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

Medica Hospitalia

Journal of Clinical Medicine

Med Hosp 2026 Vol 13 (1) March 2026 www.medicahospitalia.rskariadi.co.id

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Medica Hospitalia

Journal of Clinical Medicine

Med Hosp 2026; Vol 13 (1)

March 2026

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

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; Vol 13 (1)
March 2026

Original Articles

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Editorial

Dear Reasearchers,

Writing scientific journal articles plays a crucial role in the development of science and technology. Through articles, the researchers provide the result in a systematic and structured manner, so it can be understood and reviewed by the scientific community. This enables the exchange of accurate information and accelerates innovation in various fields, including medicine, technology, and social sciences. Journal articles also provide concrete evidence of research progress that can be used as a reference for policymaking and further development.

In the current global context, the world faces various major challenges, one of which is the geopolitical crisis in the Middle East, which has broad impact on global political and economic stability. However, this situation has not halted the progress of scientific research, particularly in the field of medicine. Researchers worldwide continue to study and develop new drugs, therapies, and medical technologies that are desperately needed to improve the quality of human life. This demonstrates that science has the power to transcend geopolitical boundaries and conflict.

Sustainable medical research is crucial, especially during times of crisis, as the need for effective health solutions becomes even more urgent. Scientific journal articles serve as a primary medium for documenting new findings and sharing knowledge among scientists globally. Scientific publications provide doctors and researchers with access to the latest information that supports the diagnosis, treatment, and prevention of disease. This is crucial for maintaining the continuity of healthcare services amidst global uncertainty.

Through a peer review process, published articles undergo rigorous evaluation by experts in the field, ensuring their quality and reliability. This is crucial to ensure that research results are not merely subjective information but are scientifically sound. Thus, journal articles provide a strong foundation for the development of credible and useful scientific knowledge.

Overall, writing scientific journal articles is a key pillar in scientific advancement, especially amidst global challenges such as geopolitical crises. Despite global instability, the passion and dedication of medical researchers remain high, striving to produce life-saving innovations. Therefore, supporting and developing a culture of scientific writing is crucial for the continued development of science and providing tangible benefits to the wider community.

Happy researching

Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; vol 13 (1) : 1–9

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Original Article

The Effect of Vitamin D Supplementation on Sputum Conversion, Erythrocyte Sedimentation Rate and Neutrophil-Lymphocyte Ratio in Pulmonary Tuberculosis Patients – A Randomized Controlled Trial

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v13i1.1290

Submitted: November 25th, 2024
Accepted: March 26th, 2026

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Abstract

Background : The health issue of pulmonary tuberculosis (TB) remains a concern in Indonesia. Vitamin D supplementation is one way to manage tuberculosis, which is a crucial case control metric. It is anticipated that vitamin D's anti-inflammatory properties will lower erythrocyte sedimentation rate (ESR) and inflammatory indicators, hence speeding up sputum conversion.
Aims : To analyze the effect of vitamin D supplementation on sputum conversion, ESR and neutrophil-lymphocyte ratio (NLR) among pulmonary tuberculosis patients
Methods : Patients with pulmonary tuberculosis who were treated as outpatients at Ulin Banjarmasin Hospital and Pekauman Health Centre between May–July 2024 and who satisfied the study's inclusion requirements were included in the randomised controlled trial. Subjects were randomly divided into 2 groups (19 subjects in the treatment group and 19 subjects in the control group) using random selection with sealed envelopes. The treatment group received antituberculosis drugs (ATD) and vitamin D supplementation at a dose of 10,000 IU/day for eight weeks after the initiation of TB therapy, while the control group received ATD and a placebo. ESR and NLR examinations were performed prior to treatment, in weeks 4 and 8, whereas sputum evaluations were conducted at weeks 2, 4, 6, and 8. Statistical Product and Service Solutions (SPSS) was used for data analysis. *P*-value <0.05 was significant statistically.
Results : The study subjects were 38 pulmonary TB patients, most of whom were women (65.0%) with an average age of 50.42 ± 18.61 years. Overall, during the 8 weeks of intervention, there was a significant effect of vitamin D supplementation on sputum conversion (OR = 1.61, 95%CI = 0.030–0.931, p = 0.037). There was no significant effect of vitamin D supplementation on NLR (regression coefficient = 0.549, 95%CI = -1.769–2.858, p = 0.641) and ESR (regression coefficient = -5.529, 95%CI = -20.658–9.599, p = 0.474).
Conclusion : Vitamin D supplementation significantly affects sputum conversion. In the 8th week, almost all subjects who initially had positive BTA became negative. But does not significantly affect ESR and NLR.

Keywords : Pulmonary Tuberculosis, Vitamin D, Sputum Conversion, Neutrophil-Lymphocyte Ratio, Erythrocyte Sedimentation Rate

INTRODUCTION

A worldwide health concern, tuberculosis (TB) is particularly prevalent in Indonesia. According to data gathered by the Republic of Indonesia's Ministry of Health (Kemenkes RI), there were 443,235 TB cases overall in 2021, and that figure rose by 503,712 cases in 2022.[1] After receiving rigorous treatment, the patient's response to treatment is evaluated by the conversion of positive acid-fast bacilli (AFB) to negative AFB. After six months of treatment, TB patients are considered to have failed therapy if their sputum does not become negative.[2]

TB treatment monitoring can also be assessed by ESR. The inflammatory process in TB causes the ESR value to increase, although it is not specific to TB infection.[3] ESR can show normal results even though the patient has TB, but the use of ESR values can still be used as an indicator of patient improvement.[3,4] NLR value can also be used to evaluate systemic inflammation.[5] Research conducted by Harun *et al*. examining NLR in TB with positive and negative AFB showed that there was a significant increase in the number of neutrophils, a decrease in lymphocytes and an increase in NLR in positive AFB TB compared to negative AFB TB.[6]

Since vitamin D is believed to play a role in the host cell immunological response to M. tuberculosis infection, vitamin D supplements are considered to be helpful in the treatment of TB. The addition of vitamin D supplementation (250 ug vitamin D/day) for 6 weeks to ATD in TB patients increased clinical improvement, as well as sputum conversion time and improved radiological images, according to research by Sugiarti *et al*. However, the dosage of vitamin D supplementation must be changed to achieve meaningful changes.[7]

There has not been much research on the effect of vitamin D supplementation on sputum conversion and inflammatory indicators such as ESR and NLR in TB patients. The purpose of this study was to assess the effect of vitamin D supplementation on sputum conversion and ESR and NLR in TB patients in Ulin Banjarmasin Hospital and Pekauman Health Centre, considering that there has been no such research in this area.

METHODS

This study was an experimental study with a randomized controlled trial study design. The study was conducted at Ulin Banjarmasin Regional Hospital and Pekauman Health Center, from May to July 2024. This research has obtained research ethics permission from the Research Ethics Commission of Lambung Mangkurat University and Ulin Banjarmasin Hospital, with permit number: No.64/PPDS.Pulmo/Litbang/RSUDU/V/2024.

The study subjects were pulmonary TB patients aged ≥18 years, diagnosed with bacteriologically confirmed pulmonary TB (TCM and AFB), Patients willingness to participate in this study by signing an informed consent. Patients who consumed vitamin D supplementation in the past month, suffered from MDR TB and lung tumors, had comorbid diseases such as kidney failure and impaired liver function, had a history of intolerance or hypersensitivity to vitamin D, and women who were pregnant, or planning to become pregnant, and were breastfeeding were excluded from this study. The sample size in this study used the unpaired numerical comparative minimum formula with the results of 19 subjects in the treatment group and 19 subjects in the control group.

After obtaining the research subjects based on the research criteria, it was then divided into 2 groups, namely the control group (given first-line ATD + placebo), and the treatment group (given first-line ATD + vitamin D) randomly, using a sealed envelope. AFB evaluation was carried out in weeks 2, 4, 6 and 8. ESR and NLR evaluations were carried out in weeks 4 and 8. Sputum conversion is defined as a change from AFB positive to negative. NLR changes were assessed based on a comparison of the mean NLR before, 4 weeks, and 8 weeks after the intervention. ESR changes were assessed based on a comparison of the mean ESR before, 4 weeks, and 8 weeks after the intervention.

After the data was collected, data analysis was carried out using the Statistical Package for the Social Sciences (SPSS) Version 29.0 software program. Subject characteristics are presented in the form of frequencies and percentages, with an assessment of differences in the characteristics of the two groups using the Chi-square test. The generalized estimating equation (GEE) was used to determine the effect of vitamin D supplementation on sputum conversion, ESR and NLR. If the p-value is <0.05, it is said to be significant.

RESULTS

Subject Characteristics

The number of subjects consisted of 38 research subjects that were included until the end of this study, and were divided into two groups, namely 19 research subjects in the control group given ATD line 1 + placebo, and 19 research subjects in the treatment group given ATD line 1 + vitamin D, without drop out subjects. Table 1 shows the characteristics of the subjects in this study.

There was no significant difference in subject characteristics between the two groups (p>0.05). There were more women in the control group compared to the treatment group. The mean age of the control group was 47.31±14.94 years and 50.42±18.61 years in the treatment group. New cases were the most dominant in this study. In both the control and intervention groups, most subjects did not have comorbidities, but some subjects did have comorbidities such as hypertension, diabetes mellitus, or others. Based on BMI, the control group was dominated

TABLE 1
Characteristics of Research Subjects

Characteristics	Control (n=19)	Intervention (n=19)	Total	*p*-value
Gender				0.051*
Men	6 (31.6%)	12 (63.2%)	18 (47.4%)	
Women	13 (68.4%)	7 (36.8%)	20 (52.6%)	
Age (meanSD)	47.31±14.94	50.42±18.61		0.228**
Case Classification				1.000***
New Case	17 (89.5%)	18 (94.7%)	35 (92.1%)	
Relaps	2 (10.5%)	0 (0%)	2 (5.3%)	
Drop out	0 (0%)	1 (5.3%)	1 (2.6%)	
Comorbid				0.794***
None	14 (73.6%)	14 (73.6%)	28 (73.6%)	
HT	0 (0%)	1 (5.3%)	1 (2.6%)	
DM	2 (10.5%)	1 (5.3%)	3 (7.8%)	
Others	3 (15.9%)	3 (15.8%)	6 (16%)	
BMI				0.194*
Underweight	12 (63.2%)	8 (42.1%)	20 (52.6%)	
Normal	7 (36.8%)	11 (57.9%)	18 (47.4%)	
Smoking				0.179*
Smoking	5 (26.3%)	9 (47.4%)	14 (36.8%)	
No Smoking	14 (73.7%)	10 (52.6%)	10 (63.2%)	
Occupation				0.972***
No Occupation	0 (0%)	3 (15.8%)	3 (5.3%)	
Employee	4 (21.1%)	4 (21.1%)	4 (21.1%)	
Businessman	4 (21.1%)	3 (15.8%)	3 (18.4%)	
Housewife	9 (47.4%)	5 (26.3%)	14 (36.8%)	
Civil Servant	0 (0%)	1 (5.3%)	1 (2.6%)	
Farmer	2 (10.5%)	3 (15.8%)	3 (13.2%)	
AFB Before Treatment				0.152***
3+	3 (15.8%)	2 (10.5%)	5 (13.2%)	
2+	7 (36.8%)	1 (5.3%)	8 (21.0%)	
1+	9 (47.4%)	16 (84.2%)	25 (65.8%)	
Gene Xpert				1.000***
Very Low	1 (5.3%)	2 (10.5%)	3 (7.3%)	
Low	9 (47.4%)	10 (52.6%)	19 (50.0%)	
Medium	7 (36.8%)	4 (21.1%)	11 (28.9%)	
High	2 (10.5%)	3 (15.8%)	5 (13.2%)	

DM: Diabetes Melitus, HT: Hypertension. *Chi Square, **Independent t-test, ***Kolmogorov Smirnov

TABLE 2
The Effect of Vitamin D Supplementation on Sputum Conversion

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
Intercept	0.465	0.2013	0.070	0.859	5.329	1	0.021
Intervention Group	0.480	0.2298	0.030	0.931	4.363	1	0.037
Control Group	0						
(Scale)	1						

Dependent variable: Sputum Conversion

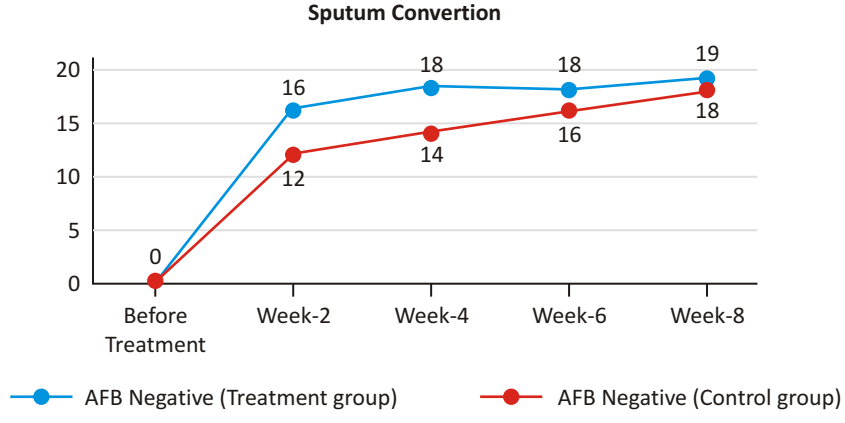

Figure 1. AFB Conversion Chart

by subjects with an underweight BMI; while the intervention group was dominated by subjects with a normal BMI. There were more non-smokers than smokers. The study subjects had various occupations, such as employee, businessman, housewife, civil servant, and farmer. Based on AFB examination before therapy, there were more subjects in the control group +1 (47.4%); as well as in the intervention group (84.2%). Based on the results of gene expert, the findings of gene expert low were more numerous than very low, medium, and high, with the number in the control group being 47.4% and in the intervention group being 52.6%.

Vitamin D and Sputum Conversion

The effect of vitamin D supplementation on sputum conversion was assessed in this study, and is presented in the Table 2.

Based on Table 2, there is a significant relationship between vitamin D supplementation and sputum conversion (p = 0.037). Figure 1 shows that more subjects experienced sputum conversion in the treatment group compared to the control group. In the second week, 12 people experienced sputum conversion in the control group and 16 people in the treatment group. In the fourth week, 14 people experienced sputum conversion in the control group and 18 people in the treatment group. In the sixth week, 16 people experienced sputum conversion in the control group and 18 people in the treatment group. In the eighth week, 18 people experienced sputum conversion in the control group and 19 people experienced sputum conversion in the treatment group.

Vitamin D and NLR

NLR was assessed before treatment, week 4 and week 8 after treatment. The following table shows the effect of vitamin D supplementation on NLR after 8 weeks.

Table 3 shows that there is no significant relationship between vitamin D supplementation and NLR (p = 0.641). The graph of NLR changes before treatment, week 4 and week 8 can be seen in Figure 2. Before treatment, the mean NLR in the control group was 7.15 and in the treatment group was 5.52. At week 4, the mean NLR in the control group was 3.52 and in the treatment group was 3.05. At week 8, the mean NLR in the control group was 2.36 and in the treatment group was 2.84.

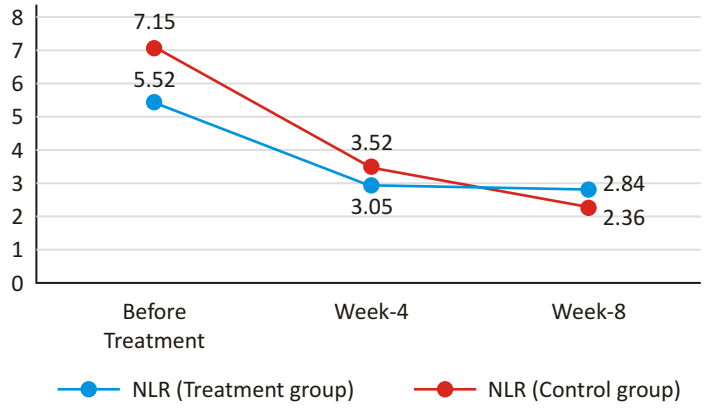

Figure 2. NLR Chart

TABLE 3
The Effect of Vitamin D Supplementation on NLR

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
Intercept	3.863	0.4030	3.073	4.653	91.881	1	0.000
Intervention Group	0.549	1.1779	-1.769	2.858	0.217	1	0.641
Control Group	0						
(Scale)	28.109						

Dependent variable: NLR

Vitamin D and ESR

ESR was assessed before treatment, week 4 and week 8. Figure 3 shows the changes in ESR before treatment, week 4 and week 8 in both groups. Before treatment, the LED in the control group was 63.63 and in the treatment group was 55.15. At week 4, the LED in the control group was 60.57 and in the treatment group was 50.36. At week 8, the LED in the control group was 42.26 and in the treatment group was 42.05.

Based on Table 4, there was no significant relationship between vitamin D supplementation and ESR ($p = 0.474$).

DISCUSSION

Sputum smear negativity (becoming non-infectious) after a specific period of anti-TB treatment initiation is a critical indicator for assessing the efficacy of anti-TB treatment in developing countries.[8] Despite the complete elimination of new TB transmission today, an estimated 5%–15% of individuals with tuberculosis (TBI) develop active TB disease during their lifetimes, thereby functioning as a vast reservoir for future TB disease.[9] Isoniazid, rifampicin, pyrazinamide, and ethambutol comprise the conventional treatment regimen for tuberculosis. The dosage must be adjusted in accordance with the patient's clinical condition, as each substance has a distinct mechanism of action. Nevertheless, this treatment is frequently confronted with a variety of obstacles, such as the emergence of substantial adverse effects. Hepatotoxicity, neuropathy, gastrointestinal disorders, and hypersensitivity reactions are potential side effects that may impact patient adherence to therapy.[10]

Recently, there has been a lot of research linking vitamin D with the prevention of tuberculosis and helping in the treatment of tuberculosis. Vitamin D (calciferol) and its metabolites are hormones and hormone precursors that can be synthesized endogenously in the appropriate biological environment. Vitamin D from plant sources is vitamin D2 (ergocalciferol), while from animal sources it is vitamin D3 (cholecalciferol). The skin is a significant source of vitamin D, which is synthesized upon exposure to ultraviolet B radiation (UV-B; wavelength, 290–320 nm). Vitamin D, whether synthesized cutaneously or absorbed from the intestine, is transported through the circulation

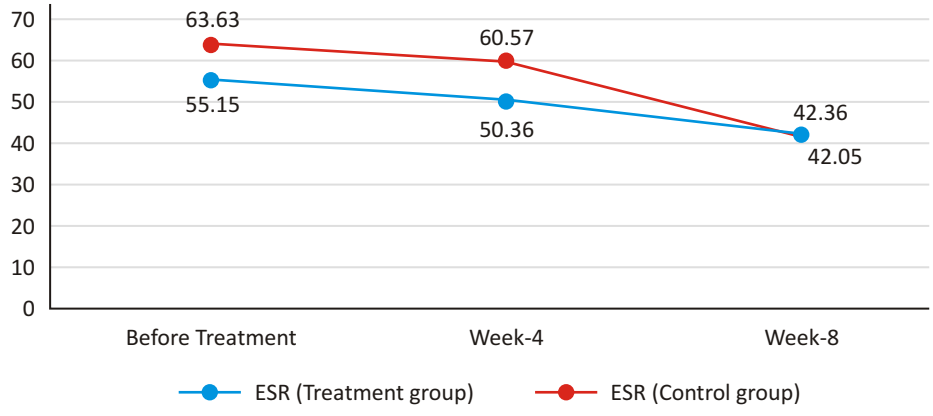

Figure 3. ESR Chart

TABLE 4
The Effect of Vitamin D Supplementation on ESR

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	Sig.
Intercept	54.491	5.7033	48.313	65.670	91.285	1	0.000
Intervention Group	-5.529	7.7186	-20.658	9.599	0.513	1	0.474
Control Group	0						
(Scale)	894.349						

Dependent variable: ESR

bound to the vitamin D-binding protein, α-globulin, which is synthesized in the liver. Vitamin D is then 25-hydroxylated in the liver by cytochrome P450 oxidase in mitochondria and microsomes to form 25-hydroxyvitamin D [25(OH)D] (calcidiol). The second hydroxylation, required for the formation of the active hormone 1,25-hydroxyvitamin D [1,25(OH)D] (calcitriol), occurs in the kidneys. 25-hydroxyvitamin D [25(OH)D] (calcidiol) is the primary circulating and stored form of vitamin D.[11]

Vitamin D enhances the antimicrobial activity of macrophages in the context of tuberculosis by promoting the production of cathelicidin and other antimicrobial peptides, as well as by supporting autophagy and phagolysosome fusion–mechanisms that are essential for the host's defense against Mycobacterium tuberculosis. Vitamin D also modulates the adaptive immune system by regulating T cell differentiation and cytokine responses, thereby assisting in the preservation of immune equilibrium. An association between low serum 25-hydroxyvitamin D levels and an increased susceptibility to infection and the development of tuberculosis has been consistently demonstrated in observational studies. It is common for individuals with active or latent tuberculosis to have lower vitamin D levels than healthy controls.[12,13] Furthermore, the biological effects of vitamin D are mediated by vitamin D receptors, also found in most tissues. In addition to its classic endocrine effects on calcium and phosphate metabolism and bone health, binding to these receptors has the potential to extend vitamin D's actions to various cell and organ systems (e.g., immune cells, the brain, breast, colon, and prostate).[11]

According to the study's findings, sputum conversion in patients with pulmonary tuberculosis is significantly impacted by vitamin D administration. Consistent with the findings of Siswanto *et al*. (2009), who found a correlation between sputum conversion and vitamin D provision, group I received 800 IU of vitamin D per day, while group 2 did not get any vitamin D. Compared to the group without receiving vitamin D, those who received it displayed negative AFB results noticeably more quickly ($p = 0.04$).[14] In that study, sputum conversion occurred as early as the first month after intervention. This conversion time was faster than in our study, where sputum conversion was seen 4 weeks after intervention. Because our study only assessed sputum conversion before, 4 weeks, and 8 weeks after

intervention, the results cannot indicate how quickly sputum conversion occurs. According to research by Sugiarti *et al*. (2018), adding 5,000 IU of vitamin D to ATD therapy enhanced radiological imaging, sputum conversion time, and clinical improvement as determined by the TB score in TB patients. To get noticeable effects, the vitamin D dosage must be increased.[15] Because it aids in regulating the immunological response to combat M. tuberculosis, vitamin D as a complement to ATD therapy also has a notable impact on clinical improvement. Vitamin D is able to phagocytose Mycobacterium tuberculosis through TLR2/1 sensitization which will increase the expression of RVD and CYP27B1, which are genes that form the 1-alpha-hydroxylase enzyme that functions to initiate vitamin D into its active metabolite form.[16]

The administration of vitamin D as a supportive treatment in addition to the present conventional short-term treatment is one alternative that should be taken into consideration in order to address the issue of TB treatment. Vitamin D contributes to respiratory system infections in the following ways: it improves mucociliary clearance function in the airways, aiding in the removal of respiratory pathogens and inflammatory mediators; it modulates inflammation by regulating adaptive and innate immune responses, suppressing excessive inflammation that may damage the respiratory tract during infections; and it lowers the risk and severity of acute respiratory infections.[17] Together with ATD that patients consumed, vitamin D acts as an immunomodulator that helps activate macrophages against Mycobacterium Tuberculosis.[8] By generating nitrogen and oxygen reactants, vitamin D has been shown to efficiently stop Mycobacterium Tuberculosis from growing in infected macrophages. It is well known that vitamin D promotes the synthesis of methyl glycol and the antimicrobial peptide β-Phenin 2, which aids in drawing T cells, neutrophils, and monocytes to the infection site. It has a major immunomodulatory effect on TB treatment.[10] Maintaining the activity of monocytes and macrophages linked to human innate immunity to certain infectious agents is the primary function of vitamin D. This function is crucial for the body's natural defense against infection, where macrophages play a significant part in pathogenesis.[13]

The active metabolite of vitamin D or calcitriol has the ability to induce an immune response to produce cathelicidin which functions as an endogenous antibiotic. The role of vitamin D in adaptive immunity is to suppress INF-y, TNF-α as inflammatory interleukins and increase IL-4 as an anti-inflammatory interleukin. The role of active metabolites of vitamin D in adaptive immunity is very necessary to suppress excessive inflammatory reactions so that it can improve and accelerate the healing of tuberculosis patients.[14,16] In addition, Vitamin D works by combining with nuclear receptors on affected cells so that abnormalities in the function and structure of the receptors or low levels of Vitamin D alter immunity to the tubercle bacillus.[18] Based on research by Riefani, *et al* (2024), various factors can increase the risk of TB, one of which is vitamin D deficiency. The results of this study showed that out of 42 research samples, there were 2 with normal vitamin D levels (4.76%), 19 with vitamin D insufficiency (45.2%), 21 with vitamin D deficiency (50%). Vitamin D levels in drug-resistant TB patients were higher than drug-sensitive TB due to differences in the number of samples and drug-resistant TB patients were more often exposed to sunlight related to their work.[19]

However, the results of this study are not in line with the study by Wang *et al*. (2018) who provided 60,000 IU of vitamin D, which showed that vitamin D supplementation did not affect AFB conversion time in TB patients.[20] The study participants were aged 23–47 years. All participants were undergoing intensive treatment at the time of entry. Vitamin D supplementation was administered for 8 weeks. Nearly 50% of the study subjects had vitamin D deficiency. This may have contributed to the differences in our results.[21] Research by Ganmaa *et al*. (2017) who conducted research on 190 patients also showed that vitamin D did not improve AFB conversion time.[21] This difference in results may be due to the fact that this study and the studies of Wang *et al* (2018) and Ganmaa *et al* (2017) did not measure vitamin D levels before the intervention, so they could not describe the initial vitamin D levels that could affect the results after the intervention.[20,21]

The results of this study indicate that there is no significant effect between vitamin D supplementation and NLR levels. They are not in line with the research of Wang *et al*. (2021) which showed that there is a relationship between vitamin D levels and NLR. The higher the vitamin D in the blood, the lower the NLR found.[20] Many studies have shown a relationship between vitamin D levels and inflammation. Research by Akbas *et al*. (2015) showed that subjects with sufficient vitamin D had lower NLR values compared to the group of subjects with vitamin D deficiency, and vice versa (p = 0.001). There isn't a clear consensus about the relationship between vitamin D and inflammatory indicators, despite the fact that the literature has highlighted the connection between vitamin D deficiency and numerous chronic inflammatory illnesses.[22]

The strong anti-inflammatory effects of 1,25-dihydroxyvitamin D, the active form of vitamin D, have been demonstrated to cause a change in response from the more inflammatory Th1/Th17 response to the less inflammatory Th2/Treg response. As a result, pro-inflammatory mediators including interferon gamma (IFN-g), TNF-a, IL-1b, IL-6, IL-8, IL-12, and IL-17 are secreted less frequently, whereas anti-inflammatory cytokines like IL-4 and IL-10 are produced more frequently.[23] Haematopoiesis in cells is influenced by

vitamin D. Vitamin D affects the early development of monocytes and granulocytes in haematopoiesis. The bioactive form of vitamin D (1,25(OH)2D3) will inhibit the development of colony-forming units of granulocyte macrophages (CFU-GM) and subsequently induce colony-forming units of macrophages during the haematopoiesis process. This will suppress the development of granulocyte cells and direct cell development towards monocytes and macrophages. The ratio of neutrophils, lymphocytes, and monocytes is altered by M. tuberculosis infection. It has been demonstrated that variations in the ratio are associated with the inhibition of M. tb growth, and they also indicate an increase in the effective immunological response.[24] Cathelicidin production from vitamin D will rise during TB infection, but this process will only take place if the body has enough vitamin D. Because of its antibacterial properties, this vitamin D can prevent germs from multiplying, which lowers neutrophils and lymphocytes and, consequently, NLR.[25]

This study evaluated ESR in addition to NLR. According to the study's findings, vitamin D supplementation and ESR do not significantly interact. This outcome is consistent with Wang *et al*. (2018)'s study, which found that vitamin D supplementation had no discernible impact on patients with pulmonary tuberculosis' ESR.[21] This, however, contradicts the findings of Kaya *et al*. (2017), who found a correlation between vitamin D levels and ESR. Patients with vitamin D insufficiency had greater ESRs than those with adequate vitamin D ($p < 0.001$), and there was a negative correlation between ESR and 25-hydroxyvitamin D levels ($r = 0.265$, $p < 0.001$).[26] ESR is an inflammatory biomarker that can rise in response to vitamin D insufficiency, according to studies by Etminan *et al*. (2020).[27]

It is known that vitamin D levels in the blood are associated with increased ESR. In accordance with the research of Etminan, *et al* (2020) showed that vitamin D deficiency is significantly associated with increased ESR. ESR has a significant effect on vitamin D levels.[27] In this study, vitamin D levels were not measured. In pulmonary TB, an inflammatory process occurs in pulmonary TB which causes positively charged acute phase proteins to neutralize the erythrocyte membrane, thereby reducing resistance and causing erythrocyte aggregation, forming rouleaux, resulting in increased ESR.[28]

By suppressing the expression of major histocompatibility complex (MHC-II) class 2 molecules on the cell surface, vitamin D has been demonstrated to improve monocyte differentiation into macrophages, stop macrophages from releasing inflammatory cytokines, and lessen the capacity of macrophages to present antigen to lymphocytes. Additionally, vitamin D inhibits the ability of T cells and monocytes to proliferate and stimulate, and it upregulates anti-inflammatory cytokines like IL-10 while downregulating proinflammatory cytokines like c-reactive protein (CRP), tumour necrosis factor-α (TNFα), interleukin (IL) 6, IL-1, and IL-8. Vitamin D may lower ESR because of these anti-inflammatory properties.[29]

The limitation of this study is that it does not include confounding variables in the statistical analysis of the relationship between independent and dependent variables, so it is difficult to see whether the confounding variables in this study can affect the results, including comorbid conditions. This study also did not mention about the diet of the subjects, including vitamin D intake from the food and sunlight exposure. Both of these variables might have confounded the results. The advantage of this study is that researchers studied inflammatory parameters, considering that research related to the effect of vitamin D supplementation on ESR and NLR in pulmonary TB patients has not been widely studied in South Kalimantan. It is hoped that this study can be used as a reference in further research.

CONCLUSION

Vitamin D supplementation can accelerate sputum conversion in pulmonary TB patients; however, it does not have a significant effect on NLR and ESR in pulmonary TB patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We would like to express our deepest gratitude to Ulin Banjarmasin Regional Hospital and Pekauman Health Center for providing time and space to assist in this research process.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; vol 13 (1) : 10–16

OPEN ACCESS

Original Article

Correlation Hemoglobin and Hematocrit Levels with Total Iron Binding Capacity (TIBC) Levels in Chronic Kidney Disease Patients

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v13i1.1387

Submitted: September 07th, 2025
Accepted: March 26th, 2025

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Abstract

Background : Chronic Kidney Failure (CKD) is a condition where the kidneys are structurally and functionally damaged characterized by a decrease in Glomerular Filtration Rate (GFR) reaching ≤ 60 ml/min/1.73m2 for more than three months. About 80 - 90% of patients with CKD experience anemia.
Aims : This research aims to determine the correlation of hemoglobin and hematocrit levels with Total Iron Binding Capacity (TIBC) levels in patients with chronic renal failure.
Methods : The research design used quantitative analysis with cross sectional method. The study used secondary data of as many as 55 respondents of chronic kidney disease patients undergoing hemodialysis. This study was conducted at the East Java Province Haji Hospital in March 2025.
Results : The normality test results showed that hemoglobin and hematocrit levels were not normally distributed ($p < 0.05$) while TIBC levels were normally distributed ($p > 0.05$). Kendall's tau b non-parametric correlation test there is no correlation between hemoglobin levels with TIBC ($r = 0.134$; $p = 0.154$), and hematocrit with TIBC levels ($r = 0.172$; $p = 0.066$).
Conclusion : The results of this study showed no correlation between hemoglobin and hematocrit levels with total iron binding capacity (TIBC) levels in chronic kidney disease patients undergoing hemodialysis at Haji Provincial General Hospital of East Java.

Keywords : Chronic Kidney Disease; Hemoglobin; Hematocrits; TIBC

INTRODUCTION

Structural and functional damage to the kidneys characterized by a decrease in glomerular filtration rate (GFR) to ≤ 60 ml/minute/1.73 m2 for more than three months is referred to as chronic kidney disease (CKD).[1] According to data from the World Health Organization (WHO), more than 843.6 million people suffered from kidney failure in 2021, and the death rate is projected to increase by 41.5% by 2040. This increase indicates that chronic kidney failure is the 12th leading cause of death worldwide.[2] The 2020 Basic Health Research (Riskesdas) results show that there are 18.613 patients with chronic kidney disease in Indonesia. East Java Province has a prevalence of 0.3% suffering from chronic kidney disease, suggesting that the prevalence of CKD patients in East Java remains relatively elevated.[3]

Disruption of kidney function can cause a decrease in the kidney's ability to filter creatinine, resulting in an increase in serum creatinine. An increase in blood creatinine levels determines whether patients with kidney dysfunction need to undergo hemodialysis or not.[4] Hemodialysis is a treatment method used to filter waste and fluids from the blood, similar to the function of normal kidneys. Hemodialysis contributes to controlling blood pressure and balancing essential mineral levels such as potassium, sodium, and calcium.[5]

Urea and creatinine can be used to diagnose kidney dysfunction, as these compounds can only be excreted by the kidneys. Urea is the final substance produced from protein metabolism taking place in the liver. Creatinine is the end product of creatine metabolism, which is a compound found in large quantities in muscles and contains nitrogen.[6]

One of the functions of the kidneys is to produce the hormone erythropoietin. Erythropoietin is a hormone used to stimulate the production of red blood cells. A reduction in erythropoietin production occurs in individuals suffering from CKD often leads to a decrease in the number of red blood cells, resulting in a decrease in hematocrit levels.[7] Approximately 80–90% of patients with chronic kidney disease experience anemia, especially in stage III. Patients with CKD are diagnosed with anemia if their hemoglobin levels are <12 g/dL for women and <13 g/dL for men.[8] In diagnosing anemia, laboratory tests such as hematology tests can be performed, including hemoglobin levels, hematocrit, red blood cell, red blood cell indices (MCV, MCH, MCHC), reticulocyte count, blood smear, and iron status tests, including Serum Iron (SI), Total Iron Binding Capacity (TIBC), Serum Ferritin, and Transferrin Saturation (ST).[9]

Previous research in 2017 showed that there was a correlation between creatinine levels and Hb (r=-0.424; *p*=0.000), RBC (r=-0.367; *p*=0.004), hematocrit (r=-0.421; *p*=0.001), Mean Corpuscular Hemoglobin (MCH) (r = -0.337; *p* = 0.009), Mean Corpuscular Hemoglobin Concentration (MCHC) (r = -0.272; *p* = 0.038), and SI (r=-0.299; *p*=0.034) in CKD patients undergoing hemodialysis at Sabratha Hospital in western Libya. The main reason for anemia in patients with CKD is the reduced production of erythropoietin (EPO) resulting from injury to the renal peritubular cells, with its occurrence rising as kidney function worsens.[10]

Previous research in 2020 showed that there was a weak correlation (r= 0.17; *p*= 0.02) between hemoglobin levels and TIBC in patients with chronic kidney failure non hemodialysis. The results of this study indicate that impaired kidney function is correlated with the severity of anemia due to various factors associated with the development of anemia in CKD patients. The average hemoglobin levels, red blood cell count, and hematocrit levels decreased significantly as kidney function deteriorated.[11]

A 2023 study indicate a weak correlation (r = 0.09; *p* = 0.684) between hemoglobin levels and Total Iron Binding Capacity (TIBC) levels in patients with stage V chronic kidney disease (CKD) undergoing hemodialysis at Toeloengredjo Hospital in Pare, Kediri. The study results indicate that low TIBC levels are not the sole cause of decreased hemoglobin levels. Hemoglobin levels decrease in CKD patients is caused by various factors, including reduced production of erythropoietin hormone, decreased longevity of red blood cells, inflammation and infection associated with hypothyroidism, advanced hyperparathyroidism, and aluminum poisoning, and most commonly due to iron and folate deficiency.[12]

METHODS

This study has obtained ethical approval from the Health Research Ethics Committee of the Haji Provincial General Hospital of East Java with certificate number: 445/56/KOM.ETIK/2025. The study design used was a quantitative analysis employing a cross-sectional approach, conducted at the Clinical Pathology Laboratory Unit of the Haji Provincial General Hospital of East Java in March 2025. The research sample was obtained using purposive sampling with criteria of patients with chronic kidney disease (CKD) undergoing hemodialysis with creatinine levels >7.0 mg/dL and aged >19 years. The study utilized secondary data from medical records and the Laboratory Information System (LIS) at the Haji Provincial General Hospital of East Java over the past five years (2021–2025), involving 55 respondents. Hemoglobin and hematocrit tests were performed using the Hematology Analyzer 5 diff (Sysmex Xn-550 and Sysmex Xn-350), and Total Iron Binding Capacity (TIBC) tests were conducted using the Cobas C-501. Data analysis was performed using SPSS version 23, followed by a normality test using the Kolmogorov-Smirnov test, and continued with a non-

parametric test using Kendall's tau-b correlation test.

RESULTS

In accordance with the results obtained from a study on the correlation between hemoglobin and hematocrit levels and total iron-binding capacity (TIBC) in 55 patients with chronic kidney disease. The study samples were obtained from secondary data taken from medical records and the laboratory information system (LIS) of patients with chronic kidney disease. Based on the study findings, there were 0 patients in 2021, 24 patients in 2022, 28 patients in 2023, 3 patients in 2024, and 0 patients in 2025 who underwent hemoglobin, hematocrit, and TIBC tests at the Clinical Pathology Laboratory of the Haji Jawa Timur Provincial General Hospital, as shown in Figure 1a.

