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Original Articles

Case Report

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Original Articles

269 Relationship Between Level of Simple Carbohydrate and Trans Fat Intake with Severity of Coronary Artery Stenosis Based on Gensini Score at Kariadi Hospital Semarang

Yudhanta Suryadilaga[1], Sodiqur Rifqi[1], Sefri Noventi Sofia[1], Niken Puruhita[2], Suhartono[3]
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There is a significant relationship between the amount of simple carbohydrate and trans fat intake and the severity of coronary artery stenosis based on the Gensini score.

280 Hypokalemia Correlates with Troponin Levels in Moderate-Severe COVID-19 Patients, Independent to Coagulation Status

Friska Anggraini Helena Silitonga[1], Nur Alaydrus[1], Andreas Arie Setiawan[1], Shila Lupiyatama[2], Charles Limantoro[1]
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In hospitalized patients with moderate to severe COVID-19, lower potassium levels were associated with elevated troponin, regardless of disease severity and without a detectable link to D-dimer status. These findings suggest hypokalemia may contribute to myocardial injury in COVID-19 and support regular monitoring and timely correction of electrolyte disturbances.

288 Improvement of Muscle Endurance in Men with Low Activity Levels After Above Anaerobic Threshold Exercise Intensity

Rudy Handoyo[1,4], Wahyu Wiryawan[2], Hari Hendriarti Satoto[3], Sri Wahyudati[1,4], Tanti Ajoe Kesoema[4], I Made Widagda[1,4], Erna Setiawati[4], Rahmi Isma Asmara Putri[4], Robby Tjandra[1,4], Naela Munawaroh[1,4], Aditya Paramitha Andini[1,4], Ratih Dwiratna Hakim[1,4], Arvin Manuel Wulur[4], Nura Eky Vikawati[4], Ellena Rachma Kusuma[4], Mela Kurnia Widyarini[4], Novritasari Setyaningrum[4]
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Aerobic exercise with intensity based on AT did not show significant differences in total SPPB score. However, aerobic exercise above AT showed a better improvement of muscle endurance in healthy adult men with low levels of physical activity.

296 Differences in The Severity of Diabetic Neuropathy Based on Electromyography in Type 2 Diabetes Mellitus Patients with and without Comorbidities

Dessy Natalia, Maria Belladonna Rahmawati, Maria Immaculata Widiastuti Samekto, Endang Kustiowati, Herlina Suryawati, Elta Diah Pasmanasari
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There is a difference in the severity of diabetic neuropathy based on EMG between patients with type 2 DM without comorbidities, with comorbid hypertension and with comorbid hypertension and hyperlipidemia. The more comorbidities, the greater the severity of diabetic neuropathy.

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Editorial

This issue covers studies ranging basic to applied science, based on scientific research. Classic topics are still relevant for discussion in research. Tuberculosis (TB), COVID-19, and urinary tract infections (UTIs) are three infectious conditions that remain major challenges in healthcare services around the world, including Indonesia. Although there were difference in their causes and transmission routes, all three have a significant impact on community morbidity and mortality, and demand serious attention from healthcare professionals and researchers.

TB, as a chronic infectious disease, continues to cause high morbidity, especially in countries with limited resources. The COVID-19 pandemic has also had a significant impact on global healthcare systems, including reducing access to and the smoothness of diagnosis and treatment.

Meanwhile, UTIs are the most common infections, especially among hospitalized patients and vulnerable populations. This condition not only worsens patients' quality of life but also carries the risk of serious complications if not managed appropriately.

The contributions from researchers, especially from the academic community, still greatly needs in Indonesia until now. Research ideas and techniques abound within this field. Our current challenge is to compile the research into a report that adheres to the principles, and disseminate in scientific publications.

Happy researching,
Editor

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OPEN ACCESS

Original Article

Association of Premedication before Blood Transfusion with Transfusion Reactions in Mohammad Hoesin Hospital Palembang

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Abstract

Background : Premedication before blood transfusion is frequently used in clinical settings, albeit its effectiveness has not been shown. Premedication is used to stop transfusion-related fever and allergy. Unwanted or unanticipated consequences connected to the administration of unstable blood products are known as transfusion reactions.
Aims : The aim of this study is to find out the association of premedication before blood transfusion with transfusion reactions.
Methods : This study is an observational analytic study with cross-sectional design, the data obtained from Mohammad Hoesin Hospital Palembang from January 1st, 2020 to December 31st, 2021.
Results : 43 patients out of 73 samples did not receive premedication before the transfusion procedure, 8 patients (18.6%) experienced transfusion reactions, and 35 patients (81.4%) did not. 35 patients who received premedication, 2 patients (5.7%) experienced transfusion reactions, and 33 patients (94.3%) did not. The incidence of transfusion reactions at Mohammad Hoesin Hospital Palembang in the 2020–2021 period was not significantly associated with pre-transfusion premedication ($p = 0.171$). It is also not associated with blood transfusion history ($p = 0.426$), blood components ($p = 0.793$), or gender ($p = 1.000$).
Conclusion : Based on this finding, there is no significant association between premedication before blood transfusion and the transfusion reactions during period of 2020–2021 at Mohammad Hoesin Hospital Palembang.

Keywords : pre-transfusion premedication; transfusion reaction; blood transfusion.

INTRODUCTION

Blood transfusion is a life-saving procedure in which a patient receives blood or blood products to replace blood lost as a result of surgery, trauma, or other illnesses that result in low blood volume or anemia.[1] Blood transfusions may be essential when a patient has experienced significant blood loss due to trauma or surgery, or when their body isn't making enough blood components. However, blood transfusions carry the risk of acute transfusion reactions.[2] Transfusion reactions are unexpected or unwanted events associated with the administration of unstable blood products. Acute transfusion reactions are categorized into two categories, immune-mediated reactions, which involve the formation of antigen-antibody complexes and non-immune-mediated reactions.[3] The most frequent acute transfusion reactions are allergy responses and fever non-hemolytic transfusion reactions (FNHTR), which are also the least harmful transfusion reactions. Within three hours after receiving a transfusion, blood donor recipients with FNHTR experience fever (defined as a temperature rise of ≥1□ above normal) and/or rigors. Within a few hours following transfusion, urticaria or other rashes, hives, wheezing, or angioedema are the most typical symptoms of allergic responses.[4,5]

According to data gathered by Switzerland's Schweizerische Heilmittelinstitut (Swissmedic), 2,032 (0.74%) complaints of adverse transfusion reactions were made for the 275,343 blood products (frozen plasma, platelet concentrates, and stored blood cells) that were transfused in 2020.[6] Among these, 3 fatalities (or 0.001% every transfusion conducted) resulted from 1,910 (0.69%) responses identified as probable transfusion reactions and 1,486 (0.54%) reactions classified as severe or severe reactions.[6] Further research conducted in 2020 using data gathered by the German Paul Ehrlich Institute (PEI) revealed that 4,400,164 blood products were transfused, with 921 (0.02%) complaints of potentially significant transfusion reactions. In this instance, the reports had no information on potential adverse effects; however, 621 (0.014%) reports showed a causal association between the delivery of blood components and 7 (0.0002%) fatalities per transfusion.[7]

Physicians commonly prescribe premedication before blood transfusion because it is believed to reduce the incidence of transfusion reactions.[8] Premedication before blood transfusion refers to the administration of medications prior to transfusion with the aim of preventing or reducing the severity of transfusion-related adverse reactions.[9] Premedication before transfusion is often used, despite limited evidence supporting its effectiveness.[8,10] Based on previous recommendations, premedication with diphenhydramine and/or acetaminophen is a standard practice to avoid moderate allergic transfusion responses and feverish nonhemolytic transfusion reactions. Randomized-controlled trials, however, have not demonstrated any advantage or effect of premedication.[11] In some developing countries, despite literature supporting the idea that premedication should only be given when transfusion reactions occur, chlorpheniramine maleate and acetaminophen are also used as premedication for preventing transfusion reactions from pre-storage leukoreduced, post-storage leukoreduced, or non-leukoreduced blood products.[12,13]

The benefit of administering premedication before transfusion remains questionable for patients.[8] Research on the use of premedication before blood transfusion to prevent transfusion reactions is limited and has never been conducted in Palembang. Therefore, this research is expected to analyze the association of premedication before blood transfusion with the transfusion reactions in Palembang and can be a reference or consideration in giving premedication before blood transfusion to patients who have a history of transfusion reactions in Palembang, especially at Mohammad Hoesin Hospital Palembang.

METHODS

Study Design

This study used observational analysis and cross-sectional design. It was conducted in the Medical Records Installation and Blood Transfusion Unit of Mohammad Hoesin Hospital Palembang. This research was conducted during September 2022 – December 2022 and have obtained ethical approval from the Faculty of Medicine, Sriwijaya University, with the number 261-2022.

Sampling

Data samples was collected with consecutive sampling in January 2020 – December 2021, involved patients who underwent blood transfusion at Mohammad Hoesin Hospital. The minimum sample size to meet the objectives of this study was calculated using the following formula:

$$n = \frac{Z_{\alpha}{}^{2} PQ}{d^{2}}$$

Based on the formula, the sample size required in this study is 67. The inclusion criteria were patients who received blood transfusions in the period January 1st, 2020 – December 31st, 2021 taken from the Medical Records Installation and Blood Transfusion Unit of Mohammad Hoesin Hospital, Palembang. Meanwhile, the exclusion criteria were (1) pediatric patients who received blood transfusions, and (2) incomplete, defective, and/or damaged patient medical record data.

In this study, the variable was catagories into premedication and non-premedication, for the variable

of the reaction of tranfusion is present and absent. The premedication given is diphenhydramine and dexamethasone, meanwhile the tranfusion reactions are all adverse side effects or adverse reactions to transfusions that often occur during or shortly after transfusion. All variables are taken from the information in the medical record.

Statistical Analysis

The collected data were processed using IBM SPSS Statistic 24 (IBM, Armonk, United States). All data is presented on a categorical scale. The data were presented descriptively using univariate analysis and then continued with bivariate analysis to determine the association between variables. The test that will be used in this study is the chi-square test.

RESULTS

The distribution of patients receiving blood transfusions based on sociodemographic factors showed in Table 1. Of the 78 patients, the subjects were predominantly aged 50–59 years (29.5%) and female (64.1%).

In Table 2, there are distribution of patients receiving blood transfusions based on blood type. The results showed that the most commonly found blood type was B (29.5%), although it was not very different from the other blood types.

Table 3 shows patients receiving blood transfusions based on blood components. The results show that the blood component most frequently used by patients is PRC (87.2%).

Table 4 shows patients who received blood transfusions based on a history of blood transfusions. Most of patients (68%) never had a history of previous transfusion.

In Table 5, there are data of patients who received blood transfusions based on a history of blood transfusions. The results showed that 78 people (100%) did not have a history of previous transfusion reactions.

Table 6 shows patients receiving blood transfusions based on the provision of premedication. It

TABLE 1
Distribution of patients receiving blood transfusions based on sociodemographic factors

Variables	Number (n = 78)	Percentage (%)
Age		
<20	5	6.4
20–29	7	9.0
30–39	14	17.9
40–49	11	14.1
50–59	23	29.5
≥60	18	23.1
Gender		
Male	28	35.9
Female	50	64.1

TABLE 2
Distribution of patients receiving blood transfusions based on blood type

Blood Type	Number (n)	Percentage (%)
A	21	26.9
B	23	29.5
O	21	26.9
AB	13	16.7
Total	78	100

TABLE 3
Distribution of patients receiving blood transfusions based on blood components

Blood Components	Number (n)	Percentage (%)
PRC	68	87.2
WE	3	3.8
TC	4	5.1
TP	2	2.6
FFP	1	1.3
Total	78	100

TABLE 4
Distribution of blood recipient patients based on blood transfusion history

Blood Transfusion History	Number (n)	Percentage (%)
0	53	68.0
1–2 times	19	24.4
3–4 times	3	3.8
≥5 times	3	3.8
Total	78	100

TABLE 5
Distribution of patients receiving blood transfusions based on a history of transfusion reactions

History of Transfusion Reaction	Number (n)	Percentage (%)
Positive	0	0.0
None	78	100.0
Total	78	100

was found that the majority of patients receiving blood transfusions were not given premedication (55.1%). All patients who received premedication were from the internal medicine ward, whereas those who did not receive premedication were from the surgical, obstetrics and gynecology (OBGYN), ear nose and throat (ENT), and emergency departments.

Table 7 shows patients who received blood transfusions based on the incidence of transfusion reactions. It was found that the majority of patients receiving blood transfusions never experience transfusion reactions before (87.2%).

Table 8 shows the association between several variables and transfusion reaction. The results of this study were analyzed using the chi-square statistical test. There is no association of gender, blood type, blood components, history of transfusion reactions, and premedication with transfusion reactions. In the other hand, there is association between the age of patients receiving blood transfusions and the transfusion reactions.

DISCUSSION

The distribution of patients receiving transfusions based on the most age was the age group 50–59 years as many as 23 people (29.5%). This is in line with a study conducted by Purwati *et al* at UTD RSUP Dr. M. Djamil Padang which showed that the distribution of the largest age group was the age group >50, with a total of 56 people (54.3%).[14] In contrast to the research conducted by Kohorst *et al* in one of the research centers in America

TABLE 6
Distribution of patients receiving blood transfusions based on the provision of premedication

Premedication	Number (n)	Percentage (%)
Positive	35	44.9
None	43	55.1
Total	78	100

TABLE 7
Distribution of patients receiving blood transfusions based on the incidence of transfusion reactions

Transfusion Reaction History	Number (n)	Percentage (%)
Positive	10	12.8
None	68	87.2
Total	78	100

which showed that the distribution of patients receiving blood transfusions based on age was the largest age group 19–25 years with a total of 84 people (41.8%).[15] This could be due to the increased risk of diseases requiring blood transfusions above the age of 50 years. The presence of conditions or diagnoses such as bleeding or cancer in adult patients over 50 is increased so that patients receiving transfusions is also increased.[16]

The patients receiving transfusions was mostly female patients as many as 50 people (64.1%). This is in line with a study conducted by Purwati *et al* at UTD Dr. M. Djamil Hospital Padang which showed that the distribution of the most gender was female, as many as 63 people (61.6%).[14] While this is not in line with a study conducted by Kohorst *et al* in one of the research centers in America which showed that the distribution of patients receiving blood transfusions based on gender was mostly male, with a total of 115 people (57.2%).[15]

Based on the literature, the exact reason for the influence of gender on the need for and consideration of blood transfusion, which is usually given to treat symptoms such as anemia, has not been determined.[17] However, it is possible that gender influences the number of blood transfusion distributions due to clinical influences such as anemia, which usually has level of hemoglobin level <12 g/dL in females and <13 g/dL in males, causing more female than male transfusion patients based on this classification because females have a lower normal lower limit than males.[18]

The most commonly found blood type was B (29.5%), although it was not very different from the other blood types. This is not in line with study by Grandi *et al* conducted in Brazil which shows that the distribution of transfusion recipients based on the most blood groups is blood group O with a total of 762 people (49.2%).[19] This is different from the study conducted by Purwati *et al* at UTD RSUP Dr. M. Djamil Padang which shows that the distribution of patients receiving blood transfusions based on the largest blood group is group A, with a total of 39 people (37.8%).[14] There is no definite basis between the number of patients receiving transfusion based on blood type because transfusion itself is given according to the indication of the patient's condition, such as in patients with acute or active bleeding, patients with symptoms associated with anemia (eg, dyspnea on exertion, weakness, tachycardia), and patients with hemoglobin level <8 g/dL. So, there is no direct impact on the distribution of patients by blood type. However, there are blood groups such as blood group O, which is a universal blood group, which indirectly makes the number of patients receiving transfusions with blood group O increase.[20]

The distribution of the most accepted blood components was packed red cell (PRC) as many as 68 recipients (87.2%). This is in line with research conducted by Grandi *et al* conducted in Brazil which shows that the distribution of patients receiving transfusions based on the most blood components is the PRC blood component as many as 1,122 people (72.5%).[19] Research by Rujkijyanont *et al* in one of the hospitals in Thailand showed different result, that the distribution of patients receiving transfusions based on the most blood components was the blood component of leukocyte poor packed red cell (LPRC) as many as 99 people (67.4%).[12] Packed red cells (PRC) can be transfused to individuals who have or are at high risk of developing symptomatic anemia in order to enhance their ability to transport oxygen.[21] According to US guidelines PRCs are

TABLE 8
The association of sociodemographic factors, blood type, blood components, transfusion history, premedication before blood transfusion with the incidence of transfusion reactions

Variables		Transfusion Reaction				Total n (%)	*p* value	95% CI	
		Yes		No					
		n	%	n	%			Lower	Upper
Gender	Male	3	10.7	25	89.3	28 (100)	1.000	0.175	3.110
	Female	7	14.0	43	86.0	50 (100)			
	Total	10	12.8	68	87.2	78 (100)			
Age	<20	3	60.0	2	40.0	5 (100)	0.021		
	21–29	0	0.0	7	100.0	7 (100)			
	30–39	2	14.3	12	85.7	14 (100)			
	40–49	0	0.0	11	100.0	11 (100)			
	50–59	2	8.9	23	91.3	23 (100)			
	≥60	3	16.7	18	83.3	18 (100)			
	Total	10	12.8	68	87.2	78 (100)			
Blood Type	A	4	19.0	17	81.0	21 (100)	0.744		
	B	3	13.0	20	87.0	23 (100)			
	O	2	9.5	19	90.5	21 (100)			
	AB	1	7.7	12	92.3	13 (100)			
	Total	10	12.8	68	87.2	78 (100)			
Blood Components	PRC	10	19.0	58	81.0	68 (100)	0.793		
	WE	0	0.0	3	100.0	3 (100)			
	TC	0	0.0	4	100.0	4 (100)			
	TP	0	0.0	2	100.0	2 (100)			
	FFP	0	0.0	1	100.0	1 (100)			
	Total	10	12.8	68	87.2	78 (100)			
Blood Transfusion History	0 times	8	15.1	45	84.9	53 (100)	0.426		
	1–2 times	1	5.3	18	94.7	19 (100)			
	3–4 times	1	33.3	2	66.7	3 (100)			
	≥5 times	0	0.0	3	100.0	3 (100)			
	Total	10	12.8	68	87.2	78 (100)			
Premedication	Non-premedicated	8	18.6	35	81.4	43 (100)	0.171	0.52	1.341
	Premedication	2	5.7	33	94.3	35 (100)			
	Total	10	12.8	68	87.2	78 (100)			

transfused if hemoglobulin is at 7 g/dL in asymptomatic patients or in patients with suspected anemia. Additionally, guidelines suggest a threshold of 8 g/dL for individuals undergoing orthopedic surgery or those with coronary artery disease.[22] This is why PRC is used more frequently than other blood components.

Most of patients in this study (68%) never had a history of previous transfusion. This is different from a

study conducted by Sanders *et al*. in the United States, which showed that the largest group of patients receiving blood transfusions were those with a prior history of transfusion, totaling 3,429 individuals (43.4%).[16] This is also different from the research conducted by Purwati *et al* at UTD RSUP Dr. M. Djamil Padang which shows that patients receiving blood transfusions based on the history of blood transfusions are the largest group of patients who have had previous transfusions before as many as 60 people (58.2%).[14] In theory, the frequency of a patient's blood transfusion history depends on their clinical diagnosis. Conditions such as thalassemia and hemophilia require patients to undergo regular transfusions, which consequently leads to a higher number of transfusions over time.[23,24] In this study, the majority of patients were found to be anemic and/or experiencing bleeding, which explains the high number of patients who had never received a blood transfusion before.

The majority of patients in this study were not given premedication (55.1%). This contrasts with a study conducted by Sanders *et al*. involving 7,900 transfusion recipients at a pediatric cancer center in the United States. The study showed that the highest proportion of transfusion reactions occurred among patients who had received premedication, totaling 5,379 individuals (67%).[16] However, this is consistent with a study conducted by Rujkiyanont *et al*. involving 147 transfusion recipients at a hospital in Thailand, which found that the largest proportion of patients, 74 individuals (50.34%), had not received premedication prior to transfusion.[12] In theory, the use of premedication prior to blood transfusion remains controversial. In the United States, premedication, particularly with antipyretics and antihistamines, is commonly administered to prevent transfusion reactions such as fever and urticaria. One large American hospital, for example, reported a premedication rate of 80%. In contrast, a healthcare facility in Canada reported a reduction in premedication use from 73% to 50% following the implementation of institutional guidelines.[11,25]

Among the 78 transfusion recipients, 68 patients (87.2%) never experienced any transfusion reactions. This is consistent with research conducted by Sanders *et al*. on transfusion recipients in the United States, which showed that the majority of patients, as many as 7,841 individuals (98.9%), did not experience transfusion reactions.[16] This is also consistent with research conducted by Rujkijyanont *et al*. at a hospital in Thailand, which showed that the majority of transfusion recipients, as many as 120 individuals (81.6%), did not experience transfusion reactions.[12] Epidemiologically, acute transfusion reactions occur in approximately 1 in 70,000 blood product transfusions. Because most patients do not exhibit symptoms, delayed transfusion reactions can be difficult to detect and are therefore underreported, making their true incidence unclear. Studies on delayed transfusion reactions vary widely in scope, with estimates ranging from approximately 1 in 800 to 1 in 11,000 transfusions. The frequency of non-immune hemolytic reactions is also uncertain, although they are believed to be relatively rare.[26]

There is significant association between age and transfusion reactions in this study. This is consistent with a study conducted by Kohorst *et al*. at, which demonstrated a significant association between age and the incidence of transfusion reactions.[15] It was reported that transfusion reactions occurred in only 2% of the general adult patient population. However, the profile of transfusion reactions may differ in immunocompromised populations.[24] In another theory, there are parameters associated with the risk of transfusion-associated circulatory overload (TACO) which are reduced cardiac and renal function, compensatory anemia, pre-existing positive fluid balance, plasma ordered to reverse anticoagulation, cancer diagnosis, and extreme age (people aged <25 or aged >74). So it can be said that younger patients and elderly patients are more susceptible to transfusion reactions such as TACO.[21]

The finding in this study showed no significant association between gender and transfusion reactions. Study conducted by Rujkijyanont *et al*. found that delayed transfusion reactions, particularly in the form of urticarial rash, occurred significantly more often in women than in men. This difference is likely attributed to the influence of estrogen on enzymes lining the blood vessels, which leads to increased nitric oxide production and may result in more prolonged and severe allergic reactions.[12]

There is no significant association between blood component and transfusion reaction. The findings of this study differ from those of a study by Sanders *et al*. conducted at a hospital in the United States, which found a significant association between premedication and the occurrence of transfusion reactions.[16] An adverse reaction or effect is an undesirable response or effect in a patient that is temporarily associated with the administration of blood or blood components.[3] Blood components should be processed from aseptically collected blood from donors who have been evaluated and meet eligibility criteria. The quality of blood components should be ensured through monitoring at all stages from donor selection to delivery at the hospital. The various blood components that can be transfused alone consist of whole blood, PRC, platelets, FFP, cryoprecipitate, apheresis platelets, and apheresis plasma.[27]

No significant association also found between blood transfusion history and transfusion reaction. The results of this study differ from those of Sanders *et al*., conducted at a hospital in the United States, which reported a significant association between a history of blood transfusion and transfusion reactions. Fever and

allergic reactions were more common among individuals with a limited history of blood transfusions and those who received transfusions in general inpatient units. Additionally, the study noted that many of the observed findings could not be fully explained by the current understanding of the pathophysiology of transfusion reactions.[16] History of blood transfusions may increase the risk of delayed hemolytic transfusion reactions (DHTRs), which are typically triggered by immune response to foreign red blood cell antigens from prior exposures, such as pregnancy or previous transfusions. [2]

In this study, there is no significant association between premedication before transfusion and the transfusion reactions (p = 0.171; p > 0.05). The results of this study are consistent with Sanders *et al*., who reported no significant association between premedication with acetaminophen and the incidence of transfusion reactions (p = 0.896; p > 0.05). The same study also found no significant association between premedication with diphenhydramine and the incidence of transfusion reactions (p = 0.054; p > 0.05).[16] Premedication before blood transfusion refers to the administration of medications prior to transfusion with the aim of preventing or reducing the severity of transfusion-related adverse reactions.[9] Premedication before blood transfusion is commonly administered clinically despite lack of evidence of its efficiency.[8] Premedication with acetaminophen and diphenhydramine was no more effective than administering a placebo in preventing transfusion responses, according to a comprehensive analysis that included randomized trials. Some retrospective investigations on premedication have produced contentious findings.[11,28]

Theoretically, the purpose of pre-transfusion premedication is to prevent fever, pruritus, and urticaria. The medication for premedication itself is administered intravenously either before or 30 minutes before transfusion. In Japan, institutional norms have not been created, and both inpatients and outpatients are premedicated in the same manner. Most experts in Japan recognize that premedication is necessary and efficient in preventing transfusion reactions.[28] The commonly used premedication is antihistamine and hydrocortisone as pre-transfusion premedication despite the lack of concrete evidence for its use.[28] This is not much different in Mohammad Hoesin Hospital where internal medicine ward patients who receive blood transfusion are given diphenhydramine and dexamethasone as pre-transfusion premedication according to the provisions of the standard operating procedure of blood transfusion in the internal medicine department.

