020) where the treatment group had lower serum homocysteine levels

TABLE 2
Serum Homocysteine Level

Information	Control N = 14 (μmol /L)	Treatment N = 15 (μmol /L)	*p*
Initial serum homocysteine	8.88 ± 7.11	4.07 ± 2.33	**0.020***
Final serum homocysteine	8.53 ± 5.55	7.07 ± 3.22	0.391*
Changes in serum homocysteine	0.81 ± 5.19	2.33 ± 2.56	0.322*
	$p = 0.842^{Y}$	$\mathbf{p = 0.013^{Y}}$	

Information: * Independent T-test, ^{Y} Paired T-test; significant when $p<0.05$

TABLE 3
Initial, final, and changes in MoCA Ina of changes in cognitive function

Information	Control N = 14	Treatment N = 15	*p*
Initial MoCA Ina	19.64 ± 5.03	14.06 ± 4.00	**0.005***
Final MoCA Ina	17.00 ± 3.96	18.40 ± 4.96	0.418*
Changes in MoCA Ina	-2.64 ± 3.69	4.33 ± 3.53	**0.000***
	$\mathbf{p = 0.016^{¥}}$	$\mathbf{p = 0.013^{¥}}$	
	z = -2.408	z = +2.405	

Information : * Independent T-test ; $^{¥}$ Paired T-test ; significant when $p < 0.05$

TABLE 4
Connection Change Level Homocysteine Serum and Factor Risk with MoCa Ina

Variables	N	Initial MoCA Ina (Mean ± SD)	Final MoCA Ina (Mean ± SD)	Changes in MoCA Ina (Mean ± SD)	MoCA Ina		Mark *p*
					Getting better	No getting better	
homocysteine Level							
Increase	24	17.4 ± 5.45	18.0 ± 4.75	0.54 ± 5.27	10	14	$p = 0.018$*
No increase	5	13.4 ± 2.60	16.4 ± 2.88	3.00 ± 1.22	5	0	$R = 0.763^{¥}$

Information : *C*hi-square* significant when $p < 0.05$, $^{¥}$ Correlation This

than the control group. In the final homocysteine examination, there was no difference between the two groups, but there was a significant increase in homocysteine levels in the treatment group based on the paired T-test (*p* 0.013), which is contrary to the theory that folic acid administration can reduce homocysteine levels.

This is inconsistent with previous studies that stated that folic acid supplementation can reduce homocysteine levels. Folate acts as a precursor for 5-methyltetrahydrofolate, a methyl donor for the remethylation of homocysteine to methionine so that homocysteine auto-oxidation that produces oxidized disulfide, two protons (H+) and two electrons (e-) that stimulate the formation of ROS is not formed. Folate deficiency indirectly causes an increase in plasma homocysteine concentrations. Folate deficiency also causes low concentrations of S-adenosyl methionine, an important methyl donor needed for epigenetic processes (gene methylation) and for the basis of processing cell metabolism (DNA and protein synthesis). Folic acid supplementation is effective for normalizing increased homocysteine levels so that it can be used to prevent cardiovascular disease. [8,14]

David S. Wald *et al*. proved that giving folic acid supplementation up to 5 mg/ day for 3 months can reduce homocysteine levels by up to 25% (or 3–12 μmol/L) in

patients known to have ischemic heart disease. In a study conducted by Wald *et al*., all subjects had high homocysteine levels, with an average of 20 µmol/L.[15] Kam S. Woo noted a decrease in homocysteine levels from 9 ± 1.7 µmol/L to 7.9 ± 2.0 µmol/L with the administration of 10 mg/day folic acid supplementation for 1 year. The increase in homocysteine levels in the treatment group in this study is still unexplained, but may be related to homocysteine metabolism itself which may involve a genetic role (polymorphism of MTHFR), side effects of other treatments (methotrexate, theophylline, phenytoin, and cyclosporine), chronic diseases (end-stage renal disease, liver dysfunction, and hypothyroidism), which should be examined in this study.[16] Increased homocysteine levels may also be related to red meat consumption and a diet high in methionine, which can be converted to homocysteine. Food groups that are high in methionine include beans, beef, lamb, pork, cheese, shellfish, soy products, eggs, milk, and nuts. Methionine levels that exceed normal levels (13 mg/kgBW) can cause increased homocysteine, and increase the risk of neurodegenerative diseases, especially Alzheimer's dementia.[6,17] In this study, no methionine levels were assessed. All elderly people received the same food from the social care facility manager, in the form of side dishes that had been arranged on plates (not taken by themselves), so it was assumed that the food intake between the two groups was no different.

Table 3 shows that there was a significant difference in the initial MoCA Ina value in the treatment group of 14.06 ± 4.00 compared to the control group of 19.64 ± 5.03, but there was no significant difference in the final MoCA Ina value. In the initial and final results, all study subjects were classified as cognitively impaired (because MoCA Ina <26), so the researchers divided the outcome of cognitive function into improved and not improved (there was no significant difference in changes in MoCA Ina in the two groups, namely an increase in MoCA Ina in the treatment group (p 0.013) and a decrease in MoCA Ina in the control group (p 0.016).

In a review compiled by I Putu Eka Widyadharma, several studies have shown that folic acid supplementation can improve cognitive function outcomes. Chen (2016) provided 1.25 mg/day folic acid supplementation for 60 days in 61 Alzheimer's patients, with improved cognitive function results (based on MMSE) $p < 0.005$.18 Ma (2016) provided 400 µg/day folic acid supplementation for 12 months in 77 Mild Cognitive Impairment patients, with improved cognitive function results (based on IQ Test and digit span test). In his study, Ma proved that consuming 400 µg folic acid supplementation for 12 months can reduce levels of IL-6, TNF-α, and Aβ-42 (β-amyloid). The presence of peripheral inflammation can cause changes in the hippocampus, including hippocampal volume. In addition, the hippocampus is also a receptor for large amounts of inflammatory cytokines, such as IL-6 and IL-1β. Thus, folic acid supplementation may potentially improve cognitive function by reducing peripheral inflammatory cytokine levels.

MoCA Ina consists of 30 points, which include several questions, grouped as follows: visual executive (7 points), naming (3 points), memory (5 points), attention (6 points), language (3 points), abstraction (2 points), and orientation (6 points). If the subject's education is ≤12 years, the total MoCA Ina score is added 1 point. Because the number of points varies for each domain, the researcher tried to analyze whether there was a relationship between differences in serum homocysteine levels and changes in cognitive function in nominal form, namely increased/unincreased serum homocysteine with improved/unimproved cognitive function. Based on the Chi square test with the nominal group division, changes in homocysteine levels had a significant difference in changes in cognitive function (p 0.018).

Pinar Oner *et al* (2023) found that homocysteine levels tended to be higher in post-COVID-19 patients compared to the control group, and higher homocysteine levels were significantly associated with decreased MoCA scores ($p < 0.001$, $r = -0.705$). This confirms that in inflammatory conditions, homocysteine levels will increase. In this study, an increase in homocysteine of 1 µmol/L was found to have a risk of decreasing the MoCA score by 0.765 points. Homocysteine is a neurotoxicant that can disrupt the integrity of the blood-brain barrier. In addition, homocysteine initiates the proinflammatory process and can cause neurological dysfunction through oxidative stress. Oxidative stress caused by homocysteine can be due to increased reactive oxygen species (ROS), inactivation of the nitric oxide synthase pathway, and lipid peroxidation, which are formed in the brain by blocking NMDA receptors.

Hyperhomocysteinemia is associated with thromboembolism and vascular damage. Thus, homocysteine can cause cognitive impairment through cerebrovascular events as well.[19]

A perfusional MRI study found that in normal individuals, hyperhomocysteinemia was associated with decreased cerebral blood flow, especially in the frontal and parietal cortex, which is not associated with other vascular risk factors. Simona Luzzi *et al*. (2021) examined the effect of homocysteine on cognitive function through several neuropsychological instruments. Hyperhomocysteine has a significant relationship with changes in performance in tasks involving memory and motor planning functions. The association of homocysteine with memory performance is thought to be due to the background that hyperhomocysteine is associated with more severe temporomedial lobe atrophy. The relationship between homocysteine and motor planning function (Luria) is still unclear, but is thought to be related to the frontal lobe.[20]

CONCLUSION

Folic acid supplementation does not affect changes in homocysteine levels (p 0.322). There is an effect of folic acid supplementation on changes in cognitive function in the elderly (p 0.000). There is an effect of changes in homocysteine levels (p 0.018) on changes in global cognitive function with r = 0.763 which shows a strong correlation.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2025; vol 12 (1) : 29–33

OPEN ACCESS

Original Article

Analysis of Risk Factors for The Severity of Hyaline Membrane Disease in Preterm Infants Based on Modality Chest X-Ray

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v12i1.1283

Accepted: November 04th, 2024
Approved: March 12th, 2025

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Abstract

Background : Hyaline membrane disease is one of the leading causes of morbidity and mortality in premature infants. Chest X-ray examination can significantly improve the diagnosis of hyaline membrane disease. This study aims to examine the relationship between risk factors and the severity of hyaline membrane disease using chest X-ray modalities.
Methods : An analytic observational study with a cross sectional and retrospective approach was conducted. Consecutive sampling of 30 preterm infants's medical records and thoracic X-ray at Dr. Kariadi Hospital Semarang was used. Data collection was carried out from April to July 2023. Statistical tests included the *Contingency Coefficient Correlation Test* and *Intraclass Correlation Coefficient* (ICC).
Results : Findings indicate that HMD severity is associated with lower birth weights ($p = 0.020$; $r = 0.392$); gestational ages ($p = 0.011$; $r = 0.420$) and maternal hypertension ($p = 0.013$; $r = 0.414$). Preeclampsia, delivery method, and gender not significantly related to the HMD severity ($p>0.05$).
Conclusion : Infant birth weight, gestational age, and maternal hypertension are significantly associated with the severity of hyalin membrane disease.

Keywords : Risk Factors, Hyaline Membrane Disease, Chest X-ray, Premature Infant

INTRODUCTION

Hyaline membrane disease, also known as respiratory distress syndrome (RDS) is a major cause of morbidity and mortality in premature infants.[1] The incidence varies internationally with rates 4.24% in Arabia; 6.4% in India; and 88.4% in Egypt.[2–4] Causes of respiratory distress include infection (68.6%), transient tachypnea of the newborn (30.7%), congenital heart defect (18%), surgery (9.6%), and hyaline membrane disease (9%). Studies show that hyaline membrane disease is particularly prevalent in India and Nigeria.[5–7] Chest x-ray examination can significantly indicate the diagnosis of hyaline membrane disease (27.36%).[8] Preterm infants less than 1500 grams are a risk factor for hyaline membrane disease.[9] Severe preeclampsia, infant gender, and cesarean delivery method are also risk factors hyaline membrane disease. For this reason, early diagnosis, supporting examinations, and appropriate interventions are very important for newborns, especially premature babies.

Diagnosis relies on clinical signs (tachypnea, cyanosis, retractions), laboratory tests (PaO2 levels below 50 mmHg), and radiological examinations.[10,11] Chest X-rays are crucial, revealing lung opacities and correlating with disease severity. The disease can be classified into four grades based on X-ray findings, ranging from ground glass appearance to homogeneous opacity.[1,12–14]

Based on the classification of grade hyaline membrane disease based on chest x-ray images and by looking at risk factors and the high mortality rate of newborns with hyaline membrane disease, researchers are interested to research on the analysis of risk factors with the severity of hyaline membrane disease in newborns based on chest x-ray modalities at Dr. Kariadi Hospital Semarang. The goal is to enhance early diagnosis and intervention, thereby reducing severity and mortality rates in affected newborns.

METHODS

The study was conducted at Dr. Kariadi Hospital Semarang from April to July 2023, using an analytic observational design with a cross-sectional, retrospective approach. Thirty subjects were selected through consecutive sampling from electronic medical records, adhering to inclusion and exclusion criteria. Inclusion criteria included premature infants diagnosed with hyaline membrane disease based on clinical and radiological exams (initial imaging) with a gestational age under 37 weeks and a birth weight below 2500 grams. Exclusion criteria involved incomplete medical records and infants who had received surfactant therapy therapy. Data was collected from the initial thoracic X-ray imaging through HER (Electronic Health Record) and subsequently evaluated by two radiologists to determine the disease grade. Descriptive analysis was employed to characterize the respondents, while bivariate analysis was conducted to assess the relationships between variables. The strength of the relationships between risk factors and disease severity was evaluated using the contingency coefficient correlation test. The reliability of the instrument in this study was assessed using inter-rater reliability (IRR). This study received ethical clearance from the Health Research Ethics Commission (KEPK) of Diponegoro University (Number 130/EC/KEPK/FK-UNDIP/IV/2023).

RESULTS

Table 1 shows that the study included 30 premature infants diagnosed with hyaline membrane disease, with 21 (70%) classified as grade I and II. Infants weighing ≤ 1500 grams comprised the largest group (56.7%), while those born at ≥ 30 weeks accounted for 66.7%. Most infants were born to mothers without hypertension (56.7%) or preeclampsia (93.3%), and cesarean section was the most common delivery method (80%). Males made up 56.7% of the sample.

Table 2 presents the results of the reliability test using the Intraclass Correlation Coefficient (ICC), yielding a va κ value of 0.889, indicating very good agreement in the grading of hyaline membrane disease. The correlation between birth weight and the severity of HMD was significant (p = 0.020; r = 0.392), reflecting a weak positive correlation, while gestational age also showed a significant moderate positive correlation with disease severity (p = 0.011; r = 0.420). In this study also indicate a correlation between maternal hypertension and the severity of hyaline membrane disease (p = 0.013; r = 0.414). However, maternal preeclampsia, delivery method, and gender did not show significant relationships with disease severity (p > 0.05).

DISCUSSION

This study identified a significant association between birth weight and the severity of hyaline membrane disease (HMD), demonstrating a weak positive correlation (p = 0.020; r = 0.392). Heavier infants exhibited milder disease, while those with lower birth weights experienced more severe cases. These findings are consistent with the research conducted by Warman *et al*., which reported a 42% incidence of HMD in infants with birth weights below 1500 grams, as well as with Melamed *et al*., who found that the majority of NICU patients with HMD weighed less than 1800 grams. Low birth weight emerged as a primary risk factor for HMD.[15,16] Additionally, Pherson *et al*. demonstrated that the severity of HMD is inversely related to gestational age, while Mansoor *et al*. confirmed a positive correlation between gestational age and birth weight. Infants with

TABLE 1
Research Subject Characteristics

Variable	n	%
Total Sample	30	100.0
Grading HMD		
I – II	21	70.0
III – IV	9	30.0
Birth Weight		
≤ 1500 grams	17	56.7
> 1500 grams	13	43.3
Gestational Age		
< 30 weeks	10	33.3
≥ 30 weeks	20	66.7
Maternal Hypertension		
Yes	13	43.3
No	17	56.7
Maternal Preeclampsia		
Yes	2	6.7
No	28	93.3
Mode of Delivery		
SC	24	80.0
Spontaneous	6	20.0
Sex		
Male	17	56.7
Female	13	43.3

TABLE 2
Conformity of Hyaline Membrane Disease Degree of Observer I and Observer II

HMD (I)	HMD (II)								Total		κ
	I		II		III		IV				
	n	%	n	%	n	%	n	%	n	%	
I	7	23.3	1	3.3	0	0	0	0	8	26.7	0.889
II	1	3.3	11	36.7	1	3.3	0	0	13	43.3	
III	0	0	2	6.7	5	16.7	0	0	7	23.3	
IV	0	0	0	0	0	0	2	6.7	2	6.7	
Total	8	26.7	14	46.7	6	20.0	5	6.7	30	100	

TABLE 3
Test of Relationship to HMD Severity

Variable	Grading HMD				*p*	r
	I – II		III – IV			
	n	%	n	%		
Birth Weight						
≤ 1500 grams	9	42.9	8	88.9	0.020£	0.392
> 1500 grams	12	57.1	1	11.1		
Gestational						
< 30 weeks	4	19	6	66.7	0.011£	0.420
≥ 30 weeks	17	81	3	33.3		
Maternal Hypertension						
Yes	6	28.6	7	77.8	0.013£	0.414
No	15	71.4	2	22.2		
Maternal Preeclampsia						
Yes	1	4.8	1	11.1	0.523£	0.116
No	20	95.2	8	88.9		
Mode of Delivery						
SC	17	81	7	77.8	0.842£	0.036
Spontaneous	4	19	2	22.2		
Sex						
Male	11	52,4	6	66.7	0.469£	0.131
Female	10	47,6	3	33.3		

£ *Contingency Coefficient*

low birth weights are often born prematurely, resulting in immature lung development and inadequate surfactant production, which contribute to respiratory distress and HMD. [11,17]

The study also identified a significant correlation between gestational age and the severity of hyaline membrane disease (HMD), demonstrating a moderate positive correlation (p = 0.011; r = 0.420). Specifically, as gestational age approaches 37 weeks, the severity of HMD diminishes. This finding is consistent with the observations of Pherson *et al*., who reported an inverse relationship between HMD severity and gestational age, and Wicaksono *et al*., who documented a 60–80% incidence of HMD in infants born at gestational ages less than 28 weeks and 15–30% incidence of HMD in infant born at 32–36 gestasional age.[15,18] Additionally, Pickerd *et al*. identified both prematurity and deficiencies in surfactant production as significant risk factors for the development of HMD. [16,19]

This study identified a significant correlation between maternal hypertension and HMD severity, with a moderate positive correlation (p = 0.013; r = 0.414). Elevated maternal blood pressure was associated with increased severity of HMD, corroborating the findings of Condo *et al*. and Wang *et al*., who emphasized the influence of maternal hypertension on neonatal outcomes. Pathological pregnancy (maternal hypertension and maternal diabetes) is associated with the incidence of hyaline membrane disease.[20,21] Efriza *et al*. also reported a significant relationship between maternal hypertension and HMD.[22] Hypertension in pregnant women can lead to vasospasm in the blood vessels, resulting in compromised blood flow that may disrupt overall circulation, including uteroplacental perfusion. This reduction in perfusion can adversely affect fetal oxygenation, increasing the risk of respiratory distress in neonates. In contrast, this study found no significant association between maternal preeclampsia, delivery method, or infant gender and the severity of hyaline membrane disease.