DISCUSSION

According to the study results presented in the Figure 1 b, it was found showed a predominance of male patients (2:1) compared to female patients. This research corresponded with the findings of the study carried out by Wayan in 2023 at Sanjiwani Gianyar Hospital on patients with CKD, which showed that the number of male patients was 48 people (60%), while female patients were 32 people (40%). This condition can be caused by male tendency to work heavier, both physically and mentally, and can also be influenced by lifestyle factors such as smoking habits, alcohol consumption, a diet high in salt and fat, and low physical activity are known to be associated with an increased risk of metabolic diseases such as hypertension, obesity, and diabetes. These conditions are major risk factors contributing to the development of chronic kidney

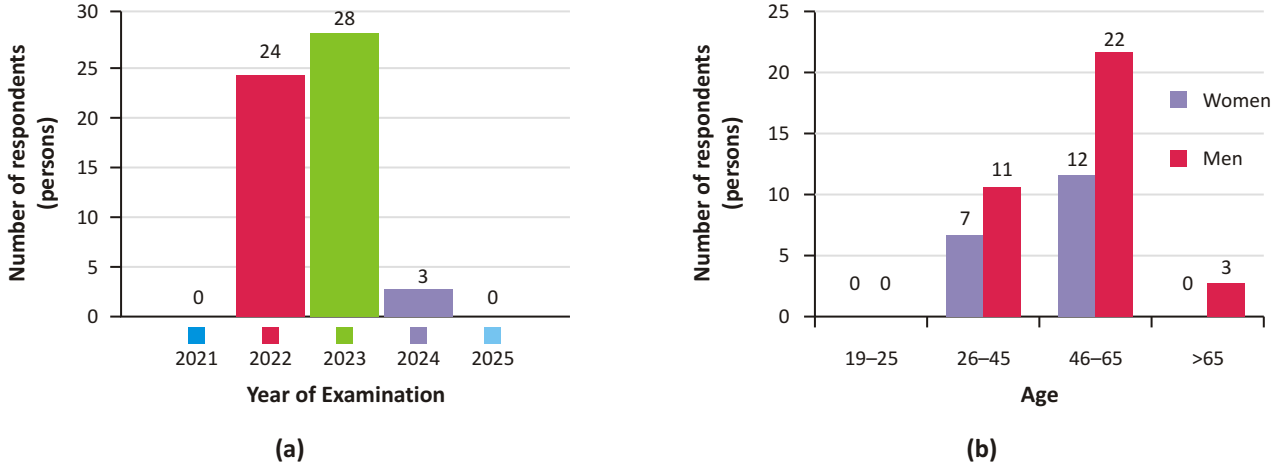

Figure 1. (a) Distribution of Respondents by Year of Examination, (b) Distribution of Respondents by Gender and Age

TABLE 1
Distribution of Respondents and Examination Results of Hemoglobin, Hematocrit, TIBC Levels

No	Characteristic Responden	N	%	Normal Value	Mean
1	Hemoglobin (g/dL)			11.2 – 17.5 g/dL	7.682 ± 1.31
	Normal	0	0		
	Mild Anemia	8	14.5		
	Moderate Anemia	33	60		
	Severe Anemia	14	25.5		
	Total	55	100		
2	Hematocrit (%)			34 – 51%	23.16 ± 3.91
	Normal	0	0		
	High	0	0		

TABLE 1. *Continued.*

No	Characteristic Responden	N	%	Normal Value	Mean
	Low	55	100		
	Total	55	100		
3	TIBC (µg/dL)			228 – 450 µg/dL	167.47 ± 48.178
	Normal	7	12.7		
	High	0	0		
	Low	48	87.3		
	Total	55	100		

TABLE 2
Kendall's tau b correlation

Variabel	(r)	(p)
Hemoglobin with TIBC	0.134	0.154
Hematokrit with TIBC	0.172	0.066

disease.[13,14]

Several epidemiological studies indicate a higher prevalence of CKD among men, partly due to occupational factors. Men tend to work in sectors involving heavy physical labor, such as construction, agriculture, mining, and manufacturing, which often involve exposure to excessive heat, chronic dehydration, and exposure to chemicals or heavy metals. This exposure triggers oxidative stress, impaired renal perfusion, and tubular damage, thereby accelerating progressive kidney function decline.[15,16]

In addition, the lower prevalence of CKD in women can be explained by the absence of testosterone or the presence of estrogen. Estrogen affects kidney function through various mechanisms, including improved metabolism, the selectivity of Angiotensin Type 2 (AT2) receptor signaling, diminished oxidative stress, and differential renin-angiotensin system (RAS). Endogenous estrogen plays a crucial role in non-communicable diseases such as CKD thanks to its ability to promote angiogenesis and vasodilation, while suppressing the production of reactive oxygen species and the development of fibrosis.[17]

Based on the age distribution in Figure 1 b, most patients with chronic kidney disease were between the ages of 46–65 (61.8%). This research corresponds with the findings of the study carried out by Lumbantobing in 2022 at Tarutung Hospital on patients with CKD who underwent hemodialysis showed that the most patients belonged in the 51–61 year age group as many as 32 patients (34.8%), this occurs because kidney function tends to decrease with age, especially if accompanied by a decline in life quality and the the presence of comorbid factors.[18]

As we age, the number of nephrons naturally decreases starting at age 40, by about 10% per decade. This decline increases the risk of CKD because the remaining nephrons must work harder (hyperfiltration) and enlarge (hypertrophy). As nephrons are lost without regeneration, the workload increases on the remaining units, leading to high intraglomerular pressure, glomerular sclerosis, tubular fibrosis, and progressive GFR decline. By the age of 70–75, the number of nephrons can decrease by up to 48% compared to younger ages, while cortical volume shrinks by only 16% due to temporary compensatory tubular hypertrophy, thereby accelerating damage in the presence of comorbid factors.[19]

Similar results were obtained from Fitri and Wahyu's research in 2022, which showed the highest prevalence of ureum and creatinine levels at the age of 40–45 years. The decline in kidney function begins to occur at the age of 40 years and above, with a decrease in function of up to 50% due to the reduced number of functioning nephrons and the absence of regeneration ability. This results in a reduced capacity of the kidney to regulate fluid output and increases the risk of protein loss through urinary excretion.[20]

In this study, 55 patients (100%) experienced anemia, with the classifications of: Mild Anemia (14.5%),

Moderate Anemia (60%), and Severe Anemia (25.5%), showing an average hemoglobin level of 7.682 g/dL. Followed by a decrease in hematocrit in all patients, with a mean hematocrit level of 23.16% as shown in Table 1. Based on hemoglobin levels, the degree of anemia can be classified into 3 categories: that mild anemia, that occurs when hemoglobin levels fall within the range of 9–10 g/dL, moderate anemia, that occurs when hemoglobin levels fall within the range of 7–8 g/dL, and severe anemia if hemoglobin levels are <7 g/dL.[21] Anemia commonly occurs in individuals with CKD and is linked to a reduced quality of life, as well as increased morbidity, mortality, and accelerated progression of CKD. The primary reason for anemia in CKD is the decreased generation of the hormone erythropoietin, which is responsible for the differentiation and development of red blood cell precursors.[22]

Based on the results of the distribution of TIBC levels in Table 1, it was found that the majority of patients had low TIBC levels (87.3%), with a mean TIBC level of 167.47 µg/dL, the TIBC level was below the normal limit. Decreased TIBC levels are found in conditions of hemochromatosis, hemosiderosis, thalassemia, hyperthyroidism, nephrotic syndrome, and anemia in chronic diseases.[23] TIBC is iron bound to the transferrin protein in plasma and plays a role in the transport of iron to the bone marrow for hemoglobin formation. The TIBC test is useful for determining the total amount of iron that can be absorbed by the transferrin protein.[24] Patients with CKD may experience chronic inflammation which can result in low TIBC levels.[12] Based on data from the Iron Disorders Institute, TIBC tends to increase when iron reserves decrease, and conversely, TIBC decreases when iron reserves increase.[25]

The majority of CKD patients in this study exhibited low TIBC levels, reflecting impaired iron metabolism due to chronic inflammation. This inflammation suppresses transferrin (an iron-carrying protein) synthesis in the liver via pro-inflammatory cytokines, thereby reducing TIBC. Furthermore, chronic inflammation also increases hepcidin levels, which inhibit iron release from macrophages and reduce iron absorption in the intestine, leading to impaired iron utilization or functional iron deficiency.[26]

The results of the Kolmogorov-Smirnov normality test in Table 2 for hemoglobin and hematocrit data, indicated that hemoglobin and hematocrit levels were not normally distributed because the *p*-value is <0.05, whereas TIBC levels showed normally distributed data because the *p*-value is >0.05. Therefore, the analysis continued with a nonparametric test, namely Kendall's tau-b.

The results of the Kendall's tau-b correlation test between Hemoglobin Levels and TIBC Levels obtained a value (r = 0.134; p = 0.154) (p> 0.05), while the correlation test between Hematocrit with TIBC Levels obtained a value (r = 0.172; p = 0.066) (p>0.05). The results of statistical test analysis showed that there were no correlation between hemoglobin and Hematocrit levels with TIBC levels in patients with CKD undergoing Hemodialysis at the Haji Hospital of East Java Province. There is no correlation between hemoglobin and hematocrit levels with TIBC levels because not all patients with chronic kidney disease experience iron deficiency anemia.[27]

This aligns with earlier studies carried out by L. V. Thang *et al* (2020) indicate a weak correlation (r = 0.17; p = 0.02) between hemoglobin and TIBC levels in non-hemodialysis chronic kidney disease patients. The results of this study indicate that decreased kidney function has a correlation with the severity of anemia due to various factors associated with the development of anemia in patients with CKD.[11]

The results of research conducted by Ekowati (2023) indicate a weak correlation (r = 0.09; p = 0.684) between Hemoglobin levels and TIBC levels in patients with grade V CKD who undergo Hemodialysis. This study's outcomes suggest that low TIBC levels are not the only cause of a decrease in hemoglobin levels. Hemoglobin levels decrease in patients with CKD is caused by many factors, including decreased production of the hormone erythropoietin, decreased longevity of red blood cells, inflammation and infection associated with hypothyroidism, advanced hyperparathyroidism, and aluminum poisoning, and most often due to iron and folate deficiency.[12]

In patients with chronic kidney disease, anemia is chiefly caused by reduced production of the hormone erythropoietin. The kidneys have a role in producing the hormone erythropoietin (EPO). This hormone is important in the process of RBC formation (erythropoiesis). Erythropoietin helps maintain the balance of the quantity of RBC within the body and ensures that tissues get enough oxygen. To maintain this balance, old red blood cells are replaced by new red blood cells.[28]

Anemia occurs when hemoglobin (Hb), hematocrit (HCT), and red blood cell counts are below normal values.[29] Hemoglobin as one of the signs to determine the decrease in the number of red blood cells (erythrocytes).[8] Hematocrit examination is one of the quality control examinations performed in the laboratory to determine the volume of erythrocytes contained in the blood. Hematocrit has a close relationship with hemoglobin levels. The higher the hemoglobin level, the hematocrit value will also increase, so that the viscosity or viscosity of the blood becomes more concentrated.[30]

The mechanism of anemia in patients with CKD is influenced by several factors. In addition to erythropoietin deficiency, anemia can also be caused by iron deficiency, which can occur due to blood loss or impaired iron absorption. In addition, the systemic

inflammation that occurs in CKD and its comorbidities causes iron storage to become ineffective. Other factors include reduced bone marrow response to erythropoietin due to uremic effects, shorter red blood cell lifespan, and vitamin B12 or folic acid deficiency.[28]

Iron plays a crucial role in oxygen binding in red blood cells and plays a vital role in various other cellular processes. Iron deficiency anemia can also be found in patients with CKD. Iron deficiency can be absolute, This condition is typically due to inadequate dietary consumption or hidden bleeding, or it may be functional, occurring when the iron demand in the erythroid bone marrow exceeds the iron supply available.[27] Patients with CKD who have anemia often maintain adequate iron levels in their bodies, but the iron is not optimally available in the bloodstream. This condition occurs due to a decrease in the amount of ferroportin (iron transport protein), so that the hemoglobin formation process is disrupted.[31]

Iron testing is important to diagnose iron deficiency or iron overload. The iron that is transferred from enterocytes to the transport protein assisted by hephaestin is called apotransferrin. When apotransferrin binds to iron, this protein turns into transferrin. TIBC is a direct measure of the amount of transferrin bound to iron in the blood. Transferrin itself is a glycoprotein that can bind two iron atoms per molecule. The amount of iron attached to transferrin indirectly reflects transferrin levels in the body. In iron deficiency conditions, the concentration of transferrin in the bloodstream is comparatively greater than that of iron, resulting in high TIBC values. Conversely, in iron overload conditions, the amount of transferrin in the blood decreases, resulting in a low TIBC value .[32,31]

CONCLUSION

According to the findings of the study regarding the correlation of hemoglobin and hematocrit levels with Total Iron Binding Capacity (TIBC) levels in patients with Chronic Renal Failure, it can be summarized that there is no correlation found between hemoglobin levels with TIBC (r = 0.134; p = 0.154), and hematocrit with TIBC levels (r = 0.172; p = 0.066) In patients with chronic kidney disease undergoing Hemodialysis at the Haji Provincial General Hospital of East Java .

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; vol 13 (1) : 17–24

OPEN ACCESS

Original Article

The Effect of Walking as A Physical Activity on Sleep Quality in The Third Trimester of Pregnancy

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Abstract

Background : Sleep disorders are common in pregnant women during the third trimester, with frequent urination being a prevalent issue due to weakened bladder muscles, leading to deteriorated sleep quality. Physical activity, such as walking, is recommended as an easy, effective, and economical way to improve sleep quality in pregnant women.
Aims : To analyze the effect of walking on sleep quality in third-trimester pregnant women at Kebakkramat I Karanganyar Health Center, Central Java.
Methods : This study used a Quasi-Experimental design with a Pretest-Posttest Control Group approach. The sample consisted of 80 third-trimester pregnant women, selected using Multistage Sampling. The Pittsburgh Sleep Quality Index (PSQI) questionnaire was used to measure sleep quality. The intervention involved walking for 20 minutes over two weeks.
Results : The analysis used the Delta score mean test between the pre-tests and post-tests for each respondent to show a significant effect of walking on sleep quality. A negative delta value shows a decrease in the PSQI score, indicating improved sleep quality for the respondent, and vice versa. The intervention group had a lower delta score mean of -3.13 compared to the control group, indicating that walking effectively improves sleep quality.
Conclusion : Walking has significant potential to improve sleep quality in third-trimester pregnant women. Pregnant women are encouraged to walk regularly and increase their knowledge about pregnancy.

Keywords : Pregnant women; sleep quality; physical activity; walking.

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v13i1.1238

Submitted: October 08th, 2024
Accepted: March 26th, 2026

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INTRODUCTION

Physical changes during the third trimester of pregnancy can lead to discomfort, including sleep disturbances, which significantly affect sleep quality in pregnant women. A study found that 88% of African-American pregnant women experienced poor sleep quality during this stage.[1] Similarly, research indicates that in Poland, the prevalence of sleep disturbances among pregnant women is estimated at 25–40%, with overall rates of sleep disturbances ranging from 84.2% to 90.5%.[2] The prevalence of sleep disturbances among pregnant women in Asia is reported to be 41.8%.[3] Data from the Basic Health Research showed that sleep disturbances in pregnant women in Indonesia reached 64%, with 65% of pregnant women in Indonesia experiencing sleep apnea.[4]

Sleep disturbances in pregnant women can be caused by various factors, such as shortness of breath, increased fetal weight, cramps during sleep, fetal movements, frequent waking to urinate, feeling too hot or cold, and back pain. The increase in progesterone hormone, which has a muscle-relaxing effect on the bladder, can also cause pregnant women to urinate frequently, ultimately negatively impacting their sleep quality.[5] Inadequate sleep in pregnant women can negatively impact both the mother and the fetus, including an increased risk of depression, preterm birth, low birth weight, increased pain during labor, and a higher potential for cesarean delivery.[1] Insufficient sleep duration in pregnant women can also result in declining health conditions, such as decreased concentration, fatigue, muscle pain, mood changes, and a tendency to become emotional.[1]

Adequate sleep is crucial for pregnant women to stay fit and healthy, enabling them to carry out daily activities, and ensuring the healthy growth of the fetus. Therefore, pregnant women need to ensure that they get enough sleep. It is recommended to sleep for 7–8 hours per day to keep the body relaxed, fit, and healthy.[6] Sleep disturbances are most common during the third trimester of pregnancy.[7] According to research, the prevalence of poor sleep quality in third-trimester pregnant women is 55.6%.[5] Various literature suggests that non-pharmacological measures recommended to improve sleep quality in pregnant women include physical activities or exercises such as swimming, yoga, pilates, pregnancy massages, relaxation, and walking. Physical activity refers to any bodily movement generated by skeletal muscles that requires energy and effort. Engaging in proper and consistent physical activity is recommended 35 times per week, with a minimum duration of 150 minutes per week.[8]

One of the easiest, most effective, and economical physical activities is walking. For pregnant women, especially in the late trimester, it is recommended to walk three times a week for 15–20 minutes.[9] Pregnant women in their late trimester who routinely walk in the morning can improve their health and that of their fetus. The high oxygen levels in the morning help the brain increase focus, thinking ability, and concentration. The amount of oxygen in the blood affects the release of serotonin in the body, which can improve mood and make them feel happier. The best time to walk is between 05:30–08:00 AM with a distance of about 500 meters.[5]

Walking provides several benefits for pregnant women related to sleep quality, including increasing stamina, reducing fatigue, and providing relaxation to the pelvic and uterine muscles. This activity helps the body become more relaxed, reduces physical tension and stress, and consequently improves sleep depth and overall sleep quality.[4] Regular physical activity during pregnancy, particularly walking, is fundamental component of maternal health that significantly improves clinical outcomes. Evidence suggests that consistent walking effectively regulates blood glucose levels, thereby reducing the risk of gestational diabetes mellitus and ensuring gestational weight gain remains within recommended medical limits.[26,27]

Furthermore, routine exercise enhances cardiovascular fitness and strengthens optimal fetal positioning and potentially shortens the duration of labor.[25] In addition to preparing the body for childbirth, low-impact activities improve systemic blood circulation, which is essential for alleviating common pregnancy related discomforts such as lower back pain and peripheral edema.[28]

Providing health counseling on the recommendation of physical activities such as walking for pregnant women is part of the midwife's authority in antenatal care for normal pregnancies, as stated in the Minister of Health Regulation (Permenkes) No. 1464/Menkes/Per/X/2010 regarding the authority possessed by midwives.

This study highlights the need to further investigate the effects of walking on sleep quality among third-trimester pregnant women, as most previous research has focused on earlier trimesters or other forms of exercise. By using the standardized Pittsburgh Sleep Quality Index (PSQI) to objectively measure outcomes, this study aims to provide stronger scientific evidence that walking is a simple, safe, and effective intervention to enhance sleep quality during late pregnancy.

Based on a preliminary study conducted, 6 out of 8 third-trimester pregnant women who completed the questionnaire had poor sleep quality and reported rarely engaging in daily physical activity. Therefore, further research is needed to determine whether physical activity such as walking can influence the sleep quality of pregnant women experiencing sleep disturbances and whether it can serve as a medical intervention to reduce the negative effects of discomfort during pregnancy.

METHODS

This study is an experimental research with a quasi-experimental design using a pretest-posttest control group design. The population in the study was 104 third-trimester pregnant women who met the inclusion criteria of being in the third trimester, healthy, and not experiencing complications during pregnancy. The exclusion criteria included pregnant women who were engaging in other exercises such as yoga, pilates, swimming, women with pregnancy risks such as premature rupture of membranes, preeclampsia, placenta previa, insomnia, and depression. The sample was selected using a multistage sampling technique, and the sample size was calculated using a categorical unpaired analytical research sample formula,[12] resulting in a sample size of 80 pregnant women based on inclusion and exclusion criteria.

The independent variable in this study is the physical activity of walking, while the dependent variable is the sleep quality of pregnant women. Data collection was carried out using primary data with the PSQI (Pittsburgh Sleep Quality Index) pre-test and post-test questionnaire instruments. After that, the data collection of PSQI questionnaire delta scores between the pre- and post-tests of each patient was calculated. Pregnant women in the intervention group were given a walking procedure eight times over two weeks in the morning between 05:30–08:00 AM for 20 minutes, covering a distance of 1–2 kilometers. The control group did not receive the walking physical activity intervention during the study. During the two weeks, the walking activity was monitored via a WhatsApp group by sending videos and a stopwatch during the walk. On the 14th day, the post-test sleep quality questionnaire was filled out, and the respondents submitted their monitoring sheets to the researchers. Data analysis was carried out by looking at the average Delta score (difference) between the pre-tests and post-tests of each respondent to determine the influence between the independent and dependent variables.

This study involved human participants and therefore required ethical due diligence. Ethical approval was obtained from the Research Ethics Committee of Dr. Moewardi Regional Hospital under number 1.344/V/HREC/2024. Prior to data collection, the researcher explained the ethical principles of the study, and participant participation was voluntary through a consent form after an explanation of the study was provided. Data confidentiality was guaranteed, and only specific group data were reported in the study results.

RESULTS

The main findings indicate that most respondents in both groups were within the productive age range (20–35 years) and had a high level of education (Table 1). The majority were multigravida, with most being unemployed. Physical activity levels were lower in the control group compared to the intervention group, with more respondents in the control group exercising less than three times per week and not accustomed to walking before pregnancy. Most respondents had a normal body mass index (BMI) and a moderate level of sedentary activity. The dominant pregnancy complaints differed between groups, with sleep difficulties more common in the control group and frequent urination reported more often in the intervention group.

TABLE 1
Respondent Characteristics Data

Respondent Characteristics	Control Group		Intervention Group		*P*-value Chi-Square
	N	%	N	%	
Age					0.735
<20 years or >35 years	4	10	6	15	
20–35 years	36	90	34	85	
Education					0.453
Low	13	32.5	9	22.5	
High	27	67.5	31	77.5	
Employment					0.654
Employed	20	50	17	42.5	
Unemployed	20	50	23	57.5	

TABLE 1. *Continued.*

Respondent Characteristics	Control Group		Intervention Group		*P*-value Chi-Square
	N	%	N	%	
Sedentary Lifestyle Level					0.050
Low (<2 hours)	0	0	4	10	
Moderate (2–5 hours)	33	82.5	25	62.5	
High (>5 hours)	7	17.5	11	27.5	
BMI					0.028
Underweight (<18.5)	2	5	8	20	
Normal (18.5–24.9)	29	72.5	21	52.5	
Overweight (25–29.9)	9	22.5	7	17.5	
Obese (>32)	0	0	4	10	
Parity					0.364
Primigravida	14	35	19	47.5	
Multigravida	26	65	21	52.5	
Pregnancy Discomforts During Third Trimester					0.957
Difficulty Sleeping	9	22.5	7	17.5	
Back Pain	7	17.5	6	15	
Frequent Urination	7	17.5	12	30	
Constipation	4	10	1	2.5	
Easily Fatigued	3	7.5	1	2.5	
Leg Cramps	8	20	11	27.5	
Uncomfortable Sleeping Position	2	5	2	5	

Statistical Significance: An alpha (α) level of 0.05 was used to determine statistical significance.

TABLE 2
Respondent Data Normality Test

Variable	Group	Test	Kolmogorov *P*-value
Sleep Quality	Intervention	Pre test	0.200
		Post test	0.000
	Control	Pre test	0.077
		Post test	0.175

Statistical Significance: An alpha (α) level of 0.05 was used to determine statistical significance.

The homogeneity test results, as shown in Table 1, revealed *p*-values >0.05 for variables such as age, occupation, parity, education, sedentary lifestyle level, and third-trimester pregnancy discomfort, indicating no significant differences between the intervention and control groups. This confirms that the characteristics of respondents in both groups were homogeneous.

The normality test results in Table 2 revealed that the post-test data in the intervention group were not normally distributed (p-value < 0.05). However, the pre-test data in the intervention group, as well as both the pre-test and post-test data in the control group, followed a normal distribution. Therefore, the statistical analyses performed included the Wilcoxon test, paired t-test, and

TABLE 3
Wilcoxon Test for Pretest and Posttest in the Intervention Group

Variable	N	*P*-value Wilcoxon
Negative Rank	32	0.000
Positive Rank	6	
Ties	2	
Total	40	

Statistical Significance: An alpha (α) level of 0.05 was used to determine statistical significance.

TABLE 4
Paired T-test for Pretest and Post-test in the Control Group

Sleep Quality Result	N	Mean ± SD	*P*-value T-test
Control Pretest	40	9.43 ± 2.97	0.000
Control Post-test	40	11.55 ± 2.43	

Statistical Significance: An alpha (α) level of 0.05 was used to determine statistical significance.

TABLE 5
Descriptive Analysis on the Effect of Walking on Sleep Quality in Pregnant Women

Group	N	Median Rank	Delta Mean Score± SD
Intervention Post-test	40	-3	-3.13 ± 3.220
Control Post-test	40	2	2.13 ± 1.667

Statistical Significance: The delta mean score is used to determine statistical significance.

the second delta score mean test for both groups.

The sleep quality score analysis using the Wilcoxon test, as presented in Table 3, yielded a *p*-value of 0.000 (<0.05), indicating a statistically significant improvement in sleep quality before and after the walking intervention in the intervention group. Out of 40 respondents in the intervention group, 32 experienced improved sleep quality, attributed to adherence to the walking intervention instructions.

The paired t-test results presented in Table 4 showed a *p*-value of 0.000 (<0.05), indicating a statistically significant difference in sleep quality between the pre-test and post-test in the control group. However, within the control group, there was an average decrease in sleep quality, with an average score reduction of 2.12, as the respondents did not receive the walking intervention.

The comprehensive analysis of sleep quality scores demonstrates that walking is effective in enhancing sleep quality among third-trimester pregnant women. A comprehensive analysis of sleep quality scores indicates that walking is effective in improving sleep quality in pregnant women in their third trimester. The results of the delta score test for the two groups showed a significant difference between the intervention group at -3.13 and the control group at 2.13, indicating that the average delta score in the intervention group was lower than in the control group. The intervention in the experimental group had a positive effect because the PSQI score decreased by an average of 3.125 points (sleep quality improved). The control group actually experienced an increase in the PSQI score of 2.125 points (sleep quality decreased). In addition, the standard deviation of the intervention group was 3.220, indicating a significant difference in effect between respondents. Meanwhile, in the control group, the standard deviation was 1.667, which was smaller, so the changes between respondents were relatively similar.

DISCUSSION

According to the analysis in Table 1, most respondents were between 20–35 years, suggesting they were within a low-risk age range for pregnancy. Regarding education, the majority had a high level of educational attainment,

with 77.5% in the intervention group and 67.5% in the control group. Pregnant women with higher education are more likely to have sufficient knowledge about pregnancy, which can psychologically prepare them for childbirth, ultimately improving sleep quality.[13]

With respect to employment status, most respondents were unemployed, comprising 50% of the control group and 57.5% of the intervention group. Unemployed mothers have more time to exercise compared to working mothers, who often lack time for physical activities such as yoga, morning walks, or swimming.[14] Employment can affect sleep quality due to work-related stress and pressure, which adds to the mental, physical, and time burden for working mothers.[15]

Most respondents also had a moderate sedentary lifestyle. Pregnant women can spend around 4.2±6.5 hours per day being sedentary, with more than a quarter exceeding eight hours per day. This lifestyle is often caused by hormonal changes that make pregnant women feel more tired, mobility difficulties due to weight gain and insufficient awareness regarding the importance of physical activity during pregnancy.[16]

Most respondents had a normal body mass index (BMI). Sleep disorders that affect sleep quality are closely related to an individual's BMI.[17] A significant correlation exists between obesity and sleep quality, with a higher BMI elevating the risk of sleep disorders, including sleep apnea, back pain, leg swelling, and GERD. Obesity can also increase insulin resistance, disrupting metabolism and leading to sleep disturbances (Sari, 2021). Therefore, the higher a person's BMI, the worse their sleep quality.[19]

In terms of parity, the majority of respondents were multigravida, accounting for 65% in the control group and 52.5% in the intervention group. Multigravida parity can affect sleep quality, as mothers who already have children must care for them in addition to themselves, which can lead to fatigue and reduced rest time.[20]

Regarding pregnancy discomfort, many respondents frequently experienced difficulty sleeping, leg cramps, and frequent urination. In the third trimester, 97.3% of pregnant women often wake up 3–11 times each night due to urination and leg cramps, which reduces sleep duration.[21] One of the psychological changes that third-trimester pregnant women experience is sleep difficulty, often due to anxiety and discomfort., and restlessness.[22]

This study shows that walking is effective in maintaining overall health, including improving sleep quality in the intervention group. Walking is an effective physical activity for pregnant women to maintain fitness during pregnancy.[23]

Walking is a suitable and beneficial form of exercise for health, including maintaining fitness, improving sleep quality, controlling blood pressure, reducing weight, managing depression, and preventing cardiovascular disease.[24]

Healthy pregnant women are recommended to engage in moderate-intensity physical activity, such as morning walks, for at least 150 minutes per week, equivalent to walking three times a week for 15–20 minutes.[9] This activity benefits sleep quality and fitness during the later stages of pregnancy. Therefore, the enhancement of sleep quality in the intervention group was due to the consistency of pregnant women in walking in the morning.

In the post-test measurement, pregnant women experienced sleep disturbances caused by discomfort in the later stages of pregnancy, such as leg cramps, difficulty sleeping, and frequent urination. This is consistent with the research showing that 55.6% of third-trimester pregnant women tend to experience a decline in sleep quality.[5] Additionally, common discomforts during pregnancy, such as frequent urination and difficulty sleeping, also contribute to this issue. The growing fetus can press on the mother's bladder, reducing its capacity and causing frequent urination and sleep disturbances.[18]

Physical changes in the third trimester can lead to psychological changes, including difficulty sleeping, which impacts the sleep quality of pregnant women during this trimester.[22] Therefore, the decline in sleep quality in the control group was due to increased sleep disturbances experienced by pregnant women and the lack of physical activity that could help improve their sleep quality.

As pregnancy progresses, various factors can disrupt a mother's sleep. Nearly all pregnant women experience poor sleep quality during the third trimester with a sleep duration of around 5-6 hours.[21] A decline in sleep quality and quantity can weaken the mother's immune system, leading to low birth weight and potential complications.[22]

Good sleep quality is essential during pregnancy to avoid the risk of complications. One solution to poor sleep is regular exercise, such as morning walks. Walking is an easy and inexpensive form of exercise that can increase oxygen levels in the blood, reduce leg swelling, and improve oxygen flow throughout the body.[10]

Additionally, walking can strengthen muscles and improve joint flexibility, preventing leg cramps and back pain.[11]

Walking can also stimulate melatonin production, helping pregnant women sleep more soundly at night. This activity supports a good sleep routine by expending energy and making the body feel healthily tired, thereby improving sleep quality and regularity.[20] Furthermore, walking can lower cortisol levels in the blood and increase endorphins and serotonin, helping women feel more relaxed, calm, and happy, and reducing depression and anxiety.[9]

Walking also helps maintain a healthy weight during pregnancy, reducing the risk of sleep disorders

related to excess weight, and preventing or managing gestational diabetes and hypertension.[10] This study is consistent with the research carried out, which showed that 88.9% of nine respondents who walked experienced improved sleep quality.[5] The study used the McNemar test with a *p*-value of 0.025, demonstrating the effectiveness of walking in enhancing sleep quality in third-trimester pregnant women. That also noted that regular exercise significantly improves sleep quality.[9]

In this study, the average delta score between pre-tests and post-tests for each respondent showed that the average delta score for sleep quality in the intervention group was -3.13, lower than the average delta score of 2.13 in the control group. This indicates that the intervention group experienced improved sleep quality after walking. Therefore, it can be concluded that walking has a positive impact on sleep quality for pregnant women in the third trimester, making it an effective primary option for improving sleep quality.

CONCLUSION

Walking positively influences sleep quality in pregnant women during the third trimester. It is advised that pregnant women adopt walking as a complementary, non-pharmacological approach to address sleep disturbances. Healthcare services should collaborate with healthcare professionals to implement walking as part of antenatal care and enhance continuous education for pregnant women. Future research could investigate other forms of physical activity or exercise to broaden the variety of accessible and affordable options that pregnant women can use to enhance their sleep quality.

ACKNOWLEDGMENT

The authors would like to express sincere gratitude to Kebakkramat I Health Center in Karanganyar, Central Java, for providing the necessary permissions and facilities to conduct this research. We also extend our deepest appreciation to all village midwives within the Kebakkramat I Health Center area for their technical assistance and coordination. Furthermore, the authors are grateful to all pregnant woman who participated as respondents for their invaluable contributions to this study.

CONFLICT OF INTEREST

The authors declare that there are no financial or non-financial conflicts of interest that could potentially influence the objectivity of this research. This work was conducted independently, and the authors have no competing interests or personal relationships that could have appeared to influence this manuscript.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; vol 13 (1) : 25–35

OPEN ACCESS

Original Article

Risk Factors for Carbapenem-Resistant Organisms Pneumonia in the Pediatric and Neonatal Intensive Care Units: A Study at Dr. Kariadi Hospital

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v13i1.1353

Submitted: June 26th, 2025
Accepted: March 26th, 2026

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Abstract

Background : Inappropriate antibiotic use has led to bacterial resistance, including carbapenem-resistant organisms (CROs), which cause severe infections in neonatal intensive care unit (NICU) and pediatric intensive care unit (PICU) patients. CRO infections are associated with high morbidity and mortality rates, with limited treatment options. Risk factors such as prolonged hospitalization, broad-spectrum antibiotic use, invasive procedures, and prior infections contribute to these cases. This study is the first in Indonesia to specifically examine CRO pneumonia risk factors in NICU and PICU children.
Objectives : This study aimed to analyze the risk factors for pneumonia caused by carbapenem-resistant organisms (CROs) in children in the pediatric and neonatal intensive care unit.
Methods : This case-control study was conducted in neonatal intensive care unit (NICU) and Pediatric Intensive Care Unit (PICU) of Dr. Kariadi Hospital, Semarang, using medical records of patients admitted between November 2022 and October 2024. This study analyzed the relationship between various risk factors, including hospitalization duration, antibiotic use, mechanical ventilation, catheterization, prior surgery, and bacterial infection history, with CRO pneumonia in NICU and PICU patients.
Results : This case-control study in NICU and PICU on 87 pediatric pneumonia patients found that 55.2% had CRO pneumonia. Multivariate analysis revealed that carbapenem use for >7 days ($p = 0.049$), mechanical ventilation ($p = 0.044$), and urinary catheterization ($p = 0.020$) were independent risk factors for CRO pneumonia.
Conclusion : CRO infections in NICU and PICU patients are highly prevalent, with prolonged carbapenem use, mechanical ventilation, and urinary catheterization as independent risk factors for CRO pneumonia.

Keywords : Antimicrobial resistance, Carbapenem-Resistant Organisms, Intensive Care Unit, pediatrics, pneumonia.

INTRODUCTION

Pneumonia is an inflammatory condition of the lung parenchyma, distal to the terminal bronchioles and causes consolidation of lung tissue and disruption of local gas exchange caused by microorganisms (bacteria, viruses, fungi, protozoa).[1] Excessive and inappropriate antibiotic use has driven an increase in pathogen resistance,[2] particularly multidrug-resistant organisms (MDROs) especially in children with pneumonia infection.[3] In recent years, infections caused by MDRO have shown a significant rise.[4] Based on expert consensus, the CDC, and ECDC, MDRO is categorized into three main types: Multi-Drug Resistance (MDR), eXtensive Drug Resistance (XDR), and Pan Drug Resistance (PDR). One of the most concerning MDRO groups is carbapenem-resistant organisms (CRO), which include carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA).[5] CRO infections is a major cause of health care-associated infections (HAIs) with a high level of resistance, making treatment difficult and significantly contributing to mortality.[6]

The WHO has designated CRO as a critical priority pathogen for the development of new antibiotics due to its increasing resistance.[7,8] Resistance of CRO occurs through various mechanisms, such as carbapenemase enzyme production and structural modifications of the bacterial cell membrane.[9] Infections caused by CRO in children primarily occur in healthcare facilities, particularly in neonatal intensive care units (NICU) and pediatric intensive care units (PICU).[10] Surveillance studies on central line-associated bloodstream infections (CLABSI) in children have reported a high prevalence of CRO, with varying resistance percentages in *Klebsiella spp., Enterobacter spp.*, and *Pseudomonas aeruginosa*.[10] Children admitted to the PICU are more vulnerable to these infections due to frequent broad-spectrum antibiotic therapy, using the invasive medical devices such as mechanical ventilation and catheters, and underlying comorbid conditions.[9,11]

Antimicrobial resistance increases morbidity, mortality, hospitalization duration, and healthcare costs. Therefore, prudent antibiotic therapy and the identification of risk factors for MDRO infections, particularly CRO, are crucial.[12] Although several studies have assessed the risk factors for CRO infections in pediatric patients, most research has focused on a single type of microorganism and general pediatric populations.[13,14] Further studies are needed to comprehensively understand the risk factors for CRO infections in intensive care unit patients. This study is the first study in Indonesia focusing specifically on CRO-related pneumonia in critically ill pediatric patients in both NICU and PICU settings. Unlike previous studies addressing general CRO infections,[15–20] our study highlights a high prevalence of CRO pneumonia-specific risk factors in NICU and PICU populations, highlighting modifiable hospital practices associated with CRO emergence.