Antihistamines, such as diphenhydramine, are commonly used as premedication before blood transfusions due to their ability to inhibit the effects of histamine, a key effector molecule involved in allergic reactions. Histamine, also known as β-aminoethyl imidazole, plays a central role in allergic transfusion reactions (ATRs) by contributing to symptoms such as flushing and tissue edema, which result from the dilation of small blood vessels and increased vascular permeability. However, it is important to recognize that histamine is only one of several bioactive mediators released by activated mast cells during an allergic response. Other substances, including leukotrienes and kinins, also contribute significantly to the overall reaction. Therefore, while antihistamines can partially alleviate allergic symptoms by targeting histamine pathways, they may not fully prevent all manifestations of ATRs due to the involvement of additional mediators.[25] It also should be noted that premedication, such as diphenhydramine, can cause side effects and may lead to significant impairment. Diphenhydramine crosses the bloodbrain barrier and exerts both anticholinergic and antihistaminic effects. These actions commonly result in drowsiness, decreased alertness, impaired cognitive function, and, in rare cases, restlessness and anxiety.[10,16,25]

Patients with a history of transfusion reactions are often prescribed premedication in an attempt to reduce the likelihood of future reactions. However, previous studies have shown no significant reduction in reaction rates with the use of premedication, even among individuals with a history of two or more transfusion reactions. Therefore, routine premedication in such cases is not recommended.[25] This is in line with this study that the incidence of transfusion reactions is not affected by the use of pre-transfusion medication.

A retrospective study by Sanders *et al*. reported a non-significant increase in the risk of transfusion reactions––such as fever and allergic responses––associated with the use of pre-transfusion medication, particularly acetaminophen and diphenhydramine. The study found no evidence that premedication effectively prevents transfusion reactions and noted that the overall incidence of febrile and allergic reactions is very low. However, the same study suggested that premedication may still be appropriate for high-risk individuals, such as those with a history of severe or unpredictable reactions.[16]

CONCLUSION

This study found no significant association between premedication before blood transfusion and transfusion reactions. These findings challenge the routine use of premedication in all transfusion recipients, particularly given the low overall rate of allergic and febrile transfusion reactions observed. Although premedication is often administered with the intention of preventing adverse reactions, the lack of clear clinical benefit, combined with the potential for medication-related side effects, calls into question its indiscriminate use in

standard transfusion protocols. Transfusion practices should be guided by evidence and individualized risk assessment rather than tradition or routine. Limiting premedication to high-risk patients, such as those with a documented history of severe or unpredictable transfusion reactions, may improve patient care and reduce unnecessary medication exposure.

CONFLICT OF INTEREST

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

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Original Article

Comparison of Genotypic (t-NGS) and Phenotypic Results for *Mycobacterium tuberculosis* Identification and Drug Susceptibility Testing (DST) against Tuberculosis

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Abstract

Background : Accurate identification and drug susceptibility testing are crucial for tuberculosis eradication and treatment, but conventional methods require over four weeks to complete. Targeted Next Generation Sequencing (t-NGS) is a promising alternative that provides results in just four days, potentially replacing traditional methods. However, the concordance between genotypic and phenotypic methods has not been widely reported.
Aims : This study aims to see the concordance between phenotypic and genotypic methods for identifying *Mycobacterium tuberculosis* and determining drug susceptibility.
Methods : Sputum samples were collected from Balai Besar Laboratorium Kesehatan Masyarakat (BBLKM) Makassar from June 2024 until July 2024. *M. tuberculosis* DNA was extracted using the Qiagen DNA mini kit, amplified with Deeplex® Myc-TB by Genoscreen, and prepared with Illumina DNA Prep. t-NGS was performed on the MiSeq Illumina platform, and sequencing results were analyzed with Deeplex® Myc-TB by Genoscreen. A comparison of genotypic and phenotypic results (Culture and Drug Sensitivity Test) was conducted using SPSS.
Results : Discrepancies were noted between phenotypic and genotypic results for two samples (Samples 16 and 18), where phenotypic results indicated non-tuberculous mycobacteria (NTM) and genotypic results identified *M. tuberculosis*. These discrepancies were not statistically significant ($p>0.05$). Additionally, a minor discrepancy was observed in isoniazid results for one sample (Sample 2), but the statistical result is not significance ($p>0.05$).
Conclusion : t-NGS is a promising alternative to conventional methods due to its shorter testing time and capability to identify novel mutations, with discrepancies compared to phenotypic results being statistically insignificant. However, its higher cost and the need for specialized expertise limit its accessibility to some laboratories.

Keywords: genotypic, *Mycobacterium tuberculosis*, phenotypic, sequencing, t-NGS

INTRODUCTION

The accurate identification of Mycobacterium tuberculosis *(M. tuberculosis)* and testing for drug susceptibility are crucial components in the diagnosis, treatment, and management of tuberculosis (TB).[1–3] TB remains one of the most pressing public health challenges globally. According to the World Health Organisation (WHO), an estimated 10 million people fell ill with TB every year, and about 1.5 million people died from the disease.[4] Indonesia is among the top two countries in the world with the highest TB burden, contributing significantly to the global case load with an estimated 969,000 new TB cases in 2022 alone.[5]

Conventional methods for TB identification and drug susceptibility testing, such as culture and phenotypic drug susceptibility testing (DST), often require significant time, usually exceeding 4–13 days.[6] This lengthy process can hinder timely diagnosis and treatment initiation, potentially worsening patient outcomes and contributing to the spread of the disease. In contrast, novel approaches such as *targeted Next-Generation Sequencing* (t-NGS) offer a promising alternative, drastically reducing diagnosis time to just 3–4 days.[6,7] This accelerated method has the potential to replace conventional techniques, providing healthcare professionals with crucial information more quickly.

Although genotypic methods such as t-NGS have shown great potential, inconsistencies remain regarding their concordance with phenotypic methods in identifying resistance to various anti-TB drugs. Previous studies have reported variable levels of agreement, often affected by mutation diversity, heteroresistance, lineage differences, and drug-specific resistance mechanisms. Moreover, most existing research has been conducted in high-resource settings or in populations with specific resistance patterns, limiting the generalizability of their findings to countries with a high TB burden such as Indonesia.

This highlights a critical research gap: comprehensive comparative data evaluating the concordance of phenotypic and genotypic DST specifically within the Indonesian context––where the burden of TB and drug-resistant TB is substantial––remain limited. The novelty of this study lies in its systematic assessment of both phenotypic and genotypic results using t-NGS within a high-burden, real-world clinical setting, providing context-specific evidence that is currently lacking in the literature. By examining concordance patterns across multiple drug classes, this study offers new insights into the reliability, strengths, and limitations of t-NGS for routine diagnostic use, particularly in settings where rapid and accurate DST results are urgently needed.

This research therefore aims to bridge the existing knowledge gap and contribute evidence that may support the broader implementation of genotypic DST approaches in national TB control strategies.

METHODS

Only sputum samples that had undergone phenotypic testing were collected. To be eligible, the samples had to meet several criteria: they had to be purulent, have a minimum volume of 500 µL, and must have undergone identification and drug susceptibility testing using conventional methods, as recorded in secondary data from the SITB database. Samples were excluded if they contained insufficient DNA, indicated by a quantification result of less than 0.1 ng/µL.

Sputum that had undergone phenotypic testing were collected from the Tuberculosis Laboratory at Balai Besar Laboratorium Kesehatan Masyarakat (BBLKM) Makassar from June 2024 until July 2024. Out of 24 sputum samples extracted, only 13 were suitable for testing (DNA quantification ± 0.1 ng/µl). Of these, 11 sputum samples were positive by microscopy, while 2 were negative by microscopy but positive by culture for non-*Mycobacterium tuberculosis* (NTM).

Five hundred microliters of sputum were placed in a microtube, then this tube was placed on a heat block at 95°C for 30 minutes. After that, the sputum was centrifuged at 3000 g for one minute. The supernatant was discarded, and the pellet was extracted to obtain the pure bacterial genomic DNA. The extraction was performed using a Qiagen DNA Mini Kit (Qiagen) according to the manufacturer's instructions, with the final elution of 60 µl and stored at -20°C until use.

DNA quantification was performed using the Qubit® 1x dsDNA HS Assay Kit by Invitrogen. The Qubit 1x dsDNA working solution was prepared at room temperature. Standard measurements were carried out by adding 190 µL of reagent to a 200 µL tube, followed by the addition of 10 µL of the standard (for standards 1 and 2). For measuring DNA samples, 198 µL of reagent was added to the tube, followed by 2 µL of the sample. The solution was homogenised by gently mixing, then incubated at room temperature for two minutes. Readings were taken using the Qubit Flex Fluorometer from Invitrogen. Quantification must be performed on all extracted samples before proceeding with sequencing. The samples with DNA quantification above 0.1 ng/mL can proceed to sequencing, whereas those below this threshold will be excluded.

Polymerase chain reaction (PCR) was performed using Deeplex Myc-TB by Genoscreen, with the following composition: 15.5 µL of Deeplex Myc-TB Master Mix, 0.2 µL Internal control, and 9 µL DNA template. Positive control, Negative control, and Internal control were followed in this step. The thermal cycler was conducted using a Bio-Rad C1000 with the following conditions: 95 °C for 2 min; 35 cycles of 95 °C for 1 min, 55 °C for 30 sec,

and 72 °C for 30 sec; 72 °C for 10 min; and hold at 4 °C.

The PCR product was purified using Agencourt AMPure XP® by Beckman CoulterTM. Seventy-five microliters of 10 mM Tris-HCl pH 7,8 was added to the PCR product, then 65 µL was added. This mix was homogenised and then incubated at room temperature for 5 minutes. The mix was placed on a magnetic rack for 5 min. The supernatant was discarded, and the beads were washed twice with 80% ethanol. The beads were resuspended using 26 µL of 10 mM Tris-HCl pH 7.8. Then the mix was homogenised and then incubated at room temperature for 2 minutes. The mix was placed on a magnetic rack for 5 min. Twenty-five microliters of suspension were transferred to a new tube. The purified amplification product was quantified again and diluted to 0.2 ng/µL in PCR-grade water for library preparation.

Library preparation and sequencing were performed using the Illumina DNA Prep and MiSeq Reagent Micro Kit V2 (Box 1 and 2) according to the manufacturer's instructions.

The FASTQ file from the machine was retrieved and analysed using Deeplex Myc-TB by the Genoscreen application.

Identification and Drug Susceptibility Testing of the sample were taken from the database of the Tuberculosis Laboratory BBLKM Makassar on Sistem Informasi Tuberkulosis (SITB) Indonesia, Ministry of Health.

All data collected from laboratory testing were statistically analysed by SPSS. Chi square test will be choose for nominal data from this research.

RESULTS

Thirteen sputum samples were sequenced using the MiSeq Illumina platform and analysed with Deeplex Myc-TB. The results are shown in Table 1. The analysis included several antibiotics recommended by WHO, such as Rifampicin (RIF), Isoniazid (INH), Pyrazinamide (PZA), Ethambutol (EMB), Streptomycin (SM), Kanamycin (KAN), Amikacin (AMI), Capreomycin (CAP), the Fluoroquinolone class (FQ), including Levofloxacin (LEV), Ofloxacin (OFX), and Moxifloxacin (MOX), Ethionamide (ETH), Linezolid (LZD), Bedaquiline (BDQ), and Clofazimine (CFZ). Two samples (15.38%) did not show identification or DST data (undetermined). According to the genotypic results, the sensitivity of FQ, LZD, AMI, CAP, and KAN was higher than that of BDQ, CFZ, SM, ETH, EMB, and PZA (Table 1). However, BDQ, CFZ, SM, ETH, EMB, and PZA showed higher sensitivity than RIF and INH (Table 1).

The phenotypic results for 13 sputum samples are shown in Table 2. Two samples were identified as Nontuberculous Mycobacteria (NTM) despite microscopy result were negative (Table 2). The antibiotics tested at the Tuberculosis Laboratory of BBLKM

TABLE 1
Genotypic result of Drugs Sensitivity Testing

Antibiotic	t-NGS result		
	% Sensitive	% Resistant	% Undetermined
RIF	0	84.62	15.38
INH	23.08	38.46	38.46
PZA	61.54	15.38	23.08
EMB	53.85	30.77	15.38
FQ	76.92	0	23.08
LZD	84.62	0	15.38
BDQ	69.23	7.69	23.08
CFZ	69.23	7.69	23.08
AMI	84.62	0	15.38
SM	53.85	15.38	23.08
ETH	53.85	15.38	23.08
CAP	76.92	0	23.08
KAN	84.62	0	15.38

% Sensitivity : showed the number of sample from 13 sample that showed the sensitivity against the antibiotics that have tested using tNGS. Undetermined : Machine can't not read the result

TABLE 2
Phenotypic result of Drugs Sensitivity Testing

Antibiotic	Identification and DST		
	% Sensitive	% Resistant	% NTM
MFX High	92.31	7.69	15.38
INH High	53.85	46.15	
INH Low	53.85	46.15	
BDQ	100	0	
CFZ	100	0	
LZD	100	0	
LFX	92.31	7.69	

% Sensitivity : showed the number of sample from 13 sample that showed the sensitivity against the antibiotics that have tested using tNGS. Undetermined : Machine can't not read the result

TABLE 3
Identification Result of 13 Sputum Sample

	Phenotypic	Genotypic
Identification result		
M. tuberculosis	84,62 %	84,62%
NTM	15,38 % (sample number 16 and 18)	0 %
Not detected	0 %	15,38% (sample number 13 and 14)
Acid Fast Bacilli (AFB) Microscopic result		
Negative	2 (Sample 16 and 18)	–
+1	4	–
+3	7	–

Makassar included moxifloxacin, isoniazid, bedaquiline, clofazimine, linezolid, and levofloxacin. These antibiotics exhibited varying sensitivities (Table 2). BDQ, CFZ, and LZD demonstrated complete (100%) sensitivity against *M. tuberculosis*, whereas both low and high concentrations of INH exhibited significantly lower sensitivity, at only 53.85% (Table 2).

The t-NGS results for 13 sputum samples obtained from the Tuberculosis Laboratory at BBLKM Makassar show both concordance and discordance with the phenotypic results. In the phenotypic results, two samples were identified as NTM, whereas the genotypic results identified 11 sputum samples as *M. tuberculosis* and 2 samples showed not detected results (Table 3).

In several samples, the genotypic drug sensitivity test results showed good concordance with the phenotypic results. However, a few samples did not exhibit good concordance because genotypic results showed uncharacterized (Table 4).

Figure 1 shows a comparison of drug resistance between genotypic and phenotypic methods, where the sample results that showed NTM, not detected, and uncharacterized were excluded.

A statistical test was conducted to evaluate the significance of both concordance and discordance across all data. The Chi-square test was chosen as the method of analysis because the data collected were categorical (nominal). The results of the Chi-square test, with a 95% confidence level, showed a significance value greater than 0.05 for the differences in phenotypic and genotypic results for tuberculosis identification and drug susceptibility testing (Table 5).

DISCUSSION

All sputum samples based on genotypic results were identified as *Mycobacterium tuberculosis* (Table 3), except for two samples (Samples 13 and 14), which were not

TABLE 4
The Drug Sensitivity Test based on Phenotypic and Genotypic Result

Code of sample	Drugs									
	BDQ		INH		CFZ		LZD		FQ as MFX	
	Phen	tNGS	Phen	tNGS	Phen	tNGS	Phen	tNGS	Phen	tNGS
1	S	S	S	S	S	S	S	S	S	S
2	S	U	R	R	S	U	S	S	S	S
5	S	S	S	S	S	S	S	S	S	S
6	S	S	R	R	S	S	S	S	S	S
8	S	S	R	R	S	S	S	S	S	S
9	S	S	S	U	S	S	S	S	S	S
11	S	S	R	R	S	S	S	S	S	S
12	S	S	S	U	S	S	S	S	S	S
13	S	ND	R	ND	S	ND	S	ND	S	ND
14	S	ND	R	ND	S	ND	S	ND	R	ND
15	S	S	R	S*	S	S	S	S	S	S
16	NTM	R*	NTM	U	NTM	R*	NTM	S*	NTM	S*
18	NTM	S*	NTM	R*	NTM	S*	NTM	S*	NTM	U

S: sensitive; R: resistant; NTM: Non Mycobacterium tuberculosis; ND: Not Detected; U: uncharecterized; *dis-concordance; Phen: Phenotypic

detected. Meanwhile, in the phenotypic results (Table 3), two samples (Samples 16 and 18) were identified as non-*Mycobacterium tuberculosis*. This indicates a discrepancy in identification between the phenotypic and genotypic results. The confirmation of phenotypic identification of *Mycobacterium tuberculosis* was based on the TB Ag MPT64 Rapid Test results by SD Bioline. The *Mycobacterium tuberculosis* complex secretes this protein, whereas NTM and Bacillus Calmette-Guerin strains with the RD2 deletion do not.[8,9] Although this rapid test has a high sensitivity (almost 100%) and specificity (almost 100%) for sample culture,[8,10,11] it has limitations. TB Ag MPT64 rapid test by SD Bioline has a limit detection on 6.90×10^4 CFU/ml.[12] Based on the microscopic results (Table 3), the two samples (NTM 16 and 18) were negative for acid-fast bacilli. Sari and Aryati demonstrated a concordance rate of 70.8% between the microscopic result and MPT64.[13] This means that the TB Ag MPT64 test may not detect *M. tuberculosis* if the bacterial load is below the limit of detection. However, in the genotypic results, *M. tuberculosis* was still identified because the amplification step in the testing process allows detection down to a limit of 200 CFU/mL.[3,14]

Genotypic analysis of Drug Sensitivity Testing (DST) was conducted using the Deeplex® Myc-TB by Genoscreen application, based on the extended WHO catalogue, which includes 13 drugs. These drugs are the first-line drugs: Rifampicin (RIF), Isoniazid (INH), Pyrazinamide (PZA), and Ethambutol (EMB); the second-line injectables: Streptomycin (SM), Kanamycin (KAN), Amikacin (AMI), and Capreomycin (CAP); the Fluoroquinolone class (FQ), including Levofloxacin (LEV), Ofloxacin (OFX), and Moxifloxacin (MOX); as well as Ethionamide (ETH), Linezolid (LZD), Bedaquiline (BDQ), and Clofazimine (CFZ).[15–17] Meanwhile, phenotypic analysis for drug sensitivity testing was conducted based on national regulations in Indonesia, which have been approved by the US FDA and recommended by the WHO in 2022.[18–20]

There was concordance in the sensitivity of several drugs when comparing phenotypic and genotypic results, except for isoniazid (Figure 1). These concordant results were obtained after excluding uncharacterised, not detected, and NTM samples from the phenotypic analysis. These findings align with recent systematic reviews reporting high overall agreement between sequencing-based DST and culture-based DST, particularly for rifampicin and fluoroquinolones.[21,22]

The genotypic test results for isoniazid indicated a lower level of drug resistance compared to the phenotypic results (Figure 1b). This discrepancy was observed in Sample 15 (Table 4). Resistance to isoniazid typically occurs due to mutations in the *katG* and *inhA* genes; however, molecular analysis showed no

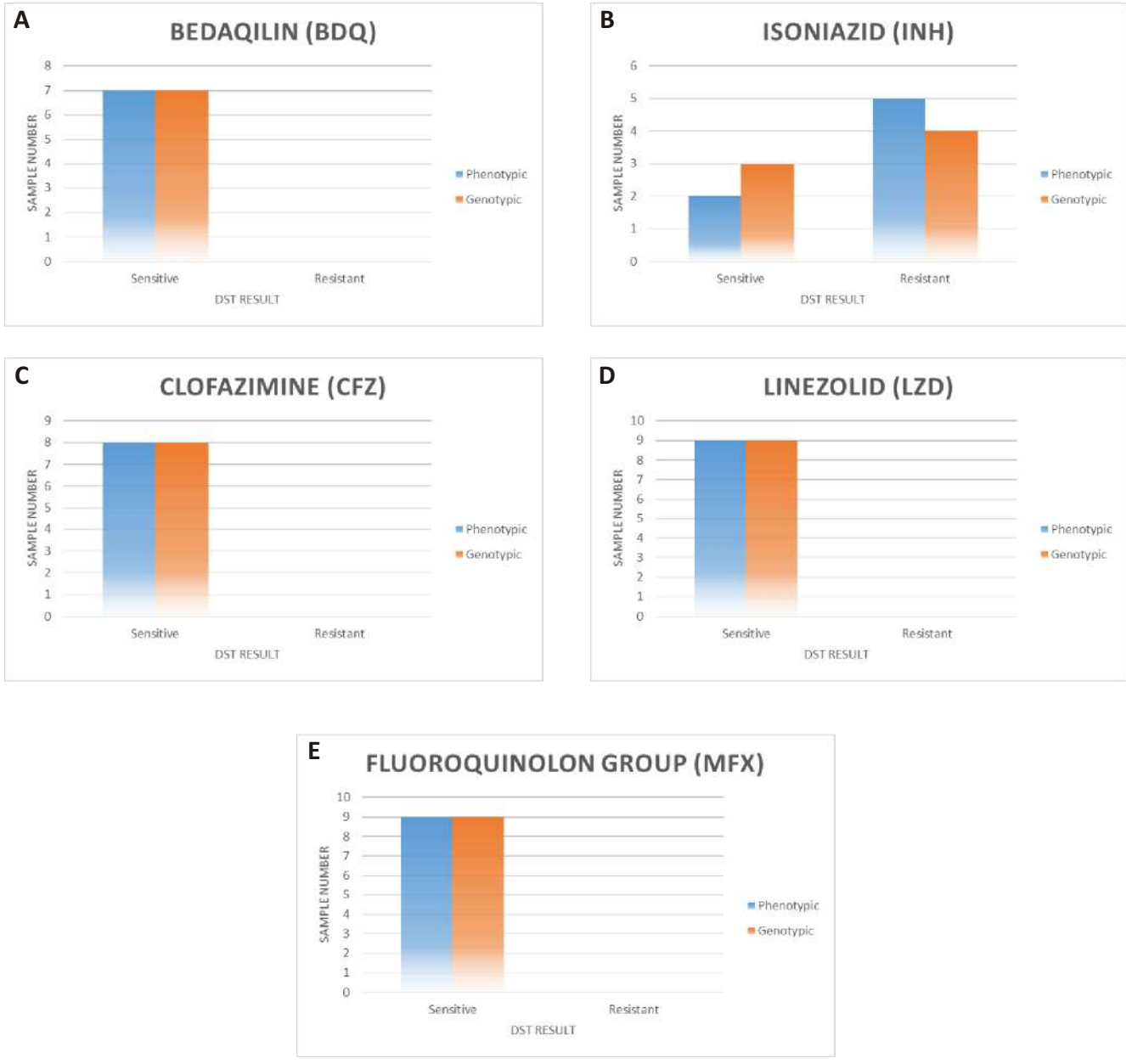

Figure 1. Comparison of the phenotypic and genotypic properties of several drugs.

mutations in these genes. Despite this, the sample exhibited phenotypic resistance to INH. This suggests that other resistance mechanisms may be involved, such as efflux pumps, slow metabolism, or impermeable cell walls.[23,24] Recent genomic studies further support the role of efflux pump mutations *(efpA, iniA)* in low-level INH resistance.[25,26]

The statistical analysis in this study revealed that the differences between phenotypic and genotypic methods for identifying *M. tuberculosis* and assessing drug susceptibility were not statistically significant, with a significance value greater than 0.05 (Table 5). This suggests a strong overall agreement between the two methods, supporting the use of genotypic approaches, such as t-NGS, as a reliable alternative to conventional phenotypic methods. These findings are consistent with results reported by previous researchers.[6,27,28] However, specific instances of discordance highlight the need for further investigation and careful interpretation of genotypic results, particularly when novel or uncharacterized mutations are involved.