CONCLUSION

There is a significant correlation between birth weight, gestational age, and maternal hypertension with the severity of hyaline membrane disease.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2025; vol 12 (1) : 34–43

OPEN ACCESS

Original Article

Evaluation of Definitive Antibiotic Therapy Effectiveness in Sepsis Patients at Tabanan Hospital, Indonesia

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v12i1.1210

Accepted: October 07th, 2024
Approved: March 13th, 2025

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Abstract

Background : The study evaluated the use of definitive antibiotics and examined the association between the causative bacteria, resistance patterns, and antibiotic regimens with clinical outcomes in sepsis. This study was aimed to assess the suitability of definitive antibiotics in sepsis patients at Tabanan Hospital, focusing on the correlation between bacterial type, antibiotics, and resistance profiles with clinical outcomes, aiming to improve sepsis management and reduce antibiotic resistance.
Methods : The observational cross-sectional study analyzed data descriptively to evaluate antibiotic-pathogen compatibility retrospectively. Chi-square tests were used for bivariate analysis of mortality-related variables. Survival analysis employed the Kaplan-Meier method.
Results : Among 112 sepsis patient records (Jan 2020 – Dec 2022), 62% received antibiotics based on bacterial sensitivity test contradiction to another 38% who were given inappropriately antibiotic. Empiric antibiotic treatment was associated with increased mortality (OR=4.379; CI 95% 1.274-15.052; *p*=0.022). Bacterial type and resistance status showed no significant association with mortality (OR=0.417; CI 95% 0.030–5.708; *p*=1.000 and OR=1.500; CI 95% 0.156–14.420; *p*=1.000, respectively).
Conclusion : Definitive antibiotic use for sepsis patients at Tabanan Hospital was mostly appropriate, and the empiric antibiotics treatment was associated with mortality, while the causal bacteria and resistance status were not significantly associated with mortality. Findings highlight the importance of transitioning from empiric to targeted therapy to potentially reduce mortality in sepsis management.

Keywords: antimicrobial stewardship, clinical outcomes, definitive antibiotics, empiric antibiotics, sepsis.

INTRODUCTION

Sepsis, as defined by the World Health Organization, represents a critical, life-threatening medical condition characterized by a dysregulated and excessive immune response to infection, culminating in potentially devastating organ dysfunction.[1] This aberrant immune response precipitates a cascade of tissue and organ damage, potentially culminating in shock, multisystem organ failure, and mortality if not promptly identified and treated. The global burden of sepsis is substantial, with an annual incidence of 731 cases per 100,000 individuals. Notably, sepsis-associated mortality rates surpass those of several other significant health conditions, including heart failure, breast cancer, colorectal cancer, and AIDS.[2] This underscores the critical nature of sepsis as a public health concern and emphasizes the urgency for improved diagnostic and therapeutic strategies.

This study aims to assess the congruence between definitive antibiotic selection and causative pathogens in sepsis cases, while also examining the relationships between bacterial species, antibiotic classes, resistance patterns, and clinical outcomes at Tabanan Hospital. The findings are intended to provide valuable insights to clinicians and hospital administrators, informing evidence-based practices for optimal definitive antibiotic utilization in sepsis management.

Healthcare institutions in developing nations frequently face significant infrastructural and resource constraints, impeding their capacity to deliver optimal care to their populations. Existing facilities often operate under suboptimal conditions, characterized by inadequate sanitation, poor ventilation, unreliable electrical supply, and insufficient lighting.[3] These deficiencies not only compromise patient safety but also create an environment conducive to the proliferation of healthcare-associated infections. Such systemic challenges can significantly impede the implementation of appropriate treatment protocols and exacerbate the risk of adverse outcomes. In Indonesia, the burden of sepsis remains particularly pronounced, with incidence rate of 30.29% and a mortality rate from 11.56% to 49%.[4] These statistics highlight the critical importance of implementing focused interventions and enhancing sepsis management protocols within Indonesia's healthcare infrastructure. The data emphasizes the pressing need for strategic improvements to address the significant burden of sepsis in the country.

According to the Surviving Sepsis Campaign (SSC) guidelines,[5] which align with the protocol at Tabanan Hospital, the primary treatment for sepsis is administering antibiotics within the first hour of diagnosis. Tabanan Hospital is a teaching hospital with 160 beds located in the district of Tabanan in Bali, Indonesia, which provides healthcare services to patients, especially treatment for sepsis. Antibiotics are one of the most important therapies in managing sepsis cases and are an effective intervention to reduce mortality.[5] Sepsis patients should be given antibiotics immediately within the first 3 hours after the diagnosis of sepsis. The effectiveness of antibiotics for sepsis patients is that it can prevent the severity of sepsis from turning into septic shock.[6] There are still many incidences of antibiotic resistance caused by the use of antibiotics in cases of sepsis. A study by Legese in 2022 reveals that there was a high incidence of multidrug resistance in Enterobacteriaceae bacteria (83.3%) and K*lebsiella pneumonia* (>80%) in several hospitals in Ethiopia on October 2019 – September 2020.[7] A study by Pradipta in 2013 found that of 25 types of antibiotics used in sepsis patients at hospitals in Bandung on May – August 2012, there was ≥ 50% resistance to 14 types of antibiotics.[8] In Bali, Multi Drug Resistant (MDR) was also found in 33 pediatric sepsis patients (52.4%) at the PICU (Pediatric Intensive Care Unit) at Sanglah General Hospital from January 2015 to April 2017.[9] Consequently, the appropriate use of antibiotics plays a very important role in preventing the occurrence of antibiotic resistance. Managing suspected sepsis requires personalized care. Immediate empiric therapy is crucial for patients with a high likelihood of infection, severe illness, or shock. The choice of empiric antimicrobials should consider infection sites, common pathogens, patient-specific resistance risk factors, and local antibiogram data.[10] The first antibiotic therapy given based on the management of SSC while waiting for culture results is empirical or broad-spectrum antibiotics.[5] Definitive antibiotics were administered once the culture results were available. The bacteria causing sepsis are also identified through a culture sampling procedure.[11]

The judicious application of definitive antibiotic therapy is important to reduce mortality rates and facilitate treatment de-escalation based on culture results and ongoing clinical laboratory data. This de-escalation process, which involves narrowing the antibiotic spectrum in response to definitive microbiological findings, is crucial in mitigating the emergence of antimicrobial resistance.[10] The selection of definitive antibiotics is contingent upon the identified pathogen and its specific resistance profile in each patient. However, discrepancies between antibiotic administration and sensitivity test results are not uncommon, potentially leading to suboptimal treatment outcomes. Inappropriate definitive antibiotic use can exacerbate antimicrobial resistance, consequently prolonging hospitalization and escalating healthcare costs.[12] Moreover, resistant infections in sepsis patients can double mortality rates, underscoring the critical nature of this issue. Therefore, a comprehensive evaluation of definitive antibiotic appropriateness in sepsis management is imperative[13] to reduce the

resistance to sepsis which can double the death rate.[14]

METHODS

Study Design and Setting

An observational research study was designed with a cross sectional performed at Tabanan Hospital from April to June 2023. The population used in this study included medical records of sepsis patients at Tabanan General Hospital who received empirical and definitive antibiotic therapy from January 2020 to December 2022. This study included sepsis patients at Tabanan General Hospital who met the inclusion and exclusion criteria. Total sampling was applied, with purposive sampling method. The research received approval from the ethical commission of Tabanan Hospital with reference number 445/220/TIMKORDIK/RSUD/2023.

Inclusion and Exclusion Criteria

The inclusion criteria of this study are all sepsis patients' medication records at Tabanan Hospitals documented thoroughly the patients' demography, diagnosed with sepsis who received empirical and definitive antibiotics, had microbiological culture sensitivity tests, and completed outcome therapy successively between January 2020 and 2022 were included as criteria. Incomplete and illiterate patient medication records were excluded from the study. All the comorbidities were documented as supporting data.

Data Analysis

The antibiotic's appropriateness was evaluated descriptively based on the culture sensitivity microbiological test result and the antibiotic use. The recommended antibiotic use is defined as a definitive antibiotic and another as an empirical antibiotic. The correlation of bacteria species, sensitivity or resistance status on the test result, and antibiotics use to the clinical outcome of the sepsis patients were analysed. Bivariate analysis was performed to determine the relationship between the variables related to mortality using the Chi-Square test. Survival analysis was conducted using the Kaplan-Meier test. The software used for the statistical test was SPSS version 29. A 95% confidence interval (CI) and p-values less than < 0.05 were considered significant. The results were presented in tables, figures, and narratives.

RESULTS

The research conducted at Tabanan Hospital from January 2020 to December 2022 involved a sample of 112 sepsis patients. After the inclusion criteria were applied, a total of 84 patients were identified, of which 71 patients received empirical antibiotic therapy and 13 patients received definitive antibiotic therapy.

The demographic and clinical characteristics of these sepsis patients are detailed in Table 1. The majority of patients were male, accounting for 48 cases (57.14%), compared to 36 female patients (42.86%). The age distribution was as follows: 9 patients (10.71%) were under 45 years old, 24 patients (28.57%) were between 45 and 60 years old, 40 patients (47.62%) were between 61 and 80 years old, and 11 patients (13.10%) were over 80 years old. Regarding comorbidities, anemia was the most prevalent, affecting 22 patients (22.62%).

Out of the 84 sepsis patients, 13 underwent culture tests. As shown in Table 2, infections caused by Gram-negative bacteria were more common, occurring in 9 patients (63.23%), compared to Gram-positive bacterial infections, which were observed in 4 patients (30.77%). This finding aligns with the general trend where the predominant cause of sepsis is Gram-negative bacteria which were about 62.2% of patients exhibiting positive blood cultures, while Gram-positive bacteria are responsible for infection in 46.8% of cases.[15]

Furthermore, in 13 patients who received definitive antibiotics, the most frequently prescribed antibiotic type was meropenem, which is a carbapenem class (Table 3). Meropenem is a broad spectrum carbapenem class of antibiotics because it works effectively on Gram-negative and Gram-positive bacteria.

Moreover, in this study, antibiotic sensitivity tests were performed on the group of patients receiving definitive antibiotics. Antibiotic sensitivity to bacteria was categorized into 3 parts, namely susceptible (S), intermediate (I), and resistant (R). Susceptible means that antibiotics can inhibit bacteria optimally, so they are effective for treatment. Intermediate means that antibiotics are less than optimal in inhibiting bacterial growth, so they are less effective for treatment, and resistance means that antibiotics are unable to inhibit bacterial growth and cannot be used for treatment. In addition, we also categorized antibiotic resistance into MDR and non-MDR; MDR if resistance occurs to three or more classes of antibiotics while if resistance occurs to less than three types of antibiotics it is classified as non-MDR. The results, based on antibiotic sensitivity to bacteria and MDR and non-MDR, all Gram-negative bacteria found as bacteria causing sepsis were sensitive to meropenem antibiotics (100%) with 6 patients categorized as MDR (Table 4), while Gram-positive bacteria were most sensitive to linezolid and vancomycin (Table 5) with only 1 patient categorized as MDR.

We also conducted an assessment of the appropriateness of the use of definitive antibiotics (Figure 1), which was seen by comparing the definitive antibiotics given to patients with the sensitivity of the

TABLE 1
Characteristics of sepsis patients using definitive antibiotics

Patients Characteristics	Number of Patients (N=84)	Percentage (%)
Gender		
Male	48	57.14
Female	36	42.86
Age		
< 45 years	9	10.71
45 – 60 years	24	28.57
61 – 80 years	40	47.62
> 80	11	13.10
Type of comorbidities*		
Anemia	19	22.62
Chronic Kidney Failure	18	21.43
Diabetes Mellitus	17	20.24
Hyperkalemia	12	14.28
Hypovolemia	9	10.71
Hyponatremia	7	8.33
Pneumonia	5	5.95
Encephalopathy	5	5.95
Heart Failure	5	5.95
Hypertension	3	3.57

*1 patient can suffer from > 1 co-morbidity

bacteria that cause sepsis, where the appropriate administration of definitive antibiotics is the administration of antibiotics that are included in the type of antibiotics that are sensitive based on the results of the sensitivity test, while the administration of definitive antibiotics is inappropriate if there is at least one antibiotic that is not included in the type of antibiotics that are sensitive based on the results of the sensitivity test. As a result, based on Figure 1, it can be seen that there were 8 patients whose used definitive antibiotics matched with sensitivity of the bacteria based on culture results (62%), obtaining that antibiotics were susceptible to bacteria. While there were 5 patients whose used definitive antibiotics did not match with the culture results (38%).

According to the Chi Square analysis, as shown in Table 6, it can be seen that the type of bacterial infection is not related to the impact of mortality (OR=0.417; 95% CI 0.030–5.708; p=1.000), and also does not show any relationship between resistance status and mortality risk in sepsis patients (OR=1.500; 95% CI 0.156–14.420; p=1.000). However, the type of antibiotic treatment is related to the clinical outcome of sepsis patients, namely alive or dead (OR=4.379; 95% CI 1.274–15.052; p=0.022).

Finally, we analyzed survival time using the Kaplan-Meier test, with the results showing that the median survival time due to sepsis in the empirical antibiotic group was 3.77 days (95% CI 2.820–5.180) and the definitive antibiotic group was 13.77 days (95% CI 9.182–14.818) (Figure 2).

DISCUSSION

Sepsis is a critical global healthcare that demands careful antimicrobial stewardship to prevent resistance. This study found a higher prevalence in males, particularly among those aged 61–80 years, highlighting a notable gender disparity.[15] This disproportionate distribution can be attributed to the differential immunomodulatory effects of sex hormones. Estrogen, predominant in females, enhances immune function, conferring a more

TABLE 2
Types of bacteria infecting sepsis patients receiving definitive antibiotic

Type of Bacteria	Specimen Used	Number of patients (N=13)	Percentage (%)
Gram-Negative			
Escherichia coli	Pus	2	15.39
Proteus mirabilis	Pus	2	15.39
Pseudomonas stutzeri	Pus	1	7.69
Enterobacter cloaceae complex	Blood	1	7.69
Providencia rettgeri	Pus	1	7.69
Klebsiella pneumoniae	Pus	1	7.69
Pseudomonas aeruginosa	Urine	1	7.69
Sub-Total		9	63.23
Gram-Positive			
Enterococcus faecalis	Blood	1	7.69
Enterococcus faecalis	Urine	1	7.69
Kocuria kristinae	Pus	1	7.69
Staphylococcus epidermidis	Pus	1	7.69
Sub-Total		4	30.77
Total		13	100

TABLE 3
Definitive antibiotics received by sepsis patients

Class of Antibiotics	Number of patients (N = 13)	Type of Antibiotics	Number of patients (N = 13)
Carbapenem	4	Meropenem	4
Glycopeptide	2	Vancomycin	2
Quinolones	2	Levofloxacin	1
		Moxifloxacin	1
Cephalosporins & Cephalosporins	1	Ceftriaxone + Cefotaxime	1
Cephalosporins & Nitroimidazoles	1	Ceftriaxone + Metronidazole	1
Cephalosporins & Aminoglycosides	1	Ceftriaxone + Amikacin	1
Quinolones & Nitroimidazoles	1	Levofloxacin + Metronidazole	1
Glycopeptide a & Aminoglycosides	1	Vancomycin + Amikacin	1
Total	13		13

robust immune response.[16] Conversely, testosterone, the primary male hormone, exhibits immunosuppressive properties, potentially predisposing men to a higher susceptibility to infections and sepsis.[17] This study also found that the most common comorbidity of sepsis patients was anemia, occuring due to inflammation, iatrogenic blood loss, and depression of serum iron levels.[17]

TABLE 4

Antibiotic sensitivity test to gram-negative bacteria based on culture results from sepsis patients given definitive antibiotics at the Tabanan Hospital in the period January 2020 – December 2022