METHODS

This case-control study was conducted in the Neonatal Intensive Care Unit (NICU) and Pediatric Intensive Care Unit (PICU) of Dr. Kariadi Hospital, Semarang, using medical records of patients admitted between November 2022 and October 2024. Children aged 1 month to 18 years with pneumonia caused by CRO or non-CRO pathogens based on culture results were included. Cases had a positive CRO culture as their first recorded infection, while controls had a positive non-CRO culture as their last recorded infection without prior CRO diagnosis. Exclusion criteria included incomplete medical records, infections caused by *Stenotrophomonas maltophilia*, or neonates under one month admitted to the NICU. A sample size of 87 patients (48 patients with CRO and 39 patients with non-CRO) was calculated using a significance level of 0.05, power of 95%, and expected odds ratio of 3.095. Consecutive sampling was applied.

Patient data included demographics (age, gender, socioeconomic status, nutritional status), clinical history, comorbidities, and prior bacterial colonization. Hospitalization details such as length of stay, invasive procedures, and antibiotic use were recorded. Information on mechanical ventilation, central venous catheterization (CVC), urinary catheterization, and surgical history was also collected.

Data analysis was performed using SPSS version 29.0.2.0 for Mac OS. Categorical variables were presented as frequencies/percentages. Chi-square and Fisher's Exact tests were used for bivariate analysis, with $p < 0.05$ considered significant. Variables with $p < 0.25$ were included in multivariate logistic regression (Backward Stepwise LR method) to determine independent risk factors, presented as odds ratios (OR) and 95% confidence intervals (CI).

This study was approved by the Ethics Committee of the Faculty of Medicine, Diponegoro University – Dr. Kariadi General Hospital (Approval No. 16426/EC/KEPK-RSDK/2025). All patient data were anonymized, confidential, and used solely for research. The study followed ethical guidelines, with all costs covered by the investigators.

RESULTS

A total of 87 pediatric patients between November 2022 to October 2024 diagnosed with pneumonia and positive bacterial cultures for Gram-negative pathogens were identified in the Neonatal Intensive Care Unit (NICU)

TABLE 1
General Characteristics of Variables

Variables	Frequency	%
Pneumonia		
CRO	48	55.2
Non-CRO	39	44.8
Gender		
Male	50	57.5
Female	37	42.5
Socioeconomic status		
High	3	3.4
Medium	42	48.3
Low	42	48.3
Age		
>10 years	17	19.5
5–10 years	6	6.9
1 month – 5 years	64	73.6
Chronic disease		
Yes	11	12.6
No	76	87.4
Malnutrition		
Yes	45	51.7
No	42	48.3
Previous bacterial colonization		
Yes	25	28.7
No	62	71.3
Length of Stay		
> 7 days	48	55.2
≤ 7 days	39	44.8
Duration of non-carbapenem antibiotic use		
> 14 days	18	20.7
≤ 14 days	69	79.3
Duration of carbapenem antibiotic use		
> 7 days	25	28.7
≤ 7 days	62	71.3
Use of mechanical ventilator		
Yes	53	60.9
No	34	39.1

TABLE 1. *Continued.*

Variables	Frequency	%
Use of central venous catheter		
Yes	50	57.5
No	37	42.5
Use of urinary catheter		
Yes	38	43.7
No	49	56.3
Use of immunosuppressant		
Yes	5	5.7
No	82	94.3
History of surgery		
Yes	20	23.0
No	67	77.0

and Pediatric Intensive Care Unit (PICU) of Dr. Kariadi General Hospital, Semarang. Among these, 48 patients (55.2%) were infected with Carbapenem-Resistant Organisms (CROs), while 39 patients (44.8%) were infected with non-CRO bacteria (Table 1). These findings indicate that the prevalence of pneumonia caused by CRO is higher than that of non-CRO infections in the NICU and PICU, highlighting the significant burden of carbapenem resistance among critically ill pediatric patients.

The majority of patients were between the ages of one month and five years (73.6%), with a male-to-female ratio of 1.35:1. Malnutrition was present in 51.7% of patients, while 12.6% had underlying chronic illnesses. A substantial proportion of CRO-infected patients had a history of prior bacterial colonization (28.7%) and prolonged hospitalization, with 55.2% of patients having a length of stay exceeding seven days (Table 1). Invasive procedures were notably more frequent among patients with CRO pneumonia, with 60.9% requiring mechanical ventilation, 57.5% undergoing central venous catheter (CVC) insertion, and 43.7% having urinary catheterization (Table 1).

Antimicrobial Resistance Patterns of CRO Isolates in the NICU and PICU

Analysis of resistance patterns showed that CRO isolates from pediatric patients in the NICU and PICU exhibited high resistance rates across multiple antibiotic classes. Most isolates demonstrated significant resistance to third-generation cephalosporins, aminoglycosides, and fluoroquinolones. Colistin remained the only antibiotic with a low resistance rate, making it the last-line therapeutic option for severe infections caused by CRO. Additionally, it was found that patients with a history of carbapenem antibiotic use for more than seven days had a significantly higher likelihood of developing CRO infections compared to those with shorter or no prior carbapenem exposure ($p < 0.001$, OR = 13.924, 95% CI: 3.778–51.290) (Table 2).

Bivariate analysis identified several risk factors significantly associated with the development of CRO pneumonia. Prior bacterial colonization ($p = 0.007$, OR = 4.875, 95% CI: 1.616–14.595), prolonged hospitalization exceeding seven days ($p <0.001$, OR = 11.020, 95% CI: 4.050–29.983), carbapenem antibiotic use for more than seven days ($p <0.001$, OR = 10.154, 95% CI: 2.747–37.538), mechanical ventilation ($p <0.001$, OR = 13.179, 95% CI: 4.606–37.702), central venous catheterization ($p <0.001$, OR = 11.030, 95% CI: 4.034–30.160), and urinary catheterization ($p <0.001$, OR = 11.000, 95% CI: 3.823–31.648) were all found to be significantly associated with CRO pneumonia (Table 2). Variables with a p-value <0.25 in the bivariate analysis were included in a multivariate logistic regression model, which determined that prolonged carbapenem antibiotic use, mechanical ventilation, and urinary catheterization were independent risk factors for CRO pneumonia. Patients who received carbapenem antibiotics for more than seven days had a 4.4-fold higher risk of developing CRO pneumonia ($p = 0.049$), those who required mechanical ventilation had a 3.8-fold increased risk ($p = 0.044$), and patients with urinary catheterization had a 4.5-fold higher risk ($p = 0.020$) (Table 3).

TABLE 2
Bivariate Analysis of General Characteristics and Pneumonia

Variables	Pneumonia				*p*	OR	95% CI
	CRO		Non CRO				
	n	%	n	%			
Gender					0.690¥	1.308	0.556 – 3.076
Male	29	60.4	21	53.8			
Female	19	39.6	18	46.2			
Socioeconomic Status					0.282‡	1.231	0.103 – 14.696
High	2	4.2	1	2.6		0.559	0.235 – 1.334
Medium	20	41.7	22	56.4			
Low	26	54.2	16	41			
Age					0.956‡	0.737	0.252 – 2.152
> 10 years	8	16.7	9	23.1		4.143	0.458 – 37.491
5 – 10 years	5	10.4	1	2.6			
1 month – 5 years	35	72.9	29	74.4			
Chronic disease					0.394£	1.494	0.404 – 5.529
Yes	7	14.6	4	10.3			
No	41	85.4	35	89.7			
Malnutrition					1.000¥	1.033	0.443 – 2.405
Yes	25	52.1	20	51.3			
No	23	47.9	19	48.7			
Previous bacterial colonization					0.007¥*	4.857	1.616 – 14.595
Yes	20	41.7	5	12.8			
No	28	58.3	34	87.2			
Length of Stay					<0.001¥*	11.020	4.050 – 29.983
> 7 days	38	79.2	10	25.6			
≤ 7 days	10	20.8	29	74.4			
Duration of non-carbapenem antibiotic use					0.172¥	2.526	0.812 – 7.852
> 14 days	13	27.1	5	12.8			
≤ 14 days	35	72.9	34	87.2			
Duration of carbapenem antibiotic use					<0.001¥*	10.154	2.747 – 37.538
> 7 days	22	45.8	3	7.7			
≤ 7 days	26	54.2	36	92.3			
Use of mechanical ventilator					<0.001¥*	13.179	4.606 – 37.702
Yes	41	85.4	12	30.8			
No	7	14.6	27	69.2			
Use of central venous catheter					<0.001¥*	11.030	4.034 – 30.160
Yes	39	81.3	11	28.2			
No	9	18.8	28	71.8			

TABLE 2. *Continued.*

Variables	Pneumonia				*p*	OR	95% CI
	CRO		Non CRO				
	n	%	n	%			
Use of urinary catheter					<0.001¥*	11.000	3.823 – 31.648
Yes	32	66.7	6	15.4			
No	16	33.3	33	84.6			
Use of immunosuppressant					0.599£	1.233	0.196 – 7.776
Yes	3	6.3	2	5.1			
No	45	93.8	37	94.9			
History of surgery							
Yes	13	27.1	7	17.9	0.453¥	1.698	0.602 – 4.787
No	35	72.9	32	82.1			

Notation:
* Significant ($p < 0.05$);
¥ Continuity Correction;
‡ Mann–Whitney (alternative χ2);
£ Fisher's Exact

TABLE 3
Multivariate Analysis of Independent Risk Factors for CRO Pneumonia

Variables	B	*p*	OR	95% CI
Previous bacterial colonization	0.198	0.816	0.643	0.137 – 3.030
Duration of treatment	-0.766	0.361	1.574	0.343 – 7.214
Duration of carbapenem antibiotic use	-1.485	0.049*	4.413	1.004 – 19.404
Use of mechanical ventilator	-1.332	0.044*	3.788	1.038 – 13.827
Use of central venous catheter	-0.271	0.766	0.635	0.259 – 9.141
Use of urinary catheter	-1.514	0.020*	4.544	1.268 – 16.285

Notation : * Significant ($p < 0.05$)

DISCUSSION

Pneumonia caused by carbapenem-resistant organisms (CROs) represents a significant proportion of infections in neonatal and pediatric intensive care units. In the present study, 48 of 87 patients (55.2%) with pneumonia were infected with CRO pathogens, whereas 39 patients (44.8%) had non-CRO bacterial infections at Dr. Kariadi General Hospital between November 2022 and October 2024. These findings are consistent with previous observations reported by Nawawi, which demonstrated that resistant pathogens predominated among intensive care unit infections. In that study, 36 cases of hospital-acquired bacterial infections were identified in the PICU among 264 admitted patients, of which 35 cases were caused by multidrug-resistant (MDR) bacteria. Although the previous study did not specifically differentiate between CRO and non-CRO pathogens, the high burden of MDR organisms in PICU-acquired infections supports the present finding that resistant bacteria, including CROs, tend to predominate over susceptible organisms in pediatric pneumonia requiring intensive care management.[21]

A meta-analysis conducted in Indonesia by Widyawati also reported that Gram-negative bacteria were the predominant pathogens causing pneumonia. *Klebsiella pneumoniae* had the highest combined prevalence of 0.21 (95% CI: 0.16–0.27), followed by

Acinetobacter baumannii with a combined prevalence of 0.20 (95% CI: 0.13–0.26) and *Pseudomonas aeruginosa* at 0.12 (95% CI: 0.09–0.15). These pathogens are strongly associated with nosocomial pneumonia, particularly in intensive care units.[22] The most common CRO pathogens include *A. baumannii, Escherichia coli*, and *K. pneumoniae*, frequently associated with Ventilator-Associated Pneumonia (VAP) and Hospital-Acquired Pneumonia (HAP). Resistance mechanisms in *A. baumannii* include β-lactamase production, efflux pumps, porin mutations, and plasmid-mediated gene transfer, while carbapenem resistance in Gram-negative bacteria generally involves β-lactamase hydrolysis, reduced PBP affinity, and altered outer membrane proteins. [23,24]

In this study, gender was not significantly associated with CRO pneumonia. Male patients constituted a slightly higher proportion in the CRO group compared to the non-CRO group, but this difference was not statistically significant (p = 0.690, OR 1.308, 95% CI 0.556–3.076). In this study, 73.6% of patients were aged 1 month–5 years, with a male-to-female ratio of 1.35:1, aligning with previous research from Hegazy (2022) that reporting higher Carbapenem-resistant Gram-negative Bacteria (CR-GNB) infection rates in males (61.4%).[13] This finding is consistent with the study from Cai (2024), where gender is not considered an independent risk factor for Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP) infection, and susceptibility is more strongly influenced by healthcare exposure and invasive procedures rather than biological sex.[25] This aligns with prior study where biological sex rarely affects colonization by multidrug-resistant organisms unless hormonal, behavioral, or exposure differences are prominent.[26]

Socioeconomic status (high, medium, low) was also not significantly associated with the occurrence of CRO pneumonia (p = 0.282).[25] Although not significantly associated, low socioeconomic status was predominant among children with CRO pneumonia (54.2%). These findings are consistent with a study by Karki *et al*., which reported that socioeconomic status was not significantly associated with pneumonia. However, these results differ from many other studies that have identified low socioeconomic status and low maternal education as risk factors for pneumonia in children. Therefore, although the results of this study did not demonstrate a significant association, socioeconomic factors are still widely recognized in the literature as important determinants of childhood pneumonia.[27]

Age distribution (>10 years, 5–10 years, and 1 month–5 years) was not significantly association with CRO pneumonia in this study (p = 0.956). These findings are consistent with the Cohort study by Espetia–Acero *et al.*, which reported no statistically significant association between CRO colonization and patient sex (p = 0.70) and similarly found that age was not a determining factor for CRO colonization in that cohort. [26] Similar results were reported by Dalfi *et al*., who found no significant association between age and pneumonia (p = 0.855).[28] Although not statistically significant, most CRO pneumonia cases occurred in children aged 1 month–5 years (72.9%). This finding is in line with a study conducted by Fadl *et al.* in Alexandria, Egypt, which reported that children under 12 months of age were independently associated with pneumonia. This may be explained by the immature immune system of infants and young children, making them more susceptible to infections such as pneumonia.[28,29] However, in the present hospital-based population, other clinical factors such as the use of invasive devices may have a greater influence on the risk of CRO infection than age alone.[26,30]

The presence of chronic disease did not significantly increase the risk of CRO pneumonia (p = 0.394, OR 1.494, 95% CI 0.404–5.529). Patients with high comorbid conditions may increased the risk although it was not statistically significant. This finding is consistent with a meta-analysis by Oktafia *et al*. and a study by Wexler *et al*., which reported that comorbidities were not significantly associated with complicated pneumonia.[31,32] However, other studies have suggested that comorbid diseases may worsen pneumonia outcomes by weakening the immune system and increasing susceptibility to severe illness.[25,33] Despite the lack of statistical significance, comorbidity remains a biologically plausible risk factor because chronic conditions can impair host defenses, increase hospitalization, and require the use of broad-spectrum antibiotics and invasive device.[30] This discrepancy may be explained by the fact that comorbid conditions in the present study were analyzed as a broad category, whereas previous studies often evaluated specific chronic diseases that may have stronger associations with CRO infections.[31,32]

Antibiotic therapy was a major contributor, with 86.4% of CRO pneumonia patients receiving broad-spectrum antibiotics, and 55.9% previously exposed to carbapenems. Prior carbapenem use (≥7 days) increased the risk of CRO infection 13.9-fold (p < 0.001, OR = 13.924, 95% CI: 3.778–51.290), while hospitalization for >7 days raised the risk 9.95-fold (p < 0.001, OR = 9.951, 95% CI: 3.738–26.507). Other significant risk factors included mechanical ventilation (OR = 13.179, p < 0.001), central venous catheterization (OR = 11.148, p < 0.001), and urinary catheterization (OR = 9.778, p < 0.001). Lin and Lan's (2014) study also mentioned that previous antibiotic use was an independent risk factor for resistance. Repeated or inappropriate antibiotic use applies selective pressure that triggers enzymatic and non-enzymatic resistance pathways. *A. baumannii* adapts and develops multidrug-resistant or even extensively drug-resistant phenotypes. This means patients previously treated with broad-spectrum or multiple antibiotics are far more likely

to acquire Carbapenem-resistant *Acinetobacter baumannii* (CRAB).[33]

According to the Infectious Disease Society of America (IDSA), major risk factors for Multi-Drug Resistant (MDR) pathogens, including CRO in VAP, include prior intravenous antibiotic use within 90 days, septic shock at the time of VAP, Acute Respiratory Distress Syndrome (ARDS), hospitalization ≥5 days before VAP, and renal replacement therapy.[23] Independent risk factors for CRAB infection in critically ill children include prior carbapenem exposure, invasive procedures, severe pneumonia, and low hemoglobin levels. Invasive procedures, particularly gastric intubation, can disrupt skin integrity, leading to bacterial translocation from the intestines to systemic circulation. Prolonged antibiotic use, especially carbapenems, increases the likelihood of genetic mutations in *A. baumannii*, driving resistance.[3]

Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP) infections pose significant challenges in children due to limited treatment options and poor prognosis. Risk factors for CRKP bloodstream infections (BSI) include age, comorbidities, prior hospitalizations, intravascular catheterization, immunosuppressive therapy, and prior antibiotic use.[7,24] Misuse and overuse of antibiotics contribute to antimicrobial resistance by promoting CRKP proliferation, with carbapenem use identified as the highest risk factor.[14] Infants and young children are vulnerable to Carbapenem-Resistant *Enterobacteriaceae* (CRE) infections, including bloodstream infections (BSI), pneumonia, and urinary tract infections (UTI).[8] ICU patients face higher transmission risks due to airborne and contact-based spread, invasive procedures, and prolonged broad-spectrum antibiotic therapy, leading to carbapenem resistance.[34]

Malnutrition showed no significant association with CRO pneumonia (p = 1.000, OR 1.033, 95% CI 0.443–2.405). Malnutrition was observed in 51.7% of patients, and 12.6% had underlying chronic conditions. This contrasts with prior evidence suggesting impaired immunity and barrier dysfunction in malnourished patients. However, cohort study from Cai (2024) reports that malnutrition alone did not independently predict CRO infection.[25] Nutritional status did not affect the probability of CRO colonization. Even though malnutrition can weaken the immune system.[26] Immunosuppressant use was not significantly associated with CRO pneumonia (p = 0.599). Previous studies focusing on CRO bloodstream infections reported that immunocompromised patients did not differ substantially from immunocompetent patients in terms of pathogen distribution, infection source, disease severity, or proportion of appropriate antimicrobial therapy.[35] Although immunosuppression is widely recognized as a risk factor for severe infection, no independent association was found.[25] Immunocompromised and critically ill patients are particularly susceptible to colonization due to compromised immune responses and disrupted physical barriers.[30]

A history of surgery was not significantly associated with CRO pneumonia (p = 0.453, OR 1.698, 95% CI 0.602–4.787). Undergoing surgery did not elevate the risk of CRO colonization. This suggests that the operating room environment adhered to strict sterility and did not contribute significantly to CRO exposure.[26] Surgery can disrupt physical barriers, alters gut microbiota, and exposes patients to perioperative antibiotics and invasive devices. These factors combine to create an environment highly conducive to CR-GNB acquisition.[30] Prolonged hospitalization (>7 days) was found in 55.2% of patients, while 28.7% had a history of prior bacterial colonization, consistent with studies linking prior CRE colonization to CRE infections.[10] A hospital stay longer than 7 days was strongly associated with CRO pneumonia (p < 0.001, OR 11.020, 95% CI 4.050–29.983). Patients with prior MDR colonization have a mortality risk exceeding 15%, and ICU stays are strongly associated with CRKP infections due to prolonged hospitalization and invasive procedures.[5,34] The longer a child remains in the hospital, the greater the exposure to contaminated environments, healthcare workers, and invasive procedures. Long of stays also increase the likelihood of receiving broad-spectrum antibiotics.[26,30]

Patients admitted to ICU infected with MDR/CRAB were higher than those in non-ICU. ICU is the center of the birth of antibiotic-resistant Gram-negative bacteria due to high antibiotic usage. *Acinetobacter baumannii* is commonly found on ventilator surfaces causing VAP. *A. baumannii*, which survives well on surfaces, frequently causes VAP and bloodstream infections in ICUs. The lack of statistical significance likely reflects the sample size, not true absence of association. Mechanistically, ICU exposure increases colonization and resistance evolution through repeated antibiotic exposure and nosocomial transmission.[33,36] Previous bacterial colonization was significantly associated with CRO pneumonia in bivariate analysis (p = 0.007, OR 4.857, 95% CI 1.616–14.595). Colonized patients act as reservoirs, and endogenous translocation is a major mechanism for secondary infection. However, in multivariate analysis, this variable lost statistical significance, suggesting that its effect may be mediated by other factors such as invasive devices and antibiotic exposure.[25] Colonization by CR-GNB itself predisposes to future CR-GNB infection.[30] Colonization is often asymptomatic but can precede infection and contribute to hospital outbreaks. Colonized patients serve as reservoirs for MDR pathogens and facilitate transmission to other patients.[37]

Patients requiring mechanical ventilation (60.9%), central venous catheters (57.5%), and urinary catheters (43.7%) had significantly higher CRO infection risks, as these procedures increase bacterial colonization and immune suppression.[14] The use of CVC was significantly associated with CRO pneumonia in bivariate analysis (p < 0.001, OR 11.030, 95% CI 4.034–30.160). CVC use might have emerged as a contributing factor.[26] Central Venous Catheters breach the skin barrier and provide direct access for microorganisms into the bloodstream or surrounding tissues. Frequent handling of the catheter and repeated access increase opportunities for contamination by resistant organisms.[30] Central Venous Catheter use is a classic invasive procedure that allows bloodstream entry of bacteria, supports biofilm formation, and increases exposure to healthcare flora.[37]

The duration of non-carbapenem antibiotic use (>14 days) was not significantly associated with CRO pneumonia (p = 0.172). This may reflect local antimicrobial-stewardship practices. The absence of correlation suggests that colonization might be more influenced by device-related exposures than antibiotic pressure in this setting.[26] Patients frequently receive broad-spectrum antibiotic therapy. Broad-spectrum antibiotic exposure promotes dysbiosis and selection of resistant bacteria. Longer durations of such antibiotics create selective pressure that favors bacterial survival and colonization.[30,37] Prolonged carbapenem use (>7 days) was a strong predictor of CRO infection, with a 4.4-fold increased risk (p = 0.049), while mechanical ventilation increased the risk 3.8-fold (p = 0.044), and urinary catheterization 4.5-fold (p = 0.020). Antibiotic exposure within the past 6–9 months increased the risk of CRAB infection, while longer ICU stays (>10 days) were associated with nosocomial infections, invasive procedures, and higher mortality rates.[13,38,39] Resistance patterns in PICU isolates showed high resistance to third-generation cephalosporins, aminoglycosides, and fluoroquinolones, supporting previous findings on CRKP and *Pseudomonas aeruginosa*.[11,34]

Exposure to carbapenem could lead to the decreased levels of OprD porin and upregulation of the multidrug efflux pump, with subsequent resistance to carbapenems. Carbapenem exposure directly drives resistance by reducing OprD porin channels, preventing antibiotics from entering the bacterium, increasing efflux pump activity, actively removing antibiotics, and creating selective pressure that favors resistant strains. Increased duration of treatment with carbapenems remained significantly associated with Carbapenem-Resistant *Pseudomonas aeruginosa* (CRPA) infection or colonization.[36] Carbapenems exert strong selective pressure against susceptible organisms, allowing carbapenem-resistant bacteria to thrive. Therefore, longer durations of carbapenem therapy significantly increase the likelihood of colonization.[30] Mechanical ventilation disrupts natural airway defenses and increases exposure to hospital pathogens, including CR-GNB. Ventilator circuits, suctioning, and frequent manipulation facilitate transmission. Thus, ventilator use correlates with higher colonization risk, especially in critically ill children.[30]

ICU setting significantly impacted the infection onset in colonized patients probably because of the use of invasive procedures such as mechanical ventilation and CVC. Ventilator dependence increases susceptibility of lower airways. Pharyngeal/nasal colonization is strongly associated with subsequent lower respiratory tract infections.[37] Ventilation bypasses natural airway defenses and provides a direct route for colonizing CRAB to enter lower respiratory tract.[40] Mechanical ventilation was highly associated with CRO pneumonia (p < 0.001, OR 13.179). In multivariate analysis, it remained an independent predictor (p = 0.044, OR 3.788). This is consistent with evidence identifying ventilator-associated pneumonia as a major clinical manifestation of CRKP infection, particularly in ICU settings, where invasive respiratory support compromises host defenses and facilitates pathogen entry.[25]

A key factor contributing to persistent bacterial infections is biofilm formation, which protects bacteria from antibiotics, particularly in ventilated patients and those with indwelling catheters.[19,41] Urinary catheters can indirectly cause pneumonia by increasing the risk of urinary tract infections (UTIs). Prolonged catheter use disrupts the natural defense mechanism of urinary flow, allowing bacteria like *Escherichia coli* and *Klebsiella pneumoniae* to ascend and cause infections. Recurrent UTIs may lead to antibiotic resistance, and in some cases, chronic bladder infections due to urine stasis. If the infection spreads into the bloodstream (bacteremia), it can reach the lungs and potentially cause pneumonia, especially in immunocompromised patients.[42,43] This study highlights the importance of antimicrobial stewardship, infection control measures, and cautious use of broad-spectrum antibiotics to reduce CRO pneumonia incidence in the PICU.

CONCLUSION

This study demonstrates that prolonged hospitalization, prior carbapenem exposure, and invasive procedures are major contributors to CRO pneumonia in critically ill pediatric patients. While our findings align with multiple studies, discrepancies in risk factor significance highlight the need for further multicenter research. Future investigations should focus on developing novel therapeutic approaches and strengthening infection control measures to combat carbapenem resistance in pediatric intensive care settings.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

ACKNOWLEDGEMENTS

The authors declare no acknowledgements of this study

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; vol 13 (1) : 36–44

OPEN ACCESS

Original Article

Correlation Between Bacterial Count and Duration of Tracheostomy Tubes Use

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v13i1.1232

Submitted: October 08th, 2024
Accepted: March 26th, 2026

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Abstract

Background : Tracheostomy tubes (TTs) are life-sustaining medical devices widely used for patients with upper airway obstruction or requiring prolonged mechanical ventilation. However, TTs serve as an indwelling substrate that promotes bacterial colonization and biofilm formation, particularly by resistant pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Despite the well-recognized clinical risks, evidence correlating the duration of TT use with quantitative bacterial load in the Indonesian hospital setting remains limited, creating a gap in local clinical guidance for tube replacement scheduling.
Aim : To analyze the correlation between TT duration of use and bacterial colony count (CFU/mL), and to identify the predominant colonizing pathogens in order to inform evidence-based infection prevention and tube replacement timing.
Methods : This cross-sectional observational study was conducted from July 2020 to January 2021 at Dr. Sardjito General Hospital, Yogyakarta, Indonesia. A total of 20 polyvinyl chloride (PVC) Portex™ tracheostomy tubes were collected via consecutive sampling from patients undergoing decannulation procedures. Bacterial cultures were performed at the Department of Microbiology, Universitas Gadjah Mada, with bacterial load expressed as colony-forming units per milliliter (CFU/mL). Spearman's rank correlation was used for statistical analysis.
Results : Mean bacterial counts (CFU × 10^3/mL) were 48.5, 9,853.83, and 28,200.00 for TT use durations of <30 days, 30–90 days, and >90 days, respectively. Spearman's rank correlation demonstrated a strong positive association between duration and bacterial count ($r = 0.70$, $p = 0.01$). *Pseudomonas aeruginosa* was the most prevalent organism, identified in 60% of tubes.
Conclusion : Duration of TT use exceeding 30 days is significantly correlated with higher bacterial colonization burden. *Pseudomonas aeruginosa* was the predominant pathogen. These findings support the recommendation for scheduled TT replacement within 30 days as an infection control measure in tracheostomized patients.

Keywords : Bacterial count, biofilm, infection control, *Pseudomonas aeruginosa*, tracheostomy tube

INTRODUCTION

Tracheostomy is one of the most commonly performed life-saving surgical procedures in critically ill patients worldwide. It provides a reliable artificial airway in patients requiring prolonged mechanical ventilation, management of upper airway obstruction, or assistance with bronchopulmonary secretion clearance. The procedure offers several clinical advantages, including reduced respiratory effort, preservation of laryngeal structures, facilitation of oral intake, improved patient comfort, and the possibility of weaning from ventilatory support. Due to advances in critical care medicine and an increasing number of patients surviving acute respiratory failure, tracheostomy utilization rates continue to rise globally.

Despite its clinical benefits, tracheostomy is not without serious complications. The tracheostomy tube (TT) itself, as an indwelling foreign body that continuously interfaces with the warm, humid, and microorganism-rich environment of the tracheal lumen, provides an ideal substrate for bacterial adhesion and biofilm formation.[1] Biofilms are structured communities of microorganisms encased within a self-produced extracellular polymeric matrix composed of polysaccharides, proteins, and extracellular DNA.[1] This protective matrix substantially increases microbial resistance to antimicrobial agents, with minimum inhibitory concentrations for biofilm-embedded bacteria reported to be 10 to 1,000 times higher than those required to kill planktonic counterparts.[1] Furthermore, bacterial cells in the deep layers of biofilms can enter a dormant metabolic state, rendering them refractory to antibiotics that target actively replicating organisms.[2]

Biofilm formation on TTs has been documented in over 90% of tubes within the first seven days of insertion.[3] A systematic review of 20 studies encompassing 981 endotracheal tubes from ICU patients confirmed that the prevalence of biofilm-producing isolates ranged from 20% to 100% (median 72%), with *Pseudomonas aeruginosa* and *Acinetobacter baumannii* emerging as the dominant biofilm-forming pathogens.[4] As the duration of tube use extends, biofilms progressively mature, increasing in thickness, structural complexity, and species diversity. The ICU environment constitutes a particularly permissive niche for biofilm development: concurrent use of broad-spectrum antibiotics selects for resistant biofilm phenotypes, invasive procedures breach mucosal barriers, and the high density of vulnerable immunocompromised patients facilitates cross-transmission of MDR organisms via contaminated devices.[5] Biofilm on TT surfaces constitutes an underestimated microbiological compartment in critically ill patients; confocal microscopy studies of ETTs from ICU patients have identified distinct biofilm morphological patterns corresponding to specific pathogens, underscoring the structural complexity of TT-associated biofilms that renders standard microbiological cultures insufficient for complete characterization.[6] Mature biofilms serve as chronic reservoirs for pathogenic microorganisms and facilitate the downstream contamination of the lower respiratory tract through microaspiration, resulting in ventilator-associated pneumonia (VAP), tracheobronchitis, or systemic sepsis.[7] VAP is among the most devastating hospital-acquired infections, affecting up to 40% of mechanically ventilated patients with a direct attributable mortality of approximately 10%.[8] Tracheostomy-associated infections contribute substantially to this burden, particularly in patients with prolonged intubation.

Among the pathogenic organisms colonizing TTs, *Pseudomonas aeruginosa* and *Staphylococcus aureus* emerge consistently as the most clinically relevant. *P. aeruginosa*, a Gram-negative opportunist, produces β-lactamases and efflux pumps that confer resistance to multiple antibiotic classes, and it secretes virulence factors that degrade TT biomaterials and promote persistent airway colonization.[9,10] *S. aureus*, particularly in its methicillin-resistant form (MRSA), adheres avidly to polymer surfaces, produces tissue-damaging toxins, and can achieve a persistent dormant state within biofilms.[11] A recent systematic review and meta-analysis of 49 studies confirmed that *Pseudomonas* was the most prevalent genus on both endotracheal and tracheostomy tubes across all conditions examined.[9]

METHODS

Study Design and Setting

This was a cross-sectional observational study conducted at the Department of Otorhinolaryngology Head and Neck Surgery, Dr. Sardjito General Hospital, Yogyakarta, Indonesia, in collaboration with the Department of Microbiology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada. The study was conducted from July 23, 2020, to January 6, 2021.

Ethical Approval

The study was approved by the Medical and Health Research Ethics Committee (MHREC) of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada / Dr. Sardjito Hospital Yogyakarta. All participants or their legal guardians provided written informed consent prior to enrollment. Patient data were stored anonymously and managed in accordance with institutional data protection protocols.

Participants and Sampling

A consecutive sampling method was employed to recruit all eligible patients presenting for decannulation during the study period. Inclusion criteria were: (1) adults aged

≥18 years; (2) previous tracheostomy for any clinical indication; (3) TT in situ for at least one day; (4) willingness to provide written informed consent. Exclusion criteria were: (1) tracheostomy tube changes performed under emergency circumstances; (2) patients who refused to participate; (3) incomplete microbiological data. A total of 20 patients were enrolled during the study period.

Tracheostomy Tube Collection and Microbiological Analysis

All TTs included in this study were polyvinyl chloride (PVC) Portex™ standard tracheostomy tubes, chosen to standardize the biomaterial variable across subjects. Upon decannulation, each removed TT was immediately placed in a sterile biohazard specimen bag and transported to the Microbiology Laboratory, Universitas Gadjah Mada, within two hours of collection to prevent post-collection bacterial changes.

In the laboratory, each tube was processed using a standardized protocol. The specimen was then subjected to three cycles of vortex mixing (30 seconds each) to dislodge adherent biofilm bacteria from the tube surface. The resulting suspension was serially diluted and plated onto Blood Agar and MacConkey Agar plates, which were incubated aerobically at 37°C for 24–48 hours. Bacterial colony counts were recorded and expressed as colony-forming units per milliliter (CFU/mL). Bacterial identification was performed using standard microbiological methods including Gram staining, colony morphology, and biochemical profiling. The independent variable was the duration of TT use, defined as the number of days from the date of tracheostomy insertion to the date of decannulation, as recorded in the patient's medical chart.

Clinical Data Collection

Patient demographic and clinical data were extracted from medical records using a standardized data collection form. Variables recorded included: patient age, sex, indication for tracheostomy, duration of TT use (categorized as <30 days, 30–90 days, and >90 days), stomal condition (presence or absence of granuloma), and history of pneumonia during the tracheostomy period.

Statistical Analysis

Descriptive statistics were used to summarize continuous and categorical variables. The Spearman's rank correlation coefficient was used to assess the association between duration of TT use and bacterial colony count (CFU/mL), chosen because the data did not meet the assumptions of normality as assessed by the Shapiro-Wilk test. A p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 25.0

RESULTS

Demographic and Clinical Characteristics

A total of 20 tracheostomized patients were enrolled in the study. Patient demographic and clinical characteristics are summarized in Table 1. The majority of participants were male (65%, n=13) with a mean age of 55.4 years (range 3275 years). The predominant indication for tracheostomy was upper airway obstruction due to malignancy (70%, n=14), followed by laryngeal or tracheal stenosis (20%, n=4), bilateral abductor paralysis of the vocal cords (5%, n=1), and prolonged use of an endotracheal tube (5%, n=1). Stomal granulation was observed in 30% of patients (n=6), and

TABLE 1
Demographic and Subject Characteristics (n=20)

Variable	n	%
Gender		
Male	13	65
Female	7	35
Tracheostomy Indication		
Upper airway obstruction (malignancy)	14	70
Bilateral abductor paralysis of vocal cord	1	5
Laryngeal/tracheal stenosis	4	20
Prolonged use of endotracheal tube	1	5
Stoma Condition		
Granuloma present	6	30
No granuloma	14	70

TABLE 1. *Continued.*

Variable	n	%
Pneumonia During Tracheostomy		
Pneumonia	5	25
No pneumonia	15	75

TABLE 2
Bacterial Count by Duration of TT Use

Sample	Duration of using	CFU (x 10 ^ 3)	Sample	Duration of using	CFU (x 10 ^ 3)
1	19	88.0	11	210	75000.0
2	14	92.0	12	48	92.0
3	34	332.0	13	3	6.0
4	20	8.0	14	63	29.0
5	242	7000.0	15	36	870.0
6	256	20000.0	16	173	28000.0
7	290	4000.0	17	270	36000.0
8	42	20000.0	18	189	15000.0
9	188	13000.0	19	623	68000.0
10	69	37800.0	20	309	16000.0

TABLE 3
Correlation Between Bacterial Count and Duration of Tracheostomy Tube Use

Correlation Test	Correlation Coefficient (r)	*p*-value	Interpretation
Spearman's Rank Correlation	0.70	0.01	Strong positive correlation

25% (n=5) had a documented episode of pneumonia during the tracheostomy period.

Bacterial Species Identified
The types of bacteria identified from TT cultures were: *Pseudomonas aeruginosa* (n=12, 60%), *Staphylococcus aureus* (n=3, 15%), a combination of *P. aeruginosa* and *S. aureus* (n=2, 10%), and other bacteria (n=3, 15%). Overall, *P. aeruginosa* was the dominant colonizing organism, present in 70% of all specimens (either alone or in combination).

Bacterial Count by Duration of TT Use
Mean bacterial counts (CFU × 10^3/mL) increased markedly with the duration of TT use. For tubes in situ for <30 days, the mean count was 48.5 × 10^3 CFU/mL; for tubes used 3090 days, the mean count was 9,853.83 × 10^3 CFU/mL; and for tubes used >90 days, the mean count was 28,200.00 × 10^3 CFU/mL. These data are illustrated in Table 2.

Correlation Analysis
Spearman's rank correlation analysis demonstrated a strong, statistically significant positive correlation between the duration of TT use and bacterial colony count (r = 0.70, p = 0.01). Results are summarized in Table 3.

DISCUSSION

The findings of this study demonstrate a strong positive correlation between the duration of TT use and the quantitative bacterial burden on TT surfaces (r = 0.70, p = 0.01), with mean bacterial counts escalating from 48.5 ×

10^3 CFU/mL in tubes used for fewer than 30 days to 28,200 × 10^3 CFU/mL in those retained for more than 90 days. This exponential increase in bacterial load reflects the natural history of biofilm maturation on polymer surfaces and has direct clinical implications for infection prevention practice.