Several results were identified as uncharacterized, including BDQ for Sample 2, INH for Samples 9, 12, and 18, CFZ for Sample 2, and FQ for Sample 18 (Table 4).

TABLE 5
Statistical result of Chi Square Test with 95% confidence level

	Significant value (*p*)
Identification	0.135
DST Test:	
BDQ	0.185
INH	0.113
CFZ	0.185
FQ as MFX	0.282
LZD	0.135

Uncharacterised variants refer to sequence variations whose association with drug resistance or susceptibility has not yet been established. Variants of uncertain significance are those that cannot yet be classified as drug-resistant or drug-susceptible according to current WHO confidence grading.[15] For instance, Sample 2 has a mutation in the rv0678 gene (Supplement 1), associated with BDQ resistance, resulting in an amino acid change from L95 to F (L95F), but this mutation remains uncharacterized. Despite this, phenotypic results indicated sensitivity to *M. tuberculosis* (Table 4).

Moreover, for samples not detected in the genotypic results (Samples 13 and 14, Table 4), the Deeplex Myc-TB analysis showed low coverage (Supplement 1). Factors such as operational techniques, including the manual extraction and library preparation processes, could have influenced these results. Therefore, professional and trained technicians are required to perform this method. While t-NGS offers faster results (within 3 days) compared to conventional methods, it is more costly and requires expertise to analyse uncharacterized samples.[27]

CONCLUSION

T-NGS shows promise as a replacement for conventional methods because the discrepancies with phenotypic results are not statistically significant, and it reduces testing time. Additionally, the genotypic method can identify promising mutations that have not been widely reported. However, not all laboratories are equipped for this method due to its higher cost and the need for experts to analyse uncharacterized samples.

CONFLICT OF INTEREST

We declare no conflict of interest

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Original Article

Validity of Leukocyte Esterase Dipstick Test Compared to Gold Standard Urine Culture in Hospitalized Children Suspected of Urinary Tract Infections

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Abstract

Background : Urinary tract infection (UTI) is an illness that affects specifically the bladder and other structures in the urinary tract. The leukocyte esterase dipstick examination is recognized for its high sensitivity but limited specificity. Additional diseases, like glomerulonephritis, can yield positive outcomes in this test. This research was conducted to determine the validity of leukocyte esterase examination in urine culture in children suspected of urinary tract infection.
Aims : To assess the accuracy of leukocyte esterase testing on urine culture in children suspected of having a .
Methods : This study employed a diagnostic test method with a cross-sectional design. Research data were obtained from medical record of pediatric patients admitted to RSUP dr. Hasan Sadikin from 2022 to 2023 with suspected urinary tract infection.
Results : The values for the diagnostic test results are follows true positive 80%, false positive 51%, true negative 25%, and false negative 40% respectively. The calculations reveal that the leukocyte esterase dip stick has a sensitivity of 67%, specificity of 33%, positive predictive value (PPV) of 61%, negative predictive value (NPV) of 38%, a positive likelihood ratio of 1.56, and a negative likelihood ratio of 0.625.
Conclusion: This study indicates that the leukocyte esterase dipstick examination has a sensitivity rate of 67%, specificity rate of 33%, PPV of 61%, and NPV value of 38%. The leukocyte esterase dipstick has a high sensitivity level and a low specificity level.

Keywords: Leukocyte Esterase; Urine Culture; Validity Test; Urinary Tract Infections; Pediatric Urinary Tract Infections.

INTRODUCTION

Urinary tract infection (UTI) is an illness that affects explicitly bladder and other structures in the urinary tract. Urinary tract infection can arise from the presence of bacteria, viruses, or other pathogens.[1] According to the 2019 Global Burden of Disease, Injury, and Risk Factor Study (GDB), there were over 404.6 million individuals worldwide who experienced urinary tract infection, resulting in the deaths of more than 236.786 individuals.[2] According to data from the Indonesian Ministry of Health in 2014, it is evident that the incidence of urinary tract infection in Indonesia is as high as 90–100 cases per 100.000 population annually. Failure to appropriately treat a urinary tract infection can lead to significant complications.[3] Urinary tract infection is not limited to adults but is also a common infection in children.[4] The majority of urinary tract infection cases (70–95%) are caused by *Escherichia coli*.[5]

Multiple diagnostic procedures can identify urinary tract infection. Urinary tract infection can be diagnosed by analyzing urine samples using urinalysis. Urinalysis is a method performed by examining and analyzing urine. Urinalysis comprises three components, among others macroscopic, microscopic, and chemical examination. Chemical examination can be conducted by determining pH levels and the presence of red blood cells, protein, nitrites, and leukocyte esterase. The urine can be chemically examined using a dipstick. Dipstick values utilized are pH, nitrite, and leukocyte esterase.[6] Leukocyte esterase can be utilized to detect white blood cells in urine. White blood cells release leukocyte esterase in reaction to present germs in urine.[7]

Leukocyte esterase dipstick examination is recognized for its high sensitivity but limited specificity. Additional diseases, like glomerulonephritis, can make the positive outcomes in this test.[7] Presently, urine culture is the established benchmark utilized for diagnosing suspected urinary tract infection.[8] A urine culture is performed by obtaining a urine specimen from an individual suspected of having an urinary tract infection.[9] The urine culture examination must be performed at a laboratory facility. Nevertheless, this unit is exclusively accessible at select health centers or primary care hospitals. Urinary tract infection can be quickly assessed using a leukocyte esterase dipstick test, which is simple and cost-effective. This inspection could decrease the quantity of negative urine samples delivered to the laboratory, thereby expediting the examination process.[10] Early detection of urinary tract infection can effectively hinder the transmission of the disease, hence decreasing the chances of developing more severe urinary tract infection. Efficient and suitable administration can alleviate the strain on healthcare resources.[7]

Leukocyte esterase dipstick examination is a cheap and fast examination. In developing countries, rapid tests such as urine dipstick tests are used for patients suspected of having urinary tract infection due to the lack of specialized laboratories with complete equipment to perform various diagnostic tests, including urine culture. The examination method using urine dipsticks has been widely used throughout the world. Many countries use it as an initial test to identify urinary tract infection in health facilities because using leukocyte esterase dipsticks is straightforward, and the examination is inexpensive, including in Indonesia, an archipelagic country with diverse geographical conditions.[25,26]

Urinary tract infections are among the most common bacterial infections in the pediatric population and may lead to significant morbidity if not diagnosed promptly. Accurate and timely identification is critical for initiating appropriate antimicrobial therapy and reducing the risk of complications. While urine culture is considered the gold standard for diagnosis, it is often inaccessible or impractical in many Indonesian healthcare facilities due to geographic and infrastructural limitations. Consequently, clinicians frequently use urine dipstick tests for leukocyte esterase as an initial screening method. The leukocyte esterase dipstick is valued for its simplicity, rapid results, cost-effectiveness, and suitability in resource-limited settings. Nevertheless, uncertainty persists regarding the sensitivity and specificity of this test for diagnosing urinary tract infections in children, especially in cases with atypical clinical presentations. This study aims to further evaluate the sensitivity and specificity of the leukocyte esterase dipstick test in diagnosing urinary tract infections in pediatric patients.

This study evaluates the diagnostic accuracy of the leukocyte esterase urine dipstick test in children with suspected urinary tract infections. By examining its sensitivity and specificity, the research aims to provide evidence-based recommendations for the use of this test as a supportive diagnostic tool in Indonesia. The results are expected to enhance the diagnosis of pediatric urinary tract infections, inform clinical practice, and support optimal resource allocation and management.

This study aimed to assess the accuracy of leukocyte esterase testing on urine culture in children suspected of having a urinary tract infection. The validity of a test is determined by calculating its sensitivity, specificity, negative predictive value, positive predictive value, positive probability, and negative likelihood using the chi-square test method. This research aims to provide a reliable reference for conducting urine exams, enabling prompt and accurate diagnosis of urinary tract infections in children suspected of having such diseases.

METHODS

This study employed a diagnostic test method with a cross-sectional design at the Central General Hospital

(RSUP) Dr. Hasan Sadikin Bandung. Secondary data from patient medical records and laboratory results were utilized as a reference. Research data were obtained from medical record of pediatric patients admitted to RSUP dr. Hasan Sadikin from 2022 to 2023 with suspected urinary tract infection. The samples used adhered to the specified inclusion requirements. Specifically, pediatric patients who presented themselves for examinations and had their urine culture findings included from RSUP Dr. Hasan Sadikin Bandung. The patient data excluded from the study were those of children suspected of urinary tract infection who did not undergo a leukocyte esterase dipstick examination and had incomplete data. The research was conducted with explicit authorization in compliance with the ethical exemption granted by the Padjadjaran University Research Ethics Committee under the reference number 331/UN6.KEP/EC/2024.

The collected data comprises results from urine culture examinations, leukocyte esterase levels from standard urine tests, and characteristics of pediatric patients suspected of having urinary tract infections. The data were analyzed using IBM's SPSS Statistics version 27 software. The chi-square test method was used to process the characteristic data. The chi-square test table compares the leukocyte esterase diagnostic test to the urine culture. Calculations are performed to ascertain the sensitivity, specificity, negative predictive value, positive predictive value, positive likelihood ratio, and negative likelihood ratio.

RESULTS

The study utilized medical data of children admitted to Dr. Hasan Sadikin Bandung Hospital suspected of having urinary tract infections. 196 samples met the inclusion criteria, whereas the exclusion criteria were not applicable. The attributes of the subject are displayed in Table 1.

The accuracy assessment of the leukocyte esterase dipstick test was conducted on 196 samples that satisfied the specified requirements and were not excluded. The test results were compared to the urine culture, considered the most reliable method (gold standard). The findings are summarized in Table 2.

The sample characteristics revealed that a significant proportion of children tested positive for urinary tract infection based on the findings from urine culture (41.3%) and leukocyte esterase dip strips (+1=5.6%; +2=8.7%; +3=28.1%; +4=1%). The majority of the children with urinary tract infection were female. The age group that had the highest number of urinary tract infection based on urine culture testing findings was the age group over 2 years, with 92 patients (14.3%). This was followed by the age group of 1–2 years, with 33 patients (16.8%), and the age group under 1 year, with 6 patients (3.1%). The leukocyte esterase dipstick examination yielded results consistent with the age groups over 2 years, with the highest incidence of urinary tract infection (1+=7.1%; +2=5.6%; +3=32.1%; +4=1.5%). This was followed by the 1-2 year age group (1+=0%; +2=2.6%; +3=9.7%; +4=0.5%) and the age group below 1 year (1+=0%; +2=2%; +3=11.2%; +4=0.5%).

The majority of the samples in the study did not exhibit any comorbidities, such as diabetes and malignancies (63.3%), followed by malignancies (2.6%) and diabetes (1%). Meanwhile, the leukocyte esterase results indicated that most research samples had no comorbidities (1+=6.6%; +2=7.7%; +3=40.8%; +4=2%). This was followed by cases of malignancy (1+=0%; +2=0.5%; +3=2.6%; +4=0%) and diabetes (1+=0.5%; +2=0%; +3=0.5%; +4=0%). Based on urine culture analysis, the percentage of samples without a history of catheter use (50.5%) was higher than that of samples with a history of catheter use (16.3%). The leukocyte esterase dipstick examination yielded results consistent with samples that did not have a prior history of catheter usage (1+=6.1%; +2=7.7%; +3=35.2%; +4=0%), compared to samples with a history of catheter use (1+=1%; +2=0.5%; +3=3.6%; +4=2%).

The analysis of the samples revealed that the predominant microorganisms were Gram-negative bacteria, as shown by both urine culture investigation (33.7%) and leukocyte esterase dipsticks (1+=1.5%; +2=1.5%; +3=19.9%; +4=0%). *Escherichia coli*, a gram-negative bacterium, was the most commonly discovered, with 51 samples. In this study, 7 samples (3.6%) had a concentration of bacteria ≥ 105 CFU/mL, whereas 2 samples (1%) had a concentration of microorganisms $<10^5$ CFU/mL. However, most medical record data, specifically 122 data points (62.2%), needed information regarding the number of bacteria in the urine culture.

According to the table, the values are true positive 80%, false positive 51%, true negative 25%, and false negative 40% respectively. The calculations reveal that the leukocyte esterase dip strip has a sensitivity of 67%, specificity of 33%, a positive predictive value (PPV) of 61%, negative predictive value (NPV) of 38%, a positive likelihood ratio of 1.56, a negative likelihood ratio of 0.625.

DISCUSSION

This study found that urinary tract infections were more common in women than in men. Female are more prone to urinary tract infection than males due to the shorter length of their urethra compared to men. This syndrome facilitates the entry of pathogenic microorganisms into the bladder. Furthermore, the anatomical positioning of the urinary system in women is in excellent proximity to the rectal region, facilitating the movement and infiltration of bacteria into the urinary tract. On the other hand, males possess a longer urethral structure, which

TABLE 1
Characteristics of Research Subjects

Patient Characteristics	Category	Total Sampel (n=196)						
		Urine Culture (1.63 ± 1.421)		Leukocyte Esterase Dipstick (1.33 ± 0.472)				
		Positive	Negative	Negative	+1	+2	+3	+4
Gender	Male	50 (25.5%)	29 (14.8%)	34 (17.3%)	3 (1.5%)	9 (4.6%)	31 (15.8%)	2 (1%)
	Female	81 (41.3%)	36 (18.4%)	42 (21.4%)	11 (5.6%)	7 (8.7%)	55 (28.1%)	2 (1%)
Age	<1 years old	6 (3.1%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)	4 (2%)	0 (0%)
	1-2years old	33 (16.8%)	8 (4.1%)	16 (8.2%)	0 (0%)	5 (2.6%)	19 (9.7%)	1 (0.5%)
	>2 years old	92 (46.9%)	57 (29.1%)	58 (29.6%)	14 (7.1%)	11 (5.6%)	63 (32.1%)	3 (1.5%)
Comorbidities	Without comorbidities	124 (63.3%)	63 (32.1%)	75 (38.3%)	13 (6.6%)	15 (7.7%)	80 (40.8%)	4 (2%)
	Diabetes	2 (1%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0%)	1 (0.5%)	0 (0%)
	Malignancy	5 (2.6%)	1 (0.5%)	0 (0%)	0 (0%)	1 (0.5)	5 (2.6%)	0 (0%)
Catheter	Without catheter	99 (50.5%)	55 (28.1%)	58 (29.6%)	12 (6.1%)	15 (7.7%)	69 (35.2%)	0 (0%)
	With catheter	32 (16.3%)	10 (5.1%)	18 (9.2%)	2 (1%)	1 (0.5%)	17 (3.6%)	4 (2%)
Type of Microorganism	Without Microorganism	0 (0%)	65 (33.2%)	25 (12.8%)	10 (5.1%)	8 (4.1%)	21 (10.7%)	1 (0.5%)
	Gram-negative bacteria	66 (33.7%)	0 (0%)	21 (10.7%)	3 (1.5%)	3 (1.5%)	39 (19.9%)	0 (0%)
	Gram-positive bacteria	16 (8.2%)	0 (0%)	6 (3.1%)	0 (0%)	3 (1.5%)	7 (3.6%)	0 (0%)
	Fungi	14 (7.1%)	0 (0%)	0 (0%)	1 (0.5%)	1 (0.5%)	4 (2%)	0 (0%)
	Others	6 (3.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.5%)	0 (0%)
	Polymicrobial	29 (14.8%)	0 (0%)	12 (6.1%)	1 (0.5%)	1 (0.5%)	12 (6.1%)	3 (1.5%)
Number of Mikroorganism	Not mentioned	122 (62.2%)	0 (0%)	46 (23.5%)	4 (2%)	8 (4.1%)	61 (31.1%)	3 (1.5%)
	$< 10^5$ CFU/mL	2 (1%)	63 (32.1%)	25 (12.8%)	10 (5.1%)	8 (4.1%)	21 (10.7%)	1 (0.5%)
	$\geq 10^5$ CFU/mL	7 (3.6%)	2 (1%)	5 (2.6%)	0 (0%)	0 (0%)	4 (2%)	0 (0%)

TABLE 2
Diagnostic Test of Leukocyte Esterase Dipstick

Leukocyte Esterase Dipstick	Urine Culture		Total (n=196)
	Positive	Negative	
Positive	80	51	131
Negative	40	25	65
Total	120	76	196
Leukocyte Esterase			
Sensitivity (%)			67
Specificity (%)			33
Positive Predictive Value (%)			23.08
Negative Predictive Value (%)			23.08
Likelihood Ratio Positive			15.38
Likelihood Ratio Negative			23.08

serves as a barrier against bacterial contamination, making it more difficult for bacteria to infiltrate the bladder than females.[10]

Urinary tract infection can occur at any age, from adults to children. Our research examined data from children suspected of having a urinary tract infection. The data was divided into three age groups, under 1 year, 1 to 2 years, and over 2 years. Our analysis revealed that children under 1 year of age were the most likely group to experience urinary tract infections. This is because the number of children under 1 year of age was higher than in the other two groups. A study revealed a higher incidence of urinary tract infection among children who utilized specific categories of diapers. Various types of diapers can lead to inadequate ventilation in the genital area, resulting in reduced airflow.[11] Infants under the age of 1 are also more vulnerable to infection.[12] According to this survey's findings, the age group above 2 years old constitutes the greatest demographic. This is because the sample size used to obtain research data for children over 2 years is larger, resulting in a higher incidence of urinary tract infection in this age group.

The study did not find a significant association between comorbidities such as diabetes mellitus (DM) and malignancies, including leukemia and preleukemia. This is evident from the findings of the urine culture analysis. The study found that only a small proportion of children with suspected urinary tract infections were also diagnosed with significant comorbid conditions, including diabetes mellitus or malignancies. Most children in this group did not exhibit evidence of these additional pathologies, underscoring the infrequency of such comorbid presentations within this clinical population. This study demonstrates that there is no substantial prevalence of diabetes and cancer among children who are suspected of having a urinary tract infection. The findings of this study contradict the previous research conducted by Regina (2023), which indicated a correlation between DM and bacteriuria, serving as a potential predictor of urinary tract infection. Patients with diabetes mellitus who have high blood sugar levels can encounter issues such as compromised immune function and urinary tract dysfunction. Elevated blood glucose levels result in glucosuria and impaired neutrophil function, heightening susceptibility to urinary tract infection.[13]

Based on urine culture analysis, the percentage of samples from individuals without a history of catheter use was higher than that of samples from individuals with a history of catheter use. Leukocyte esterase dipstick examination showed consistent results in samples without a history of catheter use, compared to samples with a history of catheter use. This study suggests that the use of catheters does not increase the likelihood of urinary tract infections in children. The prevalence of samples with a history of catheter use was quite substantial in this study. Meanwhile, based on research conducted at Medan Regional Hospital, the use of catheters increases the likelihood of urinary tract infections.[14] The majority of urinary tract infections are caused by the use of catheters. This contradicts the author's study findings.

The analysis of the samples revealed that the predominant microorganisms were Gram-negative bacteria, as shown by both urine culture investigation and leukocyte esterase dipsticks. *Escherichia coli*, a gram-negative bacterium, was the most commonly discovered. It was identified among additional microorganisms

(polymicroorganisms) or as the sole type present. *Escherichia coli* is a bacteria typically present in the normal intestinal flora. However, it can potentially cause infections in other body sections, including the digestive system and beyond, such as the urinary tract, leading to urinary tract infection. Extraintestinal *Escherichia coli* infections typically occur when *Escherichia coli* bacteria move from the intestine to other body parts. Extraintestinal *Escherichia coli* infections frequently occur in the urinary tract.[15] *Escherichia coli* has fast growth in both aerobic and anaerobic conditions. Urinary tract infection mainly result from bacterial infection when bacteria enter the urinary tract via the urethra. Subsequently, the bacteria undergo replication and adhere to the bladder. Moreover, microorganisms can infiltrate the kidneys. *Escherichia coli* possesses uropathogenic strains that can initiate urinary tract infection.[16] In the urine culture examination conducted on children suspected of urinary tract infection, other gram-negative bacterial microorganisms were found, such as *Klebsiella pneumonia, Proteus mirabilis, Pseudomonas aeruginosa, Enterobacter cloacae,* and *Morganella morganii*. Previous research found that Klebsiella pneumoniae (33.4%) is a gram-negative bacteria that is also often found in urinary tract infection patients.[27] Several other types of anaerobic bacteria were found, namely *Enterococcus faecalis, Acinetobacter baumannii, Candida albicans,* and *Candida tropicalis*.

An analysis of the data obtained from urine culture examinations indicates that, in the majority of cases, the corresponding medical records lack detailed documentation regarding the quantitative enumeration of bacterial colonies present in the samples. Specifically, most of the medical record entries related to urine cultures merely note the presence or absence of bacterial growth, without providing precise counts or concentrations. Only a limited subset of urine culture reports explicitly enumerate the number of bacteria detected. Analysis of samples with known bacterial counts revealed that most positive samples had counts of $\geq 10^5$ CFU/mL. According to Sulistiani's (2021) research, a urine culture investigation is considered positive for urinary tract infection if the number of bacteria is equal to or $\geq 10^5$ CFU/mL. This aligns with a study demonstrating that most samples containing microorganisms have findings $\geq 10^5$ CFU/mL.[17]

Millner and Becknell's earlier study established that the leukocyte esterase examination is very sensitive but lacks specificity when it comes to identifying urinary tract infection. A positive leukocyte esterase test does not always mean that there is a urinary tract infection. Several diseases, such as glomerulonephritis and appendicitis, can cause positive leukocyte esterase examination results.[8,18] These findings align with the author's research at RSUP Dr. Hasan Sadikin, demonstrating a high sensitivity (67%) and low specificity (33%) of leukocyte esterase. A high sensitivity score suggests that the leukocyte esterase dipstick can reliably identify children with a urinary tract infection. At the same time, a low specificity value shows that the leukocyte esterase dipstick cannot accurately identify patients without a urinary tract infection. Thus, leukocyte esterase is recognized as a susceptible but less specific diagnostic test for suspected urinary tract infections in children.

These findings align with the author's research at RSUP Dr. Hasan Sadikin, demonstrating a high sensitivity (67%) and low specificity (33%) of leukocyte esterase. A high sensitivity score suggests that the leukocyte esterase dipstick can reliably identify children with a urinary tract infection. At the same time, a low specificity value shows that the leukocyte esterase dipstick cannot accurately identify patients without a urinary tract infection. Thus, leukocyte esterase is recognized as a susceptible but less specific diagnostic test for suspected urinary tract infections in children.[19,20]

This study determined the NPV and PPV values to be 38% and 61%, respectively. Previous studies have established that the PPV is 44% and the NPV is 92%.[21] The PPV score of 44% suggests that the leukocyte esterase dipstick is less accurate in detecting an illness, as it is further from 100%. PPV represents the likelihood that an individual who tests positive for a disease has the ailment. PPV and NPV are utilized to assess the likelihood of an individual's illness, considering positive or negative outcomes from diagnostic tests.[22] The PPV and the NPV for both are approximately 100%. The study determined that the PPV was 61%. The study revealed that 61% of pediatric patients suspected of having a urinary tract infection were diagnosed with a urinary tract infection. The author's research has a net present value of 38%, significantly lower than 100%. The NPV indicates that 38% of children suspected of having a urinary tract infection and test negative do not indeed have a urinary tract infection. The research findings suggest that leukocyte esterase dip strips with poor NPV are unsuitable for investigating children's urinary tract infection. The outcomes of dip strip examination may differ among various study populations. The dip strip examination is not regarded as accurate for identifying urinary tract infections in children due to the potential for sample contamination. This may explain why the NPV of leukocyte esterase dip strips in children is comparatively lower.[23] The author's examination results are consistent, revealing a comparatively low NPV value.

Previous research shows that the likelihood ratio has a positive likelihood ratio (LR+) value of 2.6 and a negative likelihood ratio (LR-) value of 0.6. This value is recognized to have a negligible impact on the probability of disease.[24] This is also consistent with the research conducted by the author, which has an LR+ value of 1.56 and an LR- value of 0.625, indicating a minor influence. The LR+ value from this study only slightly increases the

likelihood that someone with a positive test result truly has a urinary tract infection. The LR-value from this study only slightly reduces the likelihood that someone with a negative test result does not have a urinary tract infection. The diagnostic test for leukocyte esterase dipstick has shown low validity. Mistakes in urinary tract infection diagnosis might also arise from faults in collecting the sample.[23] Menstrual spots and other similar situations can potentially introduce technical errors during urine collection, impacting examination results' accuracy. This can have an impact on the outcomes of the conducted research. This study was conducted with a relatively large sample size, providing sufficient statistical power. However, there was a limitation due to incomplete medical records, which reduced the number of samples available for analysis.