Cultured Bacteria	Types of Antibiotics Tested																																		Type of Antibiotics used	Suitability	Multi Drug Resistant (MDR)
	CX			CP			CD			EM			MM			AM			AC			GC			CF			TG			NF			AP			TS			MD			LF			PT					
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R			
Eschericia coli	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	–	–	1	–	–	1	–	–	–	–	–	–	–	–	Ceftriaxone & Metronidazole	Not Appropriate	Non MDR
Eschericia coli	–	–	1	1	–	–	1	–	–	1	–	–	1	–	–	–	–	1	1	–	–	1	–	–	–	–	1	1	–	–	1	–	–	–	–	1	–	–	1	–	–	1	–	–	1	–	–	Meropenem	Appropriate	MDR
Pseudomonas stutzeri	1	–	–	1	–	–	1	–	–	–	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	–	–	–	1	–	–	–	–	1	–	–	1	1	–	–	Ceftriaxone & Cefotaxime	Not Appropriate	Non MDR
Enterobacter cloaceae complex	–	–	1	–	–	1	–	–	1	1	–	–	1	–	–	–	1	1	1	–	–	–	–	1	–	–	1	1	–	–	–	–	–	1	–	–	1	–	–	–	–	–	–	–	–	Vancomycin	Not Appropriate	MDR
Proteus mirabilis	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	–	–	1	–	–	1	1	–	–	–	–	–	–	–	–	–	1	–	–	Levofloxacin & Metronidazole	Not Appropriate	MDR
Proteus mirabilis	1	–	–	1	–	–	1	–	–	–	–	–	1	–	–	–	–	1	1	–	–	–	–	1	–	–	1	–	–	–	–	–	1	1	–	–	–	–	–	–	–	–	–	–	–	–	Amikacin & Ceftriaxone	Appropriate	MDR
Providencia rettgeri	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	1	–	–	Meropenem	Appropriate	MDR
Klebsiella pneumoniae	–	–	1	1	–	–	–	–	1	1	–	–	1	–	–	–	–	1	1	–	1	1	–	–	–	–	1	1	–	–	–	–	–	–	–	1	–	–	1	–	–	–	–	–	1	–	–	Meropenem	Appropriate	MDR
Pseudomonas aeruginosa	–	–	–	1	–	–	–	–	1	–	–	–	1	–	–	1	–	–	–	–	–	1	–	–	–	–	1	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–	–	Meropenem	Appropriate	Non MDR

Abbreviations : S = *Susceptible*, I = *Intermediate*, R= *Resistant*, MDR = *MultiDrug-Resistant*;
CX = Ceftriaxone; CP = Cefepime; CD = Ceftazidime; EM = *Ertapenem*; EM = Meropenem; AM = Aztreonam; AC = Amikacin; GC = Gentamycin; CF = Ciprofloxacin; TG = Tigecycline;
NF = Nitrofurantoin; AP = Ampicillin; TS = Trimethoprim Sulfamethoxazole; MD = Metronidazole; LF = Levofloxacin; PT = Piperacillin Tazobactam

TABLE 5

Antibiotic sensitivity test to gram-positive bacteria based on culture results from sepsis patients given definitive antibiotics at the Tabanan Hospital in the period January 2020 – December 2022

Cultured Bacteria	Types of Antibiotics Tested																																		Type of Antibiotics used	Suitability	Multi Drug Resistant (MDR)
	TC			CF			MC			GC			CM			MD			MM			LF			LZ			AP			MF			AZ			SC			VM			NF			EC					
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R			
Kocuria kristinae	–	–	1	–	–	1	–	–	1	–	–	–	–	–	1	–	–	1	1	–	–	–	–	–	1	–	–	1	–	–	1	–	–	1	–	–	–	–	–	–	1	–	–	–	–	–	1	–	Moxifloxacin	Appropriate	MDR
Enterococcus faecalis	–	–	1	–	–	1	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–	–	1	–	–	–	–	–	–	–	–	1	–	–	1	–	–	1	–	–	1	–	Amikacin & Vancomycin	Not appropriate	Non MDR
Enterococcus faecalis	1	–	–	1	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	1	–	–	1	–	–	–	–	1	–	–	–	–	1	–	–	1	–	–	1	–	–	1	–	–	Levofloxacin	Appropriate	Non MDR
Staphylococcus epidermidis	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–	–	–	Vancomycin	Appropriate	Non MDR

Abbreviations : S = *Susceptible*, I = *Intermediate*, R= *Resistant*, MDR = *MultiDrug-Resistant*;
TC = Tetracycline, CF = Ciprofloxacin, MC = Methicillin, GC = Gentamycin, CM = Cefixime, MD = Metronidazole, MM = Meropenem, LF = Levofloxacin, LZ = Linezolid, AP = Ampicillin,
MF = Moxifloxacin, AZ = Azithromycin, SC = Streptomycin, VM = Vancomycin, NF = Nitrofurantoin, EC = Erythromycin

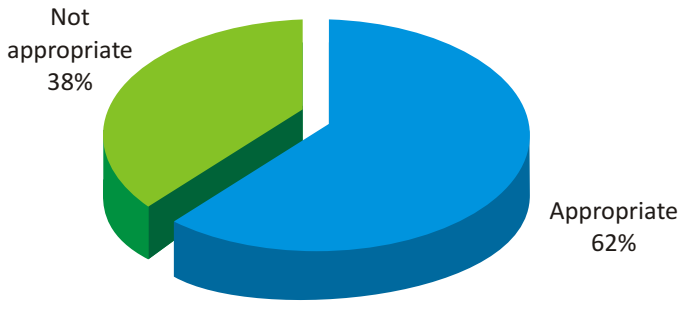

Figure 1. Appropriateness of the use of definitive antibiotics for the culture results of sepsis patients

TABLE 6
The association between bacteria types, resistance status, and antibiotic treatment type with clinical outcome of the sepsis patients

Variable	Clinical Outcome		OR	CI 95%	*p-value*
	Died	Live			
Type of Bacteria			0.417	0.030 – 5.708	1.000
Gram-positive	1 (25%)	3 (75%)			
Gram-negative	4 (44.4%)	5 (55.6%)			
Resistance Status			1.500	0.156 – 14.420	1.000
MDR	3 (42.85%)	4 (57.15%)			
Non-MDR	2 (33.33%)	4 (66.67%)			
Type of Antibiotic Treatment			4.379	1.274 – 15.052	0.022
Empiric	52 (73.24%)	19 (26.76%)			
Definitive	5 (38.46%)	8 (61.54%)			

Abbreviations: CI= Confidence Interval; OR= Odds Ratio; MDR= Multi Drug Resistant

Gram-negative bacteria are the leading cause of sepsis, responsible for 60–70% of cases, while Gram-positive bacteria account for 20–40%.[18] This aligns with research conducted in Prof. Dr. Margono Soekarjo Hospital, Purwokerto, Indonesia in 2018 identified Gram-negative bacteria in 13 patients and Gram-positive bacteria in 9 patients.[19] However, another study in Semarang, Indonesia, found that Gram-positive bacteria were the predominant cause in 83.32% of sepsis cases.[4] The most common Gram-negative bacteria at Tabanan General Hospital were *Escherichia coli* and Proteus mirabilis (15.39% each), while *Enterococcus faecalis* was the most common Gram-positive bacterium (15.39%). Similarly, a study in a Central Java hospital found *Escherichia coli* to be a prevalent cause of sepsis, and at Dr. Soetomo Hospital, Surabaya identified it as a common Gram-negative pathogen, with *Staphylococcus hominis* being the most frequent Gram-positive pathogen.[13,14]

At Tabanan Hospital, wound bed pus was the most common specimen for bacterial sensitivity testing in sepsis patients with skin infections, whereas sputum was more frequently used at Dr. Moewardi Hospital, Solo, Indonesia.[20] Definitive antibiotics are administered after identifying the causal bacteria through culture procedures, to specifically eradicate or inhibit the growth of the infectious bacteria.[11] Meropenem is a widely used definitive antibiotic for severe infections due to its broad-spectrum efficacy and minimal adverse effects, similar findings in Dr. Moewardi Hospital have been noted on frequent use of Meropenem in sepsis patients.[20,21] Meropenem, a broad-spectrum carbapenem, is effective against both Gram-negative and Gram-positive bacteria and is a preferred choice for treating severe sepsis and

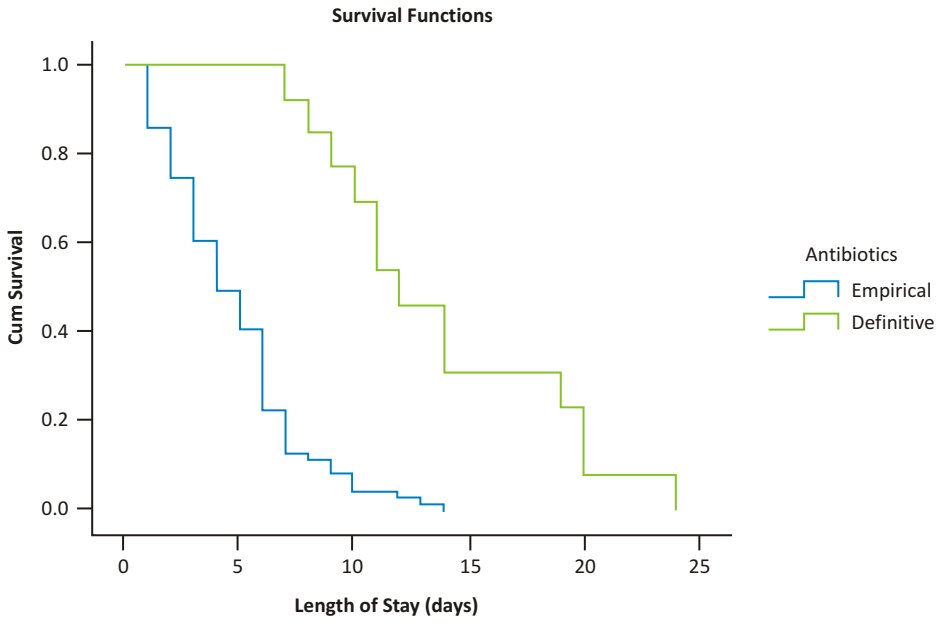

Figure 2. Kaplan Meier curves of mortality patterns in empirical and definitive antibiotic treatment of sepsis patients at Tabanan hospital in the period January 2020 - December 2022

septic shock due to its broad-spectrum efficacy and low toxicity.[21]

For antibiotic selection after culture, sensitive antibiotics are chosen based on susceptibility criteria, while bacteria classified as intermediate or resistant are considered non-sensitive. A bacterium is said to still be sensitive to antibiotics if it is included in the susceptibility criteria, and is said to be resistant if it is included in the intermediate and resistant criteria.[22] Based on the bacterial patterns found in this study, it is also known that all Gram-negative bacteria found as sepsis-causing bacteria are sensitive to meropenem antibiotics (100%). This is different when compared to research by Ramita *et al*. (2018) [23] in several hospitals, the sensitivity of sepsis-causing bacteria to meropenem was only 16.67%. Research by Ekayana *et al*. (2019)[11] showed that the highest sensitivity of sepsis-causing bacteria at Haji Adam Malik General Hospital, Medan, was to amikacin and meropenem antibiotics. Meanwhile, the highest resistance of Gram-negative bacteria occurred to ciprofloxacin. Ciprofloxacin is a type of antibiotic that quickly loses its effectiveness due to resistance problems. In addition, long-term use of ciprofloxacin antibiotics results in the growth of more resistant bacteria.[22] The highest resistance occurs in ampicillin (100%).

There was inappropriate use of antibiotics in this study. This could occur because there were patients who received combination antibiotics, where one antibiotic was in accordance with the culture results, while the other antibiotic was not in accordance with the culture results. This inaccuracy could also occur due to allergies in patients or potential drug interactions with prescribed drugs. Based on research by Sijbom *et al*. (2022),[24] allergic reactions occurred in the administration of antibiotics in the penicillin group (45%), nitrofuran (10.3%), tetracycline (7.7%), macrolide (6.7%), fluoroquinolone (5.4%), and other groups (24.9%). However, due to the limited data available in this study, this could not be traced.

The type of bacteria could be related to the clinical outcomes of sepsis patients. A cohort study by Morgan *et al*. (2016)[25] found that 90-day mortality of first-hit sepsis patients who developed a gram-negative infection was 43.6% following elective surgery and 27.9% following trauma (p<0.01), which compared with 25.6% and 20.6%, respectively, in gram-positive (p<0.05). However, there was an inverse relationship in second-hit infection. Gram-negative had a 90-day mortality of 40.4% (p<0.01), compared with 43.6% (p<0.05) in gram-positive infections. Then, Guo *et al*. (2023)26 showed sepsis patients with gram-positive infection had a higher rate of 28-day mortality (17.7% vs 15.4%; p<0.001) and in-hospital mortality (18.0% vs 15.8%; p<0.001) than gram-negative infection group. Those previous studies border with our study which indicates type of bacterial infection was not associated with mortality impact. Nowadays, the harmfulness of sepsis caused by gram-negative bacteria and gram-positive bacteria is still controversial along with pathogen-associated molecular evolution and geographic differences. So, it impacts on clinical heterogeneity of the affected individuals and the host's immune system has a crucial role in determining sepsis

prognostic.[27,28]

Increasing use of antibiotics for bacterial infections has led to the global spread of MDR. Some risk factors for the development of MDR are represented by previous exposure to broad-spectrum antibiotics, initial inappropriate antibiotic use, and colonization of resistant bacteria.[29] MDR status often causes higher morbidity and mortality. An observational study found there was significantly higher in-hospital mortality among sepsis patients with MDR than among non-MDR bacteria (40.2% vs 23.1%, p=0.001).[30] In contrast, this study showed no association between resistance status with risk of mortality in sepsis patients. Further research is needed to analyze other factors, such as inflammatory response, comorbidities, and multiple organ dysfunction, that may influence prognosis.

The bacteria type with the most MDR in this study was *Enterobacter cloacae complex*. A study by Legese *et al*. (2022),[7] showed Enterobacter cloacae complex that infects sepsis patients had the highest resistance to ampicillin, whereas most others were resistant to amikacin, ampicillin-sulbactam, aztreonam, ceftazidime, cefotaxime, ceftriaxone. It is similar to this study where the bacteria had resistance against aztreonam, ampicillin, ceftriaxone, cefepime, ceftazidime, ciprofloxacin, trimethoprim, sulfamethoxazole, and gentamicin.

Furthermore, early administration of antibiotics treatment was linked with the clinical outcomes of patients. Empiric antibiotic treatment has been shown effective for the initial treatment of sepsis.[31] Besides that, sepsis patient's treatment with a narrower antibiotic spectrum according to culture, known as definitive antibiotics, also reduces the mortality rate. A previous study showed hospitality mortality rate was 24.6% in sepsis patients in whom therapy was de-escalated and 32% in the no change of adequate empirical antibiotic group (p=0.008). De-escalation therapy also was a protective factor regarding 90-day mortality.[32] De-escalation refers to the reduction of one or more components of empirical therapy or through the switching to a narrower spectrum. In this study, type of antibiotic treatment was associated with the clinical outcomes of sepsis patients. Sepsis patients with empiric antibiotics or who did not perform a culture test have a higher mortality than the definitive antibiotic group. It is important to be aware that optimal management includes empiric therapy should be together with reassessment and subsequent definitive therapy based on cultures and antibacterial susceptibility tests.

Antimicrobial treatment impacts mortality rates, making careful prescribing essential. Strategies such as accurate diagnosis, distinguishing empiric from definitive therapy, de-escalating broad spectrum antibiotics, and identifying MDR bacteria can improve clinical outcomes and prevent worsening sepsis prognosis.

CONCLUSION

The use of definitive antibiotics for sepsis patients at Tabanan Hospital was appropriate, with the causative bacteria by 62% (8 patients) and 38% (5 patients), which was inappropriate. Sepsis patients with empiric antibiotics treatment were associated with mortality, meanwhile, the type of causal bacteria and resistance status were not significantly associated with mortality. Future sepsis research should focus on long-term antibiotic resistance trends, the impact of patient factors like comorbidities and gender on outcomes, and the effectiveness of rapid diagnostics and early treatment protocols. Collaborative multicenter studies are also crucial to gain broader insights into bacterial etiology and resistance patterns across diverse populations and healthcare settings.

Acknowledgment

Thank you to the Tabanan Hospital Medical Record Installation and all parties who have assisted in this research.

Conflict of Interest

All authors declare that they have no conflict of interest.

Abbreviations

AIDS (acquired immunodeficiency syndrome); CI (Confidence Interval); MDR (Multi Drug Resistant); OR (Odds Ratio); SSC (Surviving Sepsis Campaign).

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2025; vol 12 (1) : 44–50

OPEN ACCESS

Original Article

Comparative Effectiveness of Betahistine vs Dimenhydrinate in Reducing Dizziness Handicap Scores in Patients with Peripheral Vestibular Disorders

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v12i1.1213

Accepted: October 07th, 2024
Approved: March 18th, 2025

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Abstract

Background : Peripheral vestibular disorder is a disorder of the peripheral vestibular system. Its symptoms affect the quality of life from moderate to severe. An objective assessment is quite difficult therefore a questionnaire method has been developed such as Dizziness Handicap Inventory (DHI). Aim of the treatment is to achieved optimal quality of life by using symptomatic treatment like dimenhydrinate and betahistine. This study was aimed to prove the effectiveness of betahistine and dimenhydrinate and to compare the effectiveness in reducing DHI score

Methods : This was an intervention study with pretest and posttest control group designs, randomized control trial, double blind study at ENT-HNS Clinic, CDC Dr. Kariadi Hospital and Dr.Soetrasno Hospital Rembang. Data was collected from September 2015 to June 2016. Subject filled out the DHI pre-test questionnaire, stratified randomly divided into 2 group. One group received betahistine 12 mg / 8 hours and the other received dimenhydrinate 50 mg / 8 hours in a double-blind selection process. After 2 weeks of drug administration, subject filled out a post test questionnaire of DHI.