These results are biologically plausible and consistent with the established understanding of biofilm dynamics on indwelling medical devices, and are further explicable by the specific physicochemical properties of the tube material used in this study. All 20 TTs analyzed were polyvinyl chloride (PVC) Portex™ standard tracheostomy tubes, a standardization that eliminates biomaterial variability as a confounding factor and allows the temporal colonization trend to be attributed specifically to the duration of tube use rather than material differences.[12] PVC is the most widely used polymer for TT fabrication due to its low cost, flexibility, and ease of manufacturing; however, it possesses surface characteristics that are inherently permissive to bacterial adhesion. PVC surfaces carry a net negative surface charge under physiological conditions, and their moderately hydrophobic surface energy promotes the adsorption of host proteins – including fibronectin, fibrinogen, and albumin – within seconds of contact with the humid tracheal environment. This protein conditioning film fundamentally alters the tube surface, transforming it from an abiotic polymer into a biologically receptive substrate that presents specific ligand-binding sites for bacterial surface adhesins.[7]

The initial phase of bacterial colonization on PVC involves reversible adhesion of planktonic bacteria to this conditioned surface, mediated by weak non-covalent forces including van der Waals interactions, electrostatic attractions, and hydrophobic-hydrophobic contacts between bacterial cell surface structures and the conditioned PVC film. Importantly, PVC lacks intrinsic antimicrobial properties and does not release any bacteriostatic agents, meaning that once bacteria establish initial contact with the tube surface, there is no material-derived mechanism to interrupt the colonization process. Studies specifically examining PVC TTs have shown that *Pseudomonas aeruginosa* – the dominant organism in the present study – adheres preferentially to PVC surfaces compared to silicone or polyurethane, owing to the complementarity between the bacterium's outer membrane hydrophobicity and the surface energy characteristics of PVC.[9] Over the following days, adherent bacteria begin secreting extracellular polymeric substances (EPS), a process that is further promoted by the microscale surface roughness of PVC, which provides sheltered microniches that protect early-stage bacterial clusters from shear forces generated by airflow and suctioning. This EPS secretion marks the transition from reversible to irreversible attachment, anchoring the nascent biofilm to the PVC substrate with covalent and ionic bonds that standard cleaning and suctioning cannot disrupt.[13]

As the biofilm matures on the PVC surface, it develops complex three-dimensional architectural features including fluid-filled water channels that enable nutrient transport and metabolic waste removal throughout the biofilm depth. This structural sophistication allows deeper bacterial layers to persist in a slow-metabolizing, antimicrobial-tolerant state, protected not only by the EPS matrix but also by the structural buffering effect of the PVC tube wall itself, which physically shields the inner biofilm from mechanical disruption.[13] A critical material-specific consideration is that PVC undergoes gradual surface degradation during prolonged tracheal use: plasticizers leach from the polymer matrix over time, and mechanical abrasion from suctioning catheters progressively increases the surface roughness at the micro- and nanoscale. This degradation process, documented by Backman[12] *et al*. (2009) over a six-month observation period, creates an increasingly irregular surface topography that provides more attachment points for bacteria and greater structural complexity for biofilm anchoring, amplifying colonization beyond what would occur on a chemically and physically stable surface. By 30 days, the biofilm on PVC TTs has typically achieved a mature, structured configuration that is exponentially more resistant to both antibiotic penetration and mechanical disruption than nascent biofilms.[7] This material-specific susceptibility of PVC to progressive colonization reinforces the practical recommendation arising from this study that PVC Portex™ tubes – the standard of care in most Indonesian clinical settings – should be replaced on a scheduled basis before the 30-day threshold to prevent the establishment of this mature, treatment-resistant biofilm architecture.

The predominance of *Pseudomonas aeruginosa* (60%) in the present study is a finding of substantial clinical importance. *P. aeruginosa* is recognized as one of the ESKAPE pathogens, a group responsible for a disproportionate share of nosocomial infections and antibiotic resistance globally.[14] The high prevalence of *Pseudomonas* in this study corroborates findings from multiple international studies. A recent systematic review and meta-analysis of 49 clinical microbiology studies from 2000–2024 confirmed *Pseudomonas* as the most prevalent genus on both endotracheal and tracheostomy tubes in all patient groups and sampling methods examined.[3] Similarly, Alrabiah[15] *et al*. (2021), in a single-center retrospective study in Saudi Arabia, reported *P. aeruginosa* as the predominant post-tracheostomy organism (47.7%). Ścibik[9] *et al*. (2022) reported colonization in 97% of tracheostomy tubes within the first 24 hours of insertion, with *S. aureus*, *K. pneumoniae*, and *P. aeruginosa* as the leading pathogens.

A distinctive contribution of the present study is

its prospective, quantitative approach to measuring bacterial load across three categorical duration groups, which provides actionable data for clinical decision-making on tube replacement intervals. While most published studies report qualitative microbial profiles or resistance patterns, they rarely quantify the temporal evolution of bacterial burden in terms of CFU/mL and correlate it statistically with duration of use. The data from this study demonstrate that the transition from <30 days to 30–90 days of TT use is associated with a greater than 200-fold increase in mean bacterial count, a finding that underscores the critical importance of the 30-day threshold as a clinically meaningful decision point for scheduled tube replacement. Kumarasinghe[16] *et al*. (2020) found that colonization rates increased with the frequency of tube changes but did not provide CFU-based quantification. Saravanam[17] *et al*. (2022) conducted a prospective study on microbial profiles in tracheostomy tubes and tracheostomas in South India, reporting similar predominant organisms but without a quantitative temporal correlation analysis. The present study therefore fills a specific evidence gap by providing both the species distribution and the quantitative bacterial burden across well-defined duration categories.

This study was conducted in a tertiary hospital in Indonesia, a setting with distinct epidemiological characteristics compared to high-income countries. The study population included a high proportion of head and neck malignancy patients (70%), reflecting the local disease burden. This is clinically significant because oncologic patients often receive corticosteroids, chemotherapy, or radiotherapy that impairs local immune defenses and increases susceptibility to airway colonization. Medical device-associated biofilm infections are a growing concern in Indonesian hospitals, particularly given the increasing prevalence of multidrug-resistant organisms.[14] The diversity of tracheostomy indications also means the findings are generalizable to a broader clinical spectrum than studies restricted to ICU-ventilated patients.

The clinical implications of this study's findings are multifold. First, the strong positive correlation between duration of use and bacterial count provides a scientific basis for recommending TT replacement before 30 days of use, particularly in patients who are immunocompromised, have evidence of respiratory deterioration, or harbor known drug-resistant pathogens. Second, the 60% prevalence of *Pseudomonas aeruginosa* in this population has critical implications for empirical antibiotic selection. Lepainteur[18] *et al*. (2019) cautioned that the high prevalence of *P. aeruginosa* and *Serratia marcescens* in chronically tracheostomized patients renders amoxicillin-clavulanate ineffective as empirical therapy for lower respiratory tract infections in this population. These findings collectively underscore the need for institution-specific antibiograms and individualized antibiotic stewardship protocols in tracheostomized patients.

P. aeruginosa is a notoriously difficult pathogen to treat owing to its intrinsic and acquired resistance mechanisms, including efflux pumps (MexAB-OprM, MexCD-OprJ), outer membrane impermeability, AmpC β-lactamase overexpression, and the capacity for horizontal gene transfer of resistance determinants.[19] Reynolds and Kollef (2021) provide an updated framework for understanding the epidemiology and treatment of *P. aeruginosa* infections, emphasizing that empirical antibiotic selection must be guided by local resistance patterns and the patient's prior antibiotic exposure history. For suspected tracheostomy-associated pneumonia caused by *P. aeruginosa*, first-line empirical agents with established anti-pseudomonal activity include piperacillin-tazobactam, cefepime, and carbapenems such as meropenem or imipenem-cilastatin. Among these, piperacillin-tazobactam and cefepime are generally preferred as initial agents when susceptibility data are unavailable, given their favorable safety profiles and broad Gram-negative coverage.[19] However, both agents are susceptible to hydrolysis by extended-spectrum β-lactamases (ESBLs) and AmpC enzymes frequently expressed by *P. aeruginosa* biofilm isolates, and susceptibility testing is therefore imperative before definitive therapy is initiated.[19]

For infections caused by multidrug-resistant (MDR) or difficult-to-treat (DTR) *P. aeruginosa* strains – defined as strains resistant to all first-line antipseudomonal agents – newer β-lactam/β-lactamase inhibitor combinations represent important therapeutic advances. Ceftolozane-tazobactam and ceftazidime-avibactam have demonstrated superior activity against MDR *P. aeruginosa* compared to older agents, particularly in strains overexpressing efflux pumps or producing AmpC β-lactamases.[19] The 2024 Infectious Diseases Society of America (IDSA) guidance on the treatment of antimicrobial-resistant Gram-negative infections recommends ceftolozane-tazobactam as a preferred agent for DTR *P. aeruginosa* infections, with ceftazidime-avibactam as an alternative when metallo-β-lactamase production is suspected.[20] Colistin and polymyxin B, while historically used as last-resort agents, carry significant nephrotoxicity risk and are now reserved for pan-drug-resistant strains only when no other options exist.[21]

The choice of antibiotic must also consider the pharmacokinetic/pharmacodynamic (PK/PD) challenges posed by *P. aeruginosa* biofilms on TT surfaces. Biofilm-embedded bacteria can tolerate antibiotic concentrations 10 to 1,000 times higher than planktonic minimum inhibitory concentrations (MICs), necessitating either prolonged infusion strategies to optimize time-dependent killing (particularly for β-lactams such as piperacillin-tazobactam and

meropenem) or the use of concentration-dependent agents such as aminoglycosides (amikacin, tobramycin) or fluoroquinolones (ciprofloxacin) as combination partners.[19,20] Inhaled antibiotics, including inhaled tobramycin or colistimethate, offer the advantage of delivering very high local drug concentrations directly to the airway mucosa and TT surface, potentially overcoming the concentration barrier imposed by biofilm structure.[19] For pediatric tracheostomized patients, a systematic review by Pearce[22] *et al*. (2024) similarly concluded that anti-pseudomonal agents represent the most frequently required antibiotic class and recommended routine tracheal aspirate surveillance cultures to guide targeted therapy before overt clinical infection develops. This recommendation aligns with the present study's findings and reinforces the value of microbiological monitoring in tracheostomized patients regardless of their ventilation status.

Third, the absence of a strong association between ventilator use and biofilm formation, as observed in prior studies, suggests that the physical presence of the TT itself, rather than mechanical ventilation alone, is the primary driver of colonization. This finding challenges the common assumption that infection control efforts should focus exclusively on mechanically ventilated patients and highlights the need for equally rigorous tube hygiene and surveillance protocols in non-ventilated tracheostomized patients.[23]

The presence of stomal granulation in 30% of patients in this study requires detailed discussion, as it represents a clinically significant complication of tracheostomy that is closely intertwined with microbial colonization dynamics. Granulation tissue (granuloma) at the tracheostoma is an abnormal wound-healing response characterized by the proliferation of fibroblasts, capillary buds, and inflammatory cells, primarily macrophages and neutrophils, at the tracheal mucosal interface with the TT. The fundamental stimulus for this exuberant healing response is chronic low-grade inflammation driven by the mechanical irritation of the tube against the tracheal mucosa, exacerbated by persistent bacterial colonization and biofilm formation on the tube surface.[17]

The pathophysiological relationship between biofilm and granulation formation is bidirectional and self-reinforcing. Bacterial biofilms on the TT surface continuously release lipopolysaccharides (LPS), peptidoglycans, and other pathogen-associated molecular patterns (PAMPs) that activate toll-like receptors (TLRs) on tracheal epithelial cells and resident macrophages.[7] This activation triggers a sustained pro-inflammatory cascade involving interleukins (IL-1β, IL-6, IL-8) and tumor necrosis factor-alpha (TNF-α), which recruits circulating neutrophils and monocytes to the stoma site.[24] Paradoxically, while this inflammatory response attempts to clear the biofilm, it simultaneously promotes fibroblast proliferation and collagen deposition, the cellular mechanisms underlying granulation tissue formation. Gram-negative organisms such as *Pseudomonas aeruginosa* are particularly potent drivers of this cycle because their LPS component is a powerful TLR-4 agonist, inducing a more vigorous inflammatory reaction compared to Gram-positive cell wall components.[9] This may explain the clinical observation that patients colonized by Gram-negative organisms tend to develop more exuberant granulation than those colonized by Gram-positive flora alone.

Furthermore, the granulation tissue itself creates a microenvironment that paradoxically facilitates further bacterial colonization. The richly vascularized, irregular surface of granulation tissue provides an increased surface area and altered tissue architecture that promotes bacterial adhesion. The local hypoxia characteristic of proliferating granulation tissue also favors the selection of oxygen-tolerant and anaerobic organisms and reduces the bactericidal activity of neutrophils, whose oxidative burst mechanism requires molecular oxygen.[2] Exudate from granulation tissue provides a nutrient-rich medium that sustains bacterial growth and biofilm maturation. This self-perpetuating cycle of infection, inflammation, and granulation formation represents a key mechanism by which prolonged TT retention leads to compounding clinical complications.

In clinical practice, stomal granulation carries several important consequences that extend beyond cosmetic concern. First, granulation tissue at the stoma can partially or completely obstruct the TT lumen or the stomal opening, particularly in patients with inner cannula-style tubes, leading to increased airway resistance, difficulty with tube changes, and in severe cases, acute airway compromise. Second, granulation tissue is friable and highly vascular, making it prone to contact bleeding during suctioning, tube manipulation, or speech valve attachment, which may cause patient distress and complicate nursing care. Third, exuberant granulation at the tracheal level can contribute to tracheal stenosis, a long-term complication that may require surgical or endoscopic intervention. A study by Saravanam[17] *et al*. (2022) confirmed that patients who underwent tube changes after more than one month had significantly higher grades of granulation compared to those changed within one month, directly paralleling the bacterial load escalation observed in the present study.

The 30% prevalence of granulation in this cohort highlight the clinical utility of routine stomal assessment at each tube change as an early indicator of suboptimal TT management, excessive dwell time, or uncontrolled bacterial colonization. For patients found to have Grade 2 or higher granulation, earlier TT replacement and intensified topical hygiene protocols should be strongly considered. In refractory cases, application of silver nitrate cautery, topical corticosteroids, or surgical

excision of granulation tissue may be required to restore stomal anatomy and facilitate decannulation. These considerations reinforce the practical importance of this study's recommendation that TT replacement should occur before 30 days of use, not only to limit bacterial burden but also to prevent the cascade of stomal complications driven by chronic colonization and biofilm-mediated inflammation.[24]

From a public health perspective, the increasing prevalence of multidrug-resistant (MDR) organisms in hospital environments in Indonesia and other resource-limited settings makes biofilm management a priority. The development of antimicrobial-coated TTs, incorporating materials such as silver ions, titanium dioxide, or antimicrobial peptides, offers promising future strategies to mitigate colonization.[25] Research by Ochońska[26] *et al*. (2021) further demonstrated that *K. pneumoniae* forms genetically diverse biofilms on both PVC and polyethylene TT surfaces, reinforcing the need for biomaterial-level solutions to colonization.

CONCLUSION

This study demonstrates a strong positive correlation between the duration of TT use and bacterial colonization burden ($r = 0.70$, $p = 0.01$), with mean bacterial counts increasing more than 200-fold between tubes used for fewer than 30 days and those retained for 30–90 days. *Pseudomonas aeruginosa* was the predominant colonizing pathogen, identified in 60% of specimens. These findings provide quantitative evidence supporting the recommendation for scheduled TT replacement within 30 days as a key infection control strategy in tracheostomized patients. The findings also underscore the need for empirical antibiotic regimens with anti-pseudomonal coverage when treating suspected tracheostomy-associated respiratory infections in this population. Future research should prioritize larger prospective multicenter studies with resistance profiling to refine clinical guidelines for TT management.

ACKNOWLEDGEMENTS

The authors express sincere gratitude to the Department of Microbiology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada / Dr. Sardjito General Hospital Yogyakarta, for their invaluable collaboration and support in conducting the microbiological analyses central to this study. The authors also thank the medical and nursing staff of the Department of Otorhinolaryngology Head and Neck Surgery at Dr. Sardjito General Hospital for their assistance with patient recruitment and data collection. Special appreciation is extended to all patients who participated in this study.

CONFLICT OF INTEREST

All authors declare that they have no financial or non-financial conflicts of interest relevant to this article. The study received no external funding from pharmaceutical companies or medical device manufacturers.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; vol 13 (1) : 45–54

OPEN ACCESS

Original Article

Association Between Vitamin A and Zinc Intake with Inflammatory Markers in Pulmonary Tuberculosis

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v13i1.1222

Submitted: February 25th, 2025
Accepted: March 26th, 2025

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Abstract

Background : Indonesia has the second highest burden of tuberculosis (TB) worldwide, with an incidence of 354 per 100,000 population and approximately 969,000 cases reported in 2021. Micronutrients such as vitamin A and zinc play important roles in immune function and may influence inflammatory responses in TB. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are potential markers of systemic inflammation; however, evidence regarding their association with dietary micronutrient intake in pulmonary TB patients remains limited, particularly in Indonesia.
Aims : To examine the association between vitamin A and zinc intake and inflammatory markers in pulmonary TB patients.
Methods : A cross-sectional study was conducted among 133 pulmonary TB patients recruited consecutively from March to April 2024 at Persahabatan Hospital. Vitamin A and zinc intake were assessed using a semi-quantitative food frequency questionnaire (SQ-FFQ), while NLR and PLR values were obtained from medical records. Data normality was tested using the KolmogorovSmirnov test, and correlations were analyzed using Spearman's test. The median vitamin A intake was 105.47 RE/day and zinc intake was 7.38 mg/day, with median NLR and PLR of 2.91 and 202.08, respectively.
Results : No significant correlations were found between vitamin A or zinc intake and NLR or PLR ($p > 0.05$).
Conclusion : In conclusion, vitamin A and zinc intake were not associated with inflammatory markers in pulmonary TB patients, although host-related factors may contribute to the inflammatory response.

Keywords : Inflammation; NLR; TB; vitamin A; zinc

INTRODUCTION

Indonesia has the second-highest burden of tuberculosis (TB) globally, with an incidence of 354 per 100,000 population and approximately 969,000 cases reported in 2021. Despite ongoing national TB control programs, treatment outcomes remain suboptimal, with the treatment success rate still below the national target.[1,2] This highlights the need to explore additional modifiable factors that may influence disease progression and recovery in TB patients.

Malnutrition and TB are closely interrelated in a bidirectional manner. Poor nutritional status can impair immune function, increasing susceptibility to infection and worsening disease severity. Conversely, TB infection can lead to reduced appetite, altered metabolism, and increased energy expenditure, ultimately resulting in nutrient deficiencies. This interaction contributes to delayed recovery, higher risk of complications, and poorer treatment outcomes among affected individuals.

Micronutrients, particularly vitamin A and zinc, play essential roles in maintaining immune competence. Vitamin A is a fat-soluble vitamin involved in epithelial integrity, cellular differentiation, and regulation of both innate and adaptive immune responses. It plays a critical role in maintaining mucosal barriers and modulating the activity of T and B lymphocytes, macrophages, and antibody production. Zinc, on the other hand, is a trace element required for over 300 enzymatic reactions and is crucial for DNA synthesis, cell division, and immune cell function. Zinc deficiency has been associated with impaired phagocytosis, reduced lymphocyte proliferation, and dysregulated inflammatory responses.[3]

In the context of TB, micronutrient deficiencies are highly prevalent and may exacerbate disease progression have demonstrated that patients with active TB often have lower levels of vitamin A and zinc compared to healthy individuals. These deficiencies may impair host defense mechanisms and contribute to prolonged inflammation and delayed bacterial clearance. However, most of the existing evidence has focused on biochemical or serum levels of micronutrients rather than dietary intake, which may provide a more practical and modifiable target for intervention.

Systemic inflammation is a key feature of TB and reflects both disease severity and host immune response. In recent years, simple hematological markers such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have gained attention as indicators of inflammatory status. NLR reflects the balance between neutrophil-mediated innate immunity and lymphocyte-mediated adaptive immunity, while PLR represents the interaction between platelet activation and immune response. Enhancement NLR and PLR values have been associated with increased disease severity, poor prognosis, and treatment response in TB patients.[4,5]

Compared to conventional inflammatory markers such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), NLR and PLR are inexpensive, readily available, and can be derived from routine complete blood count examinations. This makes them particularly useful in low-resource settings, where access to advanced laboratory testing may be limited. Furthermore, these markers have been increasingly studied in various infectious and inflammatory diseases, supporting their potential clinical utility.

Despite growing interest in the role of micronutrients and inflammatory markers in TB, there remains a significant gap in the literature. Most previous studies have examined the association between serum micronutrient levels and TB outcomes, while limited research has explored the relationship between dietary micronutrient intake and inflammation. In addition, evidence from Indonesia is still scarce, despite the high burden of TB and the prevalence of nutritional deficiencies in the population.

Furthermore, the inflammatory response in TB is influenced not only by nutritional intake but also by host-related factors such as nutritional status, treatment phase, bacteriological status, and comorbid conditions, including diabetes mellitus. These factors may act as confounders and contribute to variability in inflammatory markers, yet they have not been comprehensively evaluated in relation to dietary intake in previous studies.

Therefore, this study aimed to examine the association between vitamin A and zinc intake with inflammatory markers, specifically NLR and PLR, among pulmonary TB patients at Persahabatan Hospital. This study also explored the potential influence of selected host-related factors on inflammatory responses. Understanding these relationships may provide insight into the role of nutrition in TB management and support the development of integrated strategies to improve patient outcomes. This study is among the first in Indonesia to examine dietary micronutrient intake in relation to hematological inflammatory markers in pulmonary TB patients.

METHODS

This study employed an observational analytical design with a cross-sectional approach conducted at Persahabatan National Respiratory Referral Hospital, Jakarta, Indonesia, between March and April 2024.

A consecutive sampling recruited among 133 subjects.

Inclusion criteria were adults aged ≥18 years with a confirmed diagnosis of pulmonary TB established by the attending physician based on clinical, radiological,

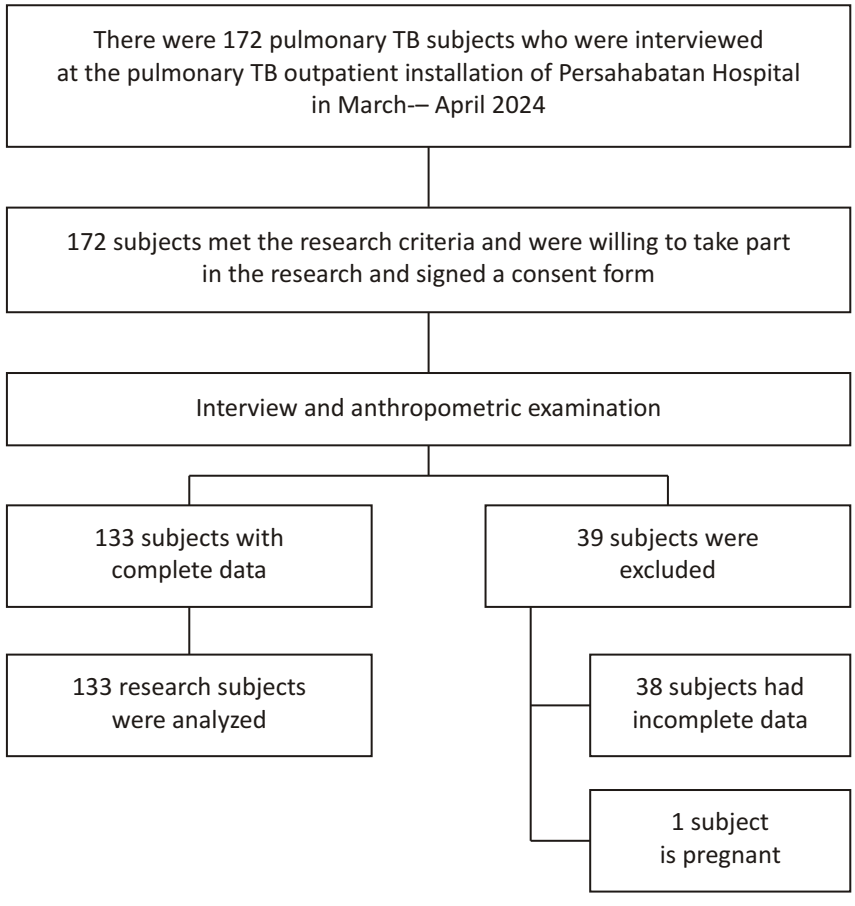

Figure 1. Research sample selection flow

and/or microbiological findings, who agreed to participate and provided written informed consent. Exclusion criteria included incomplete laboratory data (neutrophil, lymphocyte, or platelet counts), laboratory results obtained more than one month prior to data collection, pregnancy, breastfeeding, and suspected or confirmed HIV infection based on medical history or laboratory findings.

Data collection was performed through structured interviews, anthropometric measurements, and medical record review. Trained researchers conducted face-to-face interviews using standardized questionnaires to obtain information on demographic characteristics, educational level, income, smoking history, comorbidities, and medication use.

Dietary intake over the previous month was assessed using a semi-quantitative food frequency questionnaire (SQ-FFQ) consisting of commonly consumed Indonesian food items. The SQ-FFQ instrument had been previously validated in Indonesian populations. Portion sizes were estimated using a standardized food photograph atlas published by the Ministry of Health. Reported food intake was converted into grams using household measurement standards.

Nutrient intake was analyzed using NutriSurvey 2007 software based on the Indonesian Food Composition Table. Vitamin A intake was expressed as retinol equivalents (RE) per day, while zinc intake was expressed in milligrams per day.

The adequacy of micronutrient intake was determined based on the 2019 Indonesian Recommended Dietary Allowance (RDA). Vitamin A intake was categorized as adequate if ≥600 RE/day and inadequate if <600 RE/day. Zinc intake was classified as adequate if ≥8 mg/day and inadequate if <8 mg/day. The classification of micronutrient adequacy was also supported by previous studies in Indonesian populations.[26,27]

Anthropometric measurements included body weight and height, measured twice using a calibrated digital scale (SECA 876) and a ShorrBoard stadiometer with an accuracy of 0.1 cm. The average of the two measurements was used for analysis. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and classified according to the WHO Asia-Pacific criteria.

Inflammatory markers were obtained from routine complete blood count results recorded in patients' medical records. The neutrophil-to-lymphocyte ratio

(NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, while the platelet-to-lymphocyte ratio (PLR) was calculated by dividing the platelet count by the absolute lymphocyte count.

Data analysis was performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Data normality was assessed using the KolmogorovSmirnov test. Continuous variables were presented as mean ± standard deviation for normally distributed data or median (minimum–maximum) for non-normally distributed data, while categorical variables were presented as frequencies and percentages.

Correlation analysis between vitamin A and zinc intake and inflammatory markers (NLR and PLR) was conducted using Pearson correlation for normally distributed data or Spearman's rank correlation test for non-parametric data. A p-value <0.05 was considered statistically significant.

This study was approved by the Research Ethics Committee of Persahabatan Hospital (No. 0034/KEPK-RSUPP/02/2024). All participants provided written informed consent prior to enrollment. Confidentiality of participants' data was maintained throughout the study, and all procedures were conducted in accordance with ethical standards for human research.

RESULTS

A total of 133 pulmonary TB (TB) patients were included in this study. The age of participants ranged from 19 to 74 years, with a median age of 39 years, indicating a predominance of individuals in the productive age group. Male participants slightly outnumbered females, accounting for 51.9% of the sample. In terms of educational background, most subjects had a moderate level of education (57.1%), while 26.3% had low education and 16.5% had higher education.

The largest proportion of participants had normal body mass index (42.1%), followed by underweight individuals (36.8%). A smaller proportion were classified as overweight (8.3%) and obese (12.8% combined for obese I and II). These findings indicate that although a considerable number of patients had normal nutritional status, undernutrition remained highly prevalent among TB patients in this cohort.

Most participants (83.5%) had an income below the regional minimum wage, reflecting a predominantly low socioeconomic background. Regarding treatment characteristics, 46.6% of subjects were in the intensive phase of anti-TB therapy, 26.3% were in the continuation phase, and 27.1% were classified as having drug-resistant TB. Bacteriological examination showed that 51.9% of patients were positive, while 48.1% were negative at the time of data collection.

The majority of subjects (59.4%) reported no comorbidities. Among those with comorbid conditions, diabetes mellitus was the most common (15.8%), followed by cardiovascular disease (6.0%), while smaller proportions reported cancer or chronic respiratory diseases. Smoking history revealed that 57.1% of participants had never smoked, whereas 20.3% were light smokers and 16.5% were moderate to heavy smokers.

In terms of medication use, 67.7% of participants reported no additional drug consumption aside from anti-TB therapy. Among those who used concomitant medications, the most commonly reported were antihypertensive drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), and gastrointestinal medications such as antacids or proton pump inhibitors.

Dietary assessment revealed that the majority of participants had inadequate micronutrient intake. A total of 94.7% of subjects had vitamin A intake below the recommended dietary allowance, while 56.4% had inadequate zinc intake. The median vitamin A intake was 105.47 RE/day (range 4.26–1854.90), and the median zinc

TABLE 1
Characteristics of the Study Participants (n= 133)

Variables	Proportion n (%)	Median (min–max)
Age		39 (19–74)
Gender		
Male	69 (51.9)	
Female	64 (48.1)	
Level of education		
Low	35 (26.3)	
Medium	76 (57.1)	
High	22 (16.5)	

TABLE 1. *Continued.*

Variables	Proportion n (%)	Median (min–max)
Nutritional status		
Underweight	49 (36.8)	
Normal	56 (42.1)	
Overweight	11 (8.3)	
Obese I	12 (9.0)	
Obese II	5 (3.8)	
Income		
Below minimum wage	111 (83.5)	
Above minimum wage	22 (16.5)	
Treatment Phase		
Intensive Phase	62 (46.6)	
Continuation Phase	35 (26.3)	
Drug Resistant	36 (27.1)	
Bacteriological Status		
Positive	69 (51.9)	
Negative	64 (48.1)	
Comorbid		
None	79 (59.4)	
Cardiovascular disease	8 (6.0)	
Cancer	2 (1.5)	
Chronic respiratory disease	2 (1.5)	
Diabetes	21 (15.8)	
Other	20 (15.0)	
Smoking Habit		
Never	76 (57.1)	
Mild	27 (20.3)	
Moderate	22 (16.5)	
Heavy	8 (6.0)	
Drug Consumption		
None	90 (67.7)	
Antacids, PPI, H2 receptor blockers	4 (3.0)	
Nonsteroidal anti-inflammatory drugs (NSAIDs)	9 (6.8)	
Mineral Supplements (Fe, Ca, Cu)	–	
Antihypertensives (ACE inhibitors, loop diuretics, thiazides)	9 (6.8)	
Antibiotics (ciprofloxacin, tetracycline)	1 (0.8)	
Other	29 (21.8)	

TABLE 1. *Continued.*

Variables	Proportion n (%)	Median (min–max)
Vitamin A Intake		
Inadequate	126 (94.7)	
Adequate	7 (5.3)	
Zinc Intake		
Inadequate	75 (56.4)	
Adequate	58 (43.6)	

TABLE 2
Distribution of Intake of Vitamin A, Zinc, and Inflammatory markers

Variables	Median (min–max)
Vitamin A Intake (RE)	105.47 (4.26–1854.90)
Zinc Intake (mg)	7.38 (1.74–40.47)
Inflammatory markers	
NLR	2.91 (0.75–26.26)
PLR	202.08 (9.82–1516.24)

TABLE 3
Correlation between Vitamin A and Zinc Intake and Inflammatory markers

Variables	Inflammatory markers			
	NLR		PLR	
	r	*p* value	r	*p* value
Vitamin A Intake	0.077	0.379[S]	0.059	0.497[S]
Zinc Intake	0.104	0.234[S]	0.130	0.137[S]

*[S] Spearman test

intake was 7.38 mg/day (range 1.74–40.47). These findings indicate a substantial gap between actual intake and recommended levels, particularly for vitamin A.

Regarding inflammatory markers, the median neutrophil-to-lymphocyte ratio (NLR) was 2.91 (range 0.75–26.26), while the median platelet-to-lymphocyte ratio (PLR) was 202.08 (range 9.82–1516.24). These values reflect a wide variability in systemic inflammatory response among TB patients.

Correlation analysis using Spearman's test demonstrated that there was no statistically significant association between vitamin A intake and NLR (r = 0.077; p = 0.379) or PLR (r = 0.059; p = 0.497). Similarly, zinc intake was not significantly correlated with NLR (r = 0.104; p = 0.234) or PLR (r = 0.130; p = 0.137). These results indicate that dietary intake of vitamin A and zinc did not show a measurable relationship with inflammatory markers in this study population.

Further exploratory analyses were conducted to assess the potential influence of host-related factors on inflammatory markers. Patients with underweight nutritional status tended to have higher median NLR and PLR values compared to those with normal or higher BMI, suggesting a possible association between poor nutritional status and increased inflammatory response. Additionally, subjects in the intensive phase of TB treatment showed relatively higher NLR values compared to those in the continuation phase, reflecting

more active inflammation during early treatment.

Patients with comorbid diabetes mellitus also demonstrated a tendency toward higher PLR values compared to those without comorbidities. Similarly, individuals with drug-resistant TB appeared to have elevated inflammatory markers compared to drug-sensitive cases. However, these differences did not reach statistical significance in this study.

Overall, while micronutrient intake––specifically vitamin A and zinc––was largely inadequate among participants, no direct correlation was found with inflammatory markers (NLR and PLR). Instead, descriptive trends suggest that inflammatory responses in pulmonary TB patients may be influenced by a combination of nutritional status, treatment phase, and comorbid conditions rather than micronutrient intake alone.

DISCUSSION

The findings demonstrated that the majority of participants had inadequate intake of vitamin A and zinc; however, no statistically significant association was observed between micronutrient intake and inflammatory markers. These results highlight the complexity of the relationship between nutrition and immune response in TB. This finding suggests that dietary intake alone may not reflect inflammatory status in TB patients.

The high prevalence of inadequate vitamin A intake (94.7%) observed in this study is consistent with previous findings in TB populations, where micronutrient deficiencies are common due to both inadequate dietary intake and disease-related metabolic alterations.[6,28] Vitamin A plays a crucial role in maintaining epithelial integrity and modulating immune responses, particularly through its involvement in T- and B-lymphocyte differentiation and antibody production.[3] Despite its well-established immunological role, the lack of association between dietary vitamin A intake and inflammatory markers in this study suggests that intake alone may not directly reflect functional immune status in TB patients.

Similarly, more than half of the participants (56.4%) had inadequate zinc intake, which is in line with previous studies conducted in TB populations.[6,12] Zinc is essential for numerous biological processes, including DNA synthesis, cell division, and immune function. Previous interventional studies on zinc supplementation have also reported mixed effects on inflammatory outcomes.[3,23] It also plays a key role in maintaining immune integrity by supporting macrophage activity, neutrophil function, and lymphocyte proliferation. Micronutrients, including vitamin D, have also been shown to influence immune responses in TB.[31] The absence of a significant relationship between zinc intake and NLR or PLR in this study may be explained by the complex regulation of zinc metabolism during infection.

One possible explanation for the lack of significant associations is the effect of the acute-phase response during TB infection. Pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) can influence the metabolism and redistribution of micronutrients. During inflammation, both vitamin A and zinc are redistributed from circulation to tissues, resulting in decreased plasma concentrations regardless of intake.[28,29] This phenomenon may obscure the relationship between dietary intake and circulating biomarkers, including hematological inflammatory indices such as NLR and PLR.

Another important consideration is that dietary intake assessed using SQ-FFQ reflects habitual consumption rather than actual bioavailability or absorption. Factors such as dietary composition, presence of inhibitors (e.g., phytates), and individual differences in metabolism can significantly affect nutrient utilization.[13,14] For instance, zinc absorption is inhibited by phytate-rich foods, while vitamin A absorption depends on adequate dietary fat intake.[14,15] Therefore, measured intake may not accurately represent the effective nutrient status influencing immune responses.

The median NLR value of 2.91 observed in this study is consistent with previous reports indicating elevated NLR levels in TB patients.[22,37] NLR reflects the balance between innate and adaptive immune responses, where increased neutrophils indicate acute inflammation and decreased lymphocytes reflect immune redistribution.[3] Although NLR has been proposed as a useful marker for disease severity and treatment response, its relationship with nutritional factors appears to be indirect and influenced by multiple confounding variables.

Similarly, the median PLR value of 202.08 suggests an elevated inflammatory state among participants. Platelets are increasingly recognized as active participants in immune and inflammatory processes, interacting with leukocytes and contributing to cytokine release.[11] Elevated PLR has been associated with disease severity in TB and other chronic inflammatory conditions.[11] However, as with NLR, PLR may be more reflective of overall disease activity rather than specific nutritional intake.

Although no statistically significant correlations were identified, exploratory analyses in this study suggested that host-related factors may play a more prominent role in influencing inflammatory markers. Patients with underweight status tended to have higher NLR and PLR values, supporting previous evidence that malnutrition exacerbates systemic inflammation and impairs immune regulation.[1] Malnutrition can lead to reduced immune cell production and altered cytokine responses, thereby intensifying inflammatory

processes.[26,27]

Treatment phase also appeared to influence inflammatory markers. Patients in the intensive phase of anti-TB therapy demonstrated higher NLR values compared to those in the continuation phase. This finding is supported by previous studies showing that inflammatory markers tend to decrease following treatment initiation.