CONCLUSION

This study indicates that leukocyte esterase has high sensitivity (67%) and low specificity (33%), meaning it can accurately detect urinary tract infections in children, but it is not reliable for identifying children without such infection. A value of 61% PPV indicates that leukocyte esterase dipstick examination is quite good, shows that 61% of children suspected of having urinary tract infection do indeed have the condition. NPV value based on the diagnostic test is far from 100%, indicating that the leukocyte esterase dipstick is less accurate for examining urinary tract infection in children. Based on the results, it can be seen that the leukocyte esterase dipstick is less suitable for use in examining urinary tract infection in children because it has a low validity value. Therefore, leukocyte esterase dipstick examination results need to be supported by examinations using other methods to obtain more accurate urinary tract infection diagnosis results, such as nitrite examination or urine culture. In conducting similar studies in the future, it is hoped that the prevalence in the population to be used can be known with certainty to obtain more optimal results.

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CONFLICT OF INTEREST

No potential conflicts of interest that might be perceived as influencing the impartiality of the reported research.

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Original Article

Anxiety, Stress, and Depression in Recurrence of Gastritis Symptoms Among Inmates with a History of Drug Abuse in Bandung

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Abstract

Background : Drug abuse inmates in correctional institutions undergo rehabilitation programs and are supervised according to the determined sentence, thus losing their freedom. This condition causes psychosocial problems such as anxiety, stress, and depression, which may be associated with physical issues, including the recurrence of gastritis symptoms.
Aims : To identify the correlation between anxiety, stress, and depression with recurrence of gastritis symptoms in drug abuse inmates at the correctional institution.
Methods : The study used a cross-sectional design and involved 34 inmates with a history of gastritis due to drug abuse. Purposive sampling was employed to select the participants. The levels of anxiety, stress, and depression were measured with the Indonesian version of the Depression Anxiety Stress Scales (DASS-21). The Gastritis Recurrence Questionnaire evaluated the recurrence of gastritis symptoms in the inmates. The data was analyzed using descriptive statistics such as frequency distribution, and inferential analysis was conducted using the Kendal-tau test to identify correlations between the variables.
Results : The study findings indicate a correlation between anxiety, stress, and depression and the recurrence of gastritis symptoms in inmates in correctional institutions (*p-value* <0.05). Most inmates with a history of drug abuse experience psychosocial problems such as very high anxiety (29.4%) and severe stress (32.4%). At the same time, 73.5% do not experience depression.
Conclusion : Psychosocial issues like anxiety, stress, and depression have been found to contribute to the likelihood of recurrence of gastritis symptoms in inmates. The higher the levels of anxiety, stress, and depression, the greater the possibility of recurrence of gastritis symptoms. Correctional institution managers should be prepared to address these psychosocial issues to help inmates reduce the recurrence of gastritis symptoms.

Keywords : anxiety, depression, gastritis symptoms, inmate, stress

INTRODUCTION

The large number of drug abuse inmates in correctional institutions who experience psychosocial disorders causes high levels of physical health disorders. Inmates in correctional institutions are incarcerated, which causes isolation from the outside world, and they are required to follow the rules in the correctional institutions. This condition leads to psychosocial problems in inmates, such as anxiety, stress, and depression. Psychosocial issues in drug-abusing inmates can lead to physical problems, including headaches, sleep disorders, digestive issues, respiratory problems, and irregular heartbeats.[1–3]

The number of individuals abusing drugs in Indonesia has shown a concerning upward trend. According to the latest available national data from the Indonesian National Narcotics Agency, the prevalence of drug abuse among individuals aged 15–64 increased by 0.93% from 2019 to 2021, rising from 3,419,188 to 3,662,646 cases.[4] While data beyond 2021 have not been officially published as of this writing, these figures still offer relevant context to the ongoing burden of substance abuse. In the same year, 68,042 cases of drug addiction were reported in West Java Province, where this study was conducted.[4] Moreover, it was reported that approximately 96% of inmates in correctional facilities across Indonesia were incarcerated for drug-related offenses, comprising 145,413 individuals, 116,930 classified as drug dealers and 28,483 as drug users.[5] According to a preliminary study, there are a total of 1085 inmates at the Class IIA Narcotics Penitentiary in Bandung, Indonesia, with 503 prisoners of drug-related cases.

The Nurmagandi *et al*. study[1], it was found that 68.1% of inmates suffer from psychosocial problems related to anxiety disorders and stress during their sentences. Additionally, numerous studies have shown that inmates with drug-related offenses tend to experience moderate levels of anxiety, stress, and depression.[6–8] One study found that 60.5% of the 215 inmates in a correctional institution in Bandung City suffered from gastritis accompanied by psychosocial disorders.[2]

The psychosocial problems experienced by inmates who abuse drugs can lead to various physical issues such as headaches, sleep disorders, digestive problems, breathing difficulties, and irregular heartbeats.[9] These digestive problems may include symptoms of gastritis, which can reoccur due to psychosocial issues, leading to symptoms such as nausea, vomiting, and upper abdominal pain.[10] Recurrence of gastritis symptoms may be affected by diet, alcohol and smoking habits, coffee consumption, gender, age, use of nonsteroidal anti-inflammatory drugs (NSAIDs), drug use, anxiety, stress, and social environment issues.[11–15]

When inmates are sentenced to correctional institutions, they often feel isolated from the outside world, leading to loneliness, loss of self-confidence, disturbed self-concept, and decreased self-esteem.[16] Adapting to a new life and following the rules in these institutions can cause psychosocial problems. Additionally, inmates with a history of drug abuse require medical and social rehabilitation to prevent them from relapsing.[17,18] This can lead to fear of stopping drug consumption, skepticism about the effectiveness of treatment, and negative public attitudes toward drug users, resulting in increased psychosocial problems like anxiety, stress, and depression.[19,20]

Anxiety, stress, and depression are factors that cannot be controlled from outside of the person, so it's essential to identify these psychosocial factors as they can affect the recurrence of gastritis. Additionally, stress conditions are suspected to be related to the of recurrence of gastritis symptoms in both drug-abuse and non-drug-abuse individuals.[2,21] The current research on the relationship between anxiety and depression and the recurrence of gastritis in inmates, particularly those with a history of drug abuse, is limited. Therefore, this study aimed to examine the correlation between anxiety, stress, and depression and the recurrence of gastritis in drug abuse inmates at a narcotics correctional institution in Bandung.

METHODS

The study was designed as a cross-sectional study and conducted at the Class IIA Narcotics Correctional Institution in Bandung, West Java, Indonesia, from June to August 2024. The study focused on inmates with a history of drug abuse. The inclusion criteria for the study required the participants to suffer from gastritis suffer from based on a screening for symptoms of recurrence of gastritis symptoms. These symptoms included epigastric pain, nausea, vomiting, hematemesis, melena, discomfort in the upper abdomen, and a minimum imprisonment period of 3 months. The exclusion criteria were inmates under special supervision by prison officers at risk of causing disturbances.

The sampling technique employed was purposive sampling, which involved recruiting participants based on their health reports from the correctional institution clinic. Participants displaying gastritis symptoms were recruited within one week of being screened by medical personnel at the clinic. The sample size was determined using the Cochran Formula with a 90% confidence level ($z = 1.64$), an expected proportion of 15% (0.15), and an error rate of 10%, resulting in 34 people. The choice of a 90% confidence level was made due to the limited accessibility and tightly controlled setting of the correctional institution, which constrained the recruitment of eligible participants within the available

timeframe.

The study examined personal characteristics, anxiety, stress, and depression in inmates with a history of drug abuse. Personal characteristic variables included participant demographics such as age, marital status, religion, education, employment before imprisonment, length of sentence, dietary patterns during imprisonment, food triggers for gastritis, use of Non-steroidal anti-inflammatory drugs (NSAIDs), cigarette consumption, coffee drinking habits, family visits, and perceptions of adaptation to prison life. These personal characteristic variables were assessed using a demographic questionnaire developed by the researcher.

This study defines the anxiety variable as the body's response to a difficult-to-describe danger, characterized by fear that can cause physical problems such as recurrent gastritis. The stress variable refers to the body's natural reaction to changes that threaten the self and can also cause physical problems such as recurrent gastritis. In addition, the depression variable is interpreted as a prolonged dejected condition resulting from the inability to adapt to changes that can cause physical problems such as recurrent gastritis.

Anxiety, stress, and depression were measured using the Indonesian version of the Depression Anxiety Stress Scales (DASS-21), a validated 21-item instrument with three subscales (7 items each) rated on a 4-point Likert scale (0 = never, 1 = sometimes, 2 = often, 3 = very often). Higher scores indicate greater symptom severity. The DASS-21 has demonstrated strong psychometric properties, with validity coefficients ranging from 0.70 to 0.94 across subscales and a Cronbach's alpha of 0.96, indicating high reliability in the Indonesian context.[22–24]

In this study, the last variable measured was the recurrence of gastritis symptoms, which is defined as the re-emergence of gastritis symptoms caused by psychosocial problems such as anxiety, stress, and depression. The instrument used to measure the recurrence of gastritis symptoms is the gastritis symptom questionnaire created by Rodliya, which consists of 14 question items with a 4-point Likert scale. The questionnaire addresses three dimensions: general symptoms of gastritis, symptoms triggered by certain foods, and symptoms related to meal times.[25] The gastritis symptom recurrence questionnaire has demonstrated acceptable validity (r = 0.536–0.835) and high reliability (Cronbach's alpha = 0.928), ensuring its suitability for use in this population.[25]

Study questionnaires were distributed directly to participants with the assistance of prison officers. The questionnaires included a demographic survey, DASS-21, and a questionnaire about gastritis symptom recurrence. Before participants expressed their willingness to take part, they were provided with a detailed explanation of the study's purpose and their understanding was checked. Once we obtained informed consent from each participant, they filled out the written questionnaire directly. This process took between 30 to 45 minutes.

The data was analyzed descriptively, and participant characteristics were reported using frequencies and percentages. The correlation between anxiety, stress, and depression with the recurrence of gastritis symptoms in inmates was analyzed using the Kendall Tau-C test, with p <0.05 indicating statistical significance. Descriptive statistics were used in data analysis, and statistical analysis was performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Before participants completed the study questionnaire, the assessment began with a general explanation of the project's purpose and a request for written consent to indicate their willingness to participate. This study was approved by the Research Ethics Committee from Universitas 'Aisyiyah Bandung at Universitas 'Aisyiyah Bandung, Indonesia (Number 948/KEP.01/UNISA-Bandung/VI/2024).

RESULTS

Table 1 displays the characteristics of the participants in this study. Nearly half of the inmates involved were between 17 and 25 (44.1%) and single (50%). Most inmates were Muslim (97.1%) and had completed high school (55.9%). A few had worked as laborers before their imprisonment (26.5%), and most inmates had received 2–4 years (26.5%) sentence. Over 65% had knowledge of gastritis, were able to adjust to the correctional environment, were regularly visited by family, and had a consistent diet. Furthermore, over 55% had the habit of consuming spicy foods, NSAID drugs, cigarettes, and coffee.

Table 2 shows the level of anxiety, stress, depression, and relapse problems experienced by drug abuse inmates. Inmates who experience very severe anxiety reach 29.4%, and those with moderate to high stress reach 64.8%. More than 70% of inmates do not experience depression. Meanwhile, most inmates experience a relapse of gastritis symptoms while in prison.

Table 3 displays the cross-tabulation results and correlation analysis between anxiety, stress, and depression with the recurrence of gastritis symptoms in drug abuse inmates. The results show statistically significant correlations between these psychosocial variables and recurrence of gastritis symptoms. Specifically, anxiety was found to have a strong positive correlation with the recurrence of gastritis symptoms, with a Kendall Tau-c coefficient of 0.647 and a p-value of 0.000. This indicates a statistically significant relationship at the 0.01 level, meaning higher anxiety levels are strongly associated with increased recurrence of gastritis symptoms.

TABLE 1
Personal characteristics of inmates with a history of drug abuse (n=34)

Characteristics	Frequency (f)	Percentage (%)
Age		
17–25 years	14	41.2
26–35 years	15	44.1
36–45 years	3	8.8
46–55 years	1	2.9
56–65 years	1	2.9
Marital status		
Married	13	38.2
Single	17	50
Divorce	4	11.8
Religion		
Muslim	33	97.1
Christian	1	2.9
Education level		
Elementary School	7	20.6
Junior High School	7	20.6
High School	19	55.9
Bachelor	1	2.9
Occupation Before Entering Prison		
Laborer	9	26.5
Entrepreneur	8	23.5
Driver	3	8.8
Private	3	8.8
Other	8	23.5
Unemployed	3	8.8
Maximum Prison Sentence		
Less than two years	4	11.8
Two to three years	9	26.5
Four to five years	4	11.8
Six to seven years	6	17.6
Eight to ten years	7	20.6
More than 10 years	4	11.8
Exposure to gastritis information		
Yes	23	67.6
No	11	32.4

TABLE 1. *Continued*

Characteristics	Frequency (f)	Percentage (%)
Habit of consuming spicy food		
Yes	27	79.4
No	7	20.6
Diet pattern		
Regular	29	85.3
Irregular	5	14.7
Habit of using NSAID drugs		
Yes	19	55.9
No	15	44.1
Habit of consuming cigarettes		
Yes	32	94.1
No	2	5.9
Habit of consuming coffee		
Yes	29	85.3
No	5	14.7
Habit of being visited by family		
Yes	23	67.6
No	11	32.4
Ability to adapt in prison		
Yes	33	97.1
No	1	2.9

Similarly, stress showed a significant positive correlation with recurrence of gastritis symptoms (correlation coefficient = 0.522, *p*-value = 0.000), demonstrating that inmates experiencing higher stress levels were more likely to experience recurrent gastritis symptoms. In contrast, depression had a weaker but still statistically significant correlation with recurrence of gastritis symptoms (correlation coefficient = 0.280, *p*-value = 0.002), suggesting that while depression contributes to gastritis symptom recurrence, its association is less pronounced compared to anxiety and stress. The inclusion of *p*-values supports the conclusion that all three psychosocial variables, anxiety, stress, and depression, are significantly correlated with the physical manifestation of gastritis among the inmate population. These findings emphasize the importance of addressing psychosocial well-being as a preventive measure for physical health deterioration.

DISCUSSION

The study findings prove that psychosocial disorders, including anxiety, stress, and depression, are related to the recurrence of gastritis symptoms in drug abuse inmates. Anxiety, stress, and depression are psychosocial problems that are interconnected with each other.[26] Anxiety and stress are psychosocial conditions that can cause depression, which can ultimately have an impact on physical health, such as the emergence of gastritis symptoms.[27] Drug abuse inmates in correctional institutions are in a period of rehabilitation from drugs and prison sentences. In the early stages of drug rehabilitation, inmates not only stop using drugs gradually, but they also face environmental changes that make them feel bound and less free in their daily activities.

Different types of drugs affect different neurotransmitter pathways in various ways. However, most drugs affect the dopamine system.[28] Dopamine

TABLE 2
Distribution of anxiety, stress, depression, and recurrence of gastritis symptoms in inmates with a history of drug abuse (n=34)

Variable	Frequency (f)	Percentage (%)
Anxiety		
Normal	6	17.6
Low	3	8.8
Moderate	7	20.6
Severe	8	23.5
Very severe	10	29.4
Stress		
Normal	2	5.9
Low	8	23.5
Moderate	11	32.4
Severe	11	32.4
Very severe	2	5.9
Depression		
Normal	25	73.5
Mild	7	20.6
Moderate	2	5.9
Recurrence of Gastritis		
Yes	25	73.5
No	9	26.5

controls emotions, motivation, and feelings of pleasure. This is the brain's reward system. Our brains are hardwired to make sure we repeat pleasurable activities. When we do something enjoyable, we get a little dopamine, which reminds us to do it again through the brain.[29] When drug abusers stop using drugs, large amounts of dopamine are released, and the brain has difficulty keeping up with its production, and it can temporarily run out of dopamine. This causes the inmate to experience depression, increased alertness or suspiciousness, even auditory and visual hallucinations, inappropriate behavior, and psychosocial problems such as anxiety, stress, and depression.[28,30]

When experiencing psychosocial issues such as anxiety, stress, and depression, the hypothalamus may become activated, leading to the stimulation of two neuroendocrine systems: the sympathetic system and the adrenal cortex system.[31] The sympathetic nervous system responds to nerve impulses and the hypothalamus. ACTH hormone is carried through the bloodstream to the adrenal cortex, which stimulates the release of cortisol. Increased cortisol levels result in heightened gastric secretion activity (HCL).[32] Prolonged gastric secretion can lead to bodily reactions, including improved breathing, pulse rate, and blood pressure.[33] Additionally, digestive problems may arise, such as decreased appetite, bloating, a sensation of fullness in the stomach, stomach pain, nausea, and vomiting. These reactions are among the symptoms of recurrence of gastritis symptoms.[2,34] The higher the levels of anxiety, stress, and depression, the greater the likelihood of gastritis recurrence. This is supported by our findings, where 73.5% of the inmates reported experiencing recurrence of gastritis symptoms.

The high prevalence of gastritis symptoms in this study aligns with previous findings that suggest digestive disorders, especially gastritis, are common among inmates with psychosocial burdens. According to Elliya and Haryanti (2020), over 60% of inmates in a correctional facility in Sukadana, Lampung, experienced gastritis symptoms related to psychological stress.[2] Another study by Tania *et al*. (2023) reported a recurrence of gastritis symptoms rate of 68.4% among adolescents

TABLE 3
Correlation of anxiety, stress, and depression with recurrence of gastritis symptoms (n=34)

Variables	Recurrence of Gastritis		Coefficient correlation	*p*-value
	Yes - f (%)	No - f (%)		
Anxiety			0.647	0.000
Normal	2 (5.9)	4 (11.8)		
Low	0 (0.0)	3 (8.8)		
Moderate	5 (14.7)	2 (2.9)		
Severe	8 (23.5)	0 (0.0)		
Very severe	10 (29.4)	0 (0.0)		
Stress			0.522	0.000
Normal	1 (2.9)	1 (2.9)		
Low	3 (8.8)	5 (14.7)		
Moderate	8 (23.5)	3 (8.8)		
Severe	11 (32.4)	0 (0.0)		
Very severe	2 (5.9)	0 (0.0)		
Depression			0.280	0.002
Normal	16 (47.1)	9 (26.5)		
Mild	7 (20.6)	0 (0.0)		
Moderate	2 (5.9)	0 (0.0)		

Note: Statistical analysis was conducted using the Kendall Tau-C correlation test; significance was set at $p < 0.05$

facing academic and social pressure.[10] In our study, the 73.5% recurrence rate highlights how psychosocial distress in a highly restrictive correctional environment may exacerbate physiological symptoms even more than in general community populations. To help mitigate negative psychosocial and physical health consequences, including the recurrence of gastritis symptoms, it is essential to implement physical, emotional, and spiritual support strategies.

In contrast, depression showed a weaker but still statistically significant correlation with gastritis recurrence (correlation coefficient = 0.280, $p = 0.002$). This indicates that while depression contributes to gastritis symptoms, its predictive strength appears less pronounced compared to anxiety and stress. From a clinical perspective, this implies that while addressing depression remains important, interventions in correctional settings may yield greater impact by prioritizing the management of anxiety and stress. Nonetheless, comprehensive psychosocial care should include all three components to address overlapping symptomatology and underlying vulnerabilities.

Factors that can influence the recurrence of gastritis, aside from anxiety, stress, and depression, include diet, smoking habits, coffee consumption, age, use of nonsteroidal anti-inflammatory drugs (NSAIDs), and psychosocial environment issues.[11–15] In this study, 44.1% of participants were aged 26–35 years. Recurrence often occurs during productive age ranges such as 26–35 years, which aligns with our study finding that 44.1% of participants fell into this age group. At this age, individuals are typically engaged in high levels of activity and responsibility, which may increase their susceptibility to stress-related health issues such as gastritis recurrence.[12]

A majority of inmates, over 55%, have the habit of consuming spicy foods, taking NSAIDs, smoking, and drinking coffee. Diet can be a factor in the recurrence of gastritis. Foods high in saturated fat, coconut milk, spicy, processed, instant, and carbonated drinks, as well as irregular eating habits such as skipping breakfast, delaying meals, and consuming excessive or unhealthy food, can increase the production of stomach acid. This can irritate the stomach wall and cause symptoms of recurrence of gastritis symptoms. The use of NSAIDs can also affect recurrence of gastritis symptoms, as long-term use can lead to an excess of stomach acid. In our study, 85.3% of inmates reported coffee consumption, and 94.1%

smoked cigarettes, both of which are significant risk factors for gastric irritation and recurrence. Coffee can increase stomach acid due to its caffeine content, and smoking introduces nicotine, which disrupts the bicarbonate-acid balance in the stomach, further increasing acidity and the risk of mucosal damage.[35,36]

This study has several limitations. It did not explore the relationship or mediating influence between anxiety, stress, and depression. Several theories propose reciprocal effects among these variables, warranting further exploration. Another limitation lies in the relatively small sample size (n = 34), which may introduce selection bias and limit the generalizability of findings beyond the specific population of inmates with a history of drug abuse at a single correctional facility. Broader studies across diverse institutional contexts are recommended to validate and expand upon these results.

CONCLUSION

The study showed a significant relationship between anxiety, stress, and depression and the recurrence of gastritis in drug abuse inmates. The higher the levels of anxiety, stress, and depression, the more likely it was for the inmates to experience recurrence of gastritis symptoms. These psychosocial issues need to be addressed as they can lead to increased cortisol hormone levels, which in turn can cause gastric secretion (HCL) and subsequently lead to recurrence of gastritis symptoms. Therefore, interventions such as consolidating physical, emotional, and spiritual activities are necessary to address these psychosocial problems and reduce the factors contributing to recurrence of gastritis symptoms.

Based on these findings, comprehensive psychosocial and health-related interventions are highly recommended within correctional settings. First, structured mental health screening programs should be implemented routinely to detect early signs of anxiety, stress, and depression among inmates. Second, cognitive-behavioral therapy (CBT) and group counseling can be introduced as part of rehabilitation programs to help inmates develop emotional coping mechanisms. Third, stress-reduction strategies such as mindfulness-based interventions, spiritual or faith-based programs, and guided relaxation exercises can be integrated into daily correctional routines.

From a physical health perspective, dietary education and modification are essential. Correctional health services should collaborate with nutritionists to provide inmates with meals that reduce gastric irritation, such as limiting spicy food, caffeine, and NSAIDs when not clinically required. Educational workshops can also raise inmates' awareness about the relationship between psychosocial stress and gastrointestinal health. Lastly, a multidisciplinary approach involving psychologists, nurses, correctional officers, and primary care providers should be strengthened to ensure continuity of care and promote a holistic rehabilitation model. These integrative interventions are not only aimed to reduce recurrence of gastritis symptoms but also to improve the overall quality of life and mental resilience of inmates.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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Original Article

Relationship Between Level of Simple Carbohydrate and Trans Fat Intake with Severity of Coronary Artery Stenosis Based on Gensini Score at Kariadi Hospital Semarang

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Abstract

Background : Coronary artery disease accounts for 111 million (27%) out of 400 million cases of cardiovascular disease worldwide. Regular consumption of foods high in trans fats and simple carbohydrates is a major cause of increased blood lipid and glucose levels, which are key risk factors for coronary artery disease.
Aims : This researches to examine the relationship between the amount of simple carbohydrate and trans fat intake and the severity of coronary artery stenosis based on the Gensini score.
Methods : This research used a cross-sectional observational design involving 56 patients with chronic coronary syndrome who had undergone coronary angiography and were found to have stenosis in their coronary arteries. The parameters assessed included the amount of simple carbohydrate intake, trans fat intake, LDL levels, HDL levels, triglyceride levels, HbA1C levels, hs-CRP levels, oxLDL levels, and Gensini score.
Results : There was a significant relationship between the amount of simple carbohydrate intake and the severity of coronary artery stenosis based on the Gensini score (p=0.004), and between the amount of trans fat intake and the severity of coronary artery stenosis based on the Gensini score (p=0.02). Additionally, there was a significant relationship between trans fat levels and LDL levels (p=0.017), and oxLDL levels (p=0.014), but not with HDL, triglyceride, or hs-CRP levels (p>0.05). Confounding variables such as age, gender, socioeconomic status, body mass index, hypertension, diabetes mellitus, dyslipidemia, statin use, antidiabetic drug use, physical activity, and statin use showed no significant relationship (p>0.05).
Conclusion : There is a significant relationship between the amount of simple carbohydrate and trans fat intake and the severity of coronary artery stenosis based on the Gensini score.