Results : Subjects were 44 people; dimenhydrinate, 20 people (45.5%) and betahistine, 24 people (54.4%). Result showed that DHI score of post test is lower than pre test in both group with significance value of $p < 0.05$. There is no significant difference in DHI score of dimenhydrinate compared with betahistine group ($p = 0.137$).

Conclusion : Betahistine and dimenhydrinate are shown to be effective in lowering the DHI score.and betahistine not proven to be more effective.

Keywords : Peripheral vestibular disorders, Dimenhydrinate, Betahistine, Dizziness Handicap Inventory

INTRODUCTION

Peripheral Vestibular Disorders (PVD) are disorders of the peripheral vestibular system caused by changes in the sensitivity of vestibular receptors to linear and angular acceleration, asymmetric abnormalities in central vestibular activity or changes in reaching *Lobby Eye System*.[1] PVD appears more suddenly after a change in position or movement of the head, with a feeling of intense spinning or what is often called vertigo, accompanied by nausea, vomiting, sweating, can be accompanied by ringing in the ears, lack of hearing and is not accompanied by focal neurological symptoms.[2,3]

The prevalence of PVD is 5% in the adult population in one year.[4] The incidence increases every year, occurs more often in women (2.7: 1) and the incidence increases with increasing age.[5] Data from outpatient visits at Dr. Kariadi General Hospital, Semarang in 2013, recorded 255 sufferers with complaints of vertigo, 134 sufferers underwent vestibulometry examinations at *Clinic Diagnostic Centre* – Ear Nose Throat (CDC – ENT) and 63 sufferers with a diagnosis Benigna Paroxysmal Positional Vertigo (BPPV).

PVD symptoms affect the sufferer's quality of life from moderate to severe (80%). These disorders include the physical, functional and emotional nature of the sufferer.[6] Objective assessment of the severity of PVD symptoms is quite difficult, so a questionnaire method was developed to assess the quality of these complaints. One method of assessment is *Dizziness Handycap Inventory* (DHI).[7]

The DHI is a questionnaire that is useful for assessing physical abilities related to complaints of dizziness and disturbances in emotional and functional aspects. DHI has been adapted into several languages, including Swedish, Dutch, Japanese and Chinese.[8,9]

DHI contains 25 types of assessment questions with a score of 0–100, which includes 7 physical assessments, 9 functional assessments and 9 emotional assessments. DHI has been validated in several studies and proven to be related to the severity of vertigo symptoms and can measure changes or improvements in symptoms.[9]

PVD therapy seeks to achieve optimal quality of life according to the course of the disease, namely by reducing or eliminating the sensation of vertigo with minimal side effects. Therapeutic options include causative, symptomatic, rehabilitative therapy, avoiding trigger factors and lifestyle changes.[3] Symptomatic therapy is usually with vestibular suppressant drugs *(vestibulo – suppress)* given in the acute phase with the aim of alleviating vegetative symptoms without disrupting the compensation process.[10]

The class of vestibular suppressant drugs that is widely known and included in the 2013 National Formulary is class anticholinergics, antihistamines and benzodiazepines. One type of drug is dimenhydrinate, which is a first generation antihistamine with a usual dose of 50 mg per administration with a half-life of 4–6 hours, because of its strong sedation effect given 3 times a day.[10,11] Dimenhydrinate quickly causes sedation and sleep modulating effects, that needs to be taking care during their administration.[12] The highest retail price of dimenhydrinate is IDR. 30/tablets.[13] The Association of Indonesian Neurologists recommends betahistine as a choice of vestibular suppressant medication because the way it works is different and can speed up compensation.[3] Betahistine is a histamine with a usual dose of 6–24 mg per administration, half-life of 3–4 hours, given 2–3 times per day.[11] The highest retail price for betahistine is IDR. 1250/tablet.[13]

Two similar research reported that the combination of cinnarizine and dimenhydrinate reduce vertigo symptoms more quickly than betahistine.[14,15] Another research reported something different, namely that there was no significant difference between administering a combination of cinnarizine and dimenhydrinate compared to betahistine to reduce the symptoms of vertigo in Meniere's syndrome.[16] The effectiveness of betahistine compared to dimenhydrinate using the DHI score has not been studied previously.

The aim of the research is to prove the effectiveness of betahistine and dimenhydrinate and to prove that betahistine is more effective than dimenhydrinate in reducing the DHI score in patients with peripheral vestibular disorders.

METHODS

Intervention research by design *pretest and posttest control group design*. Determination of groups by double-blind random method. The output was DHI score. The research was conducted at the ENT-HNS Clinic, CDC RSUP Dr. Kariadi, ENT Clinic at Dr. Soetrasno Rembang Regional General Hospital (RSUD) for the period, at September 2015 to June 2016. Research subjects were PVD sufferers, aged between 18–60 years, cooperative and willing to take part in the research. Exclusion criteria were PVD sufferers who were receiving vestibular suppressant drug therapy, had allergic reactions to the drugs dimenhydrinate and betahistine, were taking anticholinergic drugs, antidepressants, first generation antihistamines, had contraindications to administering betahistine and dimenhydrinate, and were suffering from DM and hypertension. PVD sufferers who met the inclusion criteria were asked to sign a consent form and then their age, gender, history taking, routine physical examination, standard ear examination and vestibulometry were recorded. Every PVD sufferer is given causative therapy, rehabilitative therapy and avoidance of trigger factors and lifestyle changes. Patients filled out the DHI questionnaire before

administering the drug (pre test). Patients who were included as research subjects were then randomized by means stratified randomization and each patient was given one type of medication (dimenhydrinate 50 mg or betahistine 12 mg), taken 3 times a day for 1 week (21 items). The packaging for the medicine given was the same. Medicines are given directly by medicine officers. At the end of the second week the patient would be interviewed again to fill out the DHI questionnaire after administering the drug (post test).

Descriptive analysis was carried out for patient demographic data. Test the normality of the data using the test Saphiro-Wilk. Comparative test analysis uses paired t-test (parametric test) or Wilcoxon test (non-parametric test) and unpaired t-test (parametric test) or Mann Whitney (non-parametric test). Statistical calculations employed the SPSS computer program. The research protocol has been approved by the Medical Research Ethics Committee of FK Undip/RSUP Dr. Kariadi Semarang.

RESULTS

This research was conducted from September 2015 to June 2016 at the ENT-HNS clinic, CDC RSUP Dr. Kariadi Semarang and the ENT Clinic of Dr. Soetrasno Rembang Regional Hospital with a total of 44 research subjects. There was no research subjects drop out and all data was complete. The characteristics of the research subjects, namely the distribution of gender, age, type of PVD, as well as the percentage between the dimenhydrinate group and the betahistine group before treatment can be seen in Table 1.

The distribution of research subjects based on treatment groups was quite evenly distributed. Table 1 shows that 20 subjects received dimenhydrinate (45.5%) and 24 subjects received betahistine (54.4%). The mean pre-test DHI score in the dimenhydrinate group was 44.9 ± 15.6 and in the betahistine group 41.2 ± 4.9. There was no significant difference between the pre-test DHI scores between the two treatment groups (p<0,05). Post-test DHI scores in both groups decreased. The average DHI score for the pre-test dimenhydrinate group was 44.9 while the post-test was 6.3.

For the betahistine group, the average pre-test DHI score was 41.2 and post-test 8.3. (p<0,05). Post-test DHI scores in both groups decreased. The average DHI score for the pre-test dimenhydrinate group was 44.9 while the post-test was 6.3. For the betahistine group, the average pre-test DHI score was 41.2 and post-test 8.3. The DHI score in each group includes the total DHI score and the three sub-scores shown in Table 2.

The betahistine group shows a lower post-test DHI score than the pre-test, with a mean difference of 32.9 ± 14.3 and p value < 0.05. The sub-score E, sub-score F and sub-score P post-test are also lower than the pre-test with a mean difference of 9.7 and 12.6 and 9.3 respectively. The significance values for the three sub-scores are p<0.05. The results of this analysis are shown in Table 3.

The post-test DHI score in the dimenhydrinate group was lower than the pre-test, with a mean difference of 38.6 ± 14.8 and a significance value p<0.05. The value of each sub-score, namely the emotional sub-score, functional sub-score and physical sub-score, is lower in the post-test compared to the pre-test with the mean difference respectively being 10.4 and 14.1 and 14.0 with the significance value being p<0.05. The results of this analysis are shown in Table 4.

The post-test total DHI score of the dimenhydrinate group compared with the betahistine group provides value p = 0.137 with a mean difference of -2.0 ± 1.3. The emotional sub-score, function sub-score and post-test physical sub-score of the dimenhydrinate group compared to the betahistine group provide value p of 0.160 and 0.197 and 0.601 respectively. The results of this analysis are shown in Table 5.

The side effect most complained about was drowsiness from 10 people (7 people; dimenhydrinate group, 3 people; betahistine group) while 34 people did not have any complaints. There was no significant difference in side effects that appeared in the two treatment groups (p<0,05). The results of the analysis regarding side effects in the two treatment groups are shown in Table 6.

DISCUSSION

The distribution of research subjects based on treatment groups was fairly evenly distributed, with 20 subjects receiving dimenhydrinate (45.5%) and 24 people receiving betahistine (54.4%). The characteristics of research subjects such as gender, age, type of PVD, duration of complaints, symptoms and DHI scores in the two groups before treatment were not significantly different, which means that the characters before treatment were balanced so that the two groups were considered homogeneous, which means the two groups could be compared.

The gender frequency in this study was 25% male and 75% female. This gender proportion is almost the same as one research that aim to compare the efficacy of flunarizine and betahistine dyhidrochloride using DHI. That research found a male gender proportion of 48% and female 52%.[17] Another research also found a gender proportion of 41.6% males and 58.4% females,[18] and also provides a male to female gender ratio of 1:1.96 and is dominant in all age groups.[19] Most epidemiological research data on vertigo shows that the prevalence of vertigo is greater in women.

Many epidemiological studies show that the prevalence of vertigo is closely related to age. This study found that the largest number of research subjects was in

TABLE 1
Characteristics of research subjects

Variable	Dimenhydrinate n = 20 (45.5%)	Betahistine n=24 (54.4%)	Total	Mark *p**
Gender				
Man	6 (13.6%)	5 (11.4%)	11 (25%)	0.484**
Woman	14 (31.8%)	19 (43.2%)	33 (75%)	
Age				
21 – 30 years old	2 (10.0%)	4 (16.7%)	6 (13.6%)	0.903***
31 – 40 years old	7 (35%)	4 (16.7%)	11 (25%)	
41 – 50 years old	5 (25%)	9 (37.5%)	14 (31.8%)	
51 – 60 years old	6 (30%)	7 (29.2%)	13 (29.6%)	
Types of PVD				
BPPV	6 (30.0%)	12 (50%)	18 (40.9%)	0.091***
Syndrome Meniere	10 (50%)	11 (45.8%)	21 (47.7%)	
Labyrinthitis	4 (20%)	1 (4.2%)	5 (11.4%)	
Neuronitis vestibular	0 (0%)	0 (0%)	0 (0%)	
Complaint Duration (in weeks)				
Median	4	12	8	0.051***
Min–max	1–104	1–104	1–104	
Accompanying symptoms				
Dizzy influenced	6 (30.0%)	12 (50%)	18 (40.9%)	0.091***
Position	10 (50%)	11 (45.8%)	21 (47.7%)	
Tinnitus otorhea	4 (20%)	1 (4.2%)	5 (11.4%)	
Score DHI pre test mean±SB				
DHI total	44.9 ± 15.6	41.2 ± 14.9	42.9 ± 15.1	0.433#
Subskor E	11.1 ± 6.5	11.2 ± 6.7	11.2 ± 6.5	0.961
Sub shoes F	16.6 ± 6.5	15.8 ± 8.0	16.2 ± 7.3	0.749
Subskor P	17.1 ± 6.7	12.9 ± 5.9	14.8 ± 6.6	0.055

*p< 0.05 (significant), ** Chi-Square test, *** Mann-Whitney U test, # unpaired t-test

TABLE 2
Description of DHI scores in both pre-test and post-test groups

Mean ± SB	Dimenhydrinate		Betahistine	
	Pre test	Post test	Pre test	Post test
Score DHI	44.9 ± 15.6	6.3 ± 4.1	41.2 ± 14.9	8.3 ± 4.5
Emotion Sub Score (E)	11.1 ± 6.5	0.7 ± 1.1	11.2 ± 6.7	1.5 ± 2.0
Functional Sub Score (F)	116.6 ± 6.5	2.5 ± 2.4	15.8 ± 8.0	3.2 ± 2.2
Physical Sub Score (P)	17.1 ± 6.7	3.1 ± 2.7	12.9 ± 5.9	3.5 ± 2.7

TABLE 3
Analysis of betahistine on decreasing DHI scores in PVD sufferers

Variable	Mean ± SB	Mark *p**	Mean Difference ± SB (I 95%)
DHI total pre test – DHI total post test	41.2 ±14.9 8.3 ± 4.5	0.000	32.9 ± 14.3 (26.9 – 38.9)
Sub skor E pre test – Sub skor E pasca test	11.2 ± 6.7 1.5 ± 2.0	0.000	9.7 ± 5.9 (7.2 – 12.2)
Pre test F sub score – Post test F sub score	15.8 ± 8.0 3.2 ± 2.2	0.000	12.6 ± 8.7 (8.9 – 16.3)
Pre test P sub score – Post test P sub score	12.9 ± 5.9 3.5 ± 2.7	0.000	9.3 ± 5.6 (6.9 – 11.7)

*$p < 0.05$ (significant), Wilcoxon test

TABLE 4
Analysis of dimenhydrinate on decreasing DHI scores in PVD sufferers

Variable	Mean ± SB	Mark *p**	Mean Difference ± SB (I 95%)
DHI total pre test – DHI total post test	44.9 ± 15.6 6.3 ± 4.1	0.000	38.6 ± 14.8 (31.7 – 45.5)
Sub skor E pre test – Sub skor E pasca test	11.1 ± 6.5 0.7 ± 1.1	0.000	10.4 ± 6.3 (7.4 – 13.4)
Pre test F sub score – Post test F sub score	16.6 ± 6.5 2.5 ± 2.4	0.000	14.1 ± 6.6 (11.0 – 17.1)
Pre test P sub score – Post test P sub score	17.1 ± 6.7 3.1 ± 2.7	0.000	14.0 ± 7.1 (10.6 – 17.3)

*$p < 0.05$ (significant) Wilcoxon test

the 41–50 year age group (31.8%), more than the 51–60 year age group. Different results compared research that conducted in Romania, which showed that the demographic picture of vertigo was mostly in the 50–59 year age group (66 out of 245 samples).[20] There was no significant difference in the age of the research subjects between the two treatment groups.

The most common peripheral vestibular disorder is Meniere's syndrome (47.7%). Similar to previous study which obtained the number of Meniere's syndrome, 56% of the population with peripheral vestibular vertigo.[18] In this study, there were 3 types of PVD, namely BPPV, Meniere's syndrome and labyrinthitis, but between these three types there were no significant differences. All subjects in this study complained of dizziness with the most common accompanying symptom being tinnitus (47.7%), in accordance with the most common type of peripheral vestibular disorder in this study.

The duration of the subject's complaints in this study gave a median value of 8 weeks, with a minimum complaint of 1 week and a maximum complaint of 104 weeks. In contrast to the research that compares the efficacy and safety of betahistine dihydrochloride as treatment of recurrent vertigo, the average duration of complaints in their research was 31.6 and 32.5 months.[18] In this study, there was no difference between the two treatment groups regarding the length of complaints from research subjects thus it was not analyzed further.

Betahistine is effective in reducing the DHI score of PVD sufferers, which is shown in the decrease in the total DHI score between the pre-test and post-test and is also shown in each sub-score, namely the emotional sub-score, functional sub-score and physical sub-score ($p<0.05$). These results indicate that betahistine can be used as sole therapy to reduce vertigo complaints.