Comorbid diabetes mellitus was another factor associated with higher PLR values in this study. Diabetes is known to impair immune function and promote chronic inflammation, increasing susceptibility to TB and worsening outcomes.[21] Additionally, hyperglycemia can enhance platelet activation and inflammatory responses, potentially influencing PLR values.[2]

The findings of this study differ from some previous research that reported significant associations between serum micronutrient levels and TB outcomes. For example, studies have shown that low serum vitamin A and zinc levels are associated with worse clinical outcomes in TB patients.[12,30,31] This discrepancy may be attributed to differences in measurement methods, as this study assessed dietary intake rather than biochemical levels.

This study provides important insights into the nutritional and inflammatory profiles of TB patients in Indonesia. By focusing on dietary intake rather than biochemical measurements, it offers a practical perspective relevant for clinical and public health interventions. However, the findings also underscore the limitations of using dietary intake alone to assess the relationship between nutrition and immune function in infectious diseases.

Several limitations should be considered. The cross-sectional design limits causal interpretation, and dietary data collection using SQ-FFQ may introduce recall bias. Additionally, the absence of biochemical measurements limits the ability to fully assess micronutrient status.[13] Despite these limitations, this study contributes valuable baseline data for future research.

Future studies should consider longitudinal designs and incorporate both dietary and biochemical assessments to better understand the dynamic relationship between nutrition and inflammation in TB. Similar findings have been reported in South Asian populations, where nutritional status was associated with inflammatory markers.[32,33] Furthermore, larger sample sizes and inclusion of additional biomarkers may help clarify the observed associations.

From a clinical perspective, the findings emphasize the importance of integrating nutritional assessment into TB management. Although no direct association was found between micronutrient intake and inflammatory markers, ensuring adequate nutrient intake remains essential for supporting immune function and recovery.[32] These findings emphasize that nutritional interventions in TB should not rely solely on intake assessment but consider comprehensive host and disease-related factors.

CONCLUSION

This study found that there was no statistically significant association between dietary intake of vitamin A and zinc and inflammatory markers, as measured by neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), among pulmonary TB patients at Persahabatan Hospital. Despite the absence of a direct correlation, the findings revealed that the majority of patients had inadequate intake of these essential micronutrients, highlighting a substantial nutritional gap in this population.

The results suggest that inflammatory responses in TB are not solely influenced by micronutrient intake but are likely determined by a complex interplay of multiple host-related factors. Exploratory analyses indicated that nutritional status, phase of anti-TB treatment, drug resistance status, and comorbid conditions such as diabetes mellitus may contribute to variations in inflammatory markers. Although these associations did not reach statistical significance, they demonstrate consistent trends that align with biological plausibility and existing literature.

These findings underscore the importance of adopting a more comprehensive approach in understanding the relationship between nutrition and immune response in TB. While dietary intake alone may not directly correlate with hematological inflammatory markers, adequate micronutrient consumption remains essential for maintaining immune function, supporting recovery, and improving overall clinical outcomes. Therefore, nutritional assessment should be considered an integral component of routine TB management.

From a clinical and public health perspective, integrating nutritional evaluation and counseling into TB care may provide a low-cost and feasible strategy to support patient recovery, particularly in resource-limited settings. In addition, simple inflammatory markers such as NLR and PLR may still serve as useful adjunct tools for monitoring disease progression when interpreted alongside clinical and nutritional factors.

Future research should focus on longitudinal study designs to capture dynamic changes in both micronutrient status and inflammatory responses during treatment. The inclusion of biochemical measurements, such as serum vitamin A and zinc levels, alongside dietary assessment, would provide a more comprehensive understanding of nutrientimmune interactions. Larger, multicenter studies are also needed to confirm these findings and to further explore the combined effects of nutritional and clinical variables on

TB outcomes.

In conclusion, although no significant association was observed between vitamin A and zinc intake and inflammatory markers in this study, the high prevalence of inadequate intake and the influence of host-related factors highlight the need for integrated nutritional and clinical management strategies in TB care.

ACKNOWLEDGMENTS

We would like to thank everyone who provided guidance and contributed to the preparation of this study.

CONFLICT OF INTEREST

The authors declared there is no conflict of interest.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; vol 13 (1) : 55–63

OPEN ACCESS

Original Article

Comparison of Effectiveness Cost Therapy and Increasing Level of Haemoglobin, Ferritin in Pregnant Women with Anemia Whom are Given Iron Tablet Everyday and Every Two Days

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v13i1.1338

Submitted: February 27th, 2025
Accepted: March 26th, 2026

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Abstract

Background : Anemia is common in pregnancy, with a prevalence of 48.9% in Indonesia (Riskesdas 2018). It increases the risk of impaired fetal growth, stunting, and intellectual disorders. Iron supplementation, as recommended by *Permenkes No. 88/2014*, is a key preventive strategy. Evidence such as Moretti et al. (2015), suggests that alternate-day supplementation improves absorption due to reduced hepcidin activity.
Aim : To evaluate the effectiveness of administering iron tablets every two days in terms of treatment cost, increases in hemoglobin (Hb) and ferritin levels, and incidence of gastrointestinal adverse effects.
Methods : This was a true experimental study using a randomized prepost test control group design. The control group received iron tablets daily for two months, while the intervention group received iron tablets every two days. The study was conducted at the Obstetrics and Gynecology Polyclinic of Kariadi Central General Hospital and Halmahera Primary Health Care over eight months (December 2023 – July 2024). Each group included 23 subjects. Body weight, hemoglobin, and ferritin were measured at baseline and after two months. Adverse effects and neonatal outcomes were also documented.
Results : Baseline characteristics were normally distributed. The intervention group showed a significant increase in hemoglobin and ferritin levels, higher neonatal birth weight, and lower treatment cost and adverse effects compared to the control group ($p < 0.05$). Post-treatment differences between groups were 0.5 g/dL for hemoglobin and 17.2 ng/mL for ferritin.
Conclusion : Administering iron tablets every two days is effective in improving hemoglobin and ferritin levels in pregnant women with anemia and is also cost-effective with fewer adverse effects.

Keywords : Anemia, Cost-effective therapy, Iron Supplementation, Pregnancy

INTRODUCTION

Anemia is a common complication during pregnancy and the postpartum period. Iron deficiency anemia (IDA) in pregnancy remains a major global health concern due to its significant impact on maternal and fetal outcomes. Anemia affects an estimated 36–40% of pregnant women, with iron deficiency recognized as the leading cause, accounting for approximately half of all cases worldwide.[1,2] The burden of iron deficiency anemia among pregnant women is particularly high in Southeast Asia, where prevalence rates consistently exceed the global average. Regional estimates indicate that more than 45–50% of pregnant women in Southeast Asia are affected by anemia, with some countries reporting prevalence above 60%.[1,3]

In Indonesia, the prevalence of anemia among pregnant women is 48.9%, with the highest proportion in women aged 15–24 years (Riskesdas 2018).[4] Anemia is defined as a reduction in hemoglobin (Hb), hematocrit, or red blood cell count. In pregnancy, anemia is diagnosed when Hb is <11 g/dL in the first and third trimesters or <10.5 g/dL in the second trimester.[5] Maternal anemia increases the risk of low birth weight, preterm birth, and impaired fetal neurodevelopment. In order to prevent and treat anaemia, pregnant women should take iron supplementation during pregnancy, puerperal period and breast feeding.[6]

Anemia during pregnancy may result from acute or chronic blood loss, increased red blood cell destruction, reduced production, or a combination of these factors. Iron deficiency remains the leading cause of decline red blood cells production. The total iron requirement during pregnancy reaches approximately 1000 mg to support maternal erythropoiesis, placental development, and fetal growth, as well as blood reserve to prepare for blood loss at delivery. Thus, universal iron supplementation is advised for all pregnant woman.[5,6]

According to WHO guidelines (2012), daily iron and folic acid supplementation reduces the risk of maternal anemia, iron deficiency, preterm delivery, and low birth weight.[7] Similarly, Indonesian regulation *Permenkes No. 88/2014* recommends daily iron–folic acid tablets for at least 90 days during pregnancy.[8] However, compliance is low, from 24% of women whom receive full course of 90 iron tablets recommended, only 38.1% of them take the 90 iron tablets as prescribed, indicating that the majority of pregnant women do not fully adhere to iron tablet intake.[4] Gastrointestinal side effects such as nausea, constipation, abdominal pain, and bloating, along with limited distribution of supplements throughout Indonesia, contribute to poor adherence pregnant women to take iron-folic acid regularly.[9]

Excess iron intake may also have negative effects, including oxidative stress, alterations of the gut microbiome, hypertensive disorders, small-for-gestational-age infants, and impaired placental blood flow.[10] These concerns support the use of intermittent regimens as a potentially safer alternative. Evidence shows that oral iron given every 48 hours improves absorption compared to daily dosing, with lower adverse effects. This is largely explained by hepcidin, a liver-derived hormone that regulates systemic iron levels, particularly their absorption. Hepcidin increases after oral iron administration and suppresses absorption for up to 24 hours, thereby reducing the benefit of daily dosing.[11]

Breymann *et al*. (2017) reported that daily oral iron supplementation at 100–200 mg/day for 28 days increases hemoglobin by approximately 0.61.3 g/dL.[11] By contrast, administration of ≥60 mg iron every 48 hours (alternate-day dosing) yields significantly greater fractional iron absorption than daily or twice-daily dosing, an effect mediated by transient increases in plasma hepcidin that suppress absorption for ≤24 hours after supplementation.[12] Alternate-day dosing therefore permits hepcidin to decline between doses, enhancing iron absorption and utilization.[12,13]

Hepcidin is a peptide hormone produced by the liver that functions as the principal regulator of systemic iron homeostasis. Hepcidin synthesis is modulated by circulating iron concentration and total body iron stores. Oral iron doses of 60–240 mg acutely increase hepcidin concentrations, which in turn reduce fractional iron absorption on the same day and the following day. Consequently, James *et al*. (2021) recommend administering iron supplementation every other day rather than daily to enhance iron absorption in pregnant women.[5] During pregnancy, hepcidin concentrations reach their nadir in the third trimester, facilitating maximal iron absorption and transfer to the maternal circulation in late gestation.[6]

In addition to regulating iron homeostasis in the maternal circulation, hepcidin also regulates the transfer of iron between the maternal and fetal compartments at the syncytiotrophoblast in the placenta. Maternal transferrin-bound iron is endocytosed by syncytiotrophoblasts and released in acidified endosomes; iron is then either stored in cytosolic ferritin or exported across the basolateral membrane into the fetal circulation via the iron exporter ferroportin. Hepcidin binds ferroportin, promoting its internalization and degradation, thereby modulating iron export to the fetal circulation.[13]

The standard oral iron supplementation dose ranges from 60–120 mg of elemental iron daily, whereas therapeutic doses for iron deficiency anemia typically range from 100–200 mg per day. Oral iron preparations are broadly classified into three categories: (1) iron salts, (2) iron polymaltose complexes, and (3) liposomal iron formulations. Among these, iron salts are the most commonly used in Indonesia for both supplementation

and treatment purposes. Ferrous sulfate, in particular, is widely utilized, especially in primary healthcare settings. Optimal absorption is achieved when iron is administered on an empty stomach, preferably in conjunction with an acidic beverage, such as citrus juice.[14]

Ferritin measurement is the most specific marker of iron deficiency, with values <30 µg/L indicating deficiency and <10–15 µg/L confirming iron-deficiency anemia either in pregnant or non-pregnant women. Another type of anaemia other than iron deficient may need further examination such as blood smear, haemoglobin electrophoresis, until bone marrow puncture (BMP).[5]

Based on this background, we conducted a study comparing daily versus alternate-day oral iron supplementation in pregnant women with anemia. Outcomes assessed included maternal Hb, ferritin, gastrointestinal side effects, neonatal birth weight, and also gestational age at delivery. A cost-effectiveness analysis was also performed to evaluate the economic impact of both regimens with CEA *(Cost Effectiveness Analysis)* method.[17]

METHODS

This study was a randomized, double-blind, placebo-controlled clinical trial using a prepost test control group design. The trial compared two regimens of oral iron therapy in pregnant women with anemia, and both interventions were administered for two months :

- Control group : daily oral iron supplementation.
- Intervention group : oral iron supplementation every two days.

The study was conducted at the Obstetric Polyclinic of Dr. Kariadi Hospital and the Mother and Child Polyclinic, Halmahera Primary Health Centre. The study, including recruitment, intervention, and follow-up, lasted for eight months.

Eligibility Criteria

Pregnant women with anemia (hemoglobin 7–10.9 g/dL) were recruited. Written informed consent was obtained from all participants prior to enrolment.

Inclusion criteria:

1. Gestational age 0–20 weeks or 28–32 weeks.
2. Normal pre-pregnancy Body Mass Index (BMI).
3. Mild anemia (Hb 10–10.9 g/dL) or moderate anemia (Hb 7–9.9 g/dL).

Exclusion criteria:

1. History of hematological disorders (e.g., hemolytic anemia, thalassemia, anemia due to chronic disease).
2. Liver or kidney disease.
3. Gastrointestinal disorders (e.g., acute gastritis, inflammatory bowel disease, post-bowel resection).
4. Allergy to ferrous sulfate, vitamin B complex, or vitamin C.

Randomization was performed using a computer-generated randomization table prepared by an independent pharmacist. Participants were assigned to either the control group (daily iron) or the intervention group (alternate-day iron).

Both participants and investigators were blinded to treatment allocation. Placebo tablets, identical in appearance to the active tablets, were used to ensure blinding.

In the beginning of the study, at baseline all participants underwent measurements of body weight, hemoglobin, and serum ferritin.

- Iron supplementation: ferrous fumarate (60 mg elemental iron) combined with folic acid (400 mcg).
- Placebo: tablets identical in appearance, without iron and folic acid.
- Additional supplements for both groups: vitamin C (250 mg daily) and vitamin B12 (50 mg daily) for two months.

Participants were counselled to reduce tea consumption and increase acidic food intake to optimize iron absorption. Tablets were dispensed monthly, and participants returned for follow-up and new supplies of medication.

- Primary outcomes: changes in hemoglobin and serum ferritin levels after two months.
- Secondary outcomes: born baby weight and gastrointestinal adverse effects.

Adverse effects were recorded using a Monitoring and Evaluation (MONEV) form, completed by participants at home and collected during follow-up visits.

Participants attended two follow-up visits:

1. At 1 month: collection of MONEV forms, dispensing of new supplements.
2. At 2 months: final assessment of hemoglobin, serum ferritin, and body weight. Participants also return their second MONEV forms in this visit.

After one month of supplementation with iron–folic acid, vitamin C, and vitamin B complex, all participants in each group were scheduled for a follow-up visit at either the Obstetrics Polyclinic of Kariadi Hospital or the Maternal and Child Health Polyclinic at Halmahera Primary Health Care. During these visits, participants received a subsequent supply of ferrous sulfate, vitamin B complex, and vitamin C. They were also required to submit their MONEV forms prior to undergoing routine antenatal assessments, including physical examination and ultrasonography. At the final follow-up visit, conducted two months after initiation of supplementation, all participants underwent repeat measurements of body weight, hemoglobin levels, and serum ferritin concentrations.

After those two months follow-up, pregnancy outcomes were subsequently monitored through telephone or direct messages until delivery. We followed the pregnancy progression of both groups via telephone

or messaging, with particular attention to participants' delivery outcomes. We documented the mode of delivery, neonatal birth weight, and the infant's general health condition at birth.

The sample size was calculated using a minimum sample size formula, resulting in 46 participants : 23 in the control group and 23 in the intervention group.

In this randomized, double-blind clinical trial, predefined dropout criteria were established prior to study initiation. Participants were considered eligible for withdrawal if they experienced serious adverse events related to the intervention, demonstrated non-compliance with the study protocol (including failure to adhere to supplementation or scheduled follow-up visits), developed medical conditions necessitating discontinuation, or were lost to follow-up despite repeated contact attempts. Participants were also informed that they had the right to withdraw or discontinue their participation at any time and at any phase of the study without any consequences.

During the study period, all participants were successfully followed through to completion in accordance with the study protocol. No participants met the predefined dropout criteria, and there were no instances of withdrawal or loss to follow-up. Consequently, all enrolled participants from both the control and intervention groups were included in the final analysis.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 27. Descriptive statistics were used to summarize baseline characteristics, with continuous variables presented as mean ± standard deviation. Normality was assessed using the Shapiro–Wilk test.

For within-group (intragroup) comparisons, changes before and after the intervention were analyzed using paired t-tests for normally distributed data. Whether for between-group (intergroup) comparisons between the control and intervention groups, independent t-tests were applied for normally distributed variables. Categorical variables were compared using the Pearson chi-square test as appropriate. A p-value of <0.05 was considered statistically significant in this study.

All participants were followed prospectively until delivery. Data were systematically collected for each participant, beginning with baseline (pretest) measurements at the initial visit and continuing through to maternal and neonatal outcomes after delivery. The total duration of the study was eight months, including the period required for data analysis.

RESULTS

Data were analyzed using SPSS version 22 for Microsoft. Normality was tested using the Shapiro–Wilk test, and homogeneity was tested using Levene's test. All five parameters demonstrated normal distribution and homogeneity, allowing the use of parametric tests. For within-group comparisons (pre vs post-therapy), the paired t-test was applied. For between-group comparisons (post-therapy outcomes), the independent t-test was used.

Table 2 shows that weight, hemoglobin (Hb), and ferritin increased significantly from pre- to post-therapy within each group. When comparing post-therapy results between groups, only Hb and ferritin showed significant differences, while weight did not. This suggests that iron supplementation every two days significantly improves Hb and ferritin levels, though not maternal weight.

To assess pregnancy outcomes, gestational age at delivery and birth weight were analyzed, while maternal outcomes focused on gastrointestinal side effects. In the treatment group, 23 infants were delivered (from 23 subjects), while in the control group, 20 infants were delivered (from 23 subjects).

From Table 3, birth weight differed significantly between groups, with infants in the treatment group weighing on average 292 g more than those in the control group (p=0.028). However, there was no significant difference in mean gestational age at delivery (p=0.085).

TABLE 1
Subject characteristic in both control and treatment group

Parameter	Control Group (Mean ± SD)	Treatment Group (Mean ± SD)	*p*-value
Age (years)	27.83 ± 4.93	26.57 ± 4.73	0.930
BMI before pregnancy (kg/m²)	23.75 ± 2.94	20.76 ± 2.65	0.758
Weight pre-therapy (kg)	58.89 ± 9.30	53.87 ± 8.50	0.959
Hemoglobin pre-therapy (g/dL)	9.40 ± 0.91	9.97 ± 0.71	0.178
Ferritin pre-therapy (ng/mL)	22.36 ± 4.76	22.90 ± 5.31	0.616

TABLE 2
Subject characteristic pre and post therapy in both groups

Parameter	Control Group (Mean ± SD)	Treatment Group (Mean ± SD)	*p*-value a	*p*-value b	*p*-value c
Weight (kg)	Pre: 58.89 ± 9.30	Pre: 53.87 ± 8.50	0.000	0.000	0.207
	Post: 60.47 ± 9.30	Post: 57.04 ± 8.79			
	Δ: +1.58	Δ: +3.17			
Hemoglobin (g/dL)	Pre: 9.40 ± 0.91	Pre: 9.97 ± 0.71	0.000	0.000	0.000
	Post: 10.45 ± 1.02	Post: 11.58 ± 0.62			
	Δ: +1.05	Δ: +1.61			
Ferritin (ng/mL)	Pre: 22.36 ± 4.76	Pre: 22.90 ± 5.31	0.003	0.004	0.000
	Post: 32.84 ± 12.59	Post: 50.60 ± 11.88			
	Δ: +10.48	Δ: +27.70			

TABLE 3
Born Baby Outcomes

Parameter	Control Group (Mean ± SD)	Treatment Group (Mean ± SD)	Δ (Difference)	*p*-value
Birth weight (g)	2637 ± 513.76	2929 ± 314.57	+292 g	0.028
Gestational age at delivery (weeks)	37.55 ± 1.39	38.22 ± 1.08	+0.67 weeks	0.085

These results indicate that iron supplementation every two days may improve birth weight but does not reduce the risk of preterm labor compared with daily supplementation.

Maternal Adverse Effects

Adverse gastrointestinal effects were monitored for two months using the MONEV (Monitoring and Evaluation) form. Adverse events were classified as:

1. No symptoms
2. Mild (disappeared without medication)
3. Moderate (disappeared with medication)
4. Severe (requiring hospitalization)

No severe adverse events were reported. In the treatment group, most subjects experienced no symptoms (19/23), and only 3/23 required medication. In contrast, the control group reported higher rates of gastrointestinal discomfort. Pearson's Chi-square analysis showed a significant difference between groups (p=0.000), indicating that gastrointestinal side effects were milder in the treatment group.

The increase in Hb and ferritin was further evaluated using the N-Gain formula (Figure 1), which measures improvement relative to an ideal value (Hb: 11 g/dL; Ferritin: 70 ng/mL). Table 5 shows significant prepost improvements for hemoglobin and ferritin in both groups. However, as shown in Table 7, daily iron supplementation was effective in raising Hb only, while alternate-day supplementation was effective in raising both Hb and ferritin significantly.

To facilitate interpretation of effectiveness, the N-gain percentage was subsequently categorized into predefined effectiveness levels. In this study, the effectiveness classification proposed by Richard R. Hake (1999) was applied, as presented in Tables 6 and 7.

As shown in Table 7, daily administration of oral iron was found to be less effective in increasing serum ferritin levels, although it remained effective in improving hemoglobin levels. In contrast, alternate-day (every two days) oral iron administration resulted in significant and effective increases in both serum ferritin and hemoglobin levels.

Furthermore, the comparison of changes in hemoglobin and ferritin levels before and after therapy in both groups is illustrated in Figure 2.

Economic evaluation was performed using the Average Cost-Effectiveness Ratio (ACER) and Incremental Cost-Effectiveness Ratio (ICER). ACER is defined as the ratio of total cost to effectiveness (ACER =

TABLE 4
Maternal side effects in control and treatment group

Group	No symptoms, n (%)	Disappeared without medication, n (%)	Disappeared with medication, n (%)	Total, n
Control	6 (26.1%)	10 (43.5%)	7 (30.4%)	23
Treatment	19 (82.6%)	1 (4.3%)	3 (13.0%)	23
Total	25 (54.3%)	11 (23.9%)	10 (21.7%)	46

Chi-square test: $p<0.001$, indicating a significant difference between groups

TABLE 5
N–Gain score for haemoglobin and ferritin

Parameter	Mean Difference (Treatment – Control)	95% CI for Mean Difference	*p*-value
N-Gain Ferritin (ng/mL)	17.23	23.29 to 11.18	<0.001
N-Gain Hemoglobin (g/dL)	0.56	0.82 to 0.31	<0.001

$$\text{N-Gain} = \frac{\text{Post Test score} - \text{Pre Test score}}{\text{Ideal value} - \text{Pre Test score}}$$

Figure 1. N-Gain Formula (Hake,R.R, 1999)

cost/effectiveness), where a lower value indicates greater cost-effectiveness.[18] ICER represents the additional cost per additional unit of effectiveness between two interventions and is calculated as (Cost_intervention − Cost_control) / (Effect_intervention − Effect_control).[18,19] A negative ICER indicates that the intervention is dominant (more effective and less costly).[19]

The treatment group (every two days) showed lower ACER values for Hb (31.50 vs 143.35) and ferritin (159.18 vs 838.64) compared with the control group. For ICER, alternate-day iron supplementation reduced costs by Rp 258 for every 1% increase in effectiveness in raising ferritin (17.2 ng/mL), and by Rp 57 for every 1% increase in effectiveness in raising Hb (0.5 g/dL). These findings indicate that iron supplementation every two days is more cost-effective than daily supplementation.

DISCUSSION

Anemia in pregnancy can impair fetal growth and development. Oral iron supplementation remains the primary strategy to correct anemia during pregnancy. Daily administration of oral iron has been proven to increase hemoglobin levels significantly. However, gastrointestinal adverse effects are common, often leading to reduced compliance and potentially hindering anemia improvement. To address this, several studies have proposed alternate-day or intermittent oral iron regimens as alternatives. This study compared the effectiveness, safety, and cost efficiency of daily versus alternate-day iron supplementation in pregnant women with anemia.

Recent RCTs in pregnant populations indicate that alternate-day iron supplementation achieves similar improvements in hemoglobin levels compared to daily regimens. A 2025 randomized controlled trial reported no significant difference in hemoglobin response between alternate-day and daily supplementation in pregnant women with iron deficiency anemia.[20] These findings are consistent with a 2024–2025 meta-analysis demonstrating that intermittent regimens produce comparable increases in hemoglobin and ferritin concentrations to daily supplementation.[10] Other studies, such as Chu Lam *et al*.[21] and Von Siebenthal *et al*.[22], also reported no significant differences between alternate-day and daily supplementation in improving hemoglobin and ferritin levels.

Conversely, some recent trials suggest a potential advantage of alternate-day dosing. A 2024 randomized study showed greater short-term hemoglobin increments

TABLE 6
Effectiveness Level Criteria

No	Percentage	Interpretation
1	< 40	Not Effective
2	40 – 55	Less Effective
3	56 – 75	Quite Effective
4	> 76	Effective

TABLE 7
N-Gain percent and interpretation

No	Parameter	Mean Percent Control (%)	Mean Percent Treatment (%)	Control Interpretation	Treatment Interpretation
1	N-Gain Percent Ferritin	22.85 + 25.7	60.02 + 24.85	Less Effective	**Quite Effective**
2	N-Gain Percent Haemoglobin	133.68 + 147.05	303.26 + 351.28	**Effective**	**Effective**

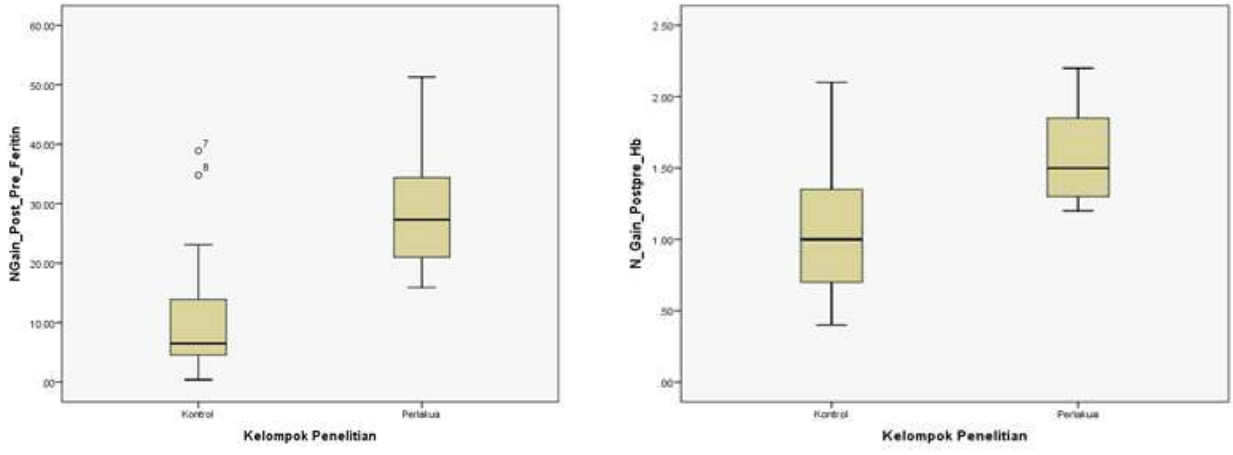

Figure 2. Histogram of N-Gain value before and after treatment

and fewer adverse effects in the alternate-day group.[23] Similarly, a 2025 clinical study reported more sustained improvement in both hemoglobin and iron stores (ferritin) with alternate-day supplementation.[24] However, these findings are not universal, and heterogeneity in study design, baseline anemia severity, and dosing regimens may explain discrepancies across studies. Overall, the current body of evidence supports a non-inferiority of intermittent dosing, with some studies suggesting superiority in specific contexts (e.g., moderate anemia or poor adherence populations).

Gastrointestinal side effects including nausea, constipation, and abdominal discomfort are common barriers to adherence in pregnant women receiving oral iron. Evidence from recent trials and meta-analyses indicates that intermittent regimens are associated with fewer adverse effects, which may improve compliance.[10] Improved adherence may, in turn, enhance overall effectiveness despite lower dosing frequency. However, not all RCTs demonstrate significant differences in side effect profiles. Some studies report similar tolerability and adherence between regimens, suggesting that patient-specific factors and iron formulation may also influence outcomes.[20]

In this study, baseline variables including maternal weight, hemoglobin, and ferritin were homogenous and normally distributed (p >0.05). Therefore, parametric tests were applied for analysis.

Paired t-tests were used to compare pre- and post-therapy changes within each group, while independent t-tests were used to evaluate differences between groups post-therapy.

Both groups showed significant increases in maternal weight, hemoglobin, and ferritin after two months of therapy. However, post-intervention comparison between groups revealed significant differences only in hemoglobin and ferritin, not in maternal weight gain. The alternate-day regimen increased hemoglobin and ferritin significantly, with N-gain analysis showing differences of 0.56 g/dL for hemoglobin and 17.23 ng/mL for ferritin compared with the daily regimen. These findings are consistent with the effectiveness interpretation criteria proposed by Hake[25], which indicated that alternate-day supplementation was effective for both hemoglobin and ferritin improvement, whereas daily supplementation was effective only for hemoglobin.

Maternal and neonatal outcomes were also assessed. Although the risk of preterm delivery was comparable between groups, infants born to mothers in the alternate-day group had a mean birth weight 292 grams higher than those in the daily group. In terms of tolerability, gastrointestinal side effects were milder in the alternate-day group, with only 3 of 23 pregnant women subjects requiring symptomatic treatment, compared to the daily group. These findings align with Karakoc *et al*.[26], who reported significantly lower rates of gastrointestinal side effects in alternate-day supplementation (15.7%) compared with daily supplementation (41.1%, $p = 0.0057$).

From a clinical perspective, these findings indicate that alternate-day iron supplementation represents a viable alternative to conventional daily dosing. This approach may be particularly beneficial for pregnant women who experience gastrointestinal intolerance, especially during the first trimester, when adherence to daily therapy is often compromised. Additionally, intermittent regimens may be advantageous in populations with poor adherence to daily supplementation, such as those in low- and middle-income countries, where limitations in medication supply and lower levels of health literacy may affect consistent intake. Furthermore, alternate-day dosing may be preferable in clinical settings where optimization of iron absorption efficiency is a priority.

Economic evaluation in this study further supported the alternate-day regimen. Cost-effectiveness analysis using ACER showed that alternate-day supplementation was more cost-effective for both hemoglobin (31.50 vs. 143.35) and ferritin (159.18 vs. 838.64). ICER analysis demonstrated that alternate-day therapy reduced costs by Rp 258 for every 17.2 ng/mL increase in ferritin and Rp 57 for every 0.5 g/dL increase in hemoglobin. These findings are supported by Taylor *et al*.[27], who showed that non-daily oral iron regimens offer comparable outcomes to daily regimens but with fewer adverse effects and lower treatment costs. To our knowledge, this is the first study in Indonesia to compare the cost-effectiveness of daily versus alternate-day oral iron supplementation in pregnant women.

CONCLUSION

This study demonstrated that alternate-day oral iron supplementation is comparable to daily supplementation in its effectiveness for increasing both hemoglobin and serum ferritin levels among pregnant women. Importantly, the alternate-day regimen was associated with several additional advantages, including a lower incidence of gastrointestinal side effects, which are commonly reported with daily iron intake and may negatively impact adherence. Improved tolerability may, therefore, contribute to better compliance with treatment protocols. Furthermore, the findings indicated a positive impact on neonatal outcomes, as reflected by improved birth weight among infants born to mothers in the alternate-day group. From an economic perspective, the reduced frequency of administration also translates into lower overall treatment costs, making this regimen particularly advantageous in resource-limited settings.

Taken together, these results suggest that alternate-day oral iron supplementation represents a practical and effective alternative to conventional daily dosing for the management of anemia during pregnancy. This approach may be especially beneficial in populations where treatment adherence and cost are significant challenges. Future studies with larger sample sizes and diverse populations are warranted to further validate these findings and support broader implementation in clinical practice.

CONFLICT OF INTEREST

The author declare no conflict of interest.

ACKNOWLEDGEMENT

We would like to express our deepest gratitude to Midwives and Nurses in Mother and Child Polyclinic in Halmahera Primary Health Centre for providing time and place in supporting the implementation of our research.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; vol 13 (1) : 64–71

OPEN ACCESS

Original Article

Correlation Between Referral Type (Emergency VS Scheduled) and Maternal Perinatal Outcome in Suspected Placenta Accreta Spectrum : A Retrospective Cohort Study in Dr. Kariadi Hospital Semarang 2020–2023

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v13i1.1366

Submitted: April 24th, 2024
Accepted: March 26th, 2026

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Abstract

Background : Maternal Mortality Rate (MMR) in Indonesia at 2023 was 189 over 100.000 live births. The most popular reason for maternal death was obstetrics hemorrhage. Obstetric hemorrhage can be caused by abnormal placentation. Abdominal delivery by cesarean section has increased recently in Indonesia. Cesarean section will increase the risk for placenta accreta spectrum, which raises maternal morbidity and mortality.
Aim : To analyze the correlation of emergency and scheduled referral with maternal and perinatal outcomes of suspected placenta accreta spectrum patients in Dr.Kariadi Hospital Semarang 2020 – 2023.
Methods : A cohort retrospective study performed in May 2024, involved 153 women with suspected placenta accreta spectrum were referred to Dr. Kariadi Hospital Semarang in 2020 – 2023, divided by emergency referral and scheduled referral groups. We use Placenta Accreta Index (PAI) Score and all patients who fulfilled the criteria of the placenta accreta spectrum based on FIGO to predict suspicious placenta accreta spectrum. Descriptive analysis included the base characteristics of the patients. Correlation analysis with maternal and perinatal outcomes using Chi Square analyze of SPSS 25.00 version.
Results : A total of 69 patients with emergency referrals and 84 patients with scheduled referrals. Mean age was 32.97, median 32(24–44), median of gestation was 3(1–6) and 3(1–9), median of gestational age was 35(22–41) and 36(32–39). The emergency referral had a higher risk for cesarean hysterectomy with OR (95%CI) 2.92 (1.51–5.67), for maternal hemorrhage with OR (95%CI) 2.34 (1.22–4.49), for blood transfusion with OR (95%CI) 6.02 (2.46–14.76), for intensive care admission with OR (95%CI) 4.39 (1.5–12.79), for prematurity with OR (95%CI) 2.56(1.32–4.92), for asphyxia with OR (95%CI) 3.41(1.56–7.47). There were significant differences between emergency and scheduled referrals for vaginal delivery (p=0.03), and perinatal mortality (p=0.04). Estimated blood loss was 1453.7 ± 1253.6 ml in emergency referral and 878.3 ± 823.7 ml in scheduled referral.
Conclusion : Emergency referrals had worse maternal and perinatal outcomes than scheduled referrals for suspicious placenta accreta spectrum patients.

Keywords : Emergency,placenta accreta, scheduled referral

INTRODUCTION

Maternal Mortality Rate (MMR) in Indonesia in 2023 was 189 over 100.000 live births.[1] It was higher than SDG's (Sustainable Development Goals) target in 2030, to decrease maternal mortality rate of 70 over 10.000 live births.[2] Most of maternal mortality at 2021 based on reason divided by related to COVID-19 as many as 2.982 cases, maternal hemorrhage 1.330 cases and hypertension in pregnancy 1.077 cases.[2] Maternal hemorrhage could be caused by the atonic uterus, abnormal placentation, obstetrics laceration, coagulopathy, other obstetrics factors such as obesity, postpartum hemorrhage history, pre-eclampsia, maternal immune, etc.[3]

The cesarean sections rates in Indonesia has increased recently. Indonesian Health Ministry Demographic Survey in 2018 gave data on the number of cesarean sections in Indonesia was 17.6% of all deliveries.[4] History of cesarean section will increase the risk of placenta accreta, the presentation for placenta accreta spectrum will increase by 0.3% from the history of one time cesarean section, and increase by 6.74% from the history of five times or more cesarean sections.[5] Placenta accreta is one of the abnormal placentation types, resulting in higher morbidity and mortality rates than other maternal hemorrhages.[6]

Placenta accreta is defined as abnormal trophoblast invasion of part or all of the placenta into the myometrium of the uterine wall. Placenta accreta spectrum, formerly known as morbidly adherent placenta, refers to the range of pathologic adherence of the placenta, including placenta accreta, placenta increta and placenta percreta. Maternal morbidity and mortality can occur because of severe hemorrhage, which often requires a blood transfusion.[7]

The efforts to improve obstetric management for the placenta accreta spectrum require good screening for diagnosing placenta accreta for preparing appropriate surgical treatment. This is important for establishing the right diagnosis when antenatal care for pregnant women with suspicion of placenta accreta spectrum. Proper diagnosis can guide in preparing scheduled referrals to tertiary hospitals as a center for placenta accreta, so patients do not suffer from emergency conditions that can increase maternal and perinatal morbidity such as massive hemorrhage, massive blood transfusion, intensive care unit admission, and even maternal death, or fetal emergency that cause asphyxia, prematurity or perinatal death.[8]

The incidences of the placenta accreta spectrum are increasing. The case report of placenta accreta spectrum in Indonesia, from Medicine Faculty of Airlangga University – Dr.Sutomo Hospital, Surabaya, there were 7 cases in 2015, 24 cases in 2016, 60 cases in 2017, 75 cases in 2018, and 83 cases in 2019, which any improvement of the number of case every year, and there were 8 patients were dead. (2,8%).[9] The incidence of placenta accreta spectrum in Kariadi Hospital also increases year by year. There were 5 cases in 2019, 4 cases in 2020, 13 cases in 2021, and 18 cases in 2022. This increasing case gives to improvement of maternal hemorrhage and other complications.