Keywords : Coronary Artery Disease, Gensini Score, Simple Carbohydrates, Trans Fats

INTRODUCTION

The prevalence of cardiovascular disease, particularly Coronary Heart Disease (CHD), continues to increase globally and is a major cause of death and reduced quality of life. Lifestyle changes, especially the consumption of fast food or processed foods high in simple carbohydrates and trans fats, are primary factors in the increase of blood lipid and glucose levels, which are major risk factors for CHD.[1,2]

The 2021 National Socioeconomic Survey (Susenas) Microdata from the Central Statistics Agency (BPS) included 339,670 respondents representing Indonesia's 271.5 million population in 2021. 14.9 million Indonesians, or 17.6%, consumed excessive amounts of sugar, with an average sugar intake of 65.12 grams per person per day. The second most consumed type of food or beverage was granulated sugar, followed by sweetened condensed milk and brown sugar. Indonesians' carbohydrate intake continued to increase from 1961 to 2013. In 1961, it was 1,439.13 kcal, and in 2013, it rose to 2,008 kcal. Despite the increase, the proportion of total calories consumed tended to decrease, from 78.9% in 1961 to 72 percent in 2013. This indicates a trend toward reducing carbohydrate intake among Indonesians. But on the other hand, there has been an increase in fat intake. For example, in 1961, the proportion of fat intake compared to total calories was 13%. In 2013, it increased to 18.7%. Similarly, protein intake increased from 7.72% to 8%. Data from the National Socioeconomic Survey (Susenas) also shows a similar trend, especially among high-income communities. On average, the poor (77.8%) consumed more carbohydrates than the wealthy (68.8 %). Total calorie intake from fat, carbohydrates, and fat also increased by 58%. In 1961, the total calorie intake was 1,824 kcal, rising to 2,883 kcal in 2013. Obesity significantly increases the risk of type 2 diabetes and premature atherothrombosis. Approximately 13% of adults in the United States (34.1 million) have diabetes (mostly type 2 diabetes), with significant variation by age, gender, race/ethnicity, and socioeconomic status, and this number is projected to increase significantly by 2050. This condition is accompanied by rising obesity, which increases the risk of type 2 diabetes and atherothrombosis. Factors such as age, gender, LDL cholesterol, smoking, and diabetes mellitus (DM) are related to the severity of coronary lesions. DM specifically accelerates CHD through vascular damage and endothelial dysfunction.[3–5,21]

Quantitatively assess the severity of CHD, the Gensini Score (GS) is used, based on coronary angiography results, to calculate the atherosclerotic plaque burden. This score is important for disease management and long-term prognosis. Nutritional intake, especially of trans fats, has a significant impact on coronary artery disease and has been shown to be a predictor of the severity of coronary artery lesions based on the Gensini Score. Trans fats trigger adverse effects through atherogenic processes, including increased pro-inflammatory cytokines and decreased nitric oxide levels. Dietary patterns high in simple carbohydrates and trans fats, such as in some traditional market snacks in Indonesia, potentially increase the risk of CHD.[6,7]

Previous research indicates that high carbohydrate and trans fat intake increases CHD risk factors such as metabolic syndrome, type II DM, and dyslipidemia. To measure nutrient intake, the Food Frequency Questionnaire (FFQ) is a valid and representative method for identifying eating habits and specific nutrient intake.[7,8,22]

Considering the important role of nutritional intake in atherosclerosis and the lack of research quantitatively linking the intake of simple carbohydrates and trans fats with the severity of coronary artery stenosis based on the Gensini Score, this study aims to investigate this relationship at Dr. Kariadi General Hospital Semarang.

METHODS

This study was an observational analytical study with a cross-sectional design. The research received ethical approval from the Health Research Ethics Committee (KEPK) of the Faculty of Medicine, Diponegoro University and Dr. Kariadi General Hospital Semarang, Number 16284/EC/KEPK-RSDK/2024, and research permit Number DP.04.01.D.X.2/9592/2924. The research sample consisted of 56 Coronary Heart Disease (CHD) patients treated at Dr. Kariadi Hospital Semarang during the period of December 2024 who came to Dr. Kariadi Hospital and met the following inclusion criteria: Patients with Chronic Coronary Syndrome, patients aged 18 years and older, patients who underwent coronary angiography and were found to have coronary artery stenosis, and patients who agreed to participate in the study by signing an informed consent form. Exclusion criteria were: Patients with a family history risk factor for CHD, patients cognitively unable to be interviewed, patients with liver disease, infection, and inflammatory diseases, patients who had undergone Percutaneous Coronary Intervention or Coronary Artery Bypass Graft surgery, and significant changes in dietary patterns for more than 1 year.

Venous blood samples were immediately taken from patients for laboratory examination of LDL, HDL, Triglycerides, HbA1c, oxLDL, and hs-CRP. The blood was centrifuged and stored at -20°C until used. Levels of LDL, HDL, triglycerides, hs-CRP (in mg/dL) and oxLDL (in ng/mL) as well as HbA1c (in %) were directly examined from venous blood the ELISA method with Abott reagent at the GAKY laboratory of Diponegoro University, Semarang. Subsequently, interviews were

conducted by bachelor-qualified nutritionists (S1) using a validated Semiquantitative Food Frequency Questionnaire (SQ FFQ) and food models, with units in grams per day (g/day), to determine the intake of simple carbohydrates and trans fats. Types of simple carbohydrates and trans fats were differentiated based on their processing method (recorded in the SQ FFQ); namely, simple carbohydrates are refined carbohydrates that have undergone processing, such as bread, noodles, pasta, glutinous rice, sugar, syrup, and ice cream. Trans fats are foods that are deep-fried, such as french fries, fried tofu, and various other fried foods. The relationship between simple carbohydrates and trans fats and the severity of coronary artery stenosis was analyzed using Spearman and Pearson tests. Confounding variables, including age, gender, hypertension status, DM status, dyslipidemia status, smoking status, physical activity level (yes/no), statin consumption, and antidiabetic drug consumption, were analyzed using multiple linear regression tests.[7,8]

RESULTS

Sample collection was conducted using consecutive sampling from December 2024. The study subjects were patients with chronic coronary syndrome who underwent coronary angiography and met the inclusion criteria at Kariadi Hospital Semarang. A total of 62 study subjects underwent coronary angiography procedures in December 2024, and there were 6 subjects who dropped out because their coronary angiography results were normal. The 56 study subjects who met the inclusion criteria underwent a questionnaire survey using the SQ-FFQ method, then had laboratory examinations for HDL, LDL, Triglycerides, HbA1C, hs-CRP, and oxLDL, and then their Gensini score was assessed from the results of the coronary angiography they had undergone. These study subjects exhibited diverse baseline characteristics with statistically significant differences, such as age, gender, socioeconomic status, physical activity level, BMI (Body Mass Index), routine medication consumption, simple carbohydrate intake, trans fat intake, energy intake, HDL levels, LDL levels, Triglyceride levels, HbA1C levels, hs-CRP levels, oxLDL levels, and Gensini score.

In Table 1 basic characteristics, the majority of study subjects were male (43 subjects, 76.8%), compared to females (13 subjects, 23.2%). The mean age of the subjects was 56.9 ± 10.21 years, with a median age of 57 years (range 37–82 years). The most common risk factor found was hypertension, experienced by 28 subjects (50.0%), followed by a history of being ex-smokers in 25 subjects (44.6%), compared to current smokers (6 subjects, 10.7%), dyslipidemia in 19 subjects (33.9%), and diabetes mellitus in 17 subjects (30.4%). The most frequently encountered highest level of education was high school (SMA), accounting for 28 subjects (50.0%), and the majority of subjects came from a middle socioeconomic level (39 subjects, 69.6%).

In anthropometric measurements, the mean body weight of the subjects was 69.8 ± 12.75 kg, mean height was 1.6 ± 0.07 meters, and the mean Body Mass Index (BMI) was 26.1 ± 4.19 kg/m². Most subjects used moderate-intensity statins, predominantly atorvastatin 20mg/day (31 subjects, 55.4%), and only a small proportion consumed anti-diabetic drugs (16 subjects, 28.6%). Additionally, the proportion of subjects reporting sufficient physical activity of 30 minutes per day, 5 times a week, was also low, at only 17 subjects (30.4%). The mean simple carbohydrate intake was only 65.5 ± 28.81 grams/day, equivalent to 262.2 ± 115.24 kcal/day. This is still below the WHO recommendation that total carbohydrate intake per day should be 40–65% of total daily calorie needs, and simple carbohydrate intake should be 10% of total daily calorie needs. Meanwhile, the mean trans fat intake was 2.1 ± 6.41 grams/day, equivalent to 25.9 ± 57.69 kcal/day, exceeding the recommended limit for trans fat intake, which is 1% of total daily calories.

In the Table 2 examines the relationship between various confounding factors and the Gensini Score, indicates that none of the tested variables demonstrated a statistically significant association. Factors such as gender, hypertension, smoking status, OAD use, and physical activity all produced p-values well above the standard significance threshold of $p<0.05$. It is particularly noteworthy that despite a substantial numerical difference in the mean Gensini Score between statin consumers (78.32±42.95) and non-consumers (36.33±27.79), the result did not achieve statistical significance ($p=0.102$). This lack of significance, especially in the statin group, may be attributed to high variability within the groups (as evidenced by large standard deviations) or a potentially underpowered study sample. Furthermore, the stated use of Spearman's correlation is an unconventional methodological choice for comparing a continuous variable between two distinct groups, where a Mann-Whitney U test would typically be more appropriate. Therefore, based on this analysis, it must be concluded that no significant relationship was found between the investigated confounding factors and the Gensini Score in this study population.

In the Table 3 the results of testing confounding variables against the Gensini score showed p-values >0.05. Thus, it can be concluded that these confounding variables did not have a significant relationship with the Gensini score. However, statin consumption and gender approached p-values < 0.25, but they could not be carried forward to multivariate analysis because they are categorical variables.

In the Table 4 simple carbohydrate intake, the p-value was 0.001 ($p < 0.05$) and the r-value was 0.420.

TABLE 1
Baseline Characteristic

Variable	Frequency (n=56)	%	Mean ± SD	Median (min – max)
Gender				
Men	43	76.8		
Women	13	23.2		
Age			56.9 ± 10.21	57 (37 – 82)
Risk Factor				
Hipertension	28	50.0		
Ex-smoker	25	44.6		
Smoker	6	10.7		
DM	17	30.4		
Dyslipidemia	19	33.9		
Menopause	4	7.1		
FH CAD	5	8.9		
Education				
SD	3	5.4		
SMP	6	10.7		
SMA	28	50.0		
S1	12	21.4		
S2	7	12.5		
Social Economic				
Low	8	14.3		
Moderate	39	69.6		
High	9	16.1		
Weight			69.7 ± 12.7	68.5 (42 – 97)
Height			1.6 ± 0.07	1.65 (1.48 – 1.85)
BMI			26.1 ± 4.19	25.92 (17.48 – 37.78)
Statin				
Non-Consumed	3	5.4		
Consumed	53	94.6		
Oral Anti-Diabetic				
Consumed	16	28.6		
Non-Consumed	40	71.4		
Physical Activity				
Yes	17	30.4		
No	39	69.6		

TABLE 1. *Continued*

Variable	Frequency (n=56)	%	Mean ± SD	Median (min – max)
Simple Cardohydrates (ccal/day)			262.2 ± 115.24	282.8 (2.0 – 565.6)
Complex Carbohydrates (ccal/day)			887.68 ± 418.16	838.8 (202.4 – 2168.8)
Total Carbohydrates (ccal/day)			1068.64 ± 394.64	976.2 (408.4 – 2204.8)
Trans Fat (ccal/day)			25.9 ± 57.69	3.8 (2.7 – 424.8)
Total Fat (ccal/day)			1079.64 ± 540.18	956.7 (396 – 2846.7)
Saturated Fat (ccal/day)			556.74 ± 287.55	489.6 (209.7 – 1548.9)
Unsaturated Fat (ccal/day)			429.12 ± 219.42	365.4 (158.4 – 1094.4)
Total Fat (ccal/day)			1079.64 ± 540.18	956.7 (396 – 2846.7)
Protein (ccal/day)			376.21 ± 118.52	312 (30 – 612.8)
Fiber (ccal/day)			42.7 ± 30.5	43.8 (19.6 – 85.8)
Energi (ccal/day)			2508.1 ± 978.35	2288.2 (1076.9 – 4813.5)
HDL (mg/dl)			38.9 ± 10.84	37.5 (18 – 86)
LDL (mg/dl)			101.9 ± 39.31	94 (27 – 195)
Trigiseride (mg/dl)			130.2 ± 105.69	103 (19 – 684)
HbA1C (%)			6.3 ± 1.25 (%)	5.8 (4.8 – 10.6)
Hs-CRP (mg/L)			5.4 ± 4.47	4.25 (0.40 – 15.60)
OxLDL (ng/ml)			74.5 ± 17.97	75.36 (24.88 – 109.01)
Gensini Score			76.1 ± 43.17	78 (8 – 164)

Information: DM : Diabetes Melitus; FH CAD : *Family History Coronary Artery Disease;* SD : Sekolah Dasar; SMP : Sekolah Menengah Pertama; SMA : Sekolah Menengah Atas; S1 : Strata-1; S2 : Strata-2; BMI : Body Mass Index; OAD : Oral Anti-Diabetic

Thus, it can be concluded that there is a significant relationship between simple carbohydrate intake and the Gensini score, with a moderate positive direction and strength. Trans fat intake, the *p*-value was 0.034 ($p < 0.05$) and the r-value was 0.283. Thus, it can be concluded that there is a significant relationship between trans fat intake and the Gensini score, with a weak positive direction and strength. LDL levels, the *p*-value was 0.044 ($p < 0.05$) and the r-value was 0.270. Thus, it can be concluded that there is a significant relationship between LDL levels and the Gensini score, with a weak positive direction and strength.Hs-CRP levels, the *p*-value was 0.020 ($p < 0.05$) and the r-value was 0.310. Thus, it can be concluded that there is a significant relationship between hs-CRP levels and the Gensini score, with a weak positive direction and strength.

OxLDL levels, the *p*-value was 0.007 ($p < 0.05$) and the r-value was 0.359. Thus, it can be concluded that there is a significant relationship between OxLDL levels and the Gensini score, with a weak positive direction and strength. Other variables in relation to the Gensini score, using the correlation test, *p*-values >0.05 were obtained; thus, it can be concluded that there was no significant relationship.

In the Table 5 the results of the Spearman's correlation test of the relationship between the amount of simple carbohydrate intake and triglyceride levels obtained a *p* value = 0.588 ($p > 0.05$) so it can be concluded that there is no significant relationship. The results of the Spearman's correlation test of the relationship between the amount of simple carbohydrate intake and HbA1C levels obtained a *p* value = 0.021 ($p < 0.05$) and r value = 0.307 (0.2 – <0.4) so it can be concluded that there is a significant relationship with the direction and strength of the relationship being weakly positive. The results of the test of the relationship between carbohydrates and hs-CRP using the Spearman's correlation test obtained a *p* value = 0.053 ($p > 0.05$) so it can be concluded that the amount of simple carbohydrate intake with hs-CRP has no significant relationship, but the amount of simple carbohydrate intake with OxLDL using the Pearson correlation test obtained a *p* value = 0.014 ($p < 0.05$) and

TABLE 2
Relation Confounding Factor with Gensini Score

Confounding Variable	Gensini Score	*p*
Gender		0.155£
Male	80.6 ± 45.83	
Female	61.1 ± 29.52	
Hypertension		0.482£
Yes	71.96 ± 39.72	
No	80.18 ± 46.73	
Smoker		0.909£
Yes	78.00 ± 48.05	
No	75.84 ± 43.01	
Statin		0.102£
Non-Consumed	36.33 ± 27.79	
Consumed	78.32 ± 42.95	
OAD		0.771£
Consumed	73.4 ± 49.09	
Non-Consumed	77.2 ± 41.20	
Physical Activity		0.858£
Yes	64.6 ± 26.55	
No	80.5 ± 44.96	

Information : £Correlation Spearman's

TABLE 3
Relation Confounding Factor with Age and BMI on Gensini Score

Variabel Perancu	Gensini Score	
	r	*p*
Age	0.093	0.494¶
BMI	0.145	0.288¶

r value = 0.328 (0.2 - <0.4) so it can be concluded that the amount of carbohydrate intake with oxLDL has a significant relationship with the direction and strength of the relationship being weakly positive.

In the Table 6 The results of the Spearman's correlation test of the relationship between the amount of trans fat intake and HDL levels obtained a *p* value = 0.299 ($p > 0.05$) so it can be concluded that there is no significant relationship. The results of the Spearman's correlation test of the relationship between the amount of fat intake and LDL levels obtained a *p* value = 0.017 ($p < 0.05$) r value = 0.318 (0.2 – <0.4) so it can be concluded that the amount of trans fat intake and LDL levels has a significant relationship with the direction and strength of the relationship being weakly positive. The results of the Spearman's correlation test of the relationship between the amount of trans fat intake and triglyceride levels obtained a *p* value = 0.410 ($p > 0.05$) so it can be concluded that there is no significant relationship. The results of the test of the relationship between fat and hs-CRP using the Spearman's correlation test obtained a *p* value = 0.053 ($p > 0.05$) so it can be concluded that there is no significant relationship between fat and hs-CRP, in OxLDL using the Spearman's correlation obtained a *p* value = 0.954

TABLE 4
Relation Variable with with Gensini Score

Variable	Gensini Score	
	r	*p*
Simple Carbohydrates	0.420	0.001¶*
Trans Fat	0.283	0.034£*
Energy	0.111	0.413£
HDL	-0.035	0.795£
LDL	0.270	0.044¶*
Trigiseride	0.028	0.839£
HbA1C	0.024	0.861£
Hs-CRP	0.310	0.020£*
OxLDL	0.359	0.007¶*

Information : *Significant ($p < 0.05$); ¶Correlation Pearson; £Correlation Spearman's

TABLE 5
Relation Simple Carbohydrates with Trigliseride, HbA1C, hs-CRP and oxLDL

Variable	Simple Carbohydrates	
	r	*p*
Trigliseride	0.129	0.344£
HbA1C	0.058	0.021£*
hs-CRP	0.144	0.053£
OxLDL	0.022	0.014¶*

Information : Normal ($p > 0.05$); *Significant ($p < 0,05$); ¶Correlation Pearson; £Correlation Spearman's

TABLE 6
Relation Trans Fat with HDL, LDL, Trigliseride, hs-CRP and oxLDL

Variable	Trans Fat	
	r	*p*
HDL	-0.141	0.299£
LDL	0.318	0.017£*
Trigliseride	0.112	0.410£
hs-CRP	0.241	0.074£
OxLDL	0.008	0.954£

Information : Normal ($p > 0.05$); *positif ($p < 0.05$); £Correlation Spearman's

($p > 0.05$) so it can be concluded that there is no significant relationship between fat and OxLDL.

In the Table 7 the results of the correlation test of the variables of the amount of simple carbohydrate intake, the amount of trans fat intake, LDL levels, hs-CRP levels and oxLDL levels meet the requirements for multivariate testing using multiple linear regression tests. The results of the multiple linear regression test on the amount of simple carbohydrate intake obtained a p value = 0.004 ($p < 0.05$) so it can be concluded that the

TABLE 7
Multivariate Results with Gensini Score

Variable	Beta	*p*
Simple Carbohydrates	0.347	0.004*
Trans Fat	0.357	0.002*
LDL	0.122	0.304
Hs-CRP	0.056	0.663
OxLDL	0.280	0.019*

Information : *Significant ($p < 0.05$)

amount of simple carbohydrate intake is a factor that influences the Gensini score. On the amount of trans fat intake, the p value = 0.002 (p <0.05) was obtained. On OxLDL levels, the p value = 0.019 (p <0.05) was obtained so it can be concluded that the amount of simple carbohydrate intake, trans fat, and oxLDL levels are factors that influence the Gensini score.

DISCCUSION

This research comprehensively investigates various factors potentially influencing the severity of Coronary Heart Disease (CHD) as measured by the Gensini score and their relationship with various important biomarkers. The primary focus is on the role of nutritional intake, specifically simple carbohydrates and trans fats, alongside an analysis of confounding variables and the methodological limitations of the study.[12,13]

The Influence of Simple Carbohydrate Intake on Gensini Score and Other Biomarkers In the demographic context, this study found that the majority of CHD patients were around 56 years old, a finding consistent with previous research that underscores the role of the aging process in the decline of normal tissue function and structure. Furthermore, it was emphasized that dietary patterns dominated by simple carbohydrates, such as those found in sweet snacks, corn syrup, and added sugars, significantly increase the risk of CHD events. Specifically, the results of Pearson correlation analysis in this study indicated a significant positive relationship with moderate strength (p=0.001; r=0.420) between the amount of simple carbohydrate intake and the Gensini score. This finding is supported by a previous meta-analysis by Jo U *et al*., which indicated that individuals with the highest carbohydrate consumption have a 1.15 times higher risk of cardiovascular disease, particularly in the context of atherosclerosis development. The average simple carbohydrate intake of the study subjects was 45.24 ± 28.81 grams/day (equivalent to 262.2 ± 115.24 kcal/day), accounting for approximately 10% of the total daily energy intake. This figure was considered to have reached or even exceeded the upper limit of the low simple carbohydrate dietary proportion recommended for CHD prevention (i.e., a maximum of 10% of total daily calories). The nature of simple or refined carbohydrates having undergone processing, lost fiber and micronutrients, and possessing smaller moleculescauses them to be absorbed more quickly, metabolized faster, and potentially trigger detrimental spikes in plasma glucose levels. Regarding other biomarkers, this study found no significant relationship between simple carbohydrate intake and levels of triglycerides, hs-CRP, or oxLDL. However, a significant positive relationship, albeit with very weak strength (p=0.021; r=0.058), was detected between simple carbohydrate intake and HbA1c levels. This finding is relevant because other research, such as by Xiao Jiao *et al*., has linked higher HbA1c levels with increased CHD severity based on the Gensini score, where hyperglycemia is known to damage the cardiovascular system and accelerate the atherosclerotic process through various mechanisms, including endothelial cell damage and oxidative stress.[12,13]

The Role of Trans Fat Intake on Gensini Score, Lipid Profile, and Inflammation Furthermore, this study also revealed a significant positive correlation, though with weak strength (p=0.034; r=0.283), between the amount of trans fat intake and the Gensini score. The consistency of this finding with previous research, such as by Li-Yun *et al*. and Samia Hadj *et al*., reinforces the idea that trans fat intake can serve as a biomarker predicting the severity of coronary artery lesions and correlates with inflammatory parameters and oxidative stress. The average trans fat intake in this study was recorded at 2.10 ± 6.41 grams/day (equivalent to 25.9 ± 57.69 kcal/day). Considering the subjects' average energy intake of 2508.12 ± 978.35 kcal/day, this trans fat intake (approximately 1% of total energy) was still within the limits recommended by the World Health Organization for adults, which is less than 1% of total daily energy intake. In relation to specific biomarkers, a significant positive relationship with weak strength was found between trans fat intake and LDL levels (p=0.017;

r=0.318). Furthermore, trans fat intake also showed a significant relationship with hs-CRP, an important inflammatory marker. Nevertheless, no significant relationship was found between trans fat intake and levels of HDL, triglycerides, or oxLDL. This difference in results compared to some other studies, such as by Zapolska *et al*., could possibly be explained by the relatively low level of trans fat intake (less than 1% of total energy) in this study's subject population.[15–17] Analysis of Confounding Variables and Their Influence on the Gensini Score This study also discussed various confounding variables that can influence the interpretation of the relationship between risk factors and the Gensini score. It was explained that confounding variables may not always show a direct relationship with the dependent variable for various reasons, including the presence of mediators, very small effects, or errors in measurement and identification. The average age of the subjects (56 years) and the predominance of males (76.8%) in this study sample align with the general demographic profile of CHD patients, where men are known to be more susceptible to atherosclerosis progression before menopause. Risk factors like hypertension, although theoretically significant, might not have shown a strong correlation with the Gensini score in this study due to the use of antihypertensive medication by a majority of the subjects, potentially modifying its effects. One of the most prominent confounding variables was statin consumption. Consistent with major studies like PARADIGM, JUPITER, and REVERSAL, statin use has been proven to be associated with a reduction in the progression rate of coronary atherosclerosis and can lower levels of inflammatory biomarkers (hs-CRP) and lipids (LDL, oxLDL). Therefore, statin consumption can be a significant co-founding factor in the analysis of the relationship between diet and atherosclerotic biomarkers. Similarly, the use of antidiabetic drugs has the potential to influence oxLDL levels, given that these medications are known to have suppressive effects on oxLDL and related inflammatory processes in diabetic patients. The relatively low level of physical activity reported by the study subjects was also noted, considering the benefits of physical activity in improving coronary blood flow and endothelial function in CHD patients. Conversely, fiber intake showed interesting results, with a significant relationship found between higher fiber intake and lower levels of hs-CRP and oxLDL, supporting the protective role of fiber in the atherosclerotic process.[18–20]

Methodological Limitations of the Research Finally, this study transparently acknowledged several methodological limitations. The use of the Semiquantitative Food Frequency Questionnaire (SQ-FFQ), which relies heavily on the subjects' recall memory regarding their simple carbohydrate and trans fat intake habits over a specific period, has the potential to introduce bias in data collection. Additionally, there was a risk of flat slope syndrome, a tendency for research subjects to provide answers that do not entirely reflect reality, for instance, by under-reporting their intake, which could affect the accuracy of the dietary intake data obtained and the overall interpretation of the research findings.[7]

Thus, this research provides an important contribution to understanding the complex interactions between diet, particularly simple carbohydrate and trans fat intake, and the severity of CHD and related biomarkers, while also considering the influence of confounding variables and acknowledging the inherent limitations in the methodology employed.[12,13]

CONCLUSION

This research presents significant findings that deepen our understanding of how daily dietary patterns directly contribute to heart health. Convincingly, the study reveals a strong relationship between the intake amount of simple carbohydrates and trans fats and the severity of coronary artery stenosis, objectively measured by the Gensini score. To ensure the accuracy and depth of data in similar future investigations, this research offers an important suggestion that the dietary intake interview process be conducted more personally and gradually, thereby building a better rapport with research subjects and yielding more valid and reliable dietary information.