The mean difference between pre-test and post-test total DHI was 32.9 ± 14.3. The mean value of this difference is higher than the mean DHI value previous study, namely 24.3 ± 20.1. The difference in mean values is because the researchers assessed DHI after 4 weeks of betahistine therapy with a betahistine dose of 16 mg, 3 times a day.[17] This difference shows that at 2 weeks

TABLE 5
Betahistine compared to dimenhydrinate on reducing the patient's DHI score Peripheral vestibular disorders

Variable	Mean ± SB	Mark *p**	Mean Difference ± SB (I 95%)
DHI total post-test kel. dimenhydrinate – DHI total post-test kel. betahistine	6.3 ± 4.1 8.3 ± 4.5	0.137	-2.0 ± 1.3 (-4.6 – 0.6)
Sub score E post test kel. dimenhydrinate – Sub score E post test kel. betahistine	0.7 ± 1.1 1.5 ± 2.0	0.160	-0.8 ± 0.5 (-1.8 – 0.2)
Sub score F post test kel.dimenhydrinate – Sub score F post test kel.betahistine	2.5 ± 2.4 3.2 ± 2.2	0.197	-0.750 ± 0.7 (-2.1 – 0.6)
P sub score post test kel.dimenhydrinate – Sub score P post test kel.betahistine	3.1 ± 2.7 3.5 ± 2.7	0.601	-0.4 ± 0.8 (-2.1 – 1.1)

*p <0.05 (significant) Mann Whitney test

TABLE 6
Side effects of administration of dimenhydrinate and betahistine

Variable	Dimenhydrinate n = 20 (45.5%)	Betahistine n=24 (54.4%)	Total	Mark *p**
Side effects				0.08
There isn't any complaint	13 (65%)	21 (87.5%)	34 (77.3%)	
Sleepy	7 (35%)	3 (12.5 %)	10 (22.7%)	
Hypersensitivity	0	0	0	
Eyes / lips dry	0	0	0	
Nausea, vomiting	0	0	0	

*p < 0.05 (significant) Mann Whitney test

betahistine therapy can reduce vertigo symptoms as indicated by a decrease in the DHI score, and increasing the time of administration of betahistine therapy will further reduce vertigo symptoms.

Dimenhydrinate is effective in reducing the DHI score of PVD sufferers, which is shown in the decrease in the total DHI score between the pre-test and post-test and is also shown in each sub-score, namely the emotional sub-score, functional sub-score and physical sub-score (p<0.05). The results of this study prove that dimenhydrinate can be used as a sole therapy for vertigo therapy.

The mean difference in total DHI pre test compared to post test was 38.6 ± 14.8. A study in Palermo designed research by administering combined dimenhydrinate therapy with cinnarizine, on the 18th day a DHI assessment was carried out and the DHI difference value was 8.5 and on the 65th day the difference was 19.3.[21] The decrease in the DHI score was smaller than in this study, this could be caused by the study using a combination of drugs while in this study monotherapy was chosen. However, this research can show a significant difference in the administration of dimenhydrinate. This proves that dimenhydrinate remains an effective therapeutic option for PVD.

The post-test total DHI score of the dimenhydrinate group compared with the betahistine group showed that there was no significant difference in the decrease in the DHI score of PVD sufferers between research subjects who received betahistine and those who received dimenhydrinate, both in total DHI scores and in sub-scores (p=0.137, 0.160, 0.197 and 0.601 respectively). This study shows that betahistine and dimenhydrinate are equally effective in reducing PVD symptoms as indicated by a decrease in DHI scores. The results of this study are similar to research that conducted in Cukurova University Medical Faculty, which reported that dimenhydrinate and betahistine were equally effective in reducing the symptoms of nystagmus in vertigo patients in different ways, so dimenhydrinate and betahistine

cannot be combined.[22] This study can recommend administering betahistine to replace dimenhydrinate in PVD therapy when PVD sufferers cannot tolerate the side effects of dimenhydrinate.

The most common side effect was drowsiness (22.7%) but it did not cause *drop out*, while 77.3% of research subjects did not complain of any side effects. In recurrent vertigo patient study, when administering betahistine for 8 weeks, 4 out of 29 subjects complained of side effects but did not cause drop out.[17] There was no statistical difference in the side effects between the two groups (p=0.08)

The limitation of this study is that it only assesses improvements in vertigo symptoms using the DHI score, which is subjective in nature. Researchers did not analyze other factors that influence vertigo complaints, such as the duration of the complaint, body metabolic factors and blood pressure.

CONCLUSION

The conclusions of this research are Betahistine and Dimenhydrinate have been proven to be effective in reducing the DHI score in patients with peripheral vestibular disorders. Betahistine was not proven to be more effective than dimenhydrinate in reducing the DHI score in patients with peripheral vestibular disorders.

SUGGESTION

The suggestion from this research is that further research is needed using samples from the same type of vestibular disorders, using different and objective measurement instruments and analyzing influencing factors.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2025; vol 12 (1) : 51–56

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Original Article

Radiologic Severity Index (RSI) Score in COVID-19 Patients After Administration of Remdesivir: A Study on High CRP and D-dimer Levels in a Group of Patients

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v12i1.1012

Accepted: August 07th, 2023
Approved: March 27th, 2025

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Abstract

Background : The COVID-19 pandemic has high mortality and morbidity. The lungs are the main target organ with a variety of symptoms ranging from asymptomatic to respiratory failure. Chest X-ray plays an important role in diagnosis, management, and prognosis. One of the chest X-ray assessment systems used is the Radiology Severity Index (RSI). Serum CRP and D-dimer levels can also be used to determine the severity of COVID-19. The aimsof this study was to examine changes in RSI scores after remdesivir therapy in COVID-19 patients with high CRP and D-dimer values.
Methods : A prospective cohort study of 64 COVID-19 patients at Dr. Kariadi Hospital Semarang from July 2020 to July 2021. Each consisted of 32 patients with high CRP (>5 mg/L) and D-dimer (>500 ng/mL) levels. Patients were given Remdesivir 200 mg therapy on day 1, followed by 100 mg/day until day 9. Chest X-rays were performed before and on day 7 after initial therapy. Patients with CHF, malignancy, autoimmune, pulmonary TB, interstitial lung disease and receiving azythromycin therapy were excluded from the study. Correlation analysis between variables was performed using the Spearman rho test and comparison test between groups. Significant results if p <0.05.
Results : There was a significant decrease in the RSI score of COVID-19 patients with high CRP and D-dimer levels after therapy, from 21.97±16.88 and 21.22±19.92 to 15.69±14.12 and 15.78±15.69, respectively (p<0.001). There was a weak significant relationship between high CRP levels and pre-therapy RSI scores (r=0.473, p=0.006) and high D-dimer levels and post-therapy RSI scores (r=0.362, p=0.041).
Conclusion : Remdesivir provides a significant correlation in the form of a decrease in RSI scores in COVID-19 patients with high CRP or D-dimer levels.

Keywords : COVID-19, CRP, D-Dimer, RSI Score, Remdesivir

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 due to the rapidity and scale of the disease's transmission. As of April 6, 2021, WHO has recorded 131,309,792 confirmed cases of COVID-19, with a death toll of 2,854,276.2 cases. The clinical manifestations of COVID-19 primarily attack the lungs, and have a wide impact on other organs of the body, such as the cardiovascular, gastrointestinal system, liver, kidneys, eyes, and skin. The most common clinical manifestations are cough, shortness of breath, fever, and sore throat. In severe cases, acute respiratory distress syndrome (ARDS), respiratory failure, and death are found. Imaging modalities play an important role in the diagnosis and management of COVID-19. Chest X-ray (CXR) is considered the first-line imaging modality for the initial triage of suspected COVID-19 cases. Although CXR is considered insensitive (CXR sensitivity is only 56%) in the early stages, CXR can be used to monitor clinical response and disease severity.[1–3]

A systematic review by Vidali *et al*., stated that most COVID-19 patients showed consolidation (68%) and ground glass opacity (GGO) (48%) with bilateral lung involvement and mostly distributed in the lower and peripheral lungs.[4] There are many CXR scoring systems to determine the severity of COVID-19, one of which is the Radiologic Severity Index (RSI). This scoring system interprets CXR changes more complexly with higher scores correlating with more severe clinical course and higher mortality.[5,6]

Characteristics of severe COVID-19 is the presence of a systemic inflammatory response, such as increased C-reactive protein (CRP) (58.3–60.7%) and increased D-dimer (46.6%). CRP levels can increase in patients with positive chest X-rays and those with severe disease, lung damage, and poor prognosis.[7] Its concentration is not affected by age, gender, or physical condition.[8] Kadek *et al*., found that confirmed COVID-19 patients with severe and critical degrees had the highest mean CRP values (133 mg/L, p <0.001) with an AUC value of 0.88 (p <0.001, 95% CI: 0.8290.948) to determine mortality.[9] In evaluating and diagnosing severe pulmonary infection, CRP levels >5 mg/L can be found.[8]

Abnormal coagulation function is one of the factors thought to be associated with the development of disease due to SARS-CoV-2 infection, which is characterized by increased D-dimer levels >500 ng/mL. D-dimer levels tend to be higher in patients with severe and critical cases than in patients with mild or moderate cases.[10] A study by Marco Francone *et al*., using CT scores to assess the level of lung involvement in patients with COVID-19 found that there was a statistically significant relationship between CT scores and D-dimer levels.[3]

One of the drugs under investigation for the treatment of COVID-19 is Remdesivir. Remdesivir is a direct-acting nucleotide-analog prodrug that inhibits ribonucleic acid (RNA) by incorporating triphosphate and interfering with the activity of viral RNA polymerase.[11] Kate *et al*., identified 55 patients treated with remdesivir for COVID-19 showed a significant decrease in CRP levels after administration of remdesivir in patients who remained non-intubated during the study period.[12]

To date, there has been little research on radiological images and biomarkers that can be used to predict the severity and death of COVID-19 patients using D-dimer and CRP levels. Reliance on CT scans places a large burden on the radiology department and this makes CXR the modality of choice. Therefore, researchers used CXR modality to describe changes in RSI scores after administration of remdesvir in COVID-19 patients with high CRP and D-dimer values.

METHODS

A prospective cohort study conducted at the Radiology Department of Dr. Kariadi Hospital Semarang, from July 2020 to July 2021 using data collected through electronic medical records. A total of 64 different patients were declared positive for COVID-19 based on clinical and laboratory (positive PCR) with age >18 years. There were 32 different patients with high CRP levels (> 5 mg/L) and 32 patients with high D-dimer levels (> 500 ng/mL). All patients received remdesivir therapy of 200 mg on the first day followed by 100 mg/day until day 9 based on disease severity and clinical response to therapy. CXR examination was performed before starting therapy and day 6 or 7 after initial Remdesivir therapy and the RSI score was calculated. Patients who received azythromycin therapy, and comorbid CHF, CKD, history of malignancy, autoimmune, pulmonary TB, or interstitial lung disease were excluded from the study.

The RSI scoring system was conducted by researchers by assessing 2 main variables from chest X-ray, namely lesion pattern and lesion area volumetrically where the right and left lung fields were each divided into 3 parts; upper zone (up to the carina), middle zone (below the carina to the upper limit of the inferior pulmonary vein), and lower zone (below the inferior pulmonary vein). The lesion pattern was divided into 3 value categories; 1 for normal lungs, 2 for GGO images, and 3 for consolidation images. The volumetric area was divided into 5 area categories; 0%, 1 for area 124%, 2 for area 2549%, 3 for area 5074%, 4 for area 75100%. RSI was obtained by multiplying the lesion pattern value and its volumetric area in each zone, with a total value between 172.[13]

Correlation analysis between variables was performed using the non-parameter Spearman rho test and the difference test between the high CRP group and

the high D-dimer group using the chi square test if the data distribution was normal or Wilcoxon if the data distribution was not normal. Data were declared significant if they obtained a p value <0.05.

RESULTS

In this study, the average age of patients was 52.95 ± 15.10 years with an age range of 21 to 87 years. The average levels of CRP and D-dimer were 11.95 ± 8.79 mg/L and 2389.69 ± 3709.76 ng/mL, respectively. There was a decrease in the average overall RSI score post-remdesivir therapy compared to pre-remdesivir therapy (15.73 ± 14.12 vs. 21.59 ± 18.32) for 24 patients in the high CRP group and 27 patients in the high D-dimer group, respectively. Further patient characteristics are described in Table 1.

Based on the results of the Spearman Rho correlation analysis in the high CRP group (Table 2), a significant weak correlation was found between high CRP levels and pre-therapy RSI score (r = 0.473, p = 0.006) and a non-significant weak correlation between high CRP levels and post-therapy RSI score and delta RSI score (high CRP with post-therapy RSI score r = 0.416, p = 0.18 and high CRP with Delta RSI score r = 0.273, p = 0.130). There was no correlation between age and high CRP

TABLE 1
Characteristics of research subjects

Variable	Mean ± SD	Median (min – max)	Amount (%)
Age (year)	52.97 ± 15.10	57 (21 87)	
Male			36 (56%)
Female			28 (44%)
CRP level (mg/L)	11.95 ± 8.79	8.63 (5.16 – 38.75)	
D-dimer level (ng/mL)	2389.69 ± 3709.76	1045 (520 – 20000)	
RSI score			
Pre- therapy	21.59 ± 18.32	20.5 (0 – 66)	
Post- therapy	15.73 ± 14.12	14.00 (0 – 54)	
Delta RSI score	5.85 ± 8.93	4.5 (-24 – 34)	
High CRP group			
Age (year)	52.97 ± 15.10	57 (21 – 87)	
Gender			
Male			17 (53.1%)
Female			15 (46.9%)
Pre therapy RSI *score*	21.97 ± 16.88	24.5 (0 – 52)	
Post therapy RSI *score*	15.69 ± 14.12	14 (0 – 47)	
Delta RSI *score*	6.28 ± 8.39	4.5 (-9 – 37)	
High D-dimer level			
Age (year)	53.34 ± 14.22	54 (18 – 73)	
Gender			
Male			19 (59.4%)
Age (year)			13 (40.6%)
Pre therapy RSI *score*	21.22 ± 19.92	15 (0 – 66)	
Post therapy RSI *score*	15.78 ± 15.69	12 (0 – 54)	
Delta RSI *score*	5.44 ± 9.56	4,5 (-24 – 34)	

*Delta = the difference between pre- and post-therapy RSI scores

TABLE 2
Spearman Rho correlation test results for the high CRP group

Variable	CRP	Pre RSI	Post RSI	Delta RSI
Age				
Correlation coefficient	0.119	0.186	0.160	0.163
P value	0.515	0.308	0.382	0.373
CRP				
Correlation coefficient		0.416	0.416	0.273
P value		0.006*	0.018	0.130
Pre RSI				
Correlation coefficient			0.906	0.578
P value			<0.001*	0.001*
Post RSI				
Correlation coefficient				0.271
P value				0.134

Note: *Significant (p <0.05)

TABLE 3
Spearman Rho correlation test results for the high D-dimer group

Variable	D-dimer	Pre RSI	Post RSI	Delta RSI
Age				
Correlation coefficient	-0.227	-0.085	-0.223	0.122
P value	0.212	0.643	0.219	0.607
CRP				
Correlation coefficient		0.331	0.362	0.200
P value		0.064	0.041*	0.273
Pre RSI				
Correlation coefficient			0.887	0.747
P value			<0.001*	<0.001*
Post RSI				
Correlation coefficient				0.439
P value				0.012*

Note: *Significant (p <0.05)

levels in COVID-19 patients, pre- and post-therapy RSI scores, and differences in RSI scores. The Wilcoxon test found a significant decrease in RSI score after remdesivir therapy in the high CRP group (21.97 ± 16.88 vs. 15.69 ± 14.12, p <0.001).

Based on the Spearman Rho correlation test in the high D-dimer group (Table 3), a low, insignificant correlation was obtained between high D-dimer levels and the RSI score pre-remdesivir therapy (r = 0.331, p = 0.064). There was no correlation between high D-dimer levels and the delta RSI score (r = 0.200, p = 0.273). The age variable was inversely correlated with pre- and post-therapy RSI values, delta RSI scores, and D-dimer levels. There was a significant decrease in the

RSI score after remdesivir administration in the high D-dimer group (21.22 ± 19.92 vs. 15.78 ± 15.69, p <0.001). Furthermore, the Fisher Exact test was performed for the difference in delta RSI scores in the high CRP and high D-dimer groups. There was no significant difference (p = 0.536) in the delta RSI score between the two groups. This shows that the therapeutic effect of remdesivir is similar in COVID-19 patients in both groups with high CRP and high D-dimer.

DISCUSSION

COVID-19 is a disease with high mortality and morbidity, especially in the elderly population and patients with comorbidities. Host factors can also affect susceptibility to infection and disease progression. The elderly and people with comorbidities are susceptible to SARS-CoV-2 and tend to develop into critical conditions. Comorbidities that increase susceptibility include hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), and cardiovascular disease. This was shown in this study, with a mean total patient age of 52.95 ± 15.10 years and age 21–87 years. Both groups of high CRP and high D-dimer indicated more severe disease conditions in COVID-19 patients and in older adult patients due to poorer immune system conditions compared to younger patients.[14–16] The gender characteristics of patients were similar, with 36 (56%) male patients and 28 (44%) female patients. COVID-19 disease can attack all genders, but women in East Asian populations are known to express higher ACE2 receptors and are therefore more susceptible to SARS-CoV-2 infection.[17]

C-reactive protein (CRP) is a protein produced by adipocytes and liver, which is associated with IL-1, IL-6, and TNF.[9] Its increase can occur in cases of hypertension, diabetes mellitus, and severe disease, so these confounding factors have been excluded from the study. The mean CRP level of patients after diagnosis was 11.95 ± 8.79 mg/L with a range of 5.16 to 38.75 mg/L. This result is lower than the results of the study by Sunil *et al*., in COVID-19 patients who had a mild CTSS picture of 21.4 (6.6 –35.4) mg / L, but there was an increase in CRP levels proportional to the increase in the degree of CTSS.[7] In the study by Geetika *et al*., CRP levels of 10.70 ± 11.08 mg / L were found to be significantly correlated with the severity as measured by the RSI score.[18] A significant decrease in the pre-therapy RSI score value was found from 21.97 ± 16.88 mg / L to 15.69 ± 14.12 mg / L post-therapy (p <0.001). Remdesivir has the effect of reducing the severity of patients in the form of a decrease in the RSI score in the high CRP group. Unfortunately, this study did not calculate the post-therapy CRP levels, so it is recommended to calculate the post-therapy CRP levels in further studies.