Although the number of placenta accreta cases has increased, there was no studies research on the correlation between referral type and the outcomes of placenta accreta spectrum. We hope this study can become the reference of referral type for suspicious placenta accreta spectrum to give proper treatment to reduce maternal and perinatal morbidity and mortality.

Placenta accreta is defined as abnormal trophoblast invasion of part or all of the placenta into the myometrium of the uterine wall. Placenta accreta spectrum, formerly known as morbidly adherent placenta, refers to the range of pathologic adherence of the placenta, including placenta accreta, placenta increta and placenta percreta.[7]

The placenta was attached tightly to myometrium in placenta accreta, so it was difficult to release it spontaneously, or there was continuous hemorrhage from the placental implantation site.[10] The histopathology discovery, absence of desidua layer or Nitabuch layer or invasion of villi chorialis into the myometrium. This definition was updated by the International Federation of Obstetrics and Gynecology, by called it with Placenta Accreta Spectrum Disorders.[10,11]

Placenta accreta spectrum can occur as a result of wound in uterine tissue, which can trigger abnormal decidualization of the endometrium or damage the local scar and an abnormal adherent placenta in the next pregnancy.[12] Placenta Accreta Spectrum was not exclusively caused by cesarean section.[13] All procedures that caused the damage in the uterus, like curettage, manual placenta, hysterocopy, endometrial ablation, myomectomy and uterine artery embolization, were related to placenta accreta in the next pregnancy.[14]

Parameter of Placenta Accreta Index Score

Parameter	Value
Previous CS ≥ 2 kali	3.0
Lacuna	
Grade 3	3.
Grade 2	1.0
Myometrium thickness ≤ 1 mm	1.0
1–3 mm	0.5
3–5 mm	0.25
Anterior placenta previa	1,0
Bridging vessels	0.5

All pregnant women should be screened for the risk of placenta accreta spectrum from anamnesis and some examination.[15] We must know the age of the mother, number of parity, history of uterine surgery, history of placenta previa, antenatal hemorrhage, etc.[7] Ultrasound, Magnetic Resonance Imaging and biological marker. Ultrasound is the first choice for placenta accreta screening because more effective, cheaper, feasible and efficient.[16] We will evaluate lacuna, myometrial thickness, myometrial integrity, retroplacental clear zone, bridging vessel, subplacental vascularity, and gap of myometrial blood flow.[17]

Martha C Rac (2014) provides a mathematical formula to make a scoring system for predicting placenta accreta spectrum by several parameters in the Placenta Accreta Index Score.[18]

METHODS

A cohort retrospective study was performed on May 2024 in Dr. Kariadi Hospital Semarang. We used the secondary data of patients medical records with suspected placenta accreta spectrum were referred to Dr. Kariadi Hospital Semarang in 2020 – 2023. The inclusion criteria were pregnant women 2nd and 3rd trimesters with Placenta Accreta Index score > 0 and all patients who fulfilled the criteria of the placenta accreta spectrum based on FIGO. The exclusion criteria were patients diagnosed with suspicious placenta accreta in Dr. Kariadi Hospital and patients with incomplete medical records.

A total of 160 patients with suspicion of placenta accreta spectrum were evaluated, then 5 patients were diagnosed with placenta accreta spectrum by Antenatal Care in Dr. Kariadi Hospital, and 2 patients had no complete medical records, so we had 153 patients that fulfilled inclusion criteria. Then divided into emergency referral and scheduled referral groups. Descriptive analysis included the the base characteristics of the patients, such as age, gestation, gestational age, fund, history of antepartum hemorrhage, history of cesarean section, history of uterine surgery, history of dilatation and curettage, history of uterine radiation, history of endometritis, placenta previa, history of manual removal of placenta, history of placenta accreta, history of Intra Uterine Device, and history of placenta previa. Kolmogorov-Smirnov test was used to analyze numeric data, if the data has an abnormal distribution, analyzed and compared to Mann-Whitney test.

The independent variable was the type of referral (emergency and scheduled referral) and the dependent variables were maternal outcomes such as cesarean hysterectomy, conservative surgery, vaginal delivery, maternal haemorrhage, blood transfusion, intensive care unit admission and maternal death, and also perinatal outcomes such as prematurity, asphyxia and perinatal death. Correlation analysis between the independent variable and a dependent variable using Chi-Square analysis of SPSS 25.00 version. Estimated blood loss and amount of transfusion between referrals analyzed with Kolmogorov-Smirnov.

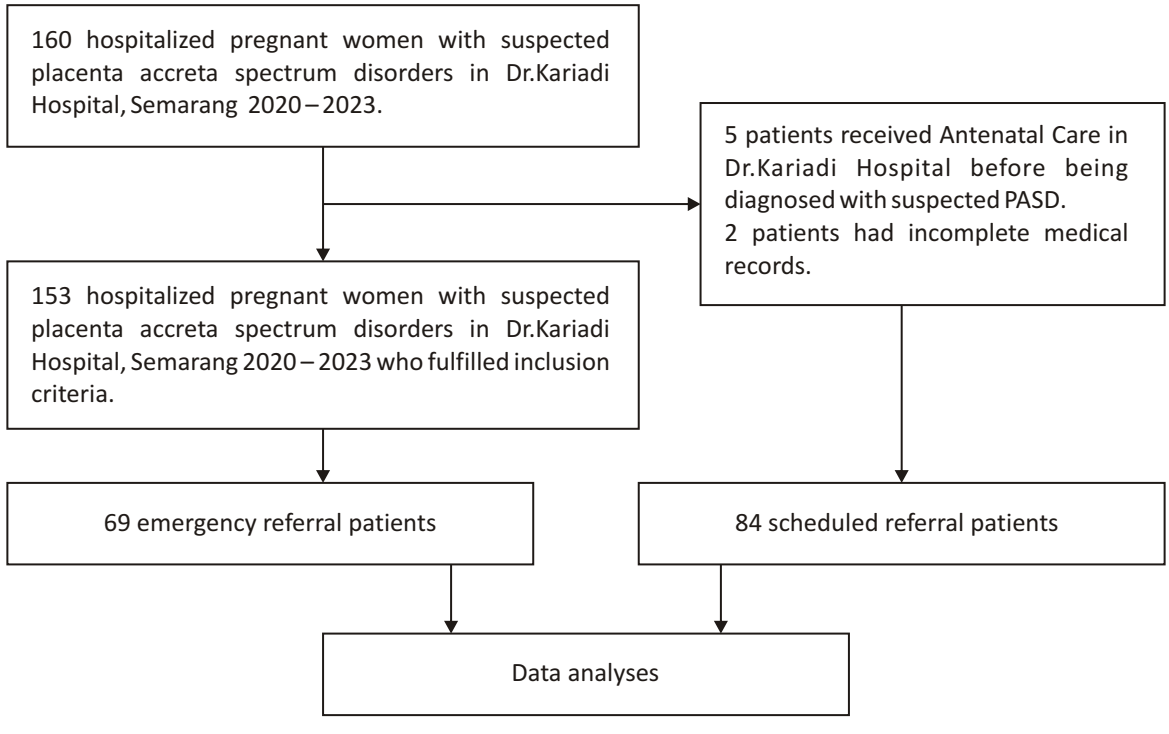

Figure 1. Flowchart of the study

RESULTS

We had 69 patients with emergency referral and 84 patients with scheduled referral. Based on the clinical characteristics of the subjects (Table 1), the mean age was 32.97, the median 32(24–44), a median of gestation was 3 (1–6) and 3 (1–9), and median gestational age was 35 (22–41) and 36 (32–39). There was significant differences between an emergency referral and scheduled referral for gestational age (p<0.01) and history of antepartum hemorrhage (p=0.02). The risk factor of the placenta accreta spectrum of the subject performed in Table 2.

From Table 3 about correlation emergency and scheduled referral with the maternal and perinatal outcome, the emergency referral had a higher risk for cesarean hysterectomy with OR (95%CI) 2,92 (1.51–5.67), for maternal hemorrhage with OR (95%CI) 2.34 (1.22–4.49), for blood transfusion with OR (95%CI) 6.02 (2.46–14.76), for intensive care admission with OR (95%CI) 4.39 (1.5–12.79), for prematurity with OR (95%CI) 2.56 (1.32–4.92), for asphyxia with OR (95%CI) 3.41 (1.56–7.47). There were significant differences between emergency and scheduled referral for vaginal delivery (p-value 0.03), and perinatal mortality (p-value 0.04).

Estimated blood loss was 1453.7 ± 1253.6 ml in emergency referral and 878.3 ± 823.7 ml in scheduled referral (Table 4). There was a significant difference in the transfusion of PRC between the two groups (p<0.01) (Table 5). Table 6 performed about histopathology results of the subjects, with overall 100 subjects (65.3%) appropriate with placenta accreta 31 (20.6%), placenta increta 54 (35,35) and placenta increta 15 (9.8%) and not examined (34.6%).

TABLE 1
Clinical characteristics of subjects

Variable	Emergency referral		Scheduled referral		*p*
	n = 69	Mean ±SD Median (min–max)	n = 84	Mean ±SD Median (min–max)	
Age (year)		3 (1–6)		32 (24–44)	0.96¥
20–35	48 (70%)		57 (68%)		
> 35	21 (30%)		27 (32%)		
Gestation		3 (1–6)		3 (1–9)	0.67‡
1	2 (3%)		1 (1%)		
2–3	45 (65%)		60 (71%)		
>3	22 (32%)		23 (27%)		
Gestational age (week)		35 (22–41)		36 (32–39)	<0.01‡*
< 28	3 (4%)		0 (0%)		
28–34	30 (44%)		18 (22%)		
>34	36 (52%)		66 (78%)		
Fund					.03¥*
JKN PBI	36 (52%)		28 (33%)		
JKN non PBI	30 (43%)		54 (64%)		
Other assurance	3 (4%)		2 (2%)		
Common	0 (0%)		0 (0%)		
Antepartum haemorrhage history					
Yes	22 (32%)		12 (14%)		
No	47 (68%)		72 (86%)		

Information : * Significant (p < 0,05); ¥ Continuity Correction; ‡ Mann-Whitney

TABLE 2
Risk of factor for placenta accreta spectrum of subjects

Risk factors for Accreta	Emergency referral (n=69)		Scheduled referral (n=84)	
	n	%	n	%
CS 1 time	23	33.3	43	51.2
CS ≥ 2 times	37	53.6	36	42.9
Placenta previa	38	55.1	31	36.9
History of curettage	22	31.9	22	26.2
History of uterine surgery	0	0	2	2.4
History of uterine radiation	0	0	0	0
History of IUD	14	20.3	12	14.3
History of removal placenta manually	0	0	0	0
History of placenta accreta	0	0	0	0
History of endometritis	0	0	0	0

TABLE 3
Correlation type of referral with maternal and perinatal outcome

Maternal and perinatal outcomes	Type of referral				*p*	OR (95%CI)
	Emergency		Scheduled			
	n	%	n	%		
Caesarean hysterectomy	41	59.4	28	33.3	0.01¥*	2.92 (1.51–5.67)
Conservative surgery	11	15.9	20	23.8	0.32¥	0.60 (0.27–1.37)
Vaginal delivery	7	10.1	0	0	0.03£*	–
Maternal haemorrhage	39	56.5	30	35.7	0.02¥*	2.34 (1.22–4.49)
Blood transfusion	62	89.9	50	59.5	<0.01¥*	6.02 (2.46–14.76)
ICU admission	15	21.7	5	6	0.01¥*	4.39 (1.51–12.79)
Maternal death	3	4.3	1	1.2	0.24£	3.77 (0.28–37.11)
Prematurity	43	62.3	33	39.3	0.01¥*	2.56 (1.32–4.92)
Asphyxia	25	36.2	12	14.3	0.03¥*	3.41 (1.56–7.47)
Perinatal death	4	5.8	0	0	0.04£*	–

Information : * Significant ($p < 0,05$); ¥ Continuity Correction; £ Fisher's Exact

DISCUSSION

The reproductive age appropriate for pregnancy, because of the minimal risk for pregnancy complications, was 20–35 years old.[19] The mean age of the subjects was 33.03 years old. The majority of gestation was 2–3, consistent with a risk factor for placenta accreta spectrum, that patients were multiparous.[7] Mean of gestational age was appropriate with timing for termination of the pregnancy with placenta accreta spectrum disorder from ACOG dan SMFM guideline (34^{+0} – 35^{+6} weeks), RCOG guideline (35^{+0} – 36^{+6} weeks), dan SOGC (34–36 weeks).[10] Patients' finances were important to prepared in every pregnancy, especially for the placenta accreta spectrum, because they need a multidisciplinary team, blood preparation, and intensive care unit admission. The

TABLE 4
Correlation type of referral with estimated blood loss

Type of referral	Estimated Blood Loss (ml)	
	Mean ± SD	Median
Emergency (n=69)	1.453.77 ± 1253.63	1000 (10 – 6000)
Scheduled (n=84)	878.31 ± 823.73	500 (200 – 4320)

TABLE 5
Correlation type of referral with type and number of transfusion

Transfusion	Type of referral	Number (kolf) Mean ± SD	*p*
PRC	Emergency	2.41 ± 1.79	<0.01*
	Scheduled	1.20 ± 1.19	
WB	Emergency	0.59 ± 1.09	0.12
	Scheduled	0.29 ± 0.59	
FFP	Emergency	0.38 ± 1.00	0.07
	Scheduled	0.11 ± 0.44	
TC	Emergency	0.07 ± 0.50	0.11
	Scheduled	0.00	

Information : *Significant ($p < 0.05$); Kolmogorov–Smirnov

TABLE 6
Histopathology results of subjects study

Histopathology	Referral type				*p*
	Emergency		Scheduled		
	n=69	%	n=84	%	
Accreta	19	27.5	12	14.3	0.07¥
Increta	29	42	25	29.7	0.06¥
Percreta	8	11.6	7	8.3	0.69¥
Not examined	13	47.6	40	47.6	<0.01¥*

Information: * Significant ($p < 0.05$); ¥ Continuity Correction

participation of patients with any health insurance shows good preparation from patients.

The estimation for antepartum haemorrhage will occur in 35 was 4.7% and will increase by gestational age, 15% at 36 weeks, 30% at 37 weeks and 59% at 38 weeks. To avoid emergency surgery, which can increase maternal and perinatal morbidity and mortality, the time of delivery is suggested at 34–35 weeks.[8]

Uterine wounds from the history of cesarean section, uterine surgery, curettage etc, were a risk factor for placenta accreta spectrum because of decidualization that results break scar breakage in the uterus and leads to abnormal invasion of the placenta in the next pregnancy.[11] Placenta previa is one of the most risk factors for placenta accreta spectrum.[12]

Placenta accreta spectrum can cause emergency

problems, both in pregnancy and delivery, because of massive hemorrhage from the placenta, so it must be given fast and adequate treatment, causing the patient to be referred by emergency referral.[8] Cesarean hysterectomy was the most common treatment applied for placenta accreta spectrum to avoid continuous hemorrhage.[13]

Finance was an important thing to prepare before the delivery of every pregnancy, especially in suspected placenta accreta, which requires more preparation, including a multidisciplinary team, blood preservation, and an intensive care unit, so it needs more finance.

The most common type of finance used in the emergency referral group was government aid insurance (52.2%), while the most common type of finance used in the scheduled referral group was non-government aid insurance (64.3%). This showed the patient's readiness for high-risk delivery finance. The most emergency referral patients registered from the emergency unit (74%), and the most scheduled referral patients registered from the policlinic. Patients with maternal and or perinatal emergencies should get emergency referral by the emergency unit in order to receive optimum and on-time treatment.

Palacios explains classification for wide placental invasion based on focal (placental invasion less than 50% of one anterior side of uterus) and diffuse (placental invasion more than 50% of one anterior side of the uterus) which shows the success of conservative surgery of the uterus in focal placenta accreta.[24] Suspicious for placenta accreta at vaginal delivery based on FIGO criteria if no separation of the placenta with synthetic oxytocin and gently controlled cord traction and attempts at manual removal of placenta result in heavy bleeding from the placental implantation site, requiring a mechanical or surgical procedure.[25] Vaginal delivery in the placenta accreta spectrum is from late diagnosis when patients get antenatal care.[8] Massive hemorrhage at placenta accreta spectrum because of separation of the placenta from its implantation site, if late to give treatment or inadequate therapy, placenta accreta spectrum can lead to another morbidity such as massive haemorrhage, massive blood transfusion, DIC *(Disseminated Intravascular Coagulation)*, ARDS *(Adult Respiratory Distress Syndrome)*, electrolyte imbalance, bladder injury, ureter lesion or kidney failure.[16]

The American College of Obstetrics and Gynecology (2012) announced a statement and opinion that the placenta accreta spectrum is a life-threatening condition and requires a multidisciplinary team. The maternal rate of placenta accreta spectrum was about 0,13% until 23%.[8]

A systematic review from the American Journal of Obstetrics and Gynecology tells us about histopathology results from placenta accreta spectrum with placenta accreta 473 from 757 (62,5%), placenta increta 117 from 757 (15,4%) and placenta percreta 167 from 757 (22,1%).[11] The histopathology result of this study was overall 100 (65,3%) subjects appropriate for placenta accreta, 31 (20,6%), placenta increta, 54 (35,35) and placenta percreta, 15 (9,8%) and not examined (34,6%).

Many newborns with prematurity were found in the emergency referral group, by the mean of gestational age, which had a significant difference between emergency and scheduled referral. The time of delivery for placenta accrete spectrum based ACOG/SMFM, FIGO, RCOG, and SOGC was 34 weeks until before 37 weeks gestational age, which includes preterm pregnancy. Several patients had a delay in diagnosis and were referred after 37 weeks.

One of the purposes of the management of placenta accreta spectrum was to deliver viable babies before mother experiences morbidity and mortality and deliver complicated fetuses as soon as possible, like fetal distress caused by antepartum hemorrhage or abruption of the placenta at placenta accreta spectrum.[8] Scheduled referral significantly decreases the probability of asphyxia in newborns from the placenta accreta spectrum.

Perinatal mortality was significantly higher in emergency referrals than in scheduled referrals. There were 2 babies with intra-uterine fetal death and 2 babies with stillbirth (p=0.039). Antepartum hemorrhage and prematurity affect to well-being of the fetus and delivered baby.[8]

To achieve a proper scheduled referral for suspected placenta accreta spectrum, accurate screening with a good medical history for risk factors of placenta accreta spectrum and ultrasound examination are needed, so when taking antenatal care with obstetricians, it could diagnose with suspected placenta accreta spectrum. An on-time scheduled referral can help to give optimal management of placenta accreta spectrum, so we can avoid maternal and perinatal morbidity and mortality. Further studies are needed to evaluate the factors that affect the referral type in placenta accreta spectrum disorders and other risk factors that impact maternal and perinatal outcomes.

We were limited by the retrospective cohort of this study. The quality of our measures may be affected by the quality of documentation available for the 4-year study period, as well as changes in documentation possible over the tenure of the project, such as implementation of an electronic medical record. So there were several confounding factors from this study.

CONCLUSION

Emergency referral had higher risk for caesarean hysterectomy, vaginal delivery, maternal haemorrhage, blood transfusion, intensive care unit, prematurity, asphyxia and perinatal mortality than scheduled referral

in placenta accreta spectrum.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We would like to express our deepest gratitude to dr.Kariadi Hospital Semarang for providing time and space to assist in this research process.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; vol 13 (1) : 72–78

OPEN ACCESS

Original Article

The Effect of an Elastic Band Resistance Training Program on Increasing Upper and Lower Limb Muscle Strength in Elderly with Sarcopenia

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v13i1.1401

Submitted: August 22th, 2025
Accepted: March 26th, 2026

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Abstract

Background : Prevention and treatment of sarcopenia are important to achieve physical health in aging, including maintaining the physical ability to live independently and carry out daily activities.
Aims : To determine the effect of a muscle-strengthening exercise program using elastic bands for 8 weeks in order to increasing muscle strength in elderly people with sarcopenia. Arm muscles (biceps and triceps) and leg muscles (quadriceps and gastrocnemius) were measured.
Methods : An intervention study with a one-group pre- and post-test design. Subjects were taken from the elderly home by as many as five women and five men. Subjects were given strengthening exercises using elastic bands in as many as 2 sets; each set was done in as many as 10 movements, and each movement was given a rest interval of 30 seconds. The elastic band strengthening exercise program was carried out three times per week, with a period of eight weeks, so that the total training was 24 sessions. Changes in muscle strength were measured using a MicroFET2 hand-held dynamometer. Furthermore, the results of muscle measurements were tested using the paired-samples T test to determine the difference in muscle strength between before and after doing the exercise program.
Results : Female and male subjects had an insignificant average age of 68.80 ± 5.12 years for women and 68.60 ± 5.64 years for men. The average BMI value in women and men had an ideal value of 24.38 ± 2.89 kg/m^2 and 24.82 ± 5.65 kg/m^2. The right limbs in the biceps, triceps, quadriceps, and gastrocnemius muscles each experienced an increase in muscle strength during the intervention, namely 2.67 kg, 2.14 kg, 1.99 kg, and 1.87 kg. Then for the left limbs, the biceps, triceps, quadriceps, and gastrocnemius muscles also experienced an increase, namely 2.96 kg, 1.42 kg, 2.28 kg, and 2.51 kg. The intervention carried out in this study can significantly increase upper limb and lower limb muscle strength (p<.05).
Conclusion : Resistance training using elastic bands routinely for 8 weeks can increase the strength of the biceps, triceps, quadriceps, and gastrocnemius muscles. This exercise can also reduce the risk of sarcopenia and improve the quality of life for the elderly. This exercise program can be a recommendation for intervention because it is economical and easy to do independently at home.

Keywords : elastic bands training; exercise; isometric muscle strength; outcome measures

INTRODUCTION

The European Working Group on Sarcopenia in Older People (EWGSOP) has suggested using the terms "presarcopenia," meaning low muscle mass, and "sarcopenia," meaning poor physical performance or low muscle mass and low muscle strength.[1] As people age, sarcopenia is expected to become one of the important factors that threaten human health and social development.[2] The cause of sarcopenia is a sedentary lifestyle or a lack of physical activity.[3,4] Efforts to maintain the physical ability to live independently while carrying out daily activities have a positive impact on preventing or reducing the risk of sarcopenia.[5,6] Sarcopenia is influenced by several interrelated factors. For example, nutritional factors, such as insufficient protein intake; treatment factors, such as long-term use of certain medications such as corticosteroids; and psychological factors, such as depression, chronic stress, and social isolation, which can lead to decreased motivation for physical activity. Therefore, muscle strengthening exercises are important for the elderly to maintain muscle fitness and health.

Muscle strength training significantly contributes to the variance of changes in sarcopenia scores, making it important for sarcopenia-related functional recovery. One type of muscle-strengthening exercise is elastic band resistance training performed by the upper[2,3] and lower limbs.[7–9] Elastic band resistance training is a low- to moderate-intensity exercise that is easy to use, economical, portable so that participants can exercise anywhere, and has safety benefits for the elderly.[10,11] Vikberg *et al*. reported that 10 weeks of instructor-led resistance training can improve functional strength and increase muscle mass in elderly adults with pre-sarcopenia.[10] Chen *et al*. reported that comprehensive exercise and progressive resistance training for 8 weeks can increase muscle mass and handgrip strength in elderly women with sarcopenia.[2] In addition, body weight-based training and elastic band strengthening training for 12 weeks in the elderly can improve body composition and muscle function.[11] The study showed positive results, including an increase in upper- and lower-limb muscle strength after strengthening exercises using elastic bands. So we speculate that elastic band resistance training can be useful for increasing muscle strength in the elderly with sarcopenia. Resistance training is also easy for seniors to do independently at home.

Resistance-based exercise programs require more research to show their effects on increasing muscle strength in the elderly. Such as hand and leg muscles, which are very important for use in daily activities. Therefore, this study aims to determine the effect of a muscle strengthening exercise program using elastic bands for 8 weeks on increasing muscle contraction strength in the elderly with sarcopenia. This study chose 8 weeks of training rather than 10 weeks or 12 weeks of training, which is shorter and has an impact on muscle development. The muscles measured were the hand muscles (biceps and triceps) and leg muscles (quadriceps and gastrocnemius), because these muscles are often used for daily activities.

METHODS

This study used an intervention study with a one-group pre- and post-test design. This study was approved by the Ethics Review Board of the Faculty of Medicine, Diponegoro University (161/EC/KEPK/FK-UNDIP/IV/2024). Participants in this study received a strengthening exercise program using elastic bands, it was carried out three times per week, for eight weeks. All participants were given details of the exercise intervention content and then signed an informed consent in accordance with the ethical standards of the Declaration of Helsinki.

All participants were elderly people with sarcopenia recruited from Pucang Gading Social Home in Semarang between April and June 2024. There were 10 participants, consisting of 5 women and 5 men. In accordance with the 2019 AWGS consensus on sarcopenia parameters, all participants were examined to determine whether they met the diagnostic criteria for sarcopenia.

The recruitment of participants in this study had additional inclusion criteria: (a) men or women over 60 years old; (b) have the ability to walk independently or use a walking aid; and (c) be willing and cooperative in the study. In addition, there were also exclusion criteria, namely: (a) having cognitive dysfunction; (b) having problems with vision, hearing, or vestibular; (c) having a worsening neurological disease, such as Parkinson's and dementia; (d) depression (the depression scale in the elderly is more than 5); (e) having a history of amputation, stroke, or fracture of the upper or lower extremities in the past year; (f) unstable metabolic, cardiovascular, and neuromuscular conditions (NYHA III-IV congestive heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension); (g) psychiatric disorders; (h) knee or hip prosthesis.

The intervention conducted in this study was a strengthening type using elastic bands for 8 weeks with a light-to-moderate intensity of around 4–7 on the OMNI-RES scale. Subjects were given strengthening exercises using elastic bands in as many as 2 sets; each set was done in as many as 10 movements, and each movement was given a rest interval of 30 seconds. The elastic band strengthening exercise program was carried out three times per week, with a period of eight weeks, so that the total training was 24 sessions (see Figure 1).

The exercise begins with warm-up exercises such as light movements and stretching exercises of the upper

Figure 1. Strengthening exercise program using elastic bands

TABLE 1
Procedure for measuring the strength of biceps, triceps, quadriceps, and gastrocnemius muscles using the MicroFET2 hand-held dynamometer

Muscle	Position	Dynamometer Position	Instruction	References
Biceps	Body in sitting position; Elbow angle 90° and arms beside the torso; Hands in supination position.	The wrist is just below the bottom crease of the wrist.	Bend your elbows with a flexion movement.	[15,16]
Triceps	Body in sitting position; Elbow angle 90° and arms beside the torso; Hands in supination position.	The dorsal surface of the wrist just below the joint.	Straighten your elbows with an extension movement.	[15,17]
Quadriceps	The body is in a sitting position; Hips & knees in 90° flexion; Hands on thighs, palmar surface upwards.	Anterior leg proximal to ankle.	Straighten out your knee.	[18–20]
Gastrocnemius	Body in sitting position; Ankle in neutral; Hands by their side palmar surface upwards.	Plantar surface of metatarsal heads.	Point your toes towards me.	[19,21]

limbs and lower limbs for 5 minutes. Then core exercises are performed with elbow flexion, elbow extension, chest press, lateral rise, hip flexion, hip extension, leg press, and ankle plantarflexion.

In this study, we used a hand-held dynamometer (MicroFET2, Hoggan Scientific, LLC, Salt Lake City, UT, USA) to measure or assess muscle strength. The muscles to be measured were the biceps muscle, the triceps muscle, the quadriceps muscle, and the gastrocnemius muscle. The subject had to produce a maximal voluntary contraction against the examiner's force, which was applied for 3–4 minutes.[12,13] A hand-held dynamometer can read muscle contraction strength with a range of 0–660 Newtons (N).[14] All subjects were tested in a sitting position. The position of the hand-held dynamometer in this study is presented in Table 1.

We processed the measurement data using SPSS software (IBM, SPSS version 25, Chicago, IL, USA) according to the following steps:

a. All data were checked to ensure that the data to be processed was normally distributed (Shapiro-Wilk test).
b. At baseline, descriptive statistics were calculated for each characteristic variable. Then, we used the

paired-samples T test to determine the difference in muscle strength before and after doing the exercise program.

c. If the *p*-value is <0.05, it indicates a difference with statistical significance and a 95% confidence interval (95% CI). Data are presented as mean ± SD unless otherwise stated.

RESULTS

Participant characteristics

In total, 10 participants met the inclusion and exclusion criteria and were included in the analysis. Participants consisted of 5 women with an average age of 68.80 ± 5.12 years and 5 men with an average age of 68.60 ± 5.64 years. Then the average BMI (body mass index) of women and men had ideal values of 24.38 ± 2.89 kg/m^2 and 24.82 ± 5.65 kg/m^2. Based on the average data, male and female participants had the same criteria, or there was no significant difference (see Table 2).

Effect of invention on biceps muscle

Bicep muscle strength experienced a significant increase before and after the intervention. The average value of the right bicep muscle increased by 2.67 kg, with a significance value of p <.001. Then, for the left bicep muscle, muscle strength increased by 2.96 kg with a significance value of p =.005. Based on these values, the average participant experienced a significant increase in muscle strength (p <.05) in the right and left bicep muscles. The intervention carried out on the biceps muscle had a positive impact on increasing muscle strength. In this study, the average left bicep muscle increased more than the right bicep muscle; see Table 3 and Figure 2.

Effect of invention on triceps muscle

Triceps muscle strength experienced a significant increase before and after the intervention. The average value of the triceps muscle in the right hand increased by 2.14 kg, with a significance value of p <.001. Then, for the

TABLE 2
Research subject data

Participants	Gender	Age (y)	Height (cm)	Weight (kg)	BMI (kg/m^2)
Subject 1	woman	71	157	61.2	24.83
Subject 2	woman	69	134	46.9	26.12^{+}
Subject 3	woman	61	142	55.5	27.52^{++}
Subject 4	woman	75	137	37.4	19.93
Subject 5	woman	68	155	56.5	23.52
Subject 6	man	66	154	65.9	27.79^{++}
Subject 7	man	71	163	48.5	18.25*
Subject 8	man	60	166	66.3	24.06
Subject 9	man	72	165	57.9	21.27
Subject 10	man	74	158	81.7	32.73^{++}

* Low level of underweight, $^{+}$ Mild degree of excess weight, $^{++}$ Severe degree of overweight

TABLE 3
Comparison of muscle strength measurements before and after performing a training program (mean ± SD, kg)

Muscle	Right limb			Left limb		
	Baseline	Week 8	*p*-Value	Baseline	Week 8	*p*-Value
Biceps	6.40 ± 1.62	9.07 ± 1.67	.000	6.51 ± 2.21	9.47 ± 3.53	.005
Triceps	4.77 ± 1.74	6.91 ± 1.67	.000	4.56 ± 2.18	5.98 ± 1.19	.039
Quadriceps	6.30 ± 2.35	8.29 ± 1.55	.009	5.43 ± 2.02	7.71 ± 2.00	.001
Gastrocnemius	5.14 ± 1.84	7.01 ± 1.62	.023	4.30 ± 1.36	6.81 ± 1.85	.010

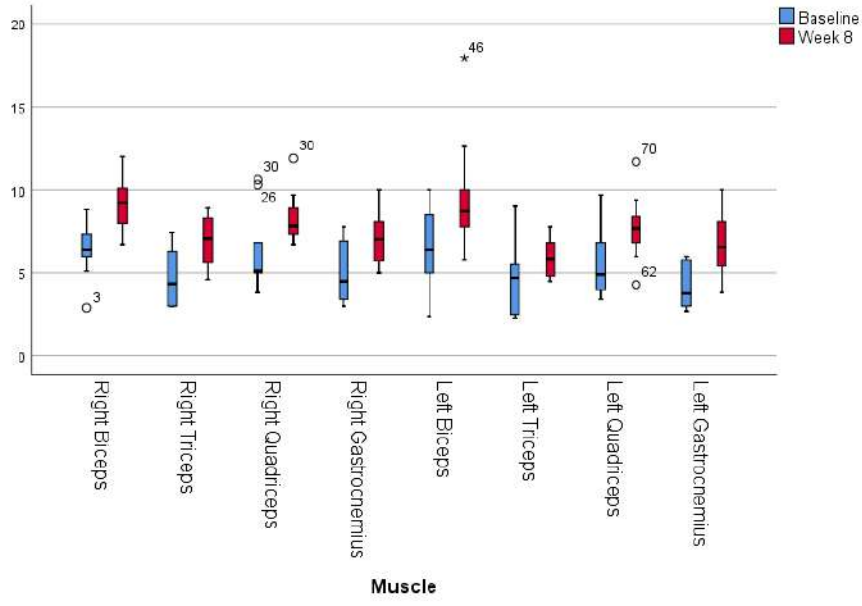

Figure 2. Changes in upper and lower limb muscle strength from baseline to the eighth week in all genders

triceps muscle of the left hand, there was an increase in muscle strength of 1.42 kg with a significance value of p =.039. Based on these values, the average participant experienced a significant increase in muscle strength (p <.05) in the triceps muscles of the right and left hands. The intervention carried out on the triceps muscles had a positive impact on increasing muscle strength. In this study, the average triceps muscle of the right hand experienced a greater increase than the triceps muscle of the left hand (see Table 3 and Figure 2).

Effect of invention on quadriceps muscle

Quadriceps muscle strength experienced a significant increase before and after the intervention. The average value of the quadriceps muscle in the right leg increased by 1.99 kg, with a significance value of p =.009. Then, for the quadriceps muscle in the left leg, there was an increase in muscle strength of 2.28 kg with a significance value of p =.001. Based on these values, the average participant experienced a significant increase in muscle strength (p <.05) in the quadriceps muscles of the right and left legs. The intervention carried out on the quadriceps muscles had a positive impact on increasing muscle strength. In this study, the average quadriceps muscle in the left leg experienced a greater increase than the quadriceps muscle in the right leg (see Table 3 and Figure 2).

Effect of invention on gastrocnemius muscle

Gastrocnemius muscle strength experienced a significant increase before and after the intervention. The average value of the gastrocnemius muscle in the right leg increased by 1.87 kg, with a significance value of p =.023. Then, for the gastrocnemius muscle in the left leg, there was an increase in muscle strength of 2.51 kg with a significance value of p =.010. Based on these values, the average participant experienced a significant increase in muscle strength (p <.05) in the gastrocnemius muscles of the right and left legs. The intervention carried out on the gastrocnemius muscles had a positive impact on increasing muscle strength. In this study, the average gastrocnemius muscle in the left leg experienced a greater increase than the gastrocnemius muscle in the right leg (see Table 3 and Figure 2).

DISCUSSION

To our knowledge, this intervention is the first report of a muscle strengthening training program using elastic bands to improve arm (biceps and triceps) and leg (quadriceps and gastrocnemius) muscle strength. All interventions were designed to be easily performed by older adults. Low muscle strength is known to independently affect quality of life in older adults,[11] predicting falls,[22] fractures, poor overall health, and mortality.[23] Therefore, the development of physical and resistance training is of interest because it can improve muscle strength in older adults.

The main finding of this study is that a muscle-building exercise program using elastic bands for 8 weeks can significantly increase the strength of biceps, triceps, quadriceps, and gastrocnemius muscles in elderly people with sarcopenia living in the elderly community. Increasing muscle strength is very important for people with sarcopenia because sarcopenia is a muscle disease (muscle dysfunction) that can interfere with daily

activities. According to EWGSOP, low muscle mass is no longer the main cause of sarcopenia; the main cause of sarcopenia is low muscle strength. Indeed, muscle strength has been shown to be a worse cause of sarcopenia than muscle mass.[24] Strengthening exercises with elastic bands can increase motor unit recruitment activity and activate Golgi tendon organs and muscle spindles, thereby increasing muscle contraction.[25] This exercise will cause the muscles to contract while holding the weight and can be increased by increasing the number of repetitions of the exercise or increasing the resistance to a higher level as needed.

Previous researchers have shown that resistance training for eight weeks has a positive effect on increasing muscle strength in the upper,[2] lower limbs[9] and delaying sarcopenia in the elderly.[2,9] The results of this study confirm our findings. This is a clinically useful finding for the elderly with sarcopenia because increasing muscle strength can have a major impact on an individual's ability to remain independent in the community.[26,27] These beneficial results can provide guidance to caregivers on how to provide exercise programs that have benefits for increasing muscle strength in the elderly.

Muscle-strengthening exercise program can also reduce the risk of sarcopenia and improve the quality of life for the elderly. This exercise program can be a recommendation for intervention because it is economical and easy to do independently at home. These findings indicate that the intervention we developed can be an effective way to encourage safer movement and reduce the risk of sarcopenia among the elderly living in the community. Therefore, we recommend that the exercise program we developed be done by the elderly at home independently. In addition, the elderly can change the pulling force of the elastic band to increase the intensity of exercise and move the limbs from head to toe when doing this exercise. Thus, this intervention can provide more benefits to improve physical performance.

The limitation of this study is that we only trained the elderly using elastic bands without any combination of other exercises. In the future, we hope to combine this exercise program with other activities, for example, gymnastics or light-weight lifting. We also aim to compare or group the elderly with different treatments so that the differences in the results of the treatments we do can be known. This research must continue to be developed to help the elderly carry out their daily activities.

Seniors can then use elastic band exercises independently at home by starting with a light warm-up, choosing a resistance band with an appropriate level of elasticity, and performing simple movements that target major muscle groups such as the arms, legs, and hips. Examples of movements include pulling up with a band to work the back and arms, squats with a band for the thighs and glutes, and stretching and strengthening muscles while standing or lying down. Exercises should be performed slowly and in a controlled manner, about 2–3 times a week, with 10–20 repetitions per movement, and interspersed with light stretches to maintain flexibility. Seniors are also advised to maintain proper posture during exercise for safety and effectiveness.