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CONFLICT OF INTEREST

The author has no conflicts of interest that could affect the results or interpretation in this report.

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Original Article

Hypokalemia Correlates with Troponin Levels in Moderate-Severe COVID-19 Patients, Independent to Coagulation Status

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Abstract

Background : Myocardial injury is a common complication of COVID-19, often marked by elevated cardiac troponin and linked to poorer outcomes. Besides recognized causes such as viral injury, inflammation, and coagulopathy, electrolyte disturbances like hypokalemia may also increase cardiac vulnerability. SARS-CoV-2 can promote potassium loss through activation of the renin angiotensin aldosterone system, but the relationship between low potassium and troponin elevation remains unclear.
Aim : To evaluate whether serum potassium levels are associated with troponin elevation in patients hospitalized with moderate to severe COVID-19, and whether this association is influenced by disease severity or D-dimer levels.
Methods : Cross-sectional study of 50 adults with moderate or severe COVID-19. Serum potassium, troponin, and D-dimer were measured once during admission. Associations were tested using independent t-tests, Mann-Whitney tests, and Fisher's exact tests, with $p < 0.05$ considered significant.
Results : Among 50 patients (39 moderate, 11 severe COVID-19), 35 (70%) had normal potassium, 12 (24%) hypokalemia, and 3 (6%) severe hypokalemia; 9 (18%) had elevated troponin. Potassium was lower in patients with elevated troponin than in those with normal levels (3.53 ± 0.53 vs. 3.99 ± 0.58 mmol/L, $p = 0.038$), and potassium status was significantly associated with troponin elevation ($p = 0.0401$). No significant differences were detected when patients were grouped by disease severity, with potassium ($p = 0.44$) and troponin ($p = 0.66$) levels similar in moderate and severe cases. D-dimer levels were not significantly different by severity ($p = 0.175$) and showed no association with potassium ($p = 0.24$) or troponin ($p = 0.91$).
Conclusion : In hospitalized patients with moderate to severe COVID-19, lower potassium levels were associated with elevated troponin, regardless of disease severity and without a detectable link to D-dimer status. These findings suggest hypokalemia may contribute to myocardial injury in COVID-19 and support regular monitoring and timely correction of electrolyte disturbances.

Keywords : COVID-19, D-dimer, Hypokalemia, Myocardial injury, Troponin

INTRODUCTION

Elevated troponin levels have become a critical marker of myocardial injury, drawing significant attention in the management of COVID-19.[1] Studies consistently link troponin elevation in these patients to severe cardiac complications,[1,2] heightened inflammation,[3] and increased mortality.[1–3] The mechanisms behind this are multifaceted, ranging from virus-induced cytokine storms and direct myocardial invasion to systemic hypoxia and a prothrombotic state.[1–3] These factors collectively place immense stress on the heart, increasing the risk of myocardial injury and adverse outcomes. Recognizing and addressing myocardial injury early could be a key step in improving prognosis for high-risk COVID-19 patients.

Among the many potential contributors to myocardial injury in COVID-19, electrolyte imbalances, particularly hypokalemia,[4,5] deserve close investigation. Hypokalemia can impair myocardial repolarization, destabilize cell membrane potentials, and reduce cardiac contractility,[6] thereby predisposing the heart to arrhythmias and ischemic injury.[7] Not only that, Hypokalemia is known to disrupt cellular electrophysiology,[8] create a pro-arrhythmic environment,[9] and potentially worsen myocardial injury.[9] Although the pathophysiological effects of hypokalemia are well recognized,[7–9] the role of hypokalemia in driving troponin elevation in COVID-19 remains unexplored, especially in the context of the frequent coagulopathy observed in these patients.[10,11] While many studies address either coagulation abnormalities[11] or electrolyte disturbances,[12] evidence on the specific interplay between hypokalemia and troponin levels within the broader setting of COVID-19 is lacking.

Building on this gap, our study investigates whether hypokalemia is associated with elevated troponin levels in COVID-19 patients. By exploring this relationship, we aim to provide deeper insight into how hypokalemia contributes to myocardial injury in an already vulnerable population. Our findings could enhance clinical decision-making and guide targeted interventions to mitigate cardiac complications. Ultimately, this work seeks to improve patient outcomes by advancing our understanding of the complex interplay between COVID-19, myocardial injury, and hypokalemia.

METHODS

This observational study employed a cross-sectional design to assess 50 patients with moderate to severe COVID-19. Patients were selected through purposive sampling from the medical records of inpatients at Dr. Kariadi Hospital, Semarang, between January and December 2021. The inclusion criteria consisted of patients aged 18 years or older with available potassium and troponin data. COVID-19 severity was classified based on clinical presentation: moderate cases included patients without symptoms of severe pneumonia who did not require oxygen supplementation, while severe cases were defined as those exhibiting severe pneumonia symptoms, requiring oxygen therapy, experiencing respiratory failure, sepsis, shock, or requiring admission to the intensive care unit (ICU). Patients with mild COVID-19 were excluded from the study.

Troponin levels were obtained from blood samples and categorized as normal (<0.1 ng/mL) or elevated (≥0.1 ng/mL). Potassium levels were similarly measured and classified as normal (>3.5 mg/dL), hypokalemia (3.0–3.5 mg/dL), or severe hypokalemia (<3.0 mg/dL). One patient with hyperkalemia (>5.0 mg/dL; 5.7 mg/dL) was retained in the dataset and included within the non-hypokalemia group for the primary comparison. Additionally, coagulation status was evaluated using D-dimer levels, with values below 500 ng/mL considered normal and values of 500 ng/mL or higher classified as elevated.

Following data collection, all information underwent a structured process of cleaning, coding, and categorization according to predefined criteria. Statistical analyses were conducted using IBM SPSS Statistics version 24, while data visualization was performed using GraphPad Prism 10.

This study was conducted following ethical guidelines and received approval from the Health Research Ethics Committee of the Faculty of Medicine, Diponegoro University, with ethical clearance number 593/EC/KEPK-RSDK/2020. Additionally, permission was granted by the Director of Dr. Kariadi Hospital. Written informed consent was obtained from all patients before their inclusion in the study. To minimize selection bias, information bias, and confounding variables, the inclusion and exclusion criteria were strictly enforced, with each subject evaluated independently by at least two examiners.

RESULTS

A total of 50 patients were included in the study (Table 1). In terms of COVID-19 severity, 39 patients (78%) presented with moderate disease, while 11 patients (22%) had severe disease. Regarding potassium levels, 35 patients (70%) had normal potassium, 12 patients (24%) had hypokalemia, and 3 patients (6%) had severe hypokalemia. The majority of 41 patients (82%) had normal troponin, whereas 9 patients (18%) had elevated levels. D-dimer was also normal in 43 patients (86%), with the remaining 7 patients (14%) showing elevated D-dimer values.

We first examined the relationship between potassium and troponin levels. Potassium reduction was

TABLE 1
Characteristics of patient data

Patient Characteristic	N	Frequency (%)	Mean ± SD / Median (min – max)
Sex			
Male	23	46	
Female	27	54	
Age			52.14 ± 14.22 years
< 50 years	20	40	
51–75 years	28	56	
>75 years	2	4	
Covid Severity			
Moderate	39	78	
Severe	11	22	
Potassium			3.908 ± 0.603 mg/dL
Normal	35	70	
Hypokalemia	12	24	
Severe Hypokalemia	3	6	
Troponin			0.00895 (0.00099 – 15.101) ng/mL
Normal	41	82	
Increased	9	18	
D-dimer			1455 (270 – 20001) ng/mL
Normal	43	86	
Increased	7	14	

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

more pronounced in patients with increased troponin levels than in those with normal troponin levels. The average potassium level was 3.99 ± 0.58 mg/dL in the normal troponin group and 3.53 ± 0.53 mg/dL in the increased troponin group. Our analysis showed a statistically significant difference between patients with elevated troponin levels than in those with normal troponin levels (Independent t-test, p= 0.038) (Fig. 1A). To further explore this relationship, we compared the distribution of potassium status across troponin groups. Among patients with normal troponin, 31 had normokalemia, 9 had hypokalemia, and 1 had severe hypokalemia. In contrast, among those with elevated troponin, 4 had normokalemia, 3 had hypokalemia, and 2 had severe hypokalemia (Table 2). Fisher's exact analysis revealed a significant association between troponin status and potassium levels (p = 0.0401) (Fig. 1B, Table 2), consistent with the results observed in Figure 1A.

Given this significant association, we next investigated whether disease severity could influence the relationship between potassium and troponin, we analyzed potassium and troponin levels by stratifying patients into moderate vs. severe disease groups. Our observations showed that the average potassium level was 3.86 ± 0.61 mg/dL in the moderate covid group and 4.06 ± 0.50 mg/dL in the severe covid group (Fig. 2A), Our analysis using independent t-test doesn't show any statistically significant difference (p=0.44). When analyzing potassium status categories (normokalemia, hypokalemia, severe hypokalemia), there was no statistically significant difference between COVID-19 severity and potassium status (Fisher's exact, p = 0.69) (Fig. 2A).

Similarly, troponin levels were not significantly influenced by COVID-19 severity. Our data shows that the median troponin levels of moderate covid patients were 0.01 ng/mL (with min 0.001 and max 15.101) and

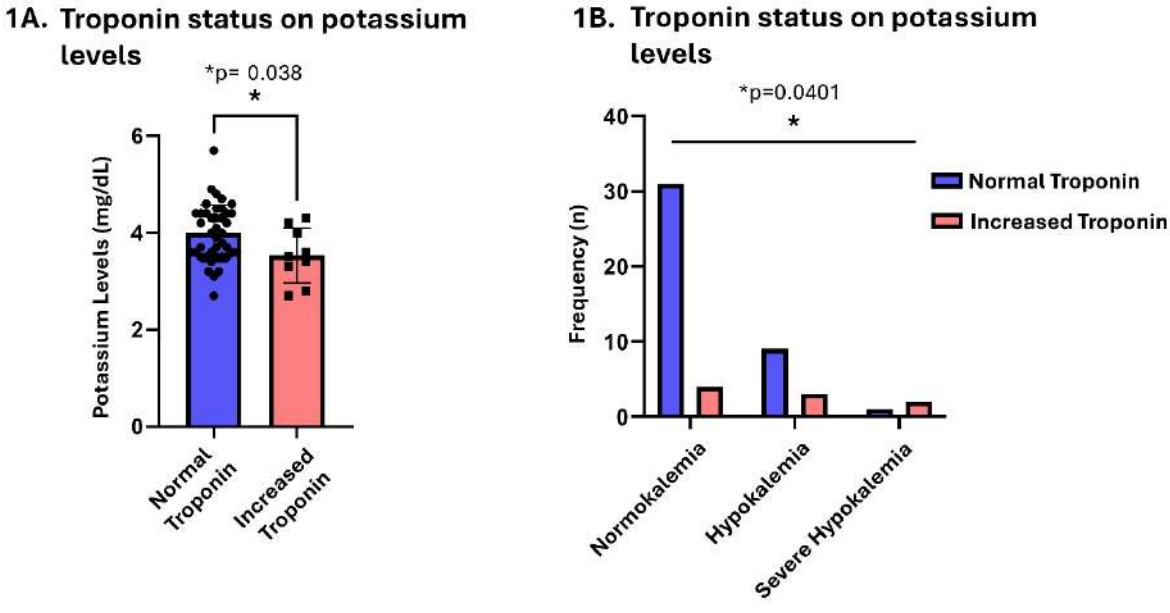

Figure 1. Relationship Between Serum Potassium Levels and Troponin Status in Patients with Moderate to Severe COVID-19. (A) Comparison between mean serum potassium levels in patients with normal vs. increased troponin. The data are presented as the mean values with error bars indicating the standard error of the mean. The analysis showed significant differences in potassium levels between normal and increased troponin groups (Independent t-test, *p= 0.038). (B) Frequency data of different potassium status categories (normokalemia, hypokalemia, and severe hypokalemia) in individuals with normal troponin (blue bars) and those with increased troponin (red bars) shows significant result (fisher's exact, *p=0.0401).

TABLE 2
Analysis of Troponin Status on Potassium Levels

	Normal Troponin (N)	Increased Troponin (N)	Fisher's exact analysis
Normal Potassium	31	4	*p = 0.0401
Hypokalemia	9	3	
Severe Hypokalemia	1	2	
Total	41	9	

Fisher's exact test was used to assess the association between potassium levels and troponin status.
p-value <0.05 was considered statistically significant.

severe covid patients were 0.008 ng/mL (with min 0.001 and max 0.157). Among moderate cases, 31 had normal troponin and 8 had increased troponin, whereas among severe cases, 10 had normal troponin and 1 had increased troponin (Fisher's exact, p = 0.66) (Fig. 2B).

Because coagulation abnormalities are a common complication of COVID-19 and may contribute to myocardial injury, we also examined whether D-dimer levels differed by disease severity. D-dimer levels tended to be higher in severe COVID-19 than in moderate cases. However, the difference did not reach statistical significance. The median D-dimer levels of moderate covid patients were 1230 ng/mL (with min 270 and max 20001) and severe covid patients were 3280 ng/mL (with min 410 and max 18910) Mann-Whitney test, p = 0.1750) (Fig. 2C). Elevated D-dimer levels were common in both groups, with no significant difference in distribution (Fisher's exact test, p = 0.99).

To further explore potential links between coagulation status and myocardial injury, we next analyzed biomarker levels according to D-dimer categories (normal vs. elevated). When troponin levels were compared between patients with normal and elevated D-dimer, the median values were similar

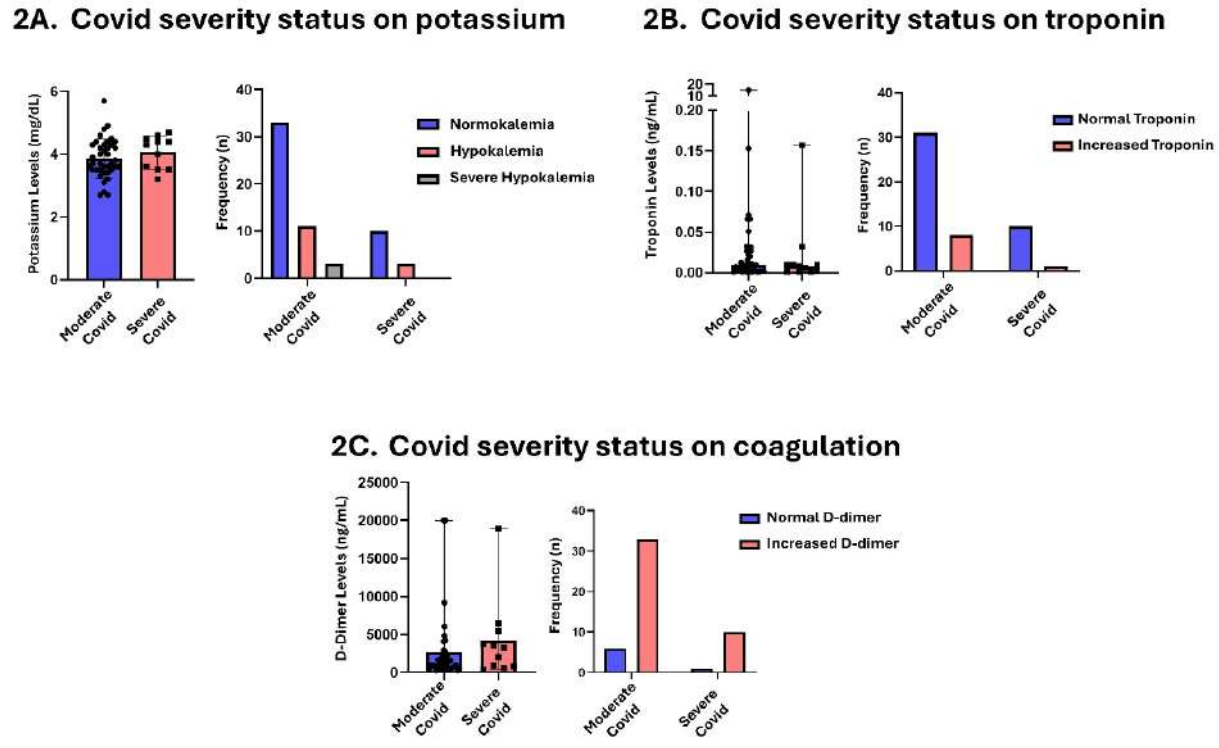

Figure 2. Association of COVID-19 Severity with Hypokalemia and Elevated Troponin. **(A) Left panel:** Comparison of serum potassium levels in moderate vs. severe COVID-19 patients. The data are presented as the mean values with error bars indicating the standard error of the mean. (Independent t-test, $p = 0.44$). The right panel further breaks down the distribution, showing how many patients with their potassium status in both groups. (Fisher's exact, $p = 0.69$). **(B) Left panel:** Comparison of serum troponin levels in moderate vs. severe COVID-19 patients. The data are shown as median number of factors with error bars representing max - min value. (Mann-Whitney, $p = 0.29$). The right panel further illustrate the distribution of patient troponin status, showing how many patients with normal or increased troponin in both groups. (Fisher's exact, $p = 0.66$). **(C) Left panel:** Comparison of D-dimer levels between patients with moderate and severe COVID-19. Data are shown as median values with error bars representing the minimum and maximum values (Mann-Whitney test, $p = 0.1750$). Right panel: Distribution of normal and increased D-dimer levels across COVID-19 severity categories (Fisher's exact test, $p = 0.99$).

(Normal D-dimer group were 0.01 ng/mL vs Elevated D-dimer group were 0.008 ng/mL), and the difference was not statistically significant (Mann-Whitney, $p = 0.91$). The proportion of patients with elevated troponin was also similar in both groups (Fisher's exact test, $p = 0.99$) (Fig. 3A).

A parallel analysis was performed for potassium levels. Mean concentrations were similar between the two D-dimer categories (Normal D-dimer group were 3.87 ± 0.61 mg/dL vs Elevated D-dimer group 4.16 ± 0.46 mg/dL) (Independent t-test $p = 0.24$), and the distribution of normokalemia, hypokalemia, and severe hypokalemia showed no meaningful variation (Fisher's exact $p = 0.79$) (Fig. 3B). These findings suggest that, within this cohort of moderate-to-severe COVID-19 patients, neither troponin nor potassium levels were influenced by coagulation status.

DISCUSSION

In this cross-sectional study of hospitalized patients with moderate to severe COVID-19, we found a notable association between hypokalemia and elevated troponin levels. This relationship persisted regardless of whether patients had severe or moderate disease, and it was not influenced by D-dimer status. These findings suggest that, for some patients, myocardial injury in COVID-19 may be linked to electrolyte disturbances rather than to the severity of respiratory illness or to overt coagulation abnormalities.

The biological link between hypokalemia and myocardial injury is well established.(8,9) SARS-CoV-2 infection can activate the renin angiotensin aldosterone system through ACE2 downregulation, leading to increased renal potassium loss.[12] Potassium depletion

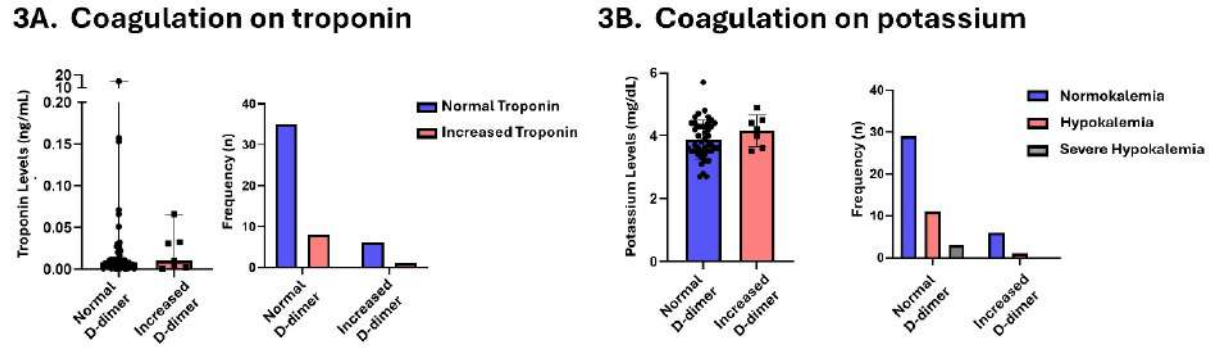

Figure 3. Association Between D-Dimer Status and Both Troponin and Serum Potassium in COVID-19 Patients. **(A) Left panel:** Comparison of serum Troponin levels in normal and increased D-dimer Covid-19 patients. The data are shown as median values with error bars representing max – min value. (Mann-Whitney, $p = 0.91$). The right panel further breaks down the distribution, showing how many patients with either normal or increased troponin. (Fisher's exact, $p = 0.99$). **(B) Left panel:** Comparison of serum potassium levels in normal vs. increased D-dimer groups. The data are presented as the mean values with error bars indicating the standard error of the mean. (Independent t-test, $p = 0.24$). The right panel further breaks down the distribution, illustrates the distribution of normokalemia, hypokalemia, and severe hypokalemia in each D-dimer category. (Fisher's exact, $p = 0.79$).

alters the electrical stability of the myocardium, delays repolarization, and increases the risk of arrhythmias.[8,9] In the setting of systemic illness and hypoxia, even modest potassium reductions can lower the threshold for myocardial injury. Our data support the possibility that correcting potassium early could reduce the risk of cardiac complications in hospitalized COVID-19 patients. Troponin serves not only as a biomarker of myocardial infarction but also of non-ischemic myocardial stress, frequently observed in systemic illness.[13,14] In the context of COVID-19, several mechanisms can lead to elevated troponin levels, including direct viral infiltration of cardiomyocytes,[3] cytokine-induced myocardial dysfunction and impaired microvascular perfusion,[3,15] oxygen supply-demand mismatch due to respiratory compromise, and coagulopathy associated with endothelial dysfunction and microthrombosis.[3,16] Our findings suggest that hypokalemia may contribute an additional myocardial stress, distinct from the classic ischemic or thrombotic pathways, by increasing cardiac vulnerability to electrical injury during systemic illness.

Interestingly, we did not find an association between D-dimer levels and troponin or potassium concentrations. While D-dimer is widely used as a marker of coagulopathy in COVID-19 on prior review,[11] is non-specific and can be influenced by many factors. In this study, most patients had D-dimer values within the normal range, which may explain the lack of statistical association. It is also possible that in moderately to severely ill but non-ICU patients, coagulation abnormalities are not the main driver of myocardial injury although our data didn't specifically analyze this possibility.