D-dimer is one of the markers of active coagulation and thrombin formation that can be used to assess the progression of SARS-CoV-2 disease. The average D-dimer level was 2389.69 ± 3709.76 ng/mL with a range of 1045 (520–20000) ng/mL. This result is much higher than the study by Herdiman *et al*., which had 58.4% of moderate clinical COVID-19 cases, obtained a range of D-dimer levels of 300-1600 ng/mL.[17] In this study, administration of remdesivir decreased the RSI score in the high D-dimer group as evidenced by a significant decrease in the pre-therapy RSI score of 21.22 ± 19.92 compared to post-therapy 15.78 ± 15.69 (p<0.001). In the study by Herdiman *et al*., it was found that increased D-dimer levels also increased the severity of radiological images (p<0.001). The presence of coagulopathy is associated with the severity of lung parenchymal involvement in COVID-19 which is caused by coagulation dysregulation due to excess inflammatory mediators. In the study by Amela *et al*., which used the CXR assessment system with the Brixia score, a significant positive correlation was found between D-dimer levels and the Brixia score (r = 0.45, p <0.001).[19]

There was no significant difference in RSI score between the high CRP and D-dimer groups (p=0.536). This may be due to increased CRP levels also in the high D-dimer group, and vice versa, considering that both of these markers increase in moderate to severe COVID-19 cases. It is known that D-dimer levels will exceed the upper limit >500 ng/mL and are significantly associated with increasingly severe disease (RR = 1.58; 95% CI = 1.25 2.00; p <0.001). In the study by Yao *et al*., D-dimer levels increased approximately 7-folds in moderate to critical COVID-19 (4.76 [2.02 – 13.3] mg/L vs. 0.6 [0.33 – 1.49] mg/L; p <0.001).17 Although no significant results were obtained, these results also indicate that remdesivir therapy has an effect on COVID-19 patients with both high CRP and high D-dimer levels. However, careful interpretation of the results is still needed considering the exclusion of groups with high CRP and D-dimer markers.

CONCLUSION

There was a significant decrease in RSI score in COVID-19 patients with high CRP levels and high D-dimer after administration of remdesivir. There was a weak significant relationship between high CRP levels and RSI score pre-remdesivir therapy, indicating that the higher the CRP levels, the higher the RSI score. There was no significant difference between the RSI score difference in the high CRP and high D-dimer groups, so remdesivir provided a similar therapeutic effect in both patients with high CRP or high D-Dimer levels.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2025; vol 12 (1) : 57–64

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Original Article

Effectiveness of Prolotherapy Injection in Elderly Patients with Knee Osteoarthritis: A Double-Blind Randomized Controlled Trial

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v12i1.1201

Accepted: October 04th, 2024
Approved: March 27th, 2025

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Abstract

Background : Knee osteoarthritis (OA) is a painful chronic disease in elderly population. Research has shown that prolotherapy is an effective pain-relieving treatment, particularly when used in combination with other therapies. The aims of this study was to evaluate the effectiveness of prolotherapy for knee OA based on The Western Ontario McMaster University OA Index (WOMAC) composite score (100 points), Knee Pain Scale, and self-reported satisfaction. We performed a randomized-controlled trial (RCT) with a double-blinded approach.

Methods : An injection saline, 10% dextrose (D10) prolotherapy, or at-home knee exercise was administered to twenty-seven elderly patients (≥60 years old) experiencing painful knee OA for at least three months. Extra- and intra-articular injections were administered at weeks 1, 4, and 7, with follow-up at weeks 11 and 15. Exercise group received in-person training and an exercise guidebook. WOMAC composite score (100 points), Knee Pain Scale, and self-reported satisfaction evaluated the outcomes. The results were considered statistically significant if $p < 0.05$.

Results : There are no significant difference in baseline among groups. At 21 weeks, all groups exhibited improved composite WOMAC scores (p <0.02) compared to baseline. After adjusting for age, sex, and body mass index, D10 prolotherapy showed a significant WOMAC score improvement at 21 weeks (p <0.04) compared to saline and exercise (score change: 16.2 ± 4.4 vs. 8.5 ± 4.3, and 9.1 ± 3.2, respectively), surpassing the minimal clinically significant difference based on WOMAC. Self-reported satisfaction with D10 prolotherapy was high without reported adverse effects.

Conclusion : When compared to saline injections and at-home exercises, D10 prolotherapy resulted in a clinically significant sustained improvement in pain, function, and stiffness scores for knee OA in elderly.

Keywords : dextrose, knee, pain, prolotherapy, osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) of the knee is a chronic condition that causes stiffness, discomfort, and functional loss of joints.[1] By 60, radiographic evidence of OA is present in most elderly.[2] Pain can originate from intra-articular structures within the joint and supportive extra-articular structures surrounding it.[3] Although multidisciplinary care is the standard, a recent comprehensive study found no significant advantages to any particular therapy.[4] Oral vitamins and conservative treatment, such as pain-relieving medication, have been studied, although their effectiveness is unclear.[5]

Prolotherapy is an injection therapy used to treat persistent musculoskeletal injuries, such as knee osteoarthritis (OA).[6] Its fundamental idea involves administering tiny amounts of an "irritant" solution to several damaged ligament and tendon insertions and nearby joint areas for several treatment sessions.[7] According to current theories, prolotherapy promotes the inflammation-induced local repair of extra and intra-articular tissue damage.[8] One injectant that is frequently utilized is hypertonic dextrose. It targets several possible pain sources in and around the injured knee joint.[9]

Despite their methodological weaknesses, one open-label study and one randomized controlled trial (RCT) indicated improved outcomes in response to prolotherapy.[10,11] Therefore, we conducted a double-blind RCT to ascertain whether elderly patients with symptomatic knee OA receiving prolotherapy would experience a more significant improvement in their knee-related quality of life than saline injections or at-home knee exercises.

METHODS

A Double-Blind Randomized Controlled Trial used in this studied. Dr. Moewardi Public Hospital Institutional Review Board approved the conduct of the study with ethical approval number 2.223/XII/HREC/2023. Adult participants aged 60 and over were recruited from RSUD Kota Banjar in West Java for this study, which took place from February to November 2023. They were then followed for nine months. Inclusion criteria were a) a diagnosis of Knee OA based on the American College of Rheumatology, b) a history of moderate-to-severe knee pain for at least three months, as defined by a score of three or higher (0 to 6 ordinal response scale) on the question, "Over the past week, what is the average severity of your left or right knee pain?", c) identification of knee OA by a radiologist on an existing knee radiograph obtained within two years of enrolment and d) tenderness of one or more anterior knee structures on physical examination.

Exclusion criteria encompassed the following conditions: pregnancy, diabetes, anticoagulation therapy, history of total knee replacement, previous knee prolotherapy, any knee injection within 3 months, opioid use, allergy or intolerance to medication, body mass index (BMI) ≥40 kg/m^2, and severe comorbidity causing participant unable to conduct exercising at home or showing up for injection visits on time. Each knee's eligibility was evaluated independently. Individuals who met the eligibility requirements consented to participate and were enrolled.

The participant was determined by Federer's formula (n-1) x (t-1) ≥15; (n, sample size of each group; t, number of groups).[12] Results showed that n ≥ 8.5, indicating nine patients in each group. The subjects were randomized by computer-generated randomization to receive injections of either saline (n = 9) or dextrose (n = 9) or to perform knee exercises at home (n = 9). Group participants and the result assessor were blinded about participants' group status. At each injection session, the blinding of the assessor and injection group participants was evaluated by asking them to identify the participant's group assignment using the options "dextrose," "saline," or "don't know." To describe the sample and assess it as a covariate for statistical analysis, baseline data on demographics, self-reported height and weight, and the degree of knee OA as visible on radiographs were gathered and evaluated according to 1-to-4-point Kellgren-Lawrence knee OA scoring method, by the hospital radiologist (A.B.A).

Injection intervention

Injections were given at 1, 4, and 7 weeks, with optional follow-up sessions at weeks 11 and 15, based on the doctor's consideration (S.K.P.). The Hospital's Pharmacy Center, located off-site, prepared dextrose and saline syringes before hand. They were blinded using an opaque paper sleeve. The injector (S.K.P.) assessed the knee, noted sore anterior knee regions, applied 2% lidocaine skin wheels for anesthetic purposes, and carried out extra- and intra-articular injections (Table 1). After the injection, participants were instructed to rest their knees for two to three days before gradually returning to regular activities. All three groups also consumed 500 mg paracetamol t.i.d. up to one week after weeks 1, 4, and 7.

At-home knee-exercise

An instructional leaflet regarding knee OA (Visual Health Information, at http://www.vhikits.com/Default.aspx) was given to participants in the exercise group.[13] It included ten at-home knee exercises that the study coordinator had demonstrated before the commencement of the study. Exercises (3 sessions per week, one session daily, 10 repetitions each) were recommended for participants to start, and they were instructed to progressively

increase therapy as tolerated over 7 weeks (5 sessions per week, 3 times daily, 15 repetitions per exercise) if wanted.

Adherence and Precautions

Call reminders were utilized to motivate and evaluate adherence to the exercise group at the same interval as injection sessions. Each time, a group member was advised not to strain or overuse their knees.

Outcome measurement

The primary outcome of this study is to assess the severity of OA by measuring pain, stiffness, and function subscales to assess OA severity by the Western Ontario McMaster University OA Index (WOMAC), a validated questionnaire. Its three subscale scores span from 0 (worst) to 96 (best), with a minimum 12-point change as the minimal clinical significant difference (MCID) of WOMAC.[14]

The secondary outcome measure is the knee pain scale (KPS). This validated questionnaire assesses the frequency and severity of knee pain (0 to 4 on an ordinal scale), with higher scores denoting worsening symptoms. 15 Independent KPS data sets were gathered for treated and untreated knees. The WOMAC and KPS scores were obtained in person at baseline before the procedure.

At 21 weeks, all participants were asked a follow-up question on treatment satisfaction: "Would you recommend the therapy you received in this study to others with knee OA like yours?" (Yes/No). Every participant had the opportunity to share qualitative remarks on their experiences.

Statistical analyses

At each evaluation week, 4, 7, 11, and 21, IBM SPSS version 22.0 for Windows performs a one-way ANOVA analysis for the mean ± SD of the three groups; significant results are further analyzed by posthoc. P value <0.05 indicated a statistical significance level.

RESULT AND DISCUSSION

Table 2 indicates that there were no significant baseline differences across the groups. The baseline WOMAC scores, x-ray reports, and overall inclusion criteria suggest that, on average, all patients had moderate severity of knee OA according to the Kellgren-Lawrence scores ranging from mild to severe. According to an analysis of the WOMAC subscale scores, D10 participants generally reported steady improvement for 21 weeks, reaching near-maximum improvement by 11 weeks. The function subscale showed the most significant increases; at 21 weeks, D10 participants reported 17.09 points, compared with 7.59 (P = 0.001) and 9.27 points (P =.002) for saline and exercise participants, respectively (Table 3 and Figure 1). Four people in the home exercise program, three saline participants, and the entire D10 said they would recommend their respective therapies.

These results align with single-arm prospective research (N = 36) that used comparable eligibility requirements and the same injection procedure.[10] Participants in that study reported similar overall effects on WOMAC and KPS outcome measures at 52 weeks despite being slightly more symptomatic at baseline. Significant improvement was also seen in the uninjected

TABLE 1
Intra- and extraarticular injections of D10 and saline

Injection	Details	Injection Approach
D10		
Intraarticular	10 cc syringe containing: 6 cc D10 4 cc lidocaine 2%	Inferomedial approach injection of 10 cc solution
Extraarticular	21 cc distributed into 3 syringes (7 cc each) containing: 5 cc D10 2 cc lidocaine 2%	The skin-sliding (withdrawal-reinsertion without puncture site removal) of 25G needle injected D10 at 3 insertions (7 cc for each site) of bone ligament.
Saline		
Intraarticular	10 cc syringe containing: 6 cc saline 4 cc lidocaine 2%	Similar to the abovementioned intraarticular approach.
Extraarticular	21 cc distributed into 3 syringes (7 cc each) containing: 5 cc saline 2 cc lidocaine 2%	Similar to the abovementioned extraarticular approach.

D10, 10% Dextrose, G, gauge.

TABLE 2
Baseline characteristics according to the intervention group

Variable	D10 (n = 9)	Saline (n = 9)	Exercise (n = 9)	*P* value
Sex, n (%)				
Male	3 (33.3)	4 (44.4)	5 (55.6)	0.73
Female	6 (66.7)	5 (55.6)	4 (44.4)	0.64
Age, mean (±SD), years	65.7 (4.8)	66.1 (5.9)	65.9 (5.1)	0.93
Pain onset, mean (±SD), months	49 (5.5)	45 (4.2)	46 (3.9)	0.09
BMI, n (%), kg/m^2				
≤ 25	1 (11.2)	0 (0.00)	1 (1.2)	0.28
25–30	3 (33.3)	2 (22.2)	4 (44.4)	
≥ 30	5 (55.5)	7 (77.8)	4 (44.4)	
History of knee therapies, n (%)				
Injection of hyaluronic acid	2 (10.53)	1 (5.55)	3 (13.04)	0.75
Injection of corticosteroid	4 (21.05)	3 (16.67)	3 (13.04)	0.68
Glucosamine	7 (34.21)	6 (33.34)	8 (34.78)	0.52
Physiotherapy	7 (34.21)	8 (44.44)	9 (39.14)	0.19
Kellgren-Lawrence OA grade				
1–2 (mild)	4	3	3	0.91
3–4 (moderate–severe)	5	6	6	0.86
WOMAC, score (SD) [range][a]				
Pain	65.2 (14.1) [34.8 – 91.9]	65.9 (15.8) [30.9 – 96.1]	61.9 (12.5) [34.5 – 89.3]	0.31
Stiffness	56.9 (18.8) [24.4 – 88.6]	53.5 (16.9) [23.9 – 86.2]	53.9 (17.3) [10.8 – 97.5]	0.07
Function	64.3 (15.5) [39.4 – 97.1]	66.2 (17.3) [34.9 – 98.5]	60.2 (11.5) [36.2 – 87.1]	0.29
KPS, score (SD)[b]				
Frequency	2.7 (0.7)	2.1 (0.9)	2.4 (0.9)	0.28
Severity	1.7 (0.7)	1.8 (0.7)	1.7 (0.8)	0.72

D10, 10% dextrose; SD, standard deviation; BMI, body mass index; OA, osteoarthritis;
WOMAC, Western Ontario McMaster University OA Index; KPS, knee pain scale.
[a]The higher score in this study indicates better knee-related quality of life. The theoretical range is 0 to 100.
[b]Higher scores indicate worse symptoms. The theoretical range of severity scores is 0 to 5, and the frequency range is 0 to 4.

contralateral knees, indicating that dextrose prolotherapy for more symptomatic knee OA may also improve the uninjected side, probably by reducing compensatory mechanisms.[10]

The direct prolotherapy mechanism generally occurs in four stages, as shown in Figure 2. When the body suffers tissue damage, it initiates a healing process through an inflammatory cascade. However, specific tissues such as ligaments, tendons, cartilage, and fibrocartilage (like the meniscus and labrum) often have limited or no blood supply, making natural healing difficult.[16] In such cases, prolotherapy is employed to encourage the healing process. Prolotherapy encourages healing through inflammation. A cellular response occurs once prolotherapy solutions are injected into the injured area. Various cells, including fibroblasts,

TABLE 3
WOMAC and KPS subscale score changes

Outcomes	Week 4	Week 7	Week 11	Week 21
WOMAC				
Pain				
D10	8.09 (3.28)	13.89 (3.43)	10.98 (3.52)	15.32 (3.51)
Saline	3.01 (2.78)	5.12 (3.33)	5.70 (3.46)	6.31 (3.33)
Exercise	3.90 (3.05)	2.99 (3.52)	4.91 (3.65)	7.92 (3.53)
P value	0.06	0.03[a]	0.04[b]	0.02[a]
Stiffness				
D10	6.98 (4.39)	14.25 (4.51)	13.25 (4.52)	14.90 (4.23)
Saline	8.52 (4.42)	9.32 (3.98)	11.98 (4.78)	11.01 (4.60)
Exercise	3.71 (4.50)	0.21 (3.27)	3.09 (4.81)	8.09 (4.96)
P value	0.09	0.01[c]	0.04[b]	0.07
Function				
D10	8.55 (3.19)	13.32 (3.25)	14.29 (3.33)	17.09 (3.12)
Saline	3.96 (3.30)	6.01 (3.36)	6.50 (3.41)	7.59 (3.36)
Exercise	4.98 (3.24)	3.94 (3.41)	4.92 (3.39)	9.27 (3.53)
P value	0.11	0.02[a]	0.03[a]	0.04[a]
KPS				
Frequency				
D10	-0.52 (0.19)	-0.82 (0.24)	-0.86 (0.26)	-1.20 (0.26)
Saline	-0.23 (0.21)	-0.31 (0.23)	-0.33 (0.24)	-0.46 (0.24)
Exercise	-0.16 (0.23)	-0.23 (0.25)	-0.14 (0.28)	-0.48 (0.26)
P value	0.23	0.01[d]	0.01[d]	0.03[d]
Severity				
D10	-0.23 (0.24)	-0.47 (0.24)	-0.53 (0.25)	-0.93 (0.24)
Saline	-0.09 (0.24)	-0.20 (0.24)	-0.15 (0.26)	-0.24 (0.26)
Exercise	-0.10 (0.25)	-0.14 (0.23)	-0.08 (0.25)	-0.31 (0.24)
P value	0.07	0.13	0.06	0.01[d]

D10 (n =9), saline (n = 9), and exercise group (n = 9) without loss to follow-up, mean (SD). D10, 10% dextrose; SD, standard deviation; BMI, body mass index; OA, osteoarthritis; WOMAC, Western Ontario McMaster University OA Index; KPS, knee pain scale.