Caregivers or healthcare professionals can integrate elastic band exercises into community or senior care programs by designing structured exercise programs tailored to the senior's physical abilities, including adjusting the intensity and frequency of the exercises. Healthcare professionals should provide direct education and training to both the senior and caregiver on safe and effective elastic band use techniques. Furthermore, caregivers can accompany the senior during the exercises to monitor safety and progress and provide motivation. This integration can also be achieved by holding regular sessions at senior centers or care facilities so that the exercises become part of a routine that supports increased muscle strength and balance, significantly reducing the risk of falls.

An exercise intervention using elastic bands effectively prevents falls and hospitalizations due to sarcopenia in older adults by improving leg muscle strength, dynamic balance, and joint flexibility. This exercise stimulates neuromuscular adaptations, resulting in stronger muscles and a more responsive sensorimotor system, which is crucial for maintaining stability and reducing fall risk. Research shows that several weeks of elastic band intervention significantly increase the strength of arm muscles (biceps and triceps) and leg muscles (quadriceps and gastrocnemius).

CONCLUSION

Resistance training using elastic bands routinely for 8 weeks can increase the strength of the biceps, triceps, quadriceps, and gastrocnemius muscles. This exercise can also reduce the risk of sarcopenia and improve the quality of life for the elderly. This exercise program can be a recommendation for intervention because it is economical and easy to do independently at home.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest related to this work.

ACKNOWLEDGEMENTS

The authors would like to thank all respondents who willingly participated in this study. Appreciation is extended to the Center for Biomechanics, Biomaterial, Biomechatronics, and Biosignal Processing (CBIOM3S) for providing facilities during the research. The authors also extend their gratitude to the Politeknik Negeri

Semarang for supporting this research.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; vol 13 (1) : 79–87

OPEN ACCESS

Original Article

The Correlation Between Social Support and Incidence of Depression in Coronary Heart Disease Patients

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Abstract

Background : Coronary heart disease can cause psychological impacts in the form of depression which, if not managed optimally, can worsen the patient's condition. One of the psychosocial factors that cause depression is low social support. Social support can strengthen individual coping with the acceptance of disease conditions in patients.
Aims : This study aims to determine the relationship between social support and depression in coronary heart disease patients at the Heart Installation of Dr. Kariadi Hospital Semarang.
Methods : This research is a descriptive quantitative correlation with a cross sectional approach. The research sample amounted to 39 respondents calculated by the Isaac and Michael formula with the sampling technique using accidental sampling. The research instruments used were Multidimensional Scale of Perceived Social Support (MSPSS) to assess social support and Beck Depression Inventory-II (BDI-II) to assess depression.
Results : The results of the Pearson Product Moment test showed a highly significant correlation between social support and depression (p = 0.000) with a value of r = -0.756 indicating a strong level of correlation with a negative correlation direction.
Conclusion : The correlation between the two variables is strong and inversely proportional where the higher the social support received, the more depressive symptoms experienced will decrease. Family education is needed to maintain and increase social support to prevent and reduce depression in coronary heart disease patients.

Keywords : social support, depression, coronary heart disease

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v13i1.1244

Submitted: October 08th, 2024
Accepted: March 31th, 2026

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INTRODUCTION

Coronary heart disease is known to be the most common cause of death among cardiovascular diseases.[1] In addition to mortality, it also contributes significantly to the global burden of disease measured by disability-adjusted life years (DALYs). DALYs represent the total number of years lost due to premature death and years lived with disability caused by a disease in a population. Coronary heart disease is therefore considered a major contributor to DALYs worldwide.[2]

In 2021 globally coronary heart disease accounts for 9.4 million deaths and 185 million DALYs. [3,4]American Heart Association (AHA)[3] report that there are 16.5 million people over the age of 20 who are affected by coronary artery disease. According to the Institute of Health Matric and Evaluation (IHME) in the Indonesian Ministry of Health[4], deaths from coronary heart disease in Indonesia were found to be 245,343 people per year.

Coronary heart disease not only causes physical complications but also has significant psychological consequences for patients.[5] The psychological impact can be in the form of impaired patient perception of their disease and the emergence of depression. The research by Amni[6] reported that most coronary heart disease patients at Dr. Hasan Sadikin Hospital, Bandung, experienced depression, including 34.4% mild, 23.3% moderate, and 4.4% severe. Severe depression may lead to feelings of helplessness and worsen the prognosis of coronary heart disease. The management of psychological conditions in chronic diseases such as heart disease that is not optimal can increase the incidence of depression which can worsen the patient's condition. Coronary heart disease patients with psychological disorders such as depression can also increase the incidence of hospital readmission and increase the length of stay index significantly.[7]

One of the psychosocial factors that cause depression is low social support.[8] Social support is very important for coronary heart disease patients to strengthen individual patient coping and help patients accept the condition of their disease so that depression does not occur.[9] Social support can be obtained from family, friends, and other significant individuals. It generally includes emotional, informational, instrumental (tangible), and appraisal support.[2]

The research in the United States on 71 respondents with heart failure disease showed a relationship between social emotional support and depressive symptoms (p = <0.001), where coronary heart disease respondents who received greater emotional support had milder depressive symptoms.[10] The research results demonstrate that social support impacts the psychological/mental well-being of coronary heart disease patients. Providing social support, including positive emotional support, can reduce depressive symptoms in coronary heart disease patients.[11]

Research on the relationship between social support and depression in coronary heart disease patients is limited in Indonesia. Based on preliminary studies conducted at Dr. Kariadi Semarang General Hospital in the Cardiac Installation, coronary heart disease patients during the 2022 period were 851 patients and from January to August 2023 it was known that 700 patients were hospitalized. Based on this phenomenon, the researcher is interested in conducting a study entitled "The Correlation between Social Support and Incidence of Depression in Coronary Heart Disease Patients" at the Heart Installation of Dr. Kariadi Hospital Semarang.

METHODS

This study is categorized as a descriptive correlation a cross sectional approach. Before starting the research, the researcher has carried out the administrative process and obtained a research permit with the number : DP.04.01/D.X.2/1421 /2024. The population in this study was the monthly average of coronary heart disease patients at the Heart Installation of Dr. Kariadi Hospital Semarang in January-August as many as 88 patients. Then, the sample was obtained through calculations using the Isaac and Michael formula of 39 respondents . The sampling technique in this study was non-probability sampling in the form of accidental sampling. This study used three instruments, a demographic questionnaire, a social support questionnaire, and the depression questionnaire. Demographic data characteristic variables in this study include; age, gender, education, marital status, occupation, income, NYHA classification, duration of coronary heart disease, and readmission.

Social support was measured using the Multi-dimensional Scale of Perceived Social Support (MSPSS) developed Zimed. The MSPSS consists of 12 items to measure perceived social support from three sources: family, friends, and significant others.[12] The MSPSS instrument uses a 7-point Likert scale, with total scores ranging from 7 to 84. Scores are categorized as low social support (12–48), moderate social support (49–68), and high social support (69–84). The Indonesian version of the questionnaire has been tested for validity and reliability, showing corrected item–total correlation values ranging from 0.365 to 0.687 (r > 0.349) and a Cronbach's alpha coefficient of 0.842, indicating good reliability.

Depression was measured using the Beck Depression Inventory-II (BDI-II) developed by by Beck, Steer and Brown. The BDI is a 21-item self-report assessment inventory that measures attitudinal characteristics and symptoms of depression. The BDI consists of three categories : negative attitudes, performance impairment, and somatic factors. The BDI

score is interpreted as follows: scores of 0–13 indicate minimal depression, 14–19 indicate mild depression, 20–28 indicate moderate depression, and 29–63 indicate severe depression. The Indonesian version of the questionnaire has demonstrated good validity, with corrected itemtotal correlation values ranging from 0.437 to 0.730 (r > 0.349), and good reliability with a Cronbach's alpha coefficient of 0.809.[13]

RESULTS

General Characteristics of Coronary Heart Disease Patient Respondents

The demographic characteristics of the respondents indicate that most participants were middle-aged adults, predominantly male, married, and a high school level of education. Most patients were also classified as NYHA II–III, indicating moderate functional limitations associated with coronary heart disease. These findings suggest that many patients remained in their productive age while experiencing physical limitations, which may increase psychological vulnerability, including the risk of depression. It is known based on the data that most of the patients are married. Marital status serve as an important source of social support for patients with chronic illnesses. Family members often play a significant role in providing emotional, informational, and instrumental support that helps patients cope with the physical and psychological burden of coronary heart disease. Adequate social support therefore reduce the likelihood of depressive symptoms and enhance patients' ability to adapt to their illness.

Univariate Analysis of Social Support Variables in Coronary Heart Disease Patients

The results of the study of social support variables with the MSPSS questionnaire instrument found that the minimum score of social support obtained by patients was 43 while the maximum score of social support obtained by patients was 78. More than half of the sample of coronary heart disease patients, there were 24 (61.5%) patients known to receive moderate social support and a small portion of 3 (7.6%) patients received low social support. The average score of social support obtained by patients in the study was 63.10 which means moderate social support with a standard deviation of 8.344 which shows that the distribution of data varies greatly.

Univariate Analysis of Depression Variables in Coronary Heart Disease Patients

The results of the study of depression variables that have been studied using the BDI-II questionnaire obtained a minimum depression score of 6 and a maximum score of 34. The majority of 16 (41%) patients experienced

TABLE 1
Demographic Data of Participants (n=39)

Variable	Classification	f	(%)	Min.	Max.	Mean	SD
Age							
Late Adulthood	36–45 years	16	41	36	65	50.41	8.315
Early Old Age	46–55 years	11	28.2				
Late Old Age	56–65 years	12	30.7				
Gender							
Male		24	61.5				
Female		15	38.5				
Last Education							
Elementary School		5	12.8				
Junior High School		9	23				
Senior High School		23	58.9				
College		2	5				
Marial Statuses							
Not yet married		3	7				
Divorce		9	23				
Married		27	69.2				

TABLE 1. *Continued.*

Variable	Classification	f	(%)	Min.	Max.	Mean	SD
Job							
Civil Servant		0	0				
Police/Army		1	2.5				
Employee/labor		12	30.8				
Self-Employed		14	35.9				
Unemployment		12	30.8				
Salary							
Low	<1.500.000	13	33.3				
Medium	1.500.000–2.500.000	19	48.7				
Moderate	2.501.000–3.500.000	7	17.9				
High	>3.500.000	0	0				
NYHA							
I		11	28.2				
II–III		26	66.7				
IV		2	5.1				
Long Term of CHD							
<1 month		4	10.3				
1-6 month		12	30.8				
>6 month		23	58.9				
Readmission							
1–3x		26	66.7				
4–6x		11	28.2				
>6x		2	5.1				
Total		39	100				

moderate depression. It was found that the average patient experienced moderate depression as evidenced by a mean value of 21.6 from the average score obtained from the BDI-II questionnaire and a standard deviation of 6.983 which showed that the data distribution was very varied.

Bivariate Analysis of Social Support Variables and Depression in Coronary Heart Disease Patients

The results of the Pearson Product Moment correlation test between social support and depression variables are *p*-value = 0.000 (<0.05) which means Ha is accepted which indicates a very significant relationship and the correlation coefficient value r = -0.756. These results mean a strong level of relationship with a negative relationship direction which means the relationship between the two variables is inversely proportional where the more social support received by coronary heart disease patients, the symptoms of depression experienced will decrease.

DISCUSSION

The majority of coronary heart disease sufferers in this study were known to be between 36–45 years (late adult group) which is still classified as productive age. Research[14] showed that coronary heart disease sufferers were in the productive age range with an age range of ≤ 40–44 years with a prevalence of 66.9% (161 of 227 respondents). Research stated that 107 of 158 patients with a prevalence of 66.7% were diagnosed with STEMI in the age range of 26 – 49 years.[15] Individuals in this age range often experience multiple responsibilities related to

TABLE 2
Data Analysis of Social Support (n = 39)

Variable	Classification	f	(%)	Min.	Max.	Mean	SD
Social Support							
Low	12–48	3	7.6	43	78	63.10	8.344
Medium	49–68	24	61.5				
High	69–84	12	30.7				
Total		39	100				

TABLE 3
Results of data analysis of depression variables in coronary heart disease patients at Dr. Kariadi General Hospital, Semarang (n = 39)

Variable	Classification	f	(%)	Min.	Max.	Mean	SD
Depression							
Minimal	0–13	6	15.3	6	33	21.6	6.983
Mild	14–19	8	20.5				
Medium	20–28	16	41				
Severe	29–63	9	23				
Total		39	100				

TABLE 4
Correlation Test of Social Support Variables with Depression

Variable	Mean ± SD	Coefficient Correlation (r)	*p*-value
Social Support	63.10 ± 8.344	-0.756	0.000
Depression	21.6 ± 6.983		

work and family roles. When diagnosed with a chronic illness such as coronary heart disease, these responsibilities create additional psychological pressure.[16] Furthermore, patients in this age group experience physical limitations as a result of their illness, including fatigue, reduced physical endurance, and restrictions in performing daily activities. These limitations can interfere with patients' ability to fulfill their social and occupational roles, which may negatively affect their self-perception and emotional well-being. Feelings of reduced independence and uncertainty about future health conditions may also increase the risk of psychological distress.[1]

It is known that most coronary heart disease sufferers are male. In line with the research of[17] conducted at Ibnu Sina Hospital Makassar, it was stated that of the 40 patients diagnosed with coronary heart disease, the highest proportion based on gender was male patients, namely 21 people (52.5%). Another study showed that the majority of coronary heart disease sufferers were male (60.4%).[18] Gender differences may influence psychological responses to illness and coping mechanisms. Male patients may be less likely to express emotional distress or seek psychological help, which may increase vulnerability to depressive symptoms. In this context, social support from family members and significant others becomes important in helping male patients manage emotional stress and adapt to health condition.[19]

More than half of the percentage of respondents have a high school education background. Setiadi's research[20] also stated that out of 118 respondents with coronary heart disease, 52 (44.1%) respondents had a high school education. The research report that out of

34 respondents with coronary heart disease, 19 (55.9%) of them had a high school/equivalent education.[21] Research conducted also stated that the majority of 4,545 (32.6%) of the 13,948 respondents with coronary heart disease had a high school education.[22] Educational background can influence a patient's understanding of their illness and their ability to access health information. Patients with better knowledge of their illness are better able to adopt effective coping strategies and seek appropriate social support.[23] Therefore, adequate health literacy can help patients manage psychological stress and reduce the risk of depression.

Married patients are known to be the most common status of coronary heart disease patients in this study. Research[24] which examined the effect of marital status on the incidence of depression in coronary heart disease patients found that out of 101 respondents, 91 (90.1%) were married and 10 (9.9%) respondents were not married. Research[10] also found that 406 (81.2%) of 500 heart disease patient respondents were married. The research repot also stated that 100 (97.1%) of 103 coronary heart disease respondents were married. Marriage is known to be a factor that is inversely related to depression because married individuals have better psychological conditions and can protect someone from external factors that can trigger depression.[5] One of the psychosocial factors that causes depression is low social support.[8] According to research,[25] it is stated that someone who is married and in a relationship is known to get high social support compared to someone who is not or has never been married. This is supported by the results of research[26] which found that respondents who were not married had a relationship with the incidence of depression (p-value = 0.037). Social support from partners/family can provide social support in the form of emotional support that can help someone reduce stress, be more compliant with the medical treatment they are undergoing, and be able to avoid depression.[27]

The income level of patients in this study was mostly classified as a moderate income level ranging from 1,500,000 – 2,500,000 per month. Research[24] found that out of 107 respondents with coronary heart disease, 61 (57%) respondents had an income of <2.8 million rupiah. In addition, the results of this study are also supported by the results of research[27] which stated that 71 (35.5%) of 200 respondents with coronary heart disease were in the moderate economic status category. However, another study[28] found that out of 950 respondents with coronary heart disease, 546 (52.6%) respondents had low economic status. Economic status may influence patients' ability to access healthcare services and manage the financial burden associated with chronic illness. Financial difficulties may increase psychological stress and potentially contribute to depressive symptoms.[29] In such situations, emotional and practical support from family members may help patients cope with both the financial and psychological challenges associated with coronary heart disease.

More than half of the patients in this study were classified in the NYHA II-III category. The study on 443 patients with angina pectoris coronary heart disease found that most of the patients were classified with NYHA II, 261 (58.9%) patients, of which 66 patients had mild depression and 26 patients had moderate depression.[30] The results of study 224 coronary heart patients found that the majority of 132 (77.2%) patients were classified as NYHA II and III, consisting of 116 (51.8%) NYHA II patients (62 of whom had depression) and 57 (25.4%) NYHA III patients (30 of whom had depression).[26] Another study[31] stated that out of 1337 coronary heart disease patients, 679 patients (52%) were classified as NYHA II and III. Depressive symptoms are more common in coronary heart disease patients with poor functional conditions who have been assessed using NYHA.[30] In coronary heart disease patients, the NYHA classification is used to categorize the extent of physical limitations experienced by coronary heart disease patients because it can affect the quality of life of coronary heart disease patients.[26] Thus, NYHA classification in patients can help health workers in assessing functional status and anticipating the emergence of depression in coronary heart disease patients with higher NYHA status.

The majority of patients in this study had been diagnosed with coronary heart disease for >6 months. The study findings that 61 (79.2) patients diagnosed for ≥6 months with coronary artery disease.[32] The results of the study by Nuraeni[24] showed that out of 107 coronary heart disease patients, 77 (72%) of them had been diagnosed for ≥ 6 months. A similar study obtained results from 81 samples of patients diagnosed with coronary heart disease < 6 months, 13 (16%) patients, then for patients diagnosed >6 months, 68 (83.9%) patients.[33] Factors that influence health related to the quality of life of heart disease patients include the length of time suffering from the disease which is associated with the symptoms that appear and depression in coronary heart disease patients. In patients with cardiovascular diseases such as coronary heart disease, symptoms of depression persist for more than 6 months after myocardial infarction, or more specifically, for ± 12 months. In addition, compared to a temporary reaction to a coronary heart disease event, depression in many patients appears months or years before the event and persists long after the event.[34]

More than half of the results of this study showed that coronary heart disease patients received moderate social support. This is in line with the results of research that out of 284 coronary heart disease patients, 115 (40.1%) patients received moderate social support.[26] Research[35] showed that out of 192 coronary heart disease patients, 124 (64.6%) patients received

sufficient/moderate social support from their families. Social support is said to be a subjective feeling felt by individuals regarding the presence or absence of actual support from other people around them.[36] Social support plays an important role in the management of heart disease.[10] This is because social support is known to be associated with quality of life and mental conditions in coronary heart disease patients.[24] The effect of social support can reduce stressors in cardiovascular patients which has an impact on reducing morbidity and mortality.[11] Adequate social support can result in reduced cortisol response to stress, better immune function, less cell aging which has an impact on reducing the risk of heart disease.[37]

The results of this study conducted at Dr. Kariadi General Hospital Semarang show that the majority of patients received moderate levels of social support. In many communities, social support for sick individuals is commonly expressed through visits, expressions of empathy, and the provision of moral or material assistance from family members, relatives, and friends.[38] In general, family is often placed at the center of social life and becomes an important source of emotional comfort and support when individuals experience health problems. These findings are consistent with the study conducted,[35] which reported that out of 192 coronary heart disease patients, 124 (64.6%) received sufficient or moderate social support from their families. This suggests that sociocultural values emphasizing care, empathy, and kinship may contribute to the availability of social support for patients with coronary heart disease.
Depression was suffered by the majority of coronary heart disease patients in this study. In line with the research[39] on coronary heart disease patients in Palestine, it showed that out of 1,022 coronary heart disease patients, 257 (25.2%) of them were included in the mild-moderate depression category. The results of a study[6] showed that out of 84 coronary heart disease patients at Dr. Hasan Sadikin Hospital, Bandung, 18 (21.4%) of them experienced mild-moderate depression. There is also another study on 175 coronary heart disease patients with myocardial infarction in Jordan, 122 (69.7%) of them experienced mild to severe depression.[40] Depression contributes to the development of several chronic medical diseases, including heart disease which results in decreased quality of life. Depression is also a factor in readmission and increased length of stay in hospital in coronary heart disease patients. Symptoms of depression often occur after the onset of acute coronary heart disease and its appearance is related to the occurrence of recurrent myocardial infarction.[40] Symptoms of depression that often appear and are almost the same as symptoms of coronary heart disease are fatigue. Fatigue that appears in heart disease patients causes the need for activity restrictions which often cause depression in patients with recurrent myocardial infarction.[41] In patients with high depression, it must be really considered because this is related to the patient's feelings of helplessness due to activity restrictions that can affect the prognosis of the coronary heart disease condition they suffer from. Coronary heart disease patients who experience depression can experience a worse prognosis and are at risk of developing major depression (Major Depressive Disorder).[6]

The results of the Pearson product moment test showed a very significant relationship between the variables of social support and depression (p-value = 0.000) with a negative relationship direction (r = -0.756) which means the relationship between the two variables is strong and inversely proportional where the more social support received by coronary heart disease patients, the symptoms of depression experienced will decrease. In line with research[32] in Indonesia showed that the results of the relationship between social support and depression in coronary heart disease patients were moderate (p = <0.005, r = -0.467). Another study by[9] in Lithuania on 129 coronary artery disease respondents showed that social support influenced the reduction of depressive symptoms in the form of fatigue experienced by coronary artery disease patients (p <0.001).

In patients with coronary heart disease, psychosocial factors have been widely highlighted because they are considered capable of causing other prognoses such as depression related to cardiovascular disease.[2] Depression is one of the common symptoms in patients with heart disease which is associated with a worsening quality of life which results in functional disorders in patients with heart disease such as decreased daily activities and decreased walking distance compared to non-depressed patients. One of the psychosocial factors that causes depression is low social support. According to[27] factors that influence the relationship between social support and depression can be associated with medical conditions experienced by patients, such as post-Acute Myocardial Infarction conditions that occur repeatedly in patients with Coronary Heart Disease.

The results of this study and previous studies show that there is a relationship between social support and depression in patients with coronary heart disease. In this study, in addition to social support factors that influence the incidence of depression, the presence of medical conditions in patients such as recurrent myocardial infarction can also be influenced by other risk factors such as: age, gender, education, marital status, occupation, income, NYHA classification, duration of coronary heart disease and readmission events can affect depression in patients with coronary heart disease.

CONCLUSION

Pearson Product Moment tests revealed a very significant

relationship between social support and depression (p=0.000) and a correlation coefficient of r=-0.756. This is interpreted as a strong level of relationship with a negative relationship direction which means the relationship between the two variables is inversely proportional where the more social support received by coronary heart disease patients, the more the symptoms of depression experienced will decrease.

CONFLICT OF INTEREST

The authors declare no conflict of interest. This study was conducted independently without financial, commercial, or personal influence, and all findings are based on objective data analysis.

AKNOWLEDGMENT

The authors would like to express their gratitude to all parties who contributed to this research. Special thanks are given to the respondents, academic supervisors, and all supporting institutions. The authors also appreciate the support from family and friends throughout the research process.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; vol 13 (1) : 88–93

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Case Report

C-Arm Assisted Surgical Foreign Body Removal in the Tongue: Evidence-Based Case Report

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p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v13i1.1340

Submitted: July 03th, 2025
Accepted: March 30th, 2026

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Abstract

Background : The term corpus alienum (foreign body) refers to an external object that should not be present within the human body. In managing such cases, X-rays are among the most important imaging modalities. To support surgical and orthopedic procedures, a mobile imaging device known as the C-Arm is often used. It provides real-time imaging during procedures involving bones or internal organs.
Case Report : A 51-year-old male presented with a staple lodged in his tongue. He previously underwent blind surgery by an oral surgeon at RSUD Salatiga, but the foreign body could not be located. The patient was referred to RSUP Dr. Kariadi Semarang and scheduled for C-Arm assisted removal under general anesthesia.
Discussion : Foreign bodies can cause discomfort and various symptoms. The C-Arm is a radiological device that provides real-time visualization using fluoroscopy and a monitor screen. With its assistance, the foreign body was accurately located and successfully removed from the tongue.
Conclusion : This case highlights the importance of imaging guidance in foreign body removal. The use of a C-Arm enabled precise localization and successful surgery after a previous failed attempt.

Keywords : corpus alienum, foreign body, C-Arm

INTRODUCTION

The term "foreign body" in the medical field refers to an external object that should not be present within the human body. The phrase originates from the Latin term "corpus alienum" and also describes the body's immune response to such objects. A rare occurrence involves foreign bodies lodged in the palate or other areas of the oral cavity, which can sometimes be misdiagnosed as other oral health conditions. Research shows that these incidents are most commonly experienced by children. The mouth serves as a primary route for foreign body accidents, especially in children under the age of three.[1,2] In managing foreign body cases, X-rays are one of the most important medical imaging methods. Despite significant advancements in medical technology, X-rays remain widely used due to their effectiveness in detecting foreign bodies, fractures, and other medical conditions. X-rays work by exposing specific parts of the body to low doses of radiation to produce internal images. This imaging technology has also evolved into fluoroscopy, which allows doctors to observe real-time moving images of internal body structures. Fluoroscopy employs continuous X-ray beams directed at specific body parts, with the images displayed on a computer screen, enabling the observation of bodily movements.[3,4]

To support procedures such as surgeries and orthopedic treatments, a mobile imaging device known as the C-Arm is often utilized. This device integrates fluoroscopy technology with computing capabilities to view, edit, store, and transfer images. The combination of these technologies ensures that X-rays and their advancements remain highly relevant and immensely helpful in patient diagnosis and treatment. The C-Arm is exceptionally beneficial and simplifies medical procedures for physicians. With its advanced features, the C-Arm minimizes errors in predicting object locations, diagnosis, and other medical actions. Most impressively, this device can provide live imaging during medical procedures and surgeries involving bones or internal organs. This ensures that surgeries and medical interventions are conducted with ease, accuracy, safety, and comfort.[4,5]

This case highlights a unique clinical scenario where a metal staple embedded in an adult patient's tongue could not be located despite a previous surgery assisted by MSCT. The object was only successfully removed through a second surgery using C-Arm fluoroscopy, a mobile imaging device capable of real-time visualization during procedures. The novelty of this case lies in demonstrating how intraoperative C-Arm assistance significantly improves the accuracy and efficiency of foreign body removal in soft tissue areas like the tongue, where conventional imaging may fall short.

Although the use of C-Arm fluoroscopy in maxillofacial surgery is uncommon, several reports have demonstrated its utility in similar contexts. One study successfully employed C-Arm fluoroscopy to extract a three-dimensional foreign object embedded approximately 5 mm deep in the intrinsic tongue musculature near the periosteum.[5] Another case utilized the device in open reduction and internal fixation of a left subcondylar mandibular fracture.[6] These findings highlight the versatility and clinical potential of C-Arm technology in enhancing surgical outcomes for complex or otherwise challenging maxillofacial cases.

This report aims to describe the diagnostic and surgical approach undertaken, evaluate the role of C-Arm fluoroscopy in improving intraoperative visualization, and provide insights for the management of comparable cases in clinical practice.

CLINICAL SCENARIO

A 51-year-old male patient presented to the Oral Surgery Department at RSUP Dr. Kariadi Semarang with a chief complaint of a staple lodged in his tongue. The patient was unaware of the staple while eating, which subsequently pierced his tongue, causing pain. The patient had previously undergone surgery with MSCT assistance for foreign body removal performed by an oral surgeon at RSUD Salatiga; however, the staple could not be located. The patient continued to experience pain and had difficulty moving his tongue, which limited him to consuming only soft foods. The patient denied a history of diabetes mellitus, hypertension, and gout. The patient was referred to RSUP Dr. Kariadi Semarang for foreign body removal with a more advanced tool for locating the foreign body (C-Arm imaging).

On clinical examination, the patient was in good general condition and fully conscious (compos mentis). Extraoral assessment revealed symmetrical facial features with no visible signs of asymmetry, edema, or hyperemia. The findings were within normal limits, indicating no outward manifestations of inflammation or infection associated with the foreign body lodged in the tongue.

Intraoral examination revealed an ulcer-like wound on the right lateral tongue region as a result of the prior surgery. Palpation detected a hard, foreign body-like sensation in the right lateral tongue region, accompanied by tenderness, hyperemia, and edema. A prior MSCT scan revealed a well-defined, hyperdense linear lesion measuring 2.27 x 0.27 cm in the right hemilingual region. Its main disadvantage is the absence of real-time visualization during surgical scissors insertion, which is typically available in conventional fluoroscopy guidance systems. Axial imaging showed the lesion to be 2.48 cm from the anterior lingual apex and 0.69 cm from the right lateral tongue edge. Sagittal imaging showed the lesion to be 1.5 cm from the superior lingual margin. A diagnosis of a foreign body in the right

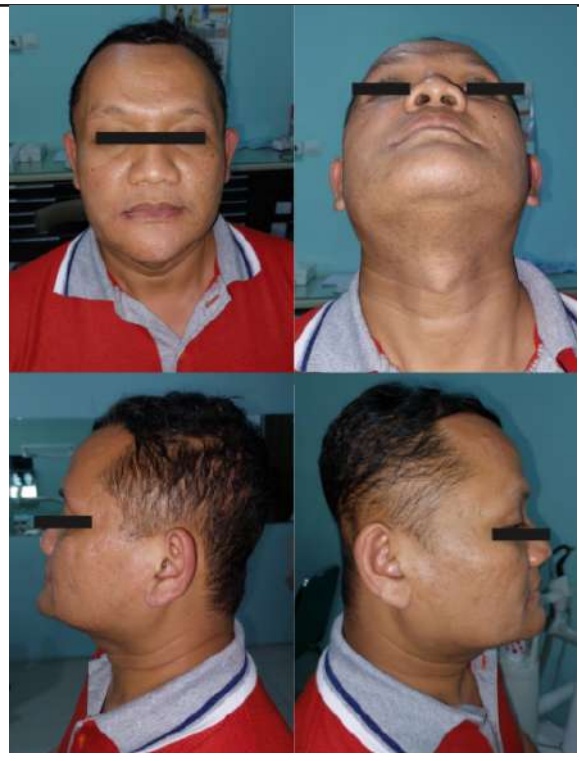

Figure 1. Extraoral examination of the patient.

lateral tongue region was established. The patient was scheduled for corpus alienum removal surgery under general anesthesia with the assistance of C-arm imaging and ultrasound guidance.

Laboratory result one day prior to the surgery showed the patient's glucose ad random level was higher than normal. The patient was referred to an internist and was prescribed 500 mg of metformin that was taken twice, in the morning and evening, the day before surgery. Aseptic preparation was carried out both extraorally and intraorally. The exact position of the foreign body was identified using C-Arm imaging to pinpoint its exact location (Figure 2a). A local vasoconstrictor (2 cc of epinephrine-containing anesthetic, such as Pehacain) was injected along the planned incision line. A mucosal incision was made on the right lateral region of the tongue, followed by blunt dissection using a Metzenbaum scissor to access the embedded object. With the aid of real-time C-Arm evaluation, the foreign body was successfully located and removed (Figure 2b). The surgical wound was then sutured using Vicryl 3.0 absorbable sutures (Figure 2c). The removed foreign body was a needle-like structure with pointed ends, measuring 2.3 cm in length (Figure 2d). Postoperatively, the patient received amoxicillin 500 mg orally every 8 hours and dexamethasone 5 mg by injection every 8 hours. Health education was provided regarding postoperative wound care, soft diet, and oral hygiene to support healing.

PROBLEM FORMULATION

Based on the clinical scenario, a focused clinical question was formulated using the PICO framework to guide evidence-based decision-making (Table 1)

The clinical question formed based on these components is: in patients with foreign bodies embedded in the tongue or head-and-neck soft tissue, does C-Arm assisted surgery, compared to conventional or blind surgical methods, improve localization accuracy and increase the success rate of foreign body removal?

SEARCH STRATEGY AND RESULTS

A systematic literature search was conducted to answer the clinical question using a structured and reproducible approach. The search was performed using electronic databases, including PubMed and ScienceDirect. The keywords used were combinations of "C-Arm Assisted Surgery," "C-Arm fluoroscopy," "foreign body," and "corpus alienum," combined with Boolean operators such as "AND" and "OR." Articles were selected based on predefined inclusion and exclusion criteria. The inclusion criteria comprised studies discussing the use of C-Arm or fluoroscopy in surgical management of foreign bodies, particularly in the head-and-neck or soft tissue regions, including case reports, case series, and clinical studies published in English. Studies were excluded if they were not relevant to the PICO question, did not involve surgical or imaging interventions, or were

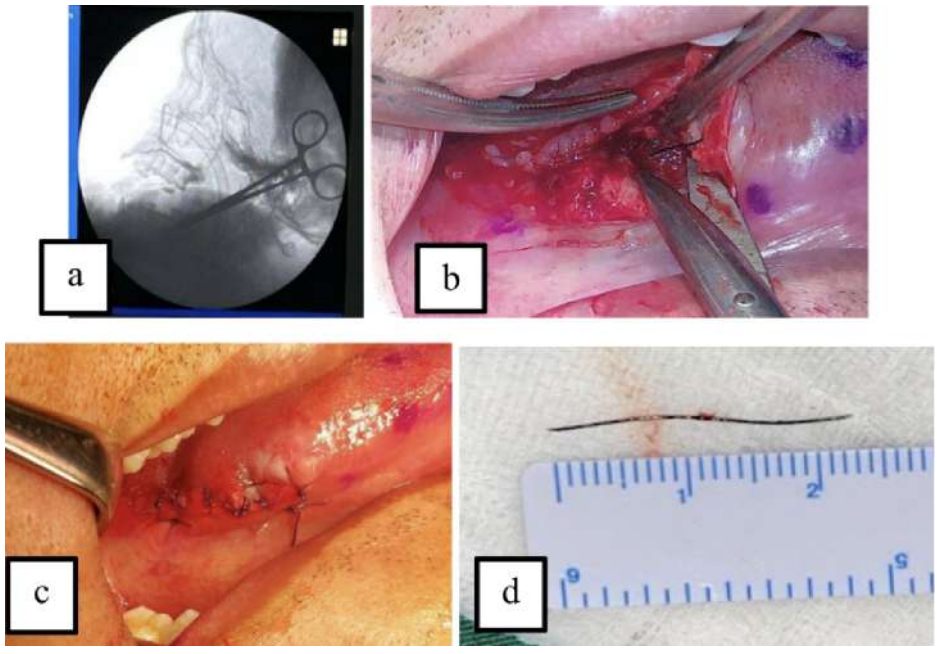

Figure 2. a. C-Arm imaging to confirm; **b.** Needle-like in tongue before removal; **c.** The wound was then sutured at the incision site; **d.** A 2,3 cm long needle with sharp ends on both sides

TABLE 1
PICO framework for guide

Problem	Intervention	Comparison	Outcome
Patients with a foreign body (corpus alienum) in the tongue or head-and-neck soft tissue that is hard to remove with conventional surgery.	C-Arm assisted surgery vs blind surgery	Accurate localization of the foreign body	Successful removal of foreign body

duplicate publications.

After screening, a total of 8 relevant articles were included for further evaluation. Most of the included studies were case reports and small clinical studies, indicating a relatively low to moderate level of evidence. However, the findings consistently supported the use of C-Arm fluoroscopy in improving intraoperative localization and facilitating successful foreign body removal.

The included study consists of an article written by Dong-Yang Ma, *et al*. A critical appraisal of this article is presented in Table 3.

DISCUSSION

A foreign body, or corpus alienum, refers to any object originating from outside the body. When such an object enters the body, it can cause discomfort and unpleasant symptoms for the patient. In this particular case, the foreign body is a metal needle that has penetrated the tongue. The patient previously underwent a procedure to remove the object at RSUD Salatiga using MSCT, but it was not successfully located. Subsequently, the patient was referred to RSUP Dr. Kariadi with the expectation that the foreign body could be identified and extracted. The patient was then scheduled for surgery under general anesthesia.

The foreign body removal surgery was performed with the assistance of radiological equipment in the form of a C-Arm. It is a radiological device used to view images or objects from a patient, which are directly observed using fluoroscopy with the help of a monitor screen. With this tool, the position of the object or examination subject inside the body can be easily detected, and it can even be viewed live like a video shoot. The advantage of the C-Arm is that it reduces costs because, during the

TABLE 2
Search queries used for literature retrieval in journal databases

Database	Keywords	Hits	Eligible
PubMed	(C-Arm Assisted Surgery) AND ((Foreign Body) OR (Corpus Alienum)	12	7
Science Direct		84	1

TABLE 3
Critical appraisal of the study

Writers (year)	Dong-Yang Ma, *et al.* (2024)	
Validity		
1.	Is this case relevant to the population of patients with foreign bodies in the tongue?	Yes. The case involves an adult patient with a staple embedded in the tongue, which could not be removed through a prior blind surgery. It is representative of patients with difficult-to-access foreign bodies in the oral cavity or head-and-neck soft tissues.
2.	Is the C-Arm intervention clearly described and reproducible?	Yes. The procedure is described in detail, including the use of real-time fluoroscopy, patient positioning, and extraction technique under general anesthesia. The standard procedure can be applied in other centers with access to a C-Arm.
3.	Are the reported data objective and consistent?	Yes. Operative outcomes are clearly documented: foreign body location, procedure duration, extraction success, and complications. However, as a single case report, external validity is limited.
Importance		
1.	Does this case support the use of real-time imaging guidance?	Yes. It provides evidence that the C-Arm assists in extracting difficult-to-access foreign bodies, relevant for oral surgery, ENT, and orthopedic practice.
Applicability		
1.	What are the limitations for clinical implementation?	It requires C-Arm facilities and trained medical personnel. As a single case, generalization is limited; larger studies or a case series are needed.

surgery, the patient does not need pre- or post-operative X-rays, as the organ to be operated on can be clearly visualized through the monitor. With the help of the C-Arm, the surgery was successfully completed, and the foreign body was removed from the patient's tongue.[7,9,10]

In the first surgery, a CT scan was performed; however, its use was still not effective in locating the patient's foreign object. This is because a CT scan can only detect foreign objects outside the operating room, requiring more time as the patient must be moved to the CT machine first, making it less practical and efficient for surgical procedures that require real-time data. In contrast, the C-Arm can be brought directly into the operating room, allowing for more real-time data acquisition. This real-time data enables the surgeon to directly visualize the position of the foreign object during surgery and adjust the surgical approach without having to pause the procedure. The use of the C-Arm is also more flexible, as it can be positioned at various angles (anterior, lateral, oblique), allowing for visualization of the foreign object from different perspectives without significantly changing the patient's position. Additionally, the radiation dose from the C-Arm is lower than that of a CT scan, allowing it to be used repeatedly if necessary during the surgical procedure.[11,12]

The staple in the patient's tongue was a 2.3 cm long needle with sharp ends on both sides. The patient was prescribed Amoxicillin 500 mg every 8 hours and Dexamethasone 5 mg every 8 hours. The patient was then instructed to maintain oral hygiene, follow a soft diet, and avoid manipulating the postoperative wound area (e.g., playing with the tongue, sucking on the surgical site, or gargling too hard). The prognosis for this case is good, provided the patient maintains oral hygiene and follows

a high-protein diet to ensure proper tissue healing.