Clinically, our results suggest that checking electrolyte levels should be a routine part of caring for patients with COVID-19. An increase in troponin is not always caused by a blocked heart artery or a blood clot; sometimes, it can be due to general body stress combined with chemical imbalances in the blood, such as low potassium. Finding and fixing these correctable problems may help lower the risk of heart injury without the need for unnecessary treatments.[3]

The clinical impact of these findings is significant because hypokalemia is a treatable condition. Unlike complications such as cytokine storms[1,16] or viral myocarditis,[3] low potassium can be identified and corrected with standard care. Early detection and correction may reduce the risk of heart injury in patients with COVID-19.[17,18] These results support routine potassium monitoring in hospitalized patients, careful use of medicines that can lower potassium such as diuretics, and, for those at high risk, consideration of preventive potassium supplementation.[4,19] The fact that this association appears even in moderate illness highlights the value of intervening early, before the disease progresses to a level that requires intensive care.

Previous reports have linked hypokalemia to worse COVID-19 outcomes, although most emphasized global severity rather than cardiac injury. The multicenter study from China showed that hypokalemia was common and tracked with poorer prognosis,[18] but it did not specifically evaluate cardiac biomarkers such as

troponin. Another study examining electrolyte imbalance in COVID-19 patients similarly found hypokalemia to be frequent and related to increased morbidity, yet it focused more broadly on metabolic disturbances rather than their relationship with myocardial injury.[12] Our analysis complements these findings by demonstrating that lower potassium is also associated with troponin elevation, and that this signal persists irrespective of disease severity and D-dimer status. Taken together, prior work underscores prevalence and prognostic relevance, while our data connect hypokalemia to a concrete marker of myocardial injury.

This study has limitations. It was conducted at a single center with a relatively small number of patients, which may limit generalizability. We did not use regression modeling, as our aim was to examine individual associations rather than adjust for multiple variables, so the influence of confounding factors cannot be excluded. Information on comorbidities, chronic medications, and baseline organ function was not available, which restricts interpretation of the results. Laboratory measurements were obtained only once, preventing assessment of temporal trends or treatment effects. Even so, the analysis provides a clear, direct view of the statistical association between potassium and troponin in COVID-19 and offers insights that may be useful in clinical care.

CONCLUSION

In hospitalized patients with moderate to severe COVID-19, lower potassium levels were associated with higher troponin concentrations, independent of disease severity and without a clear relationship to D-dimer status. These findings suggest that hypokalemia may contribute to myocardial injury through mechanisms other than coagulopathy. Given that hypokalemia is readily identifiable and correctable, routine electrolyte monitoring and timely potassium repletion should be considered as part of comprehensive inpatient management to mitigate cardiac risk.

This study did not incorporate regression modeling or adjustment for potential confounders such as ICU admission, comorbidities, medication use, or baseline organ function, and laboratory values were obtained at a single time point. Further multicenter, prospective studies with larger sample sizes, comprehensive clinical data, and serial biomarker measurements are warranted to validate these findings and to clarify the interplay between potassium balance, coagulation abnormalities, and myocardial injury in COVID-19.

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CONFLICT OF INTEREST

All the authors declare that they have no conflicts of interest that might be perceived as influencing the impartiality of the reported research.

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Original Article

Improvement of Muscle Endurance in Men with Low Activity Levels After Above Anaerobic Threshold Exercise Intensity

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Abstract

Background : Low level of physical activity can reduce physical fitness. Aerobic training can improve physical fitness. A precise aerobic training based on anaerobic threshold (AT) is recommended by American College of Sports Medicine (ACSM) whenever possible.
Methods : This was a randomized-single blinded control trial including 24 male subjects with low level of physical activity in Kariadi hospital during December 2023 until February 2024. It was randomized with a sealed envelope. Subjects were allocated in 2 groups (above AT and below AT). Physical performance was measured using SPPB score and muscle endurance that was presented using total repetition of 1RM of knee flexor muscle.
Results : There was no significant difference between two groups for total SPPB score (p=0.053). There was a significant difference of muscle endurance between two groups (p=0.010) with the above AT group resulting in higher improvements of muscle endurance (12.00 ± 5.71 vs. 6.67 ± 3.26).
Conclusion : Aerobic exercise with intensity based on AT did not show significant differences in total SPPB score. However, aerobic exercise above AT showed a better improvement of muscle endurance in healthy adult men with low levels of physical activity.

Keywords : anaerobic threshold, SPPB, endurance

INTRODUCTION

Sedentary lifestyle is a recognized risk factor for adverse cardiovascular events and multiple cardiometabolic comorbidities, and contemporary guidance emphasizes that exercise prescriptions should account for individual variability rather than rely solely on generic recommendations.[1,2] The American College of Sports Medicine (ACSM) exercise guidelines recommend aerobic exercise in these conditions, but are still considered to fail to consider wide variations, so the ACSM stresses that exercise programs should be modified based on an individual's specific health status, physical function, exercise response, and personal goals.[3] Exercise intensity is typically prescribed based on percentages of HRreserve, HRmax, VO2max, or VO2reserve. However, such prescriptions may be imprecise due to wide variability, potentially leading individuals to train at inappropriate intensitieseither failing to achieve desired physiological benefits or increasing the risk of orthopedic or cardiovascular injury.[4]

Aerobic activities such as walking, jogging, structured aerobics, swimming, and cycling are consistently recommended to improve cardiorespiratory fitness, and when performed regularly they enhance oxygen delivery and utilization by working muscles, thereby increasing aerobic capacity and functional performance. In patients with cardiovascular disease, such structured training within cardiac rehabilitation programs yields clinically meaningful benefits, but the magnitude of benefit depends on the precision of exercise intensity prescription and periodic reassessment.[5,6]

Cardiorespiratory exercise testing (CPET) is widely regarded as the most appropriate tool for individualized exercise prescription because it integrates ventilatory, cardiovascular, and metabolic responses to determine thresholds and capacities that are directly actionable for training.[7] CPET is a device that combines measurements of gas exchange, including oxygen uptake (VO2) and exhaled carbon dioxide (VCO2), with traditional exercise testing parameters such as electrocardiogram (ECG), blood pressure and peripheral oxygen saturation (SpO2), thus providing an integrative assessment of exercise response involving the pulmonary, cardiovascular, hematopoietic, neuropsychological, and musculoskeletal systems, which is not adequately reflected through measurements of individual organ system function. In fact, CPET is indicated for prescribing exercise in cardiac/pulmonary rehabilitation, CVD, pulmonary disease and as the gold standard for prescribing exercise.[8]

During exercise testing with CPET, objective assessment of Anaerobic threshold (AT) measurements is used to determine the effort made by the training subject.[9] AT is the point at which muscle O2 demand exceeds the ability of the cardiorespiratory system to supply O2. The use of AT in prescribing exercise should be more viable so that it will avoid limitations on maximal exercise testing, and can further show quantitatively the response to an exercise more accurately and is expected to ultimately improve a person's physical performance.[10–12] This approach helps bridge the gap between evidence and practice in cardiovascular rehabilitation, supporting personalized training zones that improve adherence, safety, and outcomes across cardiometabolic conditions.[7] Exercise prescription based on the anaerobic threshold (AT) obtained from cardiopulmonary exercise testing (CPET) is objective and cannot be determined solely by symptoms or signs during exercise. This method has the potential to resolve issues of under- or over-prescription of exercise intensity. It has also been recommended by the American College of Sports Medicine (ACSM) to provide beneficial physiological outcomes, reduce injury risk, and improve exercise adherence. The use of AT in exercise prescription should allow for a more accurate quantitative assessment of exercise response.[13,14]

Cardiopulmonary exercise testing (CPET) is typically performed using a cycle ergometer or treadmill. The cycle ergometer is generally safer, more suitable for a wide range of patients, allows for a more comfortable procedure, and provides accurate measurements of external work rate. The treadmill enables subjects to walk or run at controlled speeds and inclines, activates more muscle groups, induces greater oxygen desaturation, and results in higher peak oxygen uptake. In most clinical settings, the cycle ergometer is the preferred modality; however, depending on the purpose of the CPET, treadmill ergometry may be a more appropriate alternative. Another advantage of using a treadmill is that, unlike cycling, walking and running are common daily activities. Therefore, this study uses a treadmill.[15]

Currently, there are only 5 centers in Central Java that have CPET; namely Dr. Kariadi General Hospital Semarang, UNS Surakarta Hospital, Dr. Soeharso Surakarta Hospital, Moewardi Surakarta Hospital, and Semarang State University. With all the advantages of CPET, it is expected that its use can support excellent cardiac and pulmonary rehabilitation services at Dr. Kariadi General Hospital Semarang. In addition, by providing appropriate exercise prescriptions, it is expected that promotive and preventive aspects for sedentary individuals can be achieved.

METHODS

This study was a randomized single blinded control trial that included 24 male subjects with low level of physical activity in Kariadi hospital during December 2023 until February 2024. Subjects criteria were male around 25 – 35 years old, with manual muscle strength grade 5 using MRC grading scale, have low level of PA based on

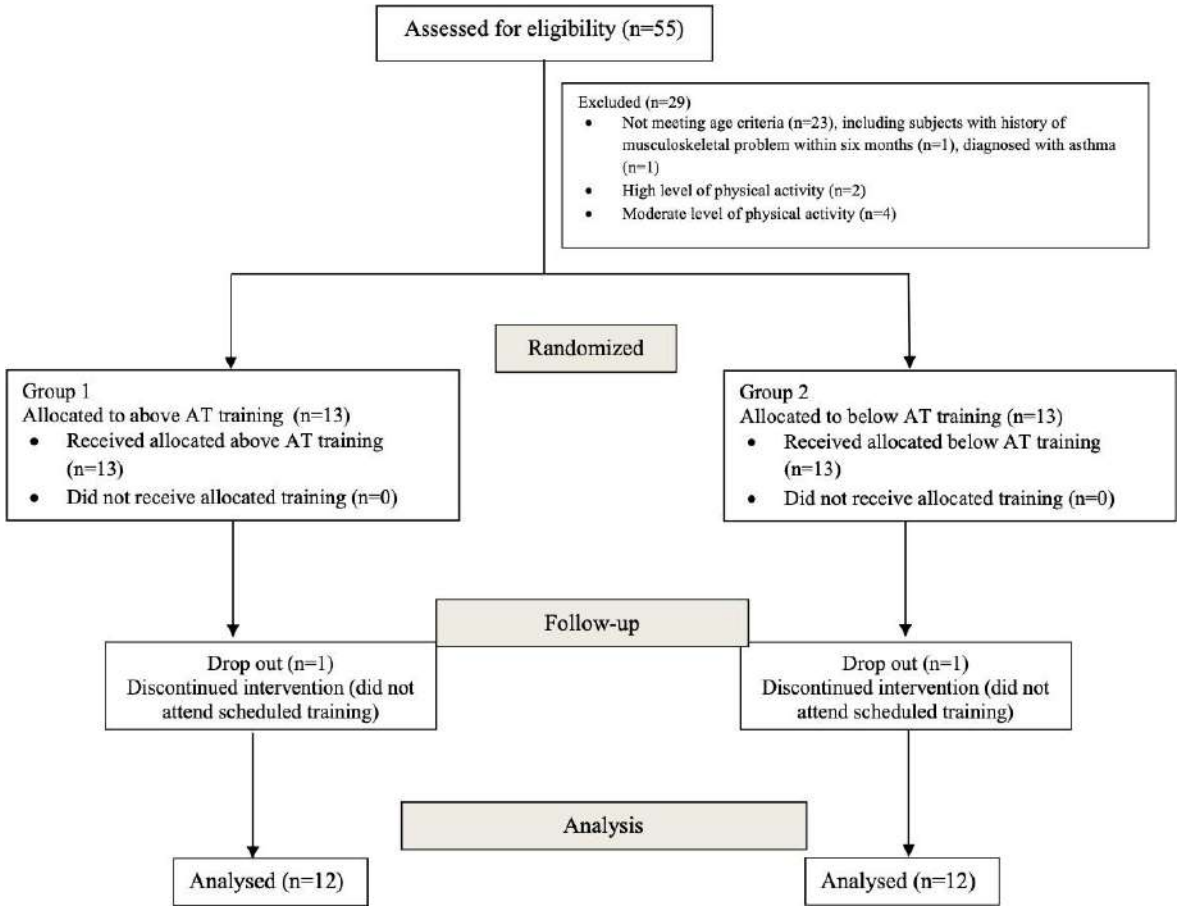

Figure 1. Enrollment based on CONSORT diagram

International Physical Activity Questionnaire Short Form (IPAQ- SF), no history of metabolic disease, cardiorespiratory disorder and history of recent neuromusculoskeletal problem (less than 6 months). Any subject meeting the criteria was given informed consent and familiarized with CPET. All of the subjects were then randomized with sealed envelope. Subjects were allocated in 2 groups (above anaerobic threshold and below anaerobic threshold). Exercise prescription based on the anaerobic threshold (AT) allows training to be individualized. Some studies suggest that when the respiratory compensation point (RCP) cannot be determined, exercise intensity can be prescribed at 20% above the AT. Other research involving healthy sedentary individuals has categorized AT-based prescriptions into groups above, below, and near the AT. Baseline data from these studies indicate that the "near AT" group typically trains within ±10% of the AT. Therefore, in this study, the training range was set between 10% and 20% above the AT.[14,16,17]

All the eligible subjects were evaluated for physical performance, lower muscle endurance, and CPET (to decide the AT for intensity prescription) before intervention. Both groups were given aerobic exercise training based on the AT from the CPET. First groups were given exercise with the range 10–20% above AT. Second group were trained with the range 20–10% below AT. The assessment of physical performance by using SPPB was obtained using the balance function, 5x chair stand, and 4- meter walking.[18] The balance function data had a range of scores 0 to 4. The 4-meter walking data had a score range of 1–4 points (score 1 if > 8.7 seconds, 2 if 6.21–8.7 seconds, 3 if 4.82–6.2 seconds, 4 if <4.82 seconds). The 5 times chair stand test had a range of score from 0–4 points (point 4 if the time data obtained was <11.19 seconds, point 3 if it was 11.2–13.69 seconds, point 2 if it was 13.7–16.69 seconds, 1 if it was >16.7 seconds, and 0, if it was >60 seconds). Thus, the highest SPPB score was 12 and the lowest was 0. The lower extremity endurance was presented as total repetition of 1-RM which could be performed by subjects for dominant knee flexor based on subject preferences.[19,20] It was measured by entree. The SPPB and lower endurance measurement were done before intervention and after 4 weeks intervention. The

diagram consort was shown at Figure 1. All data were analyzed descriptively and analytically.

RESULTS

From the 26 subjects involved, all of them were active residents at varying levels from the Physical Medicine and Rehabilitation study program (38.5%), Surgery (3.85%), Neurosurgery (7.7%), Internal Medicine (11.5%), Neurology (11.5%), Microbiology (3.85%), Cardiology (7.7%), Ophthalmology (3.85%), Anatomical Pathology (3.85 %), and Clinical Nutrition (7.7%). The subjects were divided into two groups, namely the training group above AT and the training group below AT. Both groups received exercise with the same frequency, in which 3 times a week intervention for 4 weeks was given. The pre-intervention of SPPB and 1-RM muscle endurance was carried out 1 day before the intervention and post-intervention assessment was carried out 1 day after the last intervention. There were no complications, either musculoskeletal or cardiorespiratory injuries, during the study. Until the end of the study, the data analyzed was 24 subjects. The data was input into sample codes in SPSS ver.26 app for Windows. Characteristic distribution for IPAQ score was analyzed using the Mann-Whitney test, while the others using the independent-t test. The comparison of exercise intensity on total SPPB score was analyzed using the Mann-Whitney test, and the independent-t test on muscle endurance. Demographic and clinical characteristics of research subjects in both

TABLE 1
Characteristic distribution of all subjects

Variable	Groups		*p* value
	Above AT	Below AT	
IPAQ Score	520.25 ± 72.68	447.50 ± 122.28	0.192‡
Age	31.17 ± 2.44	31.33 ± 2.06	0.858§
Body weight (BW)	70.06 ± 5.21	74.00 ± 6.76	0.245§
Body Height (BH)	170.75 ± 3.08	170.08 ± 4.06	0.655§
BMI	24.37 ± 1.67	25.59 ± 2.27	0.150§

‡Mann-Whitney; §Independent-t

TABLE 2
Absolute changes with training for below AT group in total SPPB score, balance score, gait speed, chair stand test, and muscle endurance

Variable	Groups		*p*
	Above AT	Below AT	
Total SPPB score			
Baseline	520.25 ± 72.68	447.50 ± 122.28	0.192‡
After training	31.17 ± 2.44	31.33 ± 2.06	0.858§
p	70.06 ± 5.21	74.00 ± 6.76	0.245§
Delta	170.75 ± 3.08	170.08 ± 4.06	0.655§
Muscle endurance			
Baseline	9.67 ± 10.44	8.33 ± 6.24	0.908‡
After training	21.67 ± 11.69	15.00 ± 7.53	0.111§
p	<0.001¶*	<0.001¶*	
Delta	12.00 ± 5.71	6.67 ± 3.26	0.010§*

‡Mann-Whitney; †Wilcoxon, ¶Paired t, §Independent t

groups are shown in Table 1. The comparison of baseline and after training in above AT and below AT groups were presented in Table 2.

DISCUSSION

Based on the data in Table 1, the characteristics of the subjects in both groups were not significantly different. It showed that the characteristics of the study subjects in both groups were homogeneous. Of all candidate subjects (n = 55 subjects) without considering inclusion or exclusion criteria, 49% had low levels of physical activity. Our finding was almost similar with other study in Malaysia using the same instrument which found that 41.4% of students ranging from 18–25 years old had low levels of physical activity.[21] Other studies also shown that around 40% and 45.6% of health professionals tend to have low levels of physical activity in Africa and Malaysia. A cohort study in the UK showed that 25–34 years old respondents had the highest proportion (45%) of low levels physical activity.[22,23] The reasons why the health professionals in this age group have low levels of physical activity were due to lack of free time, long working hours and negligence.[24,25] Other study assume that young doctors are very busy because related to financial building issue and social life that cause them have little time to exercise.[26]

The sample in this study comprised individuals whose body mass index (BMI) ranged from normal to overweight according to WHO criteria.[27] The distribution of BMI and other anthropometric measures (body weight and height) did not differ statistically between the two groups, indicating homogeneity at baseline and reducing the likelihood that differences in body size confounded the observed effects of the intervention. This is inferred that the exercise intervention effects on functional outcomes were unlikely to be driven by baseline differences in body composition or somatic size; nevertheless, this study did not perform formal statistical analyses of the relationships between BMI or other anthropometrics and outcomes such as SPPB or muscle endurance. A recent study has examined associations between anthropometric characteristics and muscle endurance or performance tests, highlighting that body composition and segmental anthropometrics can influence strength and endurance measures and the interpretation of functional tests like the SPPB, but findings vary by age, sex, and activity level and underscore the need for population specific analyses.[28] To the best of our knowledge, there remains limited published data specifically addressing how BMI or simple anthropometric measures affect SPPB scores and knee flexor 1 RM endurance outcomes in young male individuals with low physical activity, which supports the rationale for reporting our results while acknowledging this gap for future targeted investigation.

Although the Short Physical Performance Battery (SPPB) was originally developed and remains most widely validated for identifying mobility limitations and predicting adverse outcomes in older adults, interest has grown in applying the SPPB to younger and clinical populations to explore how sedentary behavior and disease processes influence functional performance across the lifespan.[29]

In general, the effect of exercise on SPPB scores had been studied in the elderly, with few studies correlates the relationship of SPPB to younger ages, especially young sedentary. One study used the SPPB to evaluate the associations with sedentary activity in multiple sclerosis patients ranging from young to old age. Among young multiple sclerosis patient (20–39 years), the SPPB summary score was associated with sedentary behavior patterns (ρ range between −0.354 and −0.350, $p < 0.05$), but not with volume ($\rho = -0.289$, $p > 0.05$). The SPPB balance, gait, and strength component scores were not associated with volume or sedentary behavior patterns.[30,31]

The Short Physical Performance Battery is a method for assessing physical performance and has been shown to predict fall risk in the elderly. A cross-sectional study with two research groups, namely healthy young adult women aged 19–23 years and healthy elderly women aged 59-66 years showed that the total score of the SPPB test for young adults was 10,950 ± 0.959 and for the elderly 9,225 ± 1,310 (p = 0.000). In that study, the correlation test between age and the 4-m walking test was weakly correlated r = 0.367 (p = 0.001), with the chair stand test was weakly correlated r = 0.494 (p = 0.000), and with the total score of the SPPB test was strongly correlated r = -0.557 (p = 0.000). It showed that aging causes a decrease in muscle mass and strength as seen from a decrease in physical performance through the SPPB test.[32] Our study showed no correlation between aerobic treadmill training in both above and below AT with total SPPB score. This could be because the samples in our study who were young sedentary had initial SPPB scores that were already high and normal so that an increase in SPPB score could no longer be observed (ceiling effect). These observations are reinforced by recent population and intervention studies showing that task□specific, higher□resolution functional tests or instrumented gait and balance measures are often more needed to detect change in younger, higher□performing groups.[33]

Exercise prescription based on the anaerobic threshold (AT) emphasizes peripheral vascularization and the recruitment of active muscle groups to maintain a steady-state aerobic metabolism. The AT represents a physiological tipping point where the body transitions from purely aerobic energy production to a mix of aerobic and anaerobic metabolism. Training at or just below this threshold allows the body to operate efficiently, with minimal lactate accumulation, while maximizing oxygen

delivery and utilization in the working muscles. From a physiological standpoint, this training intensity stimulates adaptations in the peripheral musculature, particularly in the capillary networks and mitochondrial density. These adaptations enhance the muscles' ability to extract and utilize oxygen, which is essential for sustaining prolonged aerobic activity without fatigue. The concept of steady-state metabolism refers to a condition where oxygen supply meets the metabolic demands of the muscles, allowing for a stable internal environment during exercise. Peripheral adaptations, such as increased capillarization and improved oxidative enzyme activity, are critical for maintaining steady-state aerobic metabolism during submaximal exercise intensities. These changes acts in optimizing oxygen delivery to impaired or deconditioned muscles. Exercising based on anaerobic threshold enhances the muscles' metabolic flexibility, allowing for more efficient energy production and reduced reliance on anaerobic glycolysis. This metabolic efficiency is directly linked to improved endurance and reduced fatigue, especially in clinical populations with compromised cardiovascular or muscular function.[34]

The exercise-induced adaptation in skeletal muscle fibers is specific to the type of exercise stimulus i.e., endurance exercise. The adaptation is the result of an increase in the number of specific proteins (calcineurin, CaMK, AMPK, p38, and NFκB). These proteins result in activation of PGC-1α. All of the signaling pattern results in fast-to-slow fiber type shift, synthesis of antioxidant enzymes, and mitochondrial biogenesis. Increased mitochondria number decreases lactate and ion hydrogen formation to maintain the blood pH. Aerobic exercise increases endogenous antioxidants in trained muscles which protects muscle fibers against free-radical mediated damage and fatigue during prolonged exercise. The regular exercise results in less disruption of the blood pH during submaximal work as muscles produce less lactate and hydrogen ions.[35–39] No previous study is yet to show this fatigue tolerance as muscle endurance which is measured by maximum repetition.

However, our study has some limitations such as small sample size that result in no control subject without intervention in this study. Moreover, blinding could not be implemented to all subjects since they were medical professionals who previously have a prior knowledge about exercise training. The last, physical performance measurement using the SPPB score may not be appropriate for young subjects with previously high performance.

Besides all the limitations mentioned, this research offers a new perspective because there has been no previous empirical study that provides new information related to a more precise prescription such as CPET. The aerobic exercise with precise prescription above each individual AT results in a better muscle endurance outcome in adult men with low levels of physical activity, acting as a promotive and preventive effort for diseases caused by sedentary life. Until now, there has been no previous research that specifically examined the clinical outcomes of precision prescriptions on muscle endurance, so this study has significant novelty value.

This research highlights a foundational gap in precision exercise prescription using CPET for improving muscle endurance, especially regarding peripheral adaptations. It may represent emerging information about improvement of muscle endurance through precision aerobic exercise prescription using CPET, which is expected to be both effective and safe. Most of exercise protocols based on AT are studied primarily from a systemic perspective. There is lack of study concerning peripheral muscle endurance adaptation. That kind of study will provide data about understanding local muscle fatigue, recruitment patterns, and oxygen utilization, which are directly linked to endurance capacity.