[a] D10 surpassed saline and exercise (both $P<0.05$), with no significant differences between saline and exercise ($P>0.05$).

[b] D10 surpassed exercise ($P<0.05$), with no significant differences between saline vs. D10 and saline vs. exercise (both $P>0.05$).

[c] D10 surpassed exercise ($P<0.05$), and saline surpassed exercise ($P<0.05$), with no significant differences between D10 vs. saline ($P>0.05$).

[d] D10 score change was more than saline and exercise score change (both $P<0.05$), with no significant difference between saline vs. exercise score ($P>0.05$).

endothelial cells, and myofibroblasts, form new blood vessels and eventually produce collagen, strengthening and repairing the tissue.[17] The last stage of healing is tissue remodeling. The tissue continues to reshape for several months following an injury or prolotherapy. The new tissue that forms closely resembles and functions like the original tissue before the injury. The associated pain diminishes as the tissue regains strength comparable to the original.[18] Thus, in OA patients, mechanical-induced remodeling may be more destructive than irritative

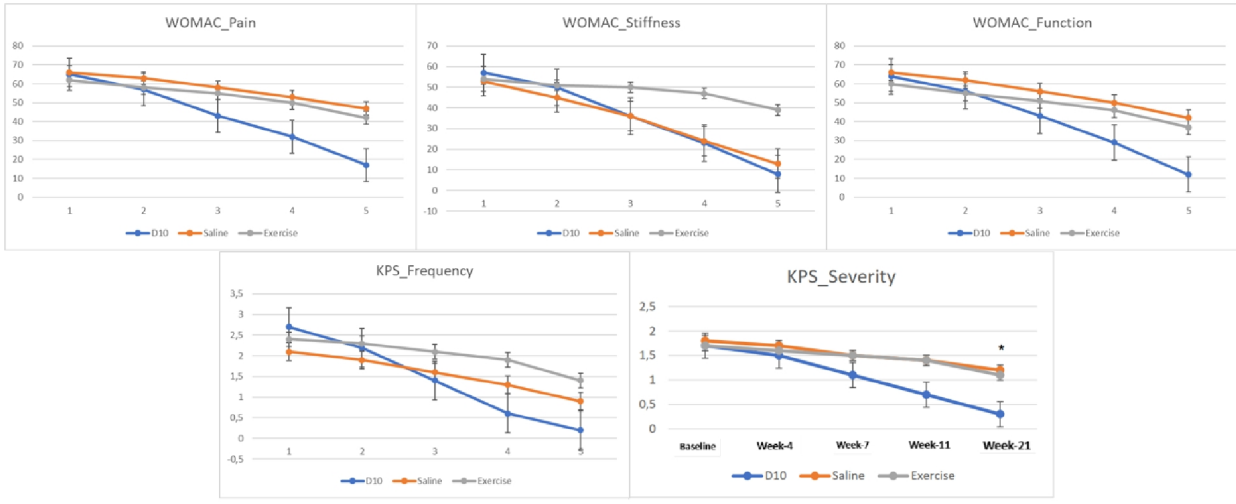

Figure 1. The overall group demonstrated WOMAC and KPS-associated line declines, with significant details in Table 3. The changes within week 1–4 in WOMAC and KPS subscale outcomes among D10 (n =9), saline (n = 9), and exercise group (n = 9) were without loss to follow-up.

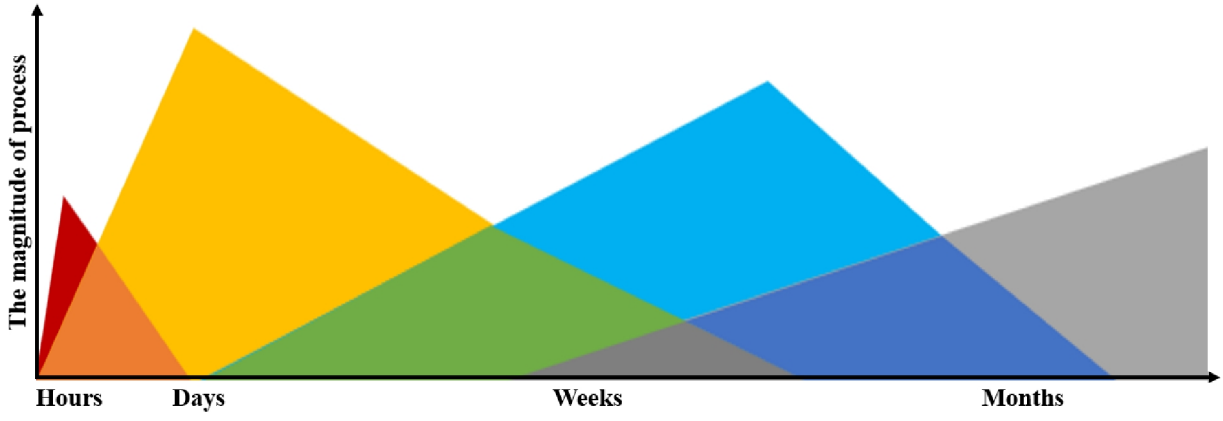

Figure 2. The biological process of prolotherapy treatment**.** Bleeding (red), inflammation (yellow), proliferation (blue), and remodeling (grey). Prolotherapy usually lasts four to six weeks to achieve a minimum practical effect.

substance-induced remodeling, such as that utilized in dextrose prolotherapy because mechanical loading can exacerbate the condition of tissues that are already vulnerable to mechanical damage.[19]

Despite the research conducted to date, the exact mechanism of dextrose prolotherapy remains unclear. Researchers have proposed three possible processes.[20] The core concept behind prolotherapy is to promote tissue regeneration and repair by using irritants to induce inflammation. According to one study, 10% dextrose appears to help heal articular cartilage abnormalities in rabbits.[20] Researchers have demonstrated that encouraging the growth of fibroblasts with 20% dextrose has a healing effect on damaged Achilles tendons in rats.[21] Additionally, there is conflicting data regarding the pro-chondrogenic potential of dextrose prolotherapy. Through direct arthroscopic visualization and cartilage biopsy, it was found that intra-articular dextrose prolotherapy improved knee cartilage quality in a manner consistent with chondrogenesis.[22]

Furthermore, dextrose may have a direct pain-modulating effect, which may have a direct impact. In a double-blind, randomized controlled trial involving patients with persistent low back pain accompanied by either gluteal or leg discomfort, caudal epidural dextrose of 5% dextrose, administered without local anesthetic, resulted in a reduction of pain. Notably, analgesia began to take effect as soon as 15 minutes after the injection, supporting the hypothesis that dextrose can have a sensorineural direct impact.[23]

This study has several limitations, including a tiny sample size. However, the effect size of prolotherapy is significant enough to identify differences between the groups. The sample size was inadequate for identifying uncommon side effects, such as drug intolerance or infrequent complications related to injections. This investigation did not compare prolotherapy with the most intervention used, such as intraarticular corticosteroid and hyaluronic acid injections. Confirmation in a more significant effectiveness study, including biomechanical and imaging outcomes, will be necessary to evaluate the potential for disease modification and determine prolotherapy's clinical value.

CONCLUSION

Based on our findings, prolotherapy injection significantly improved knee osteoarthritis symptoms compared to saline and exercise interventions. Patients in the D10 group exhibited a more significant reduction in WOMAC scores ($p < 0.05$), indicating better pain relief and functional recovery. Additionally, the KPS subscale outcomes showed a substantial enhancement in physical performance among prolotherapy recipients ($p < 0.05$), suggesting its potential as an effective therapeutic option for elderly patients with knee osteoarthritis. Given these results, prolotherapy could be considered a viable non-surgical intervention, particularly for individuals seeking pain management and functional improvement. Further studies with larger sample sizes and extended follow-up periods are recommended to confirm these findings and explore long-term benefits.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2025; vol 12 (1) : 65–70

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Case Report

Radiologic Features of Anencephaly : A Serial Case Report

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v12i1.1186

Accepted: September 19th, 2024
Approved: March 21th, 2025

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Abstract

Background : Anencephaly is a lethal central nervous system anomaly characterized by absence of cerebral structures and cranial vault. It is the most common open neural tube defect that occurs in 0.5 – 2 per 1,000 live births. This anomaly can be detected as early as 11 weeks of pregnancy by transvaginal ultrasonography. Micronutrient deficiency, such as anemia and folic acid deficiency, was known to be the potential risk factor for anencephaly.
Case Report : We reported 4 cases of anencephaly diagnosed using ultrasonography during pregnancy. All patients were referred to Dr. Kariadi General Hospital from private hospitals in Central Java. There are 3 out of 4 cases were diagnosed in the first trimester and 1 case was diagnosed in the third trimester. Ultrasonography features showed typical signs of anencephaly including 'frog eyes sign', 'Mickey mouse sign' and acrania. All of the patients underwent termination of pregnancy with variable route of delivery according to condition and gestational age.
Discussion : Routine antenatal ultrasonography is recommended for early detection of fetal viability and other congenital anomalies including anencephaly. Ultrasonography is able to detect typical findings of anencephaly and therefore is able to accurately establish the diagnosis. Advanced imaging technique such as MRI is unnecessary unless diagnosis using ultrasonography is indeterminate. Enforcement of diagnosis of anencephaly is very important due to determining its definitive treatment, in which termination of pregnancy.
Conclusion : Presented various radiologic features of anencephaly using ultrasonography may clinicians will be able to diagnose this anomaly in earlier age of pregnancy. So, definitive treatment can be done and complications during pregnancy can be prevented.

Keywords : Anencephaly, neural tube defect, ultrasonography

INTRODUCTION

Anencephaly is a lethal central nervous system anomaly characterized by absence of cerebral structures and cranial vault. This anomaly is a result of an open neural tube defect which occurs in 23rd to 28th days after conception.[1] Anencephaly is the most common open neural tube defect with incidence of 0.5 – 2 per 1,000 live births. Females are affected more frequently with a ratio of 4 : 1. The susceptibility of females has been suggested to result from the difference between male and female embryos in some specific aspects of the neurulation process. Anencephaly is relatively more common in Caucasian than in Asian. The etiology is unclear but there are possible risk factors including advanced maternal age, diabetes mellitus, antiepileptic drugs, radiation and chromosomal anomalies.[2]

The pathogenesis is still controversial, either a failure of closure of the neural tube or reopening after closure has been hypothesized. Other anomalies, such as vertebral anomalies, omphalocele and other systemic anomalies, are often associated with anencephaly and can be detected using ultrasonography as early as 11 weeks of pregnancy. Despite the ability to diagnose using ultrasonography, advanced imaging modality such as magnetic resonance imaging (MRI) is required in indeterminate cases.[3] Anencephaly is uniformly lethal. Fatal complications include stillbirth or death shortly after birth. Once the diagnosis is made, patients should be offered termination of pregnancy. Ability to detect anencephaly using ultrasonography is required so that definitive treatment in which termination of pregnancy can be done with minimal maternal morbidity.[4] In this serial case series, we present various radiologic features of anencephaly using ultrasonography so that clinicians will be able to diagnose this anomaly in earlier age of pregnancy. Hence, maternal complications and morbidity can be prevented.

CASE REPORTS

In this article, we presented 4 cases of pregnancy with anencephaly fetus. We present the resume of all patients' sociodemographic data is shown in Table 1. All patients were primipara with age under 30 years old and referred to Dr. Kariadi General Hospital from private hospitals in Central Java. 3 out of 4 cases were diagnosed in the first trimester and 1 case was diagnosed in the third trimester. Ultrasonography features showed typical signs of anencephaly including 'frog eyes sign', 'Mickey mouse sign' and acrania.

Case #1

27 y.o female was referred to Dr. Kariadi General Hospital with a suspicion of anencephaly fetus from ultrasonography examination at private hospital (Table 1). Personal history was unremarkable with no history of anemia or vaginal bleeding during pregnancy. Laboratory examination showed normal hemoglobin levels (Table 2). Ultrasonography was first performed at 12 weeks of pregnancy showing intrauterine single fetus with acrania. Examination was then repeated at 15 weeks of pregnancy showing intrauterine single fetus with normal fetal biometry, fetal heart rate and fetal movement. On sagittal plane, ultrasonography showed 'frog eyes sign' and on coronal plane, ultrasonography showed 'Mickey mouse sign' (Figure 1). Diagnosis of anencephaly was made and patients was offered termination of pregnancy (Table 2).

Case #2

28 y.o female was referred to Dr. Kariadi General Hospital with a suspicion of anencephaly fetus from ultrasonography examination at private hospital (Table 1). Personal history was unremarkable with no history of anemia or vaginal bleeding during pregnancy. Laboratory examination showed normal hemoglobin

TABLE 1
Sociodemographic data

Variable	Case 1	Case 2	Case 3	Case 4
Patient's age	27 y.o	28 y.o	27 y.o	27 y.o
Husband's age	30 y.o	29 y.o	29 y.o	30 y.o
Parity	Primipara	Primipara	Primipara	Primipara
Referral	Yes	Yes	Yes	Yes
Origin of referral	Private hospital	Private hospital	Private hospital	Private hospital
Hospital billing	Private insurance	Private insurance	Private insurance	Personal expense
Gestational age	15 weeks	13 weeks	28 weeks	14 weeks
Gestational age at timeof diagnosis	12 weeks	12 weeks	26 weeks	11 weeks

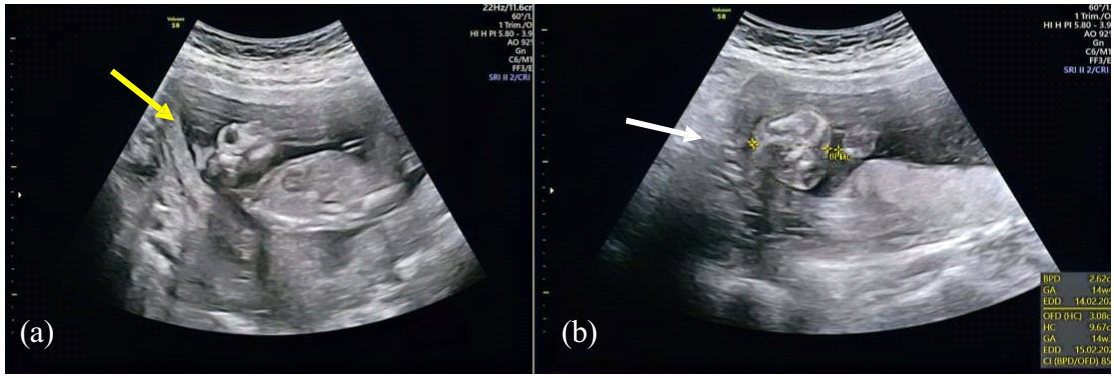

Figure 1. (a) Ultrasonography on sagittal plane showed prominent orbital structure with absence of cerebral hemisphere and cranial vault, resembling an appearance of frog eyes (yellow arrow). (b) On coronal plane, ultrasonography showed an appearance of 'Mickey mouse sign' (white arrow).

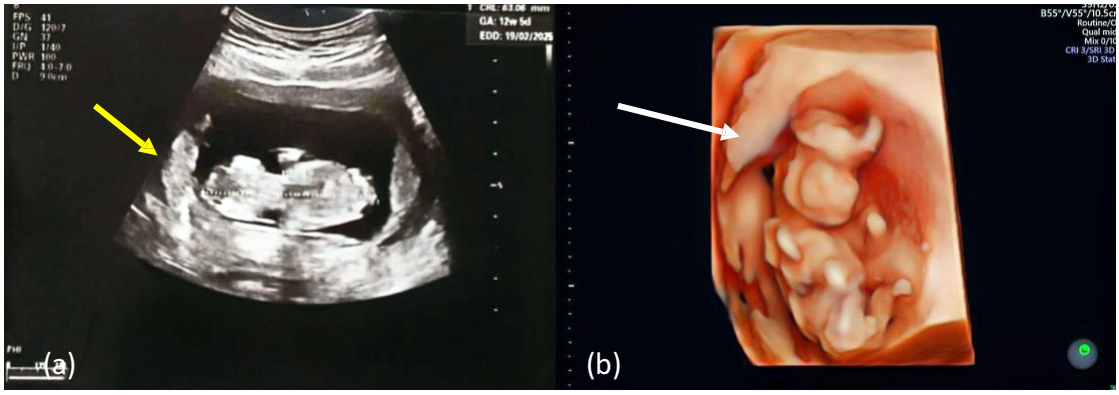

Figure 2. (a) Ultrasonography on coronal plane showed prominent orbital structure with absence of cerebral hemisphere and cranial vault, resembling an appearance of frog eyes (yellow arrow). (b) On 3D ultrasonography examination, absence of cranial vault was clearly shown (white arrow).