Unlike previous studies that primarily focus on foreign bodies in more accessible areas of the oral cavity, this case involves a rare instance of a metallic foreign object embedded deep within the tongue of an adult patient. Notably, despite the use of MSCT in a prior surgical attempt, the foreign body remained undetected and unretrieved. This report highlights the added value of intraoperative C-Arm fluoroscopy, which enabled real-time visualization and successful removal of the object without the need for repeated exploratory procedures. To our knowledge, documentation of C-Arm utilization in soft tissue foreign body extraction in the tongue remains limited in the literature, making this report a meaningful contribution to clinical practice and imaging-guided surgical techniques.

CONCLUSION

A foreign body in the tongue can cause significant discomfort and functional limitations. In this case, C-Arm fluoroscopy enabled accurate intraoperative localization and successful removal of the object after a previous attempt using MSCT had failed. This case highlights the effectiveness of C-Arm as a real-time imaging tool for managing soft tissue foreign bodies when other imaging modalities are insufficient.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We would like to express our gratitude to Dr. Kariadi Central General Hospital for providing support and assistance during the preparation of this evidence-based case report.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; vol 13 (1) : 94–101

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Case Report

A Free-Floating Technique Simplifies Lower Face Thread Lift for Premature Lower Face Aging: An Evidence-Based Case Report

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Abstract

Background : Skin aging is a complex biological process influenced by a combination of endogenous (intrinsic) and exogenous (extrinsic) factors. A Thread Lift is a cosmetic procedure that lifts and tightens sagging tissue while enhancing facial contours, using threads made from the same material utilized in surgical wound closure. This case report aims to present a new, simplified thread lift technique available to dermatologists today, covering preventive measures, cosmetic strategies, topical and systemic therapeutic agents, and invasive procedures.
Case : A 40-years-old man, a contractor and heavy smoker who participates in outdoor sports, is frequently exposed to the sun. He has complained of sagging in the lower cheek area for the past year. A thread lift treatment was performed. On the patient's second visit, a thread lift was conducted after marking an anchoring pattern in the retaining ligament and injecting 2% lidocaine at the entry point of the lateral face area. This was followed by tumescent anesthesia using a 25G cannula along the thread lift marking. The entry point was opened using an 18G needle, and the bevel-down thread lift was inserted above the mandibular angle into the subcutaneous layer without injuring the facial muscles as per the marking. The thread lift protocol used a thread (thread 6D cog PDO threads with needles). After the thread lift is inserted into the marionette line, pull on the entry point slowly until the thread lift elevates the epidermis to the subcutaneous layer, achieving repositioning of the lower face.
Conclusion : The free-floating Thread lift technique is an aesthetic procedure with a quick healing process and minimal side effects that help prevent premature aging, making it simple and suitable for all dermatologists to perform.

Keywords : Lower Face Aging, Premature Aging, Thread Lift, Simplify Thread Lift

p-ISSN: 2301-4369 e-ISSN: 2685-7898
https://doi.org/10.36408/mhjcm.v13i1.1377

Submitted: June 26th, 2025
Accepted: March 30th, 2026

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INTRODUCTION

Aging is the decline in function of the entire body. Any multicellular organism exposed to solar energy will undergo changes resulting in aging.[1-4] Aging can be defined as the deterioration of physiological functions necessary for survival that affects all individuals. Aging can be divided into physiological aging, which is based on increasing age, and premature aging, which is caused by extrinsic factors such as sun exposure and lifestyle.[5-7] The aging of the skin, particularly in the facial area, is a multifaceted process that involves both intrinsic and extrinsic mechanisms, leading to various structural and physiological changes in the skin. Intrinsic aging is associated with programmed aging and cellular aging, caused by endogenous oxidative stress and cellular damage.[8-10] As age increases, exposure to free radicals, sun radiation, and lifestyle choices can accelerate the aging process, resulting in what is known as premature aging. This phenomenon poses a concern for individuals who are conscious of their appearance and health.[11]

A thread lift study is a non-surgical procedure found in databases like PubMed, Google Scholar, Cochrane Library, and ScienceDirect using search keywords: "Thread lift" OR "Suture lift" and "PDO" OR "Polydioxanone" and "Lower face" OR "Jowl sagging" AND "Premature aging." It identified 450 articles, but only 13 studies are related to this topic (see Figure 1). Table 1 shows recent 5-year studies on thread lift, including criteria and outcomes. This procedure lifts drooping and aging skin while stimulating collagen production to renew the face or neck and combat early aging. It raises and firms sagging tissue, emphasizing facial contours with threads made from the same material used in surgical wound closures. When placed under the skin, the thread can tighten tissue and add volume to the area. Although various thread lift techniques are used clinically, no single method combines simplicity with effectiveness results.[1,12,13]

Therefore, we emphasize the use of a simplified free-floating thread lift technique for facial rejuvenation, focusing on thread types, patient selection, and how to

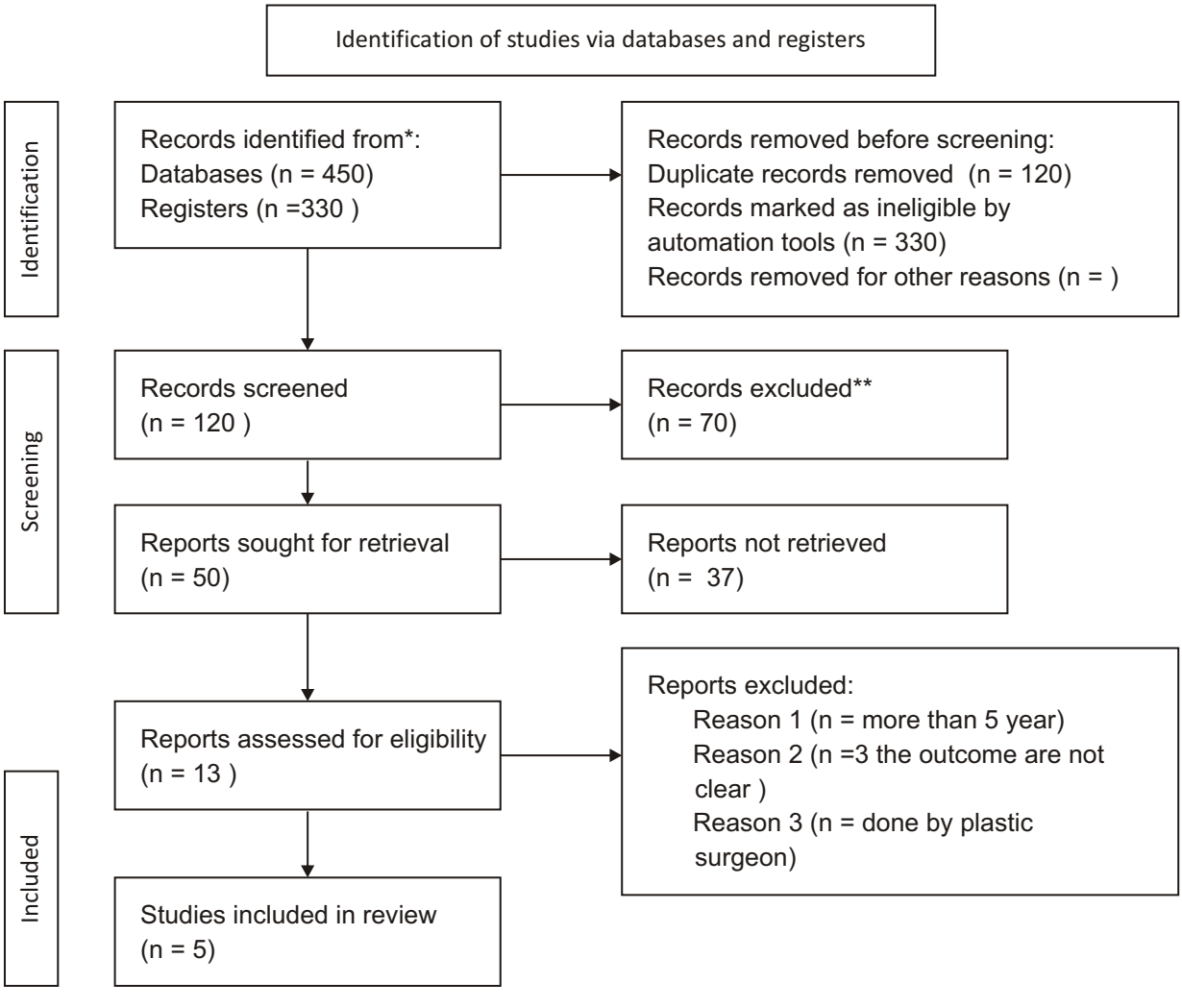


Figure 1. Flow diagram of literature searching

TABLE 1
A systematic literature review was carried out over the past 5 years

No.	Study Author & Year	Inclusion Criteria	Exclusion Criteria	Primary Outcomes
1.	Liao *et al*. (2024)	Middle-aged and elderly individuals (40-65 years) with facial skin laxity and nasolabial folds.	History of facial surgery, severe systemic diseases, or active skin infections.	Significant improvement in facial rejuvenation; combined use with fillers increased maintenance duration.
2.	Tavares *et al.* (2022)	Patients aged 3069 years with gravitational ptosis (type I, II, or III laxity).	Skin diseases, hemophilia, use of anticoagulants, or history of malignant blood diseases.	WSRS score improved from 3.88 to 2.36 after 2 years; high patient satisfaction (GAIS score 4.01).
3.	Ojha *et al*. (2025)	Patients seeking minimally invasive facial lifting using various suture materials (PDO, PLLA, PCL).	Follow-up less than 12 months or prior major facial reconstructive surgery.	Comparison of complication rates: Swelling (16%), Skin dimpling (7%), and Ecchymosis (26%).
4.	Wan *et al.* (2024)	Individuals with subzygomatic arch (lateral cheek) depression or forehead volume loss.	Previous permanent fillers, severe skin thinning, or unrealistic aesthetic expectations.	Effective volume migration and tissue displacement; successful forehead and lateral cheek augmentation.
5.	Clinical Study to Evaluate Safety and Effectiveness of Noble Lift® Lifting adsClinical	BMI 18.5–30; requiring aesthetic treatment of mid-face/lower-face with resorbable threads.	Severe malar fat sagging, resorbable fillers within 12 months, or known bleeding disorders.	Non-inferiority of new thread models; primary endpoint measured by GAIS score at month 3.

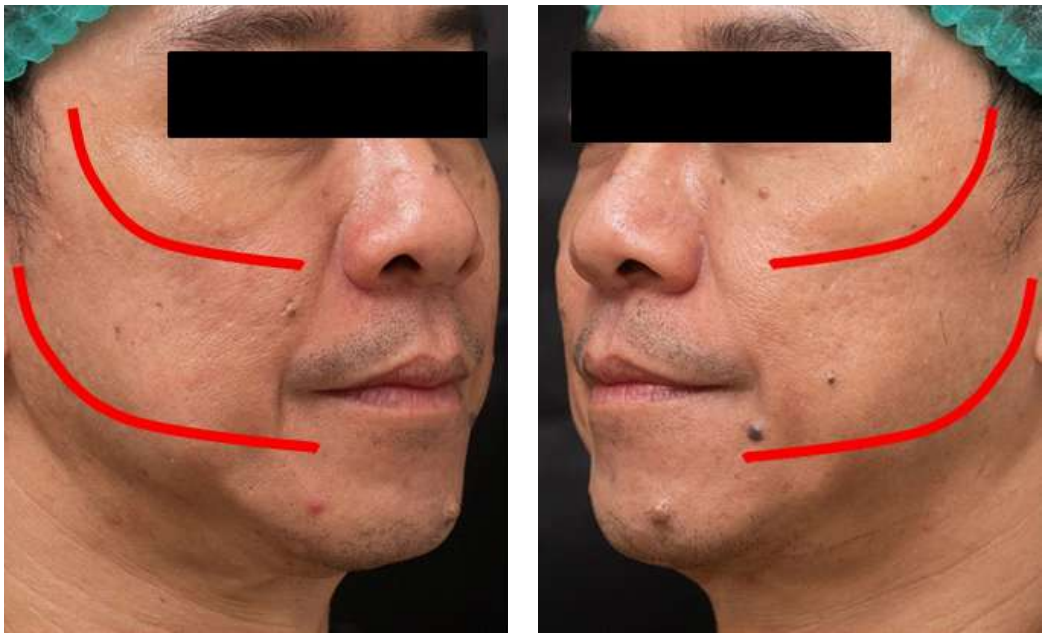
choose the right technique for individuals showing signs of premature facial aging. This case report aims to introduce a new, easier thread lift method available to dermatologists today, covering preventive measures, cosmetic strategies, topical and systemic therapeutic agents, and invasive procedures.

CASE PRESENTATION

A 40-year-old man, a contractor, heavy smoker, and outdoor sports enthusiast, is frequently exposed to the sun. He has complained of sagging in the lower cheek area for the past year (Figure 2).

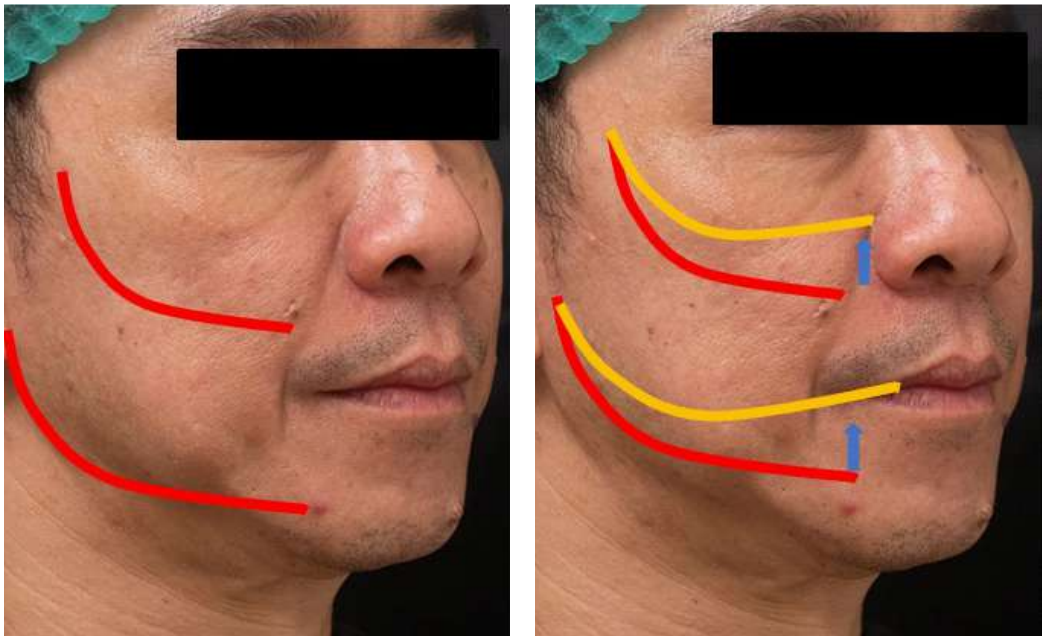
Six months before the examination, the patient practiced self-care by adjusting their diet, reducing sun exposure, and using sunscreen; however, complaints persisted. Non-invasive treatments such as laser and ultrasound have been performed, but there has been no significant improvement. Currently, the patient visits the dermatology clinic for consultation. From the consultation results, it was observed that the skin texture was widened, there were large pores, uneven skin color, hyperpigmentation, and sagging in the pre-jowl area (lower face), which are signs typically seen in facial skin aged 50 years. Facial analysis (photography in the Frankfurt position) and action planning were conducted, including advice to discontinue blood-thinning medications in preparation for the thread lift procedure. The procedure done on patient's second visit, A lower face thread lift was performed to correct premature lower facial aging characterized by pre-jowl sulcus formation, marionette line deepening, and mandibular contour laxity. Pre-procedural assessment included a comprehensive facial analysis with standardized photography obtained in the Frankfurt horizontal plane to evaluate facial symmetry, degree of soft-tissue ptosis, and lower facial contour deformities. The treatment objective was to reposition descended soft tissue in the pre-jowl and marionette regions using a superolateral lifting vector anchored to the lateral facial retaining ligament complex. The patient was advised to discontinue medications and supplements associated with increased bleeding risk, including anticoagulants, antiplatelet agents, non-steroidal anti-inflammatory drugs, vitamin E, and herbal supplements, for at least 57 days prior to the procedure. Written informed consent was obtained.

The procedure start (Figure 3) with patient's was positioned in a semi-recumbent position (30–45°) to allow optimal visualization of gravitational tissue descent and



Right Side **Left Side**

Figure 2. Premature aging of the lower face with markings (red lines) of sagging or drooping of the facial skin.



A. Marking Before **B. Target Lifting**

Figure 3. (A) Mapping with marker (red line) before the procedure, **(B)** lower face lift (yellow line) with skin tightening level (blue arrow) as the target face lift

to facilitate accurate vector planning. The treatment area, including the lateral cheek, mandibular border, and pre-jowl region, was prepared using povidone-iodine solution followed by 70% alcohol to maintain strict aseptic conditions. Facial markings were performed with the patient in an upright position. The entry point was located in the lateral facial region superior to the mandibular angle, an area considered relatively safe due to its distance from major neurovascular structures. The target zone included the marionette line and pre-jowl

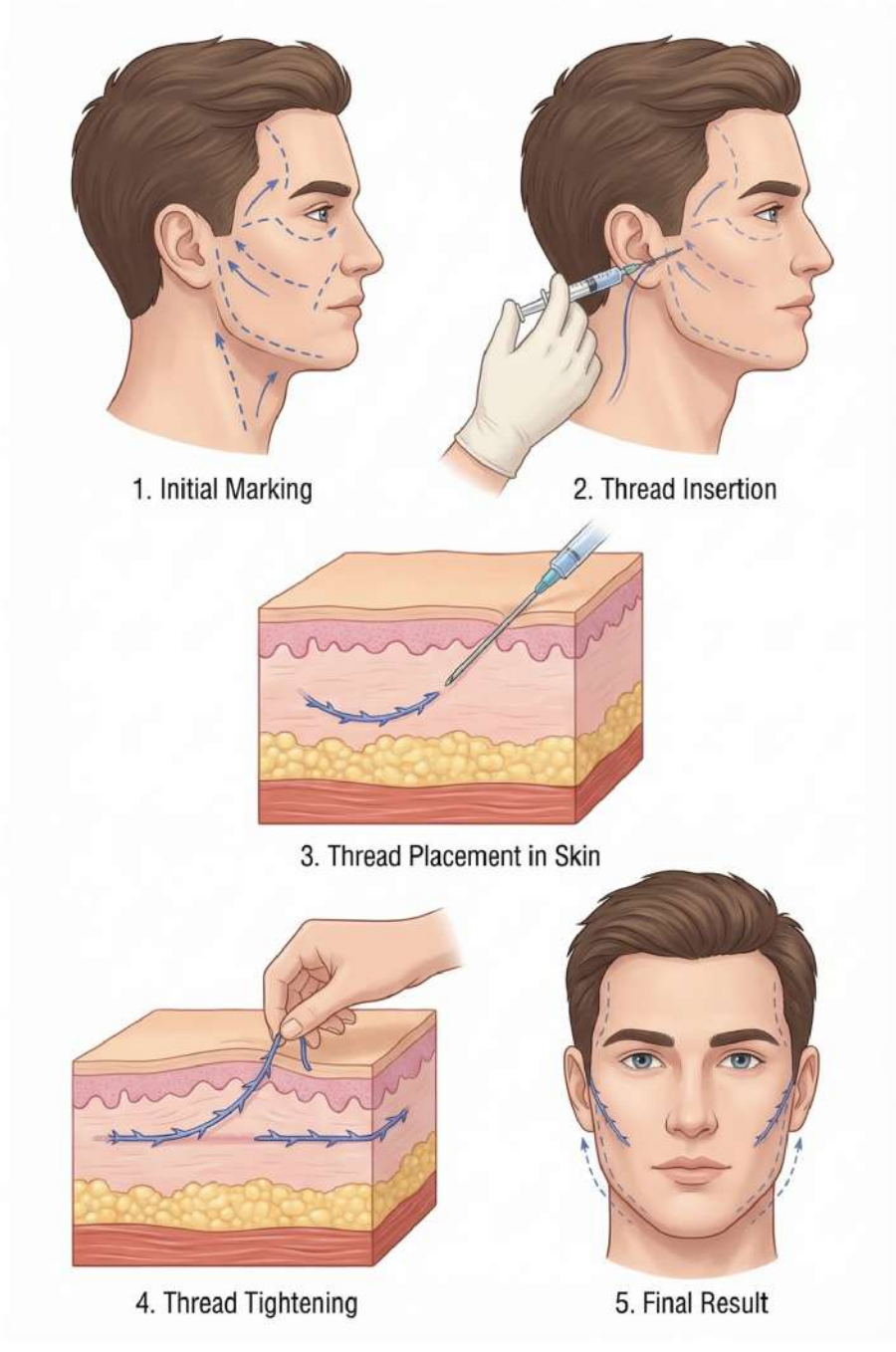


Figure 4. The illustration of "free-floating Thread lift technique Procedure" (Step-by-Step)

sulcus. The lifting vectors were designed in a superolateral direction toward the zygomatic retaining ligament and lateral temporal fascia, structures that provide strong anchoring support for mechanical lifting.

Special attention was given to avoiding critical anatomical danger zones during thread placement. The thread trajectory was planned to remain within the subcutaneous plane superficial to the superficial musculoaponeurotic system (SMAS) to minimize the risk of injury to deeper neurovascular structures. Care was taken to avoid the course of the facial artery, which typically runs along the anterior border of the masseter muscle before crossing the mandibular border toward the nasolabial fold. In addition, the insertion pathway was planned to avoid the marginal mandibular branch of the facial nerve, which runs inferior to the mandibular border and supplies the depressor muscles of the lower lip. Maintaining a superficial subcutaneous plane and lateral

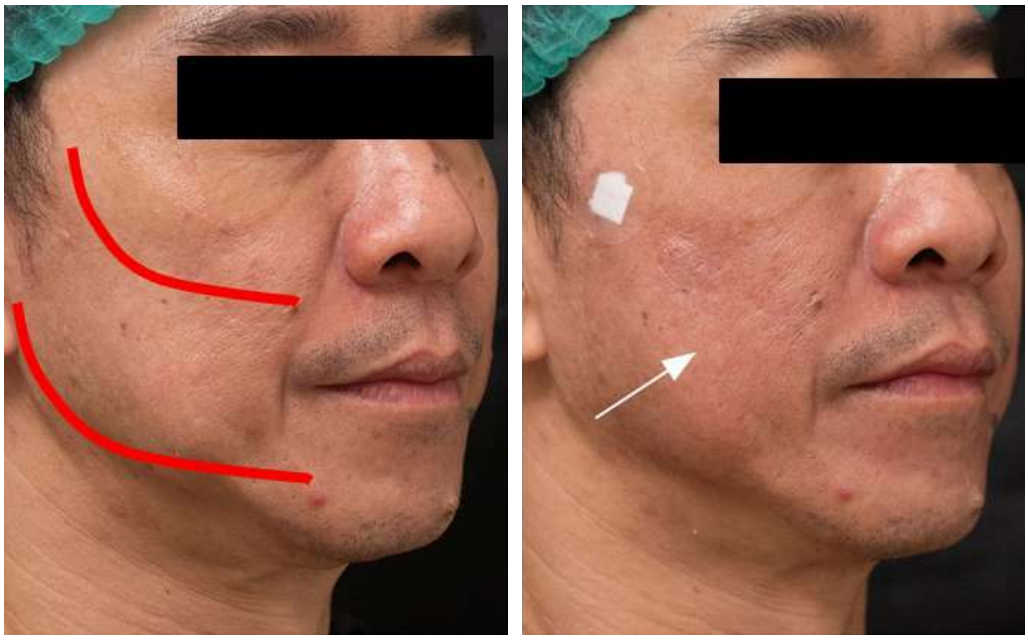


Figure 5. Before and after view of thread lift on the lower face

entry point helped reduce the risk of nerve injury and vascular complications. Topical anesthesia (Figure 3A & 3B) using lidocaine 9% cream was applied to the treatment area for approximately 10–15 minutes to reduce procedural discomfort. After removal of the topical anesthetic, local infiltration with 2% lidocaine was administered at the entry point. Tumescent anesthesia containing lidocaine was subsequently injected along the marked thread pathway using a 25-gauge cannula, providing hydrodissection within the subcutaneous layer, improving patient comfort, and facilitating atraumatic thread passage. A skin entry point was created using an 18-gauge needle, allowing smooth introduction of the thread needle into the subcutaneous tissue. The thread lift procedure used Thread 6D, a bidirectional, barbed polydioxanone (PDO) thread designed for mechanical lifting and stimulation of collagen neogenesis. Each thread measured 19–21 cm in length with an approximate needle gauge of 19G, allowing adequate reach from the lateral entry point to the marionette and pre-jowl regions. A total of two threads were inserted on each side of the lower face following the pre-marked vectors.

The thread needle was inserted through the entry point and advanced along the pre-marked path within the subcutaneous layer above the SMAS, carefully avoiding penetration into deeper muscle tissues. The thread was guided toward the marionette line and pre-jowl area using a free-floating technique, allowing the cog barbs to catch onto the fibrous septa within the subcutaneous fat. Once the thread reached the target location, the needle was removed while keeping the thread in place. Gentle tension was applied from the entry point to activate the cog barbs and lift the sagging tissues mechanically. This maneuver repositioned the soft tissue upward and outward, enhancing the contour of the jawline and reducing the prominence of the marionette line and pre-jowl depression. After achieving the desired lifting effect, the excess thread at the entry site was trimmed flush with the skin surface. Gentle manual molding of the treated area was performed to minimize irregularities and ensure smooth contouring of the lifted tissue. The patient was then asked to sit upright to evaluate the immediate lifting effect and to assess facial symmetry, skin dimpling, or tension irregularities. The same procedure was subsequently performed on the contralateral side to achieve balanced bilateral lifting. Following completion of the procedure, the treated areas were carefully examined for immediate complications, including bleeding, hematoma formation, skin dimpling, or thread extrusion. Standardized post-procedure photographs were obtained to document the immediate aesthetic outcome.

Post-procedure instructions (Figure 5) included avoiding excessive facial movements, vigorous chewing, facial massage, and strenuous physical activity for at least one week. Patients were also advised to sleep in a supine position with the head elevated and avoid external pressure on the treated areas for approximately two weeks. Follow-up visits were scheduled to monitor healing, evaluate treatment outcomes, and identify any delayed complications.

DISCUSSION

Skin aging is a complex biological process influenced by a combination of intrinsic (endogenous) and extrinsic (exogenous) factors. Premature lower facial aging is characterized by soft tissue descent, loss of skin elasticity, and the development of structural changes such as the marionette line and pre-jowl sulcus. These changes are commonly associated with intrinsic aging, environmental exposure, and lifestyle factors, including chronic ultraviolet radiation and smoking. In the present case, the patient exhibited features of lower facial aging that were disproportionate to chronological age, likely related to prolonged sun exposure and smoking, both of which contribute to collagen degradation, elastin fragmentation, and reduced dermal structural integrity.[14,15]

Thread lifting with polydioxanone (PDO) cog threads has become a minimally invasive alternative to surgical rhytidectomy for correcting mild to moderate facial ptosis. PDO threads deliver an immediate mechanical lift by engaging barbed structures within the subcutaneous fibrous septa. Besides providing mechanical support, PDO materials promote neocollagenesis, fibroblast growth, and tissue remodeling during biodegradation. The hydrolysis of PDO threads generally takes about 6–8 months, during which collagen buildup and fibrosis around the thread help maintain lifting and skin tightening effects.[16]

In this case, 6D cog PDO threads were selected because of their multidirectional barbed configuration, which offers stronger tissue anchoring and enhanced lifting ability compared to mono or smooth threads. Using bidirectional cog threads allows the barbs to engage surrounding soft tissue structures, thereby redistributing the gravitational forces responsible for lower facial sagging. Placement within the subcutaneous layer superficial to the superficial musculoaponeurotic system (SMAS) enables effective tissue repositioning while reducing the risk of injury to deeper anatomical structures. Anatomical considerations are crucial for the safety and success of thread lift procedures. The lower face contains vital neurovascular structures, including the facial artery and the marginal mandibular branch of the facial nerve. The facial artery generally runs along the anterior border of the masseter muscle before crossing the mandibular border toward the nasolabial fold, while the marginal mandibular nerve travels inferior to the mandibular border to innervate the depressor muscles of the lower lip. In this technique, the entry point was positioned in the lateral facial region above the mandibular angle, and the thread was advanced in a superficial subcutaneous plane. This approach helps reduce the risk of neurovascular injury while ensuring effective engagement of fibrous septa within the subcutaneous tissue. The lifting vectors used in this case were directed superolaterally toward the zygomatic retaining ligament complex, which provides a stable anchoring point for soft tissue suspension. Retaining ligaments of the face serve as structural support systems that connect the superficial soft tissues to deeper fascial layers and the periosteum. Utilizing these anatomical structures as anchoring points enhances the stability of thread fixation and improves the durability of lifting outcomes. The vector orientation is particularly important in the correction of pre-jowl deformity, as it allows redistribution of sagging tissue toward areas of stronger ligamentous support. The free-floating insertion technique used in this procedure enables the cog barbs to engage the fibrous septa within the subcutaneous adipose layer without rigid fixation at the distal endpoint. This technique allows gradual tissue repositioning while reducing the risk of excessive tension or skin dimpling. Following activation of the barbs through gentle traction, the lifted tissues are repositioned along the predetermined vector, resulting in improved mandibular contour and reduction of the marionette line.[17]

Previous studies have reported that thread lifting procedures using PDO cog threads are associated with high patient satisfaction and relatively low complication rates when performed with proper anatomical knowledge and technique. The most common adverse events include transient swelling, bruising, mild pain, and temporary skin dimpling. More serious complications, such as nerve injury, infection, or thread extrusion, are uncommon but may occur if the procedure is performed in an incorrect anatomical plane or near major neurovascular structures.[18–21]

Although thread lifting offers several advantages, including minimal invasiveness, short recovery time, and immediate aesthetic improvement, the longevity of results remains limited compared with surgical facelifting procedures. The durability of PDO thread lifting is influenced by multiple factors, including thread type, insertion technique, patient age, skin quality, and lifestyle factors such as smoking and sun exposure.[12,19,22–25]

CONCLUSION

Although natural aging is genetically determined, extrinsic aging can be prevented. Aesthetic dermatology should contribute to “healthy aging,” not only in cosmetic terms by attempting to erase the traces of time on the skin but also by playing an important role in preventing premature aging. This simple technique can regenerate and delay skin aging by combining knowledge of potential local and systemic therapies, instrumental devices, and non-invasive procedures. Mapping prior to implementing thread tightening procedures can boost every dermatologist's confidence and help achieve an excellent facelift without serious

complications in cases of premature lower facial aging. Overall, this case demonstrates that the use of multidirectional cog PDO threads with a superolateral vector anchored to the lateral facial retaining ligaments can provide effective correction of premature lower facial aging with minimal complications when performed with careful anatomical planning and proper technique.

ACKNOWLEDGMENTS

The figure of this manuscript was created in Illustrae.co website

CONFLICTS OF INTEREST

There are no conflicts of interest.

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Medica Hospitalia
Journal of Clinical Medicine
Med Hosp 2026; Vol 13 (1)
March 2026

AUTHOR GUIDELINE

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Research manuscript should adhere guidelines as follow:

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

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

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

Methods :
1. Explains research design, settings and time
2. Explains population and sample, sampling technique, sample size (equation doesn't need to be enclosed), inclusion and exclusion criteria.
3. For clinical trial, explains randomization and conceal allocation, and Kappa test if conducted and detailed investment
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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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Discussion :
1. Discusses all relevant findings and its association with practice. There is no redundant repetition of findings already presented in the results section.
2. Is compared with previous study findings.
3. Mentions research strengths/weaknesses and its impact on findings.

Conclusion :
1. Should answer research question
2. Should be based on research findings, not quotation
3. Can provide suggestion for future research

References :
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4. Is presented in English

Introduction :
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2. Is supported by relevant and strong references

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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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Direktorat Jenderal Pendidikan Tinggi, Riset dan Teknologi
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Kutipan dari Keputusan Direktorat Jenderal Pendidikan Tinggi, Riset dan Teknologi
Kementerian Pendidikan, Kebudayaan, Riset, dan Teknologi Republik Indonesia

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

Nama Jurnal Ilmiah

Medica Hospitalia : Journal of Clinical Medicine

E-ISSN: 26857898

Penerbit: RSUP Dr. Kariadi Semarang

Ditetapkan Sebagai Jurnal Ilmiah

TERAKREDITASI PERINGKAT 3

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

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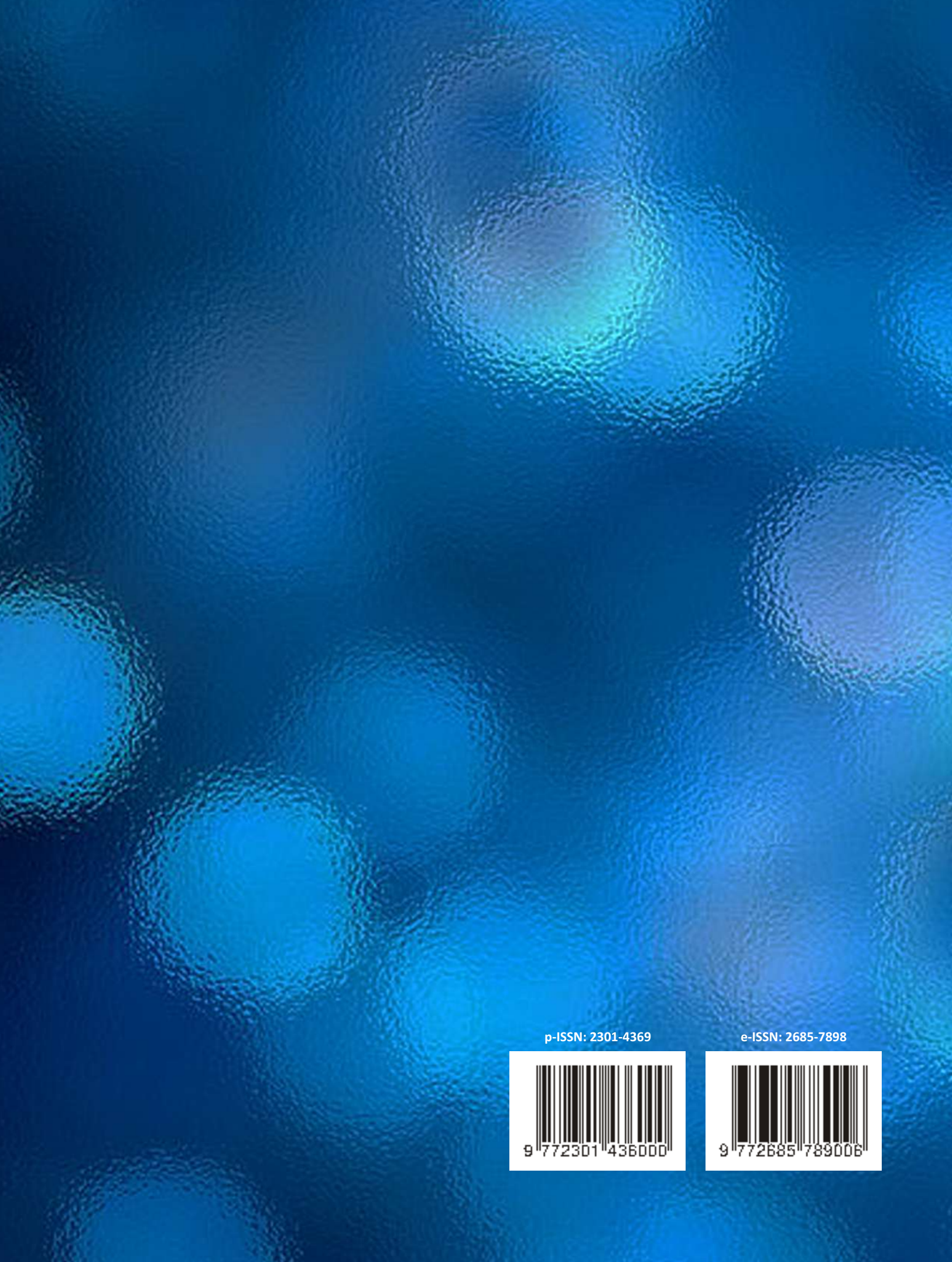

p-ISSN: 2301-4369

e-ISSN: 2685-7898