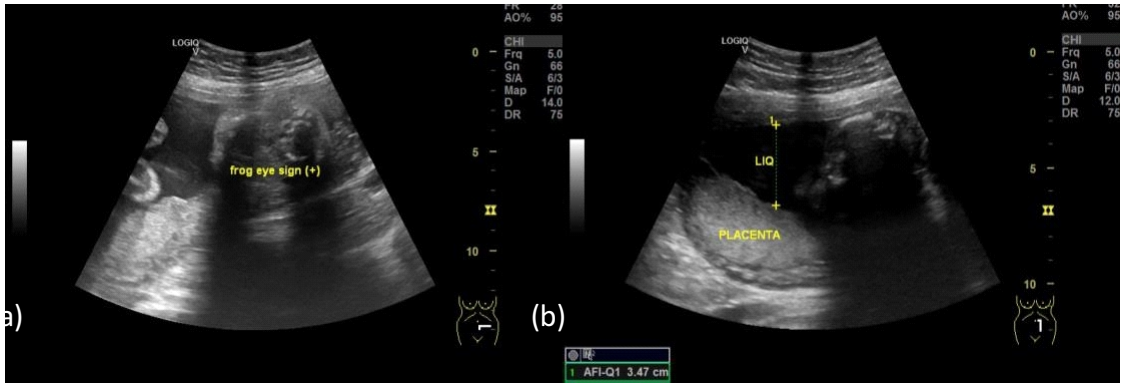

Figure 3. (a) Ultrasonography on coronal plane showed prominent orbital structure with absence of cerebral hemisphere and cranial vault, resembling an appearance of frog eyes. (b) No signs of polyhydramnios showed by normal AFI and single pocket depth.

levels (Table 2). Ultrasonography was first performed at 12 weeks of pregnancy showing intrauterine single fetus with acrania. Examination was then repeated at 13 weeks of pregnancy showing intrauterine single fetus with normal fetal biometry, fetal heart rate and fetal movement. On coronal plane, ultrasonography showed 'frog eyes sign' and 3D ultrasonography showed absence of cranial vault (Figure 2). Diagnosis of anencephaly was made and patients was offered termination of pregnancy. (Table 2).

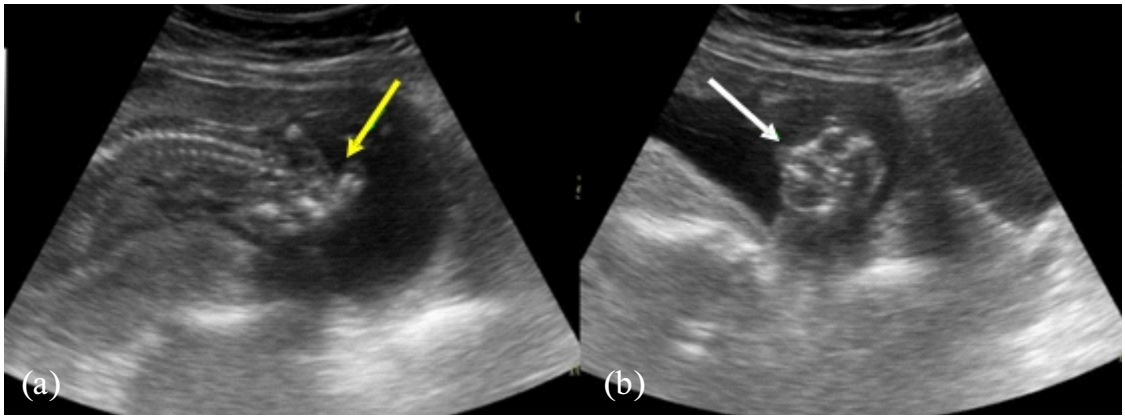

Figure 4. (a) Ultrasonography on sagittal plane showed absence of cranial vault (yellow arrow). (b) On coronal plane, prominent orbits were clearly shown (white arrow).

TABLE 2
Clinical data

Variable	Case 1	Case 2	Case 3	Case 4
Laboratory (hemoglobin)	12.3g/dL (normal)	12.5g/dL (normal)	10g/dL (low)	9.1 g/dL (low)
Treatment	Termination of pregnancy	Termination of pregnancy	Vaginal delivery	Spontaneous vaginal delivery
Length of stay	n/a	n/a	3 days	3 days

Case #3
27 y.o female was referred to Dr. Kariadi General Hospital with a suspicion of anencephaly fetus from ultrasonography examination at private hospital (Table 1). Personal history was unremarkable. Laboratory examination showed low hemoglobin level (Table 2). Ultrasonography was first performed at 11 weeks of pregnancy showing intrauterine single fetus with no congenital anomalies. Examination was then repeated at 26 weeks of pregnancy showing intrauterine single fetus with normal fetal biometry, fetal heart rate and fetal movement. On coronal plane, ultrasonography showed 'frog eyes sign' and normal amniotic fluid index (AFI) with no signs of polyhydramnios (Figure 3). Diagnosis of anencephaly was made and patients was offered termination of pregnancy. Prior to the planned termination date, patient felt periodic contraction with reduced fetal movement. Physical examination showed no fetal heart rate and diagnosis of intrauterine fetal death was made. Vaginal delivery was done to reduce maternal complications and morbidity (Table 2).

Case #4
27 y.o female was referred to Dr. Kariadi General Hospital with a suspicion of anencephaly fetus from ultrasonography examination at private hospital (Table 1). Personal history was unremarkable. Laboratory examination showed low level of hemoglobin (Table 2). Ultrasonography was first performed at 11 weeks of pregnancy showing intrauterine single fetus with acrania. Examination was then repeated at 14 weeks of pregnancy showing intrauterine single fetus with normal fetal biometry, fetal heart rate and fetal movement. 'Frog eyes sign' and acrania was discovered and diagnosis of anencephaly was made (Figure 4). Patient was offered termination of pregnancy but prior to the planned termination date, patientcame to emergency department with complaint of vaginal bleeding. Patient was having a spontaneous vaginal delivery and no additional curettage therapy was needed (Table 2).

We present the resume of all patients' clinical data is shown in Table 2. 2 out of 4 patients were present with anemia with low level of hemoglobin below 10 g/dL. Two patients underwent termination of pregnancy using curettage method and two other patients underwent vaginal delivery as the method of pregnancy termination.

DISCUSSION

The neural tube closes within the first 28 days of development. Fusion starts in the mid region and then extends in both directions to form the neural tube. The ends of the tube, called the anterior and posterior

neuropores, close later. Failed closure of the anterior neuropore results in anencephaly, whereas failed closure of the posterior neuropore results in spina bifida. Both pathology was classified as open neural tube defect in which anencephaly is the most common and the most lethal congenital anomaly with worst prognosis. The etiology is still unknown andvarious factors known to play a role in increasing the risk of anencephaly. Among those factors, folate deficiency is known to be the most important in neural tube fusion process. [5,6]

We reported 4 cases of primipara patients with age range below 30 years old and present with anencephaly fetus. The age of these patients is still considered as optimal age for risk-free pregnancy in which below 35 years old. Therefore, primipara conditions are not a risk factor for anencephaly, but primiparas with reproductive age tend to have micronutrient deficiencies such as anemia, vitamin B12 deficiency and folate deficiency. In this case report, we found 2 patients with anemia characterized by low level of hemoglobin. Anemia and folate deficiency are two related conditions in which folate deficiency can cause normochromic macrocytic anemia and both can be major risk factors for anencephaly. Providing iron and folate supplements to pregnant women is recommended and able to reduce the risk of neural tube defect. The recommended dose is 400 µg per day for 1 month before pregnancy and for patients with a history of anencephaly the recommended dose is 4 mg per day. [7,8]

The first line modality in diagnosing anencephaly is using ultrasonography examination. Ultrasonography will be able to discover typical signs of anencephaly such as 'frog eyes sign', 'Mickey mouse sign' and acrania. These typical signs are due to defects in the scalp and calvarium and the absence of both cerebral hemispheres. In addition to these signs, polyhydramnios can also be found in anencephaly as an indirect sign due to impaired swallowing ability in fetus. These ultrasonography features can be detected at as early as 11 weeks of pregnancy using transvaginal ultrasonography.[9] We reported 4 patients in which 3 of them were diagnosed with anencephaly in first trimester, whereas 1 of them were diagnosed in third trimester. Ultrasonography of the 4 patients in this case report showed the absence of cerebral hemispheres and cranial vault making an appearance of 'Mickey mouse sign' and prominent orbital structures making an appearance of 'frog eyes sign'. Both features support the diagnosis of anencephaly using ultrasonography examination. Although ultrasonography examination can diagnose anencephaly accurately, there are still some exceptions that require more advanced imaging modalities, such as MRI. MRI is used in indeterminate case where ultrasonography is not be able to confirm anencephaly and to rule out other possible differential diagnosis. Absence of cerebral hemisphere can accurately depicted using MRI and presence of differential diagnosis such as exencephaly can be ruled out using this modality (Figure 4). In this case report, all four patients could be diagnosed accurately using ultrasonography examination so that MRI examination was no longer needed. [10,11]

Anencephaly can also be diagnosed using alpha fetoprotein (AFP) level examination in amniotic fluid and maternal blood serum as additional examination. In pregnancies with anencephaly and other open neural tube defects, there is an increase in AFP due to AFP produced in liver and fetal yolk sac can easily escape into the amniotic fluid and maternal circulation through defect. But due to its invasiveness measuring AFP levels in amniotic fluid, the examination was not done in our patients. [14,15]

Reinforcement of diagnosis of anencephaly is very important due to determining its definitive treatment, in which termination of pregnancy. In this case report, all 4 patients underwent termination of pregnancy with variable route of delivery according to each patients' condition and gestational age. The third case underwent vaginal delivery due to intrauterine fetal death and the fourth case underwent spontaneous vaginal delivery with no additionalcurettage therapy needed. The first two cases were planned to have termination of pregnancy. The route of delivery is chosen according to the patient's gestational age with the least maternal complications and morbidity rate, in which vaginal delivery. The very low life expectancy with a mortality rate of 100% in anencephaly makes termination of pregnancy the definitive management. However, there are also several cases of anencephaly that are born alive with the longest life expectancy being 28 days. This is due to an intact brain stem in anencephaly so that the baby can breathe spontaneously, respond to light and move its extremities. In cases of babies with anencephaly who are born alive, supportive therapy is still given according to the baby's condition. [16]

CONCLUSION

Ultrasonography is the first line modality in diagnosing anencephaly. Routine antenatal ultrasonography is recommended for early detection of fetal viability and other congenital anomalies. Ultrasonography is required to detect anencephaly. Hence, complications and mortality during pregnancy can be prevented.

ABBREVIATIONS

AFP = amniotic fluid index ; AFP = alpha feto protein ; MRI = magnetic resonance imaging.

ETHICAL APPROVAL AND INFORMED CONSENT

Written informed consents were already taken and signed by all patients and their family members . All data collection tools were used anonymously to maintain confidentiality of data. Participation in the study was on a fully voluntary basis.

DISCLOSURE

All authors declare that they have no conflicts of interest.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2025; Vol 12 (1)
March 2025

AUTHOR GUIDELINE

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Title :
1. Is neither too long nor too short, approximately 12–14 words
2. Describes research design
3. Contains no abbreviation unless standard

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1. Is well structured (background, aim, method, result, conclusion)
2. Consists of maximum 250 words
3. Consists of 3-8 keywords
4. Is presented in English

Introduction :
1. Consists of 2 paragraphs/parts. The first paragraph consists of research background (research justification): what have been known and what need to be added. The second paragraph consists of hypothesis or research aim.
2. Is supported by relevant and strong references

Methods :
1. Explains research design, settings and time
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3. For clinical trial, explains randomization and conceal allocation, and Kappa test if conducted and detailed investment
4. Thoroughly explains method, instrument, measurement technique and data collection
5. Explains data analysis with proper tests according to data, significance and confidence interval
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1. Is presented in a logical sequence
2. Presents subject characteristics (in a table). For clinical trial, subject characteristic of each group before trial are presented
3. Explains subjects who drop out and the reasons. If possible, provides consort diagram
4. Maximum 3-4 tables
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2. Is compared with previous study findings.
3. Mentions research strengths/weaknesses and its impact on findings.

Conclusion :
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2. Stresses new or rare cases or new therapies or procedures
3. Provides patient's picture (if necessary), investigations such as radiology or laboratory or others as needed. Pictures/photos size minimum 300 dpi.
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Kementerian Pendidikan, Kebudayaan, Riset, dan Teknologi Republik Indonesia

Nomor 105/E/KPT/2022
Peringkat Akreditasi Jurnal Ilmiah Periode 1 Tahun 2022

Nama Jurnal Ilmiah

Medica Hospitalia : Journal of Clinical Medicine

E-ISSN: 26857898

Penerbit: RSUP Dr. Kariadi Semarang

Ditetapkan Sebagai Jurnal Ilmiah

TERAKREDITASI PERINGKAT 3

Akreditasi Berlaku selama 5 (lima) Tahun, yaitu
Volume 8 Nomor 2 Tahun 2021 Sampai Volume 13 Nomor 1 Tahun 2026

Jakarta, 07 April 2022
Plt. Direktur Jenderal Pendidikan Tinggi,
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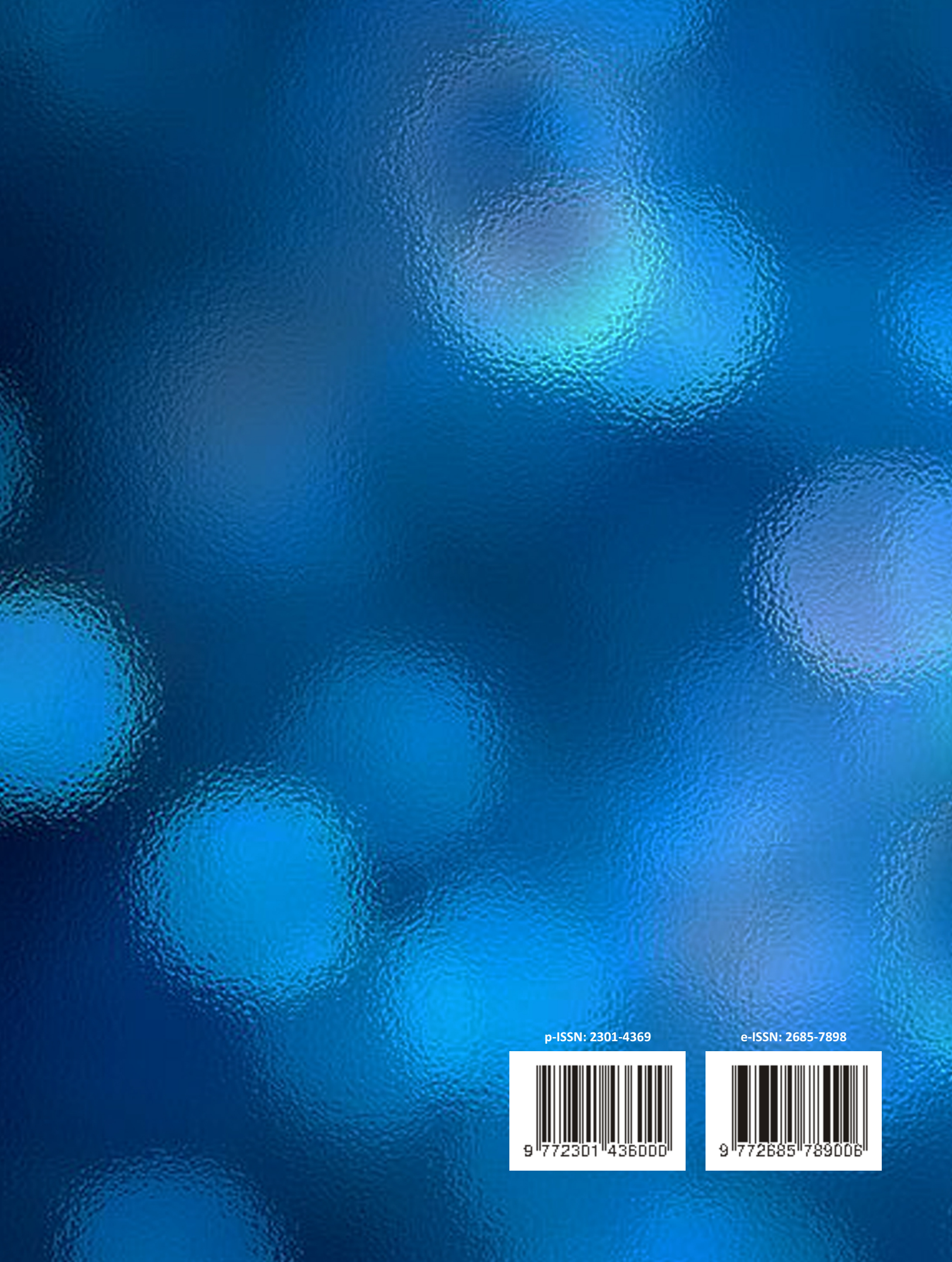

p-ISSN: 2301-4369

e-ISSN: 2685-7898