This research encourages further study to close a gap which is a notable absence of research applying aerobic capacity assessments to samples with musculoskeletal or neurological impairments. These populations often present with specific conditions, making it imperative to tailor exercise prescriptions based on objective physiological data. The use of CPET in these groups could offer a more accurate and individualized approach to rehabilitation, enhancing safety and efficacy.

The ideas presented in this study are expected to serve as a foundation for future research. It would allow for the development of protocols that are both physiologically sound and functionally relevant, ultimately improving patient outcomes. Researchers and clinicians can develop more refined and targeted exercise prescriptions which can be ensured as effective and safe.

CONCLUSION

Aerobic exercise with intensity based on AT did not show significant differences in total SPPB score. However, aerobic exercise above AT showed a better improvement of muscle endurance in healthy adult men with low levels of physical activity.

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CONFLICT OF INTEREST

There is no conflict of interest regarding this manuscript.

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Original Article

Differences in The Severity of Diabetic Neuropathy Based on Electromyography in Type 2 Diabetes Mellitus Patients with and without Comorbidities

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Abstract

Background : Diabetic neuropathy is one of the most common complications of type 2 Diabetes Mellitus. Hyperglycemia causes axonal abnormalities and impaired schwan cell metabolism. Hypertension and hyperlipidemia associated with atherosclerosis, lipid metabolism and arterial compliance. This study aims to determine the difference in the severity of diabetic neuropathy based on electromyography between type 2 DM patients with and without comorbidities.
Methods : This study used a cross sectional design. A total of 78 diabetic neuropathy subjects from Outpatient Installation of Dr. Kariadi Hospital Semarang were divided into 3 groups, 26 subjects without comorbidities, 25 subjects with comorbid hypertension and 27 subjects with comorbid hypertension and hyperlipidemia. Inclusion criteria were aged 40–80 years, distal symmetrical polyneuropathy classification, without comorbid and with comorbid hypertension and hyperlipidemia. Exclusion criteria were patients with chemotherapy, HNP, CKD stage 5, incomplete medical records. Data were analyzed using Kruskal-Wallis comparative test.
Results : There is a difference in the severity of diabetic neuropathy based on EMG between type 2 DM patients without comorbidities and with comorbidities (p<0.01). No difference in the severity between patients with type 2 DM without comorbidities and with comorbid hypertension (p 0.058). There is a difference in the severity between patients with type 2 DM without comorbidities and with comorbid hypertension and hyperlipidemia (p<0.01).
Conclusion : There is a difference in the severity of diabetic neuropathy based on EMG between patients with type 2 DM without comorbidities, with comorbid hypertension and with comorbid hypertension and hyperlipidemia. The more comorbidities, the greater the severity of diabetic neuropathy.

Keywords : Type 2 Diabetes Mellitus, Diabetic Neuropathy, Electromyography, Hypertension, Hyperlipidemi

INTRODUCTION

Diabetes mellitus is a major metabolic disorder, where almost more than 1 billion people suffer from diabetes worldwide.[1] Diabetes mellitus is characterized by hyperglycemia and glucose intolerance.[2] Type 2 diabetes mellitus can cause microvascular and macrovascular complications. One of them is diabetic neuropathy. Diabetic neuropathy is the most common cause of neuropathy worldwide and is estimated to affect approximately half of people with diabetes, increasing morbidity, impairing quality of life and increasing mortality. The underlying pathophysiology of diabetic neuropathy is the result of hyperglycemia and microangiopathy. There is many type of diabetic neuropathy, however, distal symmetric sensorimotor polyneuropathy is the most common form. Thist suggests than the disease primarily involves the most distal regions of the body, particularly the feet, while the term "symmetric" implies that the signs and symptoms are present on both sides of the body.[3,4] Hyperglycemia increases vascular endothelial resistance, decreased neurovascular flow, decreased myoinositol in the nervous system and oxidative stress which cause neuronal, axonal and metabolic abnormalities of schwan cells that interfere with axonal transport processes.[5,6]

Hyperlipidemia is a metabolic problem associated with abnormal lipid metabolism which is directly related to cell membranes and affects the myelin sheath. Hyperlipidemia resulting in vascular lumen stenosis and impairment of microcirculation, which consequently leads to ischemia of peripheral nerves. In cases of hyperlipidemia, hyperstimulation of glutamatergic receptors may occur, disrupting intracellular calcium homeostasis and leading to toxic calcium accumulation that subsequently causes neuronal damage. Hyperlipidemia is also associated with increased leves of plasma oxLDL, which binds to oxLDL receptor on the neuronal membrane and activates NOXes in cells. Activation of NOXes leads to the generation of ROS within neurons, resulting in cellular oxidative stress.[7]

Hypertension is also associated with the severity of diabetic neuropathy. There are two main pathologies of hypertension, namely atherosclerosis and decreased arterial compliance. Vascular tone may increase due to enhanced stimulation of α-adrenoreceptors or elevated levels of peptides such as angiotensin or endothelin. The final pathway involves an increase in cytosolic calcium within vascular smooth muscle cells, leading to vasoconstriction. Several growth factors, including angiotensin and endothelin, contribute to the proliferation of vascular smooth muscle cells, a process known as vascular remodeling. This is associated with impaired microvascular flow, characterized by reduced endothelium-dependent vasodilatation and decreased nitric oxide (NO) levels in hypertensive condition. There is an association between diabetic neuropathy and comorbid factors of hypertension and hyperlipidemia. A study conducted by Lingning Huang *et al*., demonstrated that systolic blood pressure and HbA1C levels in patients with diabetic peripheral neuropathy were found to be higher than in the non-DPN group.[8–11]

Age is a risk factor for diabetic polyneuropathy. Several study groups have demonstrated that age serves as an independent factor in -patients with diabetic polyneuropathy, indicating a progressive increase in its prevalence with each decade of life. Several study found that female patients with diabetes have a higher risk of developing diabetic polyneuropathy compared to male patients. Height is also associated with diabetic polyneuropathy due to length-dependent pattern of the disease, which is related to the length of the nerve fibers. In diabetic neuropathy, these disorders are more often found in sensory nerves than in motor nerves, which is related to the morphology of these nerves.[12–14] From the examination of nerve conductivity in diabetic neuropathy patients, we often found demyelination disorders with a decrease in amplitude associated with axonopathy.

Studies comparing the severity of diabetic neuropathy based on multiple comorbidities remain limited because prior research only focused with single comorbidity such as hypertension or dyslipidemia. The purpose of this study was to determine the differences in the severity of diabetic neuropathy based on electromyographic examination between patients with type 2 diabetes mellitus without comorbidities, type 2 diabetes mellitus with comorbid hypertension and type 2 diabetes mellitus with comorbid hypertension and hyperlipidemia, then determine the relationship between distal latency and amplitude in diabetic neuropathy patients with and without comorbidities and analyze differences in the severity of diabetic neuropathy based on age, height and HbA1C in type 2 diabetes mellitus patients with and without comorbidities. Therefore, this study provides novelty by evaluating the severity of diabetic neuropathy using electrophysiological parameters between patient without comorbidities, with hypertension and with both hypertension and hyperlipidemia.

METHODS

This study is an analytical descriptive study with a cross sectional approach and was conducted at the Outpatient Installation and Medical Records of Dr. Kariadi Hospital Semarang. This study was approved by the Health Research Ethics Committee (HREC) of the Faculty of Medicine, Diponegoro University, under Ethical Clearance number 600/EC/KEPK/FK-UNDIP/XII/2023. All costs related to the research were covered by the researcher. The identities of the subjects were kept confidential throughout the study.

The population of this study were patients with type 2 diabetes mellitus with diabetic neuropathy who received treatment at Dr. Kariadi Hospital Semarang for the period January 1, 2021 – December 31, 2023. The sample size for this study was determined using the formula for unpaired categorical analytical studies and met the criteria for statistical testing. The calculation yielded a required sample size of 25 subjects per group.

The inclusion criteria were diabetic neuropathy patients aged 40–80 years, diabetic neuropathy patients with distal symmetrical polyneuropathy classification, diabetic neuropathy patients without comorbidities and with comorbid hypertension and hyperlipidemia, while the exclusion criteria in this study were diabetic neuropathy patients with a history of chemotherapy, diabetic neuropathy patients with Hernia Nucleus Pulposus (HNP), diabetic neuropathy patients with CKD stage 5 (eGFR <15 mL/min/1. 73 m) or doing hemodialysis, and incomplete medical records.

The severity of diabetic neuropathy in this study is based on electromyographic examination which is measured based on latency, amplitude and nerve conductivity on the unilateral side and based on the number of peripheral nerves involved. Where grade 0 is no nerve involved, grade 1 is mild if the sensory nervus suralis is involved, grade 2 is moderate if the sensory nervus suralis and motor of the peroneal nerve and or tibial nerve are involved, grade 3 is moderate to severe, if the suralis nerve, peroneal nerve, tibial nerve and sensory median and or ulnar nerve are involved, while grade 4 is severe if the suralis nerve, peroneal nerve, tibial nerve, sensory and motor median and or ulnar nerve are involved.

The collected data were analyzed using SPSS Statistics for Windows version 26. Data analysis was conducted in two stages: descriptive statistics and analytical statistics. To evaluate differences in the severity of diabetic neuropathy, an unpaired categorical comparative test was employed using the Chi-square test when assumptions were met. If the assumptions were not fulfilled, the KruskalWallis test was applied as an alternative. The data collected were then divided into 3 groups of neuropathy patients, namely diabetic neuropathy patients without comorbidities, with comorbid hypertension and with comorbid hypertension and hyperlipidemia. In this study, data regarding HbA1C, age of the subject which was divided into 3 groups, namely 40–50 years, 51–60 years and ≥ 61 years, and height of the subject were included.

RESULTS

From data collection through medical records on patients with a diagnosis of diabetic neuropathy who received treatment at the neurology clinic and underwent electromyographic examination at Dr. Kariadi Hospital from 2021 to 2023, 78 subjects were obtained who met the inclusion criteria. After that, they were grouped into groups of diabetic neuropathy patients without comorbidities as many as 26 people, diabetic neuropathy patients with comorbid hypertension as many as 25 people, and diabetic neuropathy patients with comorbid hypertension and hyperlipidemia as many as 27 people.

This study included 78 patients with diabetic neuropathy who fulfilled the inclusion criteria. The mean age of the participants was 56 years, and the majority were female. Based on the duration of diabetes mellitus (DM), the majority of cases were found in patients with a disease onset of ≥5 years. The mean body mass index (BMI) was 25.14 and the mean HbA1C level was 8.17. Differences in electromyography results in diabetic neuropathy patients in this study were associated with severity. Severity is measured based on latency, amplitude and nerve velocity. The severity of diabetic neuropathy based on electromyographic examination is divided based on the number of peripheral nerves involved.

Table 2 shows the result of p=0.001. There is significant difference between the severity of diabetic neuropathy in DM subjects without comorbidities, DM subjects with comorbid hypertension, and DM subjects with comorbid hypertension and hyperlipidemia.

Table 3 shows the result of p=0.058. There is no statistically significant difference between the severity of diabetic neuropathy in DM subjects without comorbidities and DM subjects with comorbid hypertension.

Table 4 shows the results of p<0.01. There is significant difference between the severity of diabetic neuropathy in DM subjects without comorbidities and DM subjects with comorbid hypertension and hyperlipidemia.

Table 5 shows that there is a significant correlation between latency and amplitude in patients with DM without comorbidities with a very strong correlation in Median Sensory Nerve (rho -0.903) and Suralis Sensory Nerve (rho -0.894). There was a strong correlation in Ulnar Sensory Nerve (rho -0.692) and moderate correlation in Median Motoric Nerve (rho - 0.411). Beside that, there is a significant correlation between distal latency and amplitude in patients DM with comorbidities with a very strong correlation in Suralis Sensory Nerve (rho - 0.956), strong correlation in Median Sensory Nerve (rho -0.774) and Ulnar Sensory Nerve (rho -0.676). There was a moderate correlation in Median Motoric Nerve (rho -0.423), Peroneal Motoric Nerve (rho -0.594) and Tibial Motoric Nerve (rho -0.507).

Based on theory, age, height and HbA1C are factors that can affect the severity of diabetic neuropathy in both DM patients without comorbidities and with comorbidities (Table 6).

TABLE 1
Demographic and Clinical Characteristics of Subjects

Variable	Frequency	%	Mean ± SD	Median (Min–Max)
Demographics Data				
Age (year)			56.09 ± 8.53	56.5 (40–74)
40-50	20	25.6		
51-60	32	41		
≥ 61	26	33.3		
Gender				
Male	33	42.3		
Female	45	57.7		
Clinical Data				
Group of diseases				
DM	26	33.3		
DM and hypertension	25	32.1		
DM, hypertension & hyperlipidemia	27	34.6		
DM onset				
< 5 years	29	37.2		
≥ 5 years	49	62.8		
Weight			65.92 ± 11.79	65 (33–100)
Height			161.77 ± 7.3	160 (145–180)
IMT			25.14 ± 4	24.7 (15.7–39.06)
HbA1C			8.17 ± 2.23	7.55 (5.2–17.6)

TABLE 2
Differences in Severity of Diabetic Neuropathy in DM Subjects without comorbid, comorbid hypertension and comorbid hypertension and hyperlipidemia

		Group of Diseases			*P* Value
		DM (n=26)	DM & hypertension (n=25)	DM, hypertension & hyperlipidemia (n=27)	
Severity of Diabetic Neuropathy	Grade 1	4 (100%)	0 (0%)	0 (0%)	0.001*
	Grade 2	5 (41.7%)	5 (41.7%)	2 (16.7%)	
	Grade 3	13 (40.6%)	11 (34.4%)	8 (25%)	
	Grade 4	4 (13.3%)	9 (30%)	17 (56.7%)	
	Total	26 (33.3%)	25 (32.1%)	27 (34.6%)	

Notes : *significant ($p < 0.05$) using Kruskal-Wallis test

TABLE 3
Differences in Severity of Diabetic Neuropathy in DM Subjects without Comorbidities and with Comorbid Hypertension

		Group of Diseases		*P* Value
		DM (n=26)	DM & hypertension (n=25)	
Severity of Diabetic Neuropathy	Grade 1	4 (100%)	0 (0%)	0.058
	Grade 2	5 (50%)	5 (50%)	
	Grade 3	13 (54.2%)	11 (45.8%)	
	Grade 4	4 (30.8%)	9 (69.2%)	
	Total	26 (51%)	25 (49%)	

Notes : *significant ($p < 0.05$) using Kruskal-Wallis test

TABLE 4
Differences in Severity of Diabetic Neuropathy in DM Subjects without Comorbidities and with Comorbid Hypertension and Hyperlipidemia

		Group of Diseases		*P* Value
		DM (n=26)	DM, hypertension & hyperlipidemia (n=27)	
Severity of Diabetic Neuropathy	Grade 1	4 (100%)	0 (0%)	< 0.01*
	Grade 2	5 (71.4%)	2 (28.6%)	
	Grade 3	13 (61.9%)	8 (38.1%)	
	Grade 4	4 (19%)	17 (81%)	
	Total	26 (49.1%)	27 (50.9%)	

Notes : *significant ($p < 0.05$) using Kruskal-Wallis test

TABLE 5
Correlation between Distal Latency and Amplitude in DM Subjects without Comorbidities and with Comorbidities

		DM without Comorbidities		DM with Comorbidities	
	Amplitude Score	rho	*p*	rho	*p*
Distal Latency	Median Sensory Nerve	-0.903	< 0.01	-0.774	< 0.01
	Ulnar Sensory Nerve	-0.692	< 0.01	-0.676	< 0.01
	Median Motoric Nerve	-0.411	0.037	-0.423	0.002
	Ulnar Motoric Nerve	0.304	0.130	-0.173	0.219
	Suralis Sensory Nerve	-0.894	< 0.01	-0.956	< 0.01
	Peroneal Motoric Nerve	-0.249	0.220	-0.594	< 0.01
	Tibial Motoric Nerve	-0.301	0.136	-0.594	< 0.01

Notes : *significant ($p < 0.05$) using Spearman Correlation test

TABLE 6
Differences in Severity of Diabetic Neuropathy by Age Group in DM Subjects with and Without Comorbidities

Variable	Severity of Diabetic Neuropathy					Total	*P* Value
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4		
DM without comorbidities							
Age 40–50	0 (0%)	2 (33.3%)	1 (16.7%)	3 (50%)	0 (0%)	6	
Age 51–60	0 (0%)	1 (8.3%)	4 (33.3%)	5 (41.7%)	2 (16.7%)	12	0.405
Age ≥ 61	0 (0%)	1 (12.5%)	0 (0%)	5 (62.5%)	2 (25%)	8	
Height	0	164.25 ± 5.38	163 ± 5.43	158.15 ± 7.24	162.25 ± 5.32		0.394
HbA1C	0	8.05 ± 2.9	8.26 ± 2.6	7.85 ± 2.26	10.23 ± 5.23		0.903
DM with comorbidities							
Age 40–50	0 (0%)	0 (0%)	2 (14.3%)	6 (42.9%)	6 (42.9%)	14	
Age 51–60	0 (0%)	0 (0%)	4 (20%)	7 (35%)	9 (45%)	20	0.511
Age ≥ 61	0 (0%)	0 (0%)	1 (5.6%)	6 (33.3%)	11 (61.1%)	18	
Height	0	0	162.43 ± 9.48	160.95 ± 7.4	163.3 ± 7.43		0.74
HbA1C	0	0	8.16 ± 2.15	7.88 ± 1.61	8.24 ± 1.94		0.389

Notes : *significant ($p < 0.05$) using Kruskal-Wallis test

Table 6 shows there is no significant difference between age, height and HbA1C with the severity of diabetic neuropathy. However, the older age group (age ≥ 61 years) was found to have more grade 3 (62.5%) and grade 4 (25%) diabetic neuropathy. For height, grade 3 diabetic neuropathy was 158.15 ± 7.24 and grade 4 diabetic neuropathy was 162.25 ± 5.32. While based on HbA1C levels obtained for grade 4 of 10.23 ± 5.23.

In the group of DM subjects with comorbidities also showed the results there is no significant difference between groups of age, height and HbA1C with the severity of diabetic neuropathy. In the older age group (age ≥ 61 years), there were more grade 3 (33.3%) and grade 4 (61.1%) diabetic neuropathy. For height, grade 3 diabetic neuropathy was found at 160.95 ± 7.4 and grade 4 diabetic neuropathy at 163.3 ± 7.43. While based on HbA1C levels 8.24 ± 1.94.

DISCUSSION

This study involved 78 diabetic neuropathy patients who met the inclusion criteria. Based on demographic data, the majority of patients with diabetic neuropathy in this study were female (57.7%). A study conducted by Dipika Bansal *et al*. which also reported that most patients were female (50.7%). This finding is consistent with studies by Yanhui Lu *et al*. and Zohaib Igbal *et al*., which demonstrated that female patients with diabetes mellitus are more likely to develop diabetic neuropathy compared to males. Furthermore, their study found that women have a threefold higher risk of developing diabetic neuropathy than men. This difference may be related to higher physical activity levels among men. But, there is another study who reported that the onset of diabetic neuropathy occurs earlier in men than in women. This may be attributed to greater exposure to stressors and a decline in androgen hormens in male patients with diabetes mellitus, as these hormones exert neuroprotective effects on both the central and peripheral nervous systems.[15]

In this study, the average age of diabetic neuropathy patients in this study was 56.09 years. This agrees with the study of Fipika Bansal *et al* in 2014 obtained similar results, namely the average age of patients with diabetic neuropathy was 57.1 years.[15] This is also in accordance with studies which state that diabetic neuropathy tends to occur at the age of more than 50 years.[1] Hyperglycemia conditions take time to cause damage to the nerves so that increasing age is indirectly related to an increased risk of diabetic neuropathy in patients with type 2 diabetes mellitus.[1,16]

In this study there was a significant difference between the severity of diabetic neuropathy in Diabetes Mellitus patients without comorbidities and Diabetes Mellitus patients with comorbidities. Some comorbidities are associated with the severity of diabetic neuropathy such as hyperlipidemia, smoking, hypertension and obesity. This is in agreement with the study of Shafina

Sachedina *et al*, who found that some of the comorbidities were associated with the severity of diabetic neuropathy in patients with type 2 diabetes mellitus.[17]

There was no statistically significant difference between the severity of diabetic neuropathy in patients with DM without comorbidities and DM with comorbid hypertension. However, the data showed that the number of patients with grade 4 severity was higher among patients who also had comorbid hypertension. In addition, there were no cases of grade 1 diabetic neuropathy in patients with diabetes mellitus with comorbid hypertension. This is in agreement with the study of Shafina Sachedina *et al*, who found that hypertension did not provide a significant difference with the severity of diabetic neuropathy in patients with type 2 DM.[17] However, this result is different from the study of Lingning Huang *et al*, where a significant difference was found between diabetic neuropathy patients in DM patients with and without hypertension.[8] Meanwhile, the results of a study conducted by Sethi Y, et. al where found that hypertension is a modifiable risk factor for the development of diabetic neuropathy in patients with type 2 DM.[18] Hypertension is associated with decreased nerve perfusion, endoneural hypoxia and structural changes in nerve microvasculature. Growth factors such as angiotensin and endothelin also cause vascular remodelling where there is an increase in vascular smooth muscle and associated with changes in vasoconstriction function and decreased vasodilation or vascular elasticity and associated with the occurrence of subclinical atherosclerosis due to impaired arterial compliance.[8]

There was a statistically significant difference between the severity of diabetic neuropathy in patients DM and DM with comorbid hypertension and hyperlipidemia. Hypertension and hyperlipidemia are 2 important cardiovascular risk factors as predictors of severe diabetic complications.[19] Based on a study by Nidhi Yadav *et al*., diabetic neuropathy patients with hyperlipidemia showed differences in the severity of diabetic neuropathy. The progression and severity of diabetic neuropathy is related to factors including elevated triglycerides, smoking, hypertension and obesity. The presence of hypertension is associated with vascular remodeling and leads to impaired perfusion in the nerve vasculature.[18] Meanwhile, hyperlipidemia is associated with oxidative stress in the dorsal root ganglia which plays a major role in the occurrence of neurodegeneration in diabetes.[17]

This study found a significant correlation between distal latency and amplitude in patients with DM without comorbidities with a very strong correlation in Median Sensory Nerve and Suralis Sensory Nerve. In addition, there was a strong correlation in Ulnar Sensory Nerve and a moderate correlation in Median Motoric Nerve. In DM patients with comorbidities, there was a significant correlation between distal latency and amplitude with a very strong correlation in Suralis Sensory Nerve, strong correlation in Median Sensory Nerve and Ulnar Sensory Nerve. In addition, there was also a moderate correlation in Median Motoric Nerve, Peroneal Motoric Nerve, and Tibial Motoric Nerve. In DM patients, sensory nerve abnormalities are more prominent than motor nerve abnormalities. The vulnerability in sensory nerves is associated with thinner and longer nerve types compared to motor nerves.[20,21]

Latency is related to the presence or absence of myelin destruction while amplitude is related to axonal. Amplitude indicates how many nerve fibers are stimulated.[12,22] Study from Ruchi *et al*, found that axonal-type damage of the ulnar nerve was found in patients with diabetic neuropathy and type 2 diabetes mellitus. In a study conducted by Anwar H. Siddique *et al*., the amplutides of the median and sural nerves were significantly lower in patients with symptomatic diabetic neuropathy compared to those with asymptomatic diabetic neuropathy.[20] Another study demonstrated a decrease in sensoryh and motor nerve amplitudes due to axonopathy, which is more commonly observed in diabetic patients. Axonal neuropathy results in reduced amplitude, whereas demyelinating neuropathy is characterized by slowed conduction. Previous studies have shown that diabetic neuropathy involves both of these components. Study by Raju Panta *et al*, found that a decrease in the amplitude of the sensory nerve was often found in demyelinating lesions, a decrease in the amplitude of the Suralis Nerve examination indicates axonal loss which is often also found in demyelinating disorders. The presence of amplitude disorders (axonal neuropathy) is the most powerful measure related to the severity of neuropathic disorders.[23]

When associated with age, there was no significant difference between DM patient groups without comorbidities and with comorbidities. However, descriptively, it was found that the older age group had more grade 3 and 4 diabetic neuropathy severity in both the DM without comorbidities and with comorbidities groups. This may be related to medication compliance in elderly patients and the association with other risk factors such as HbA1C variability and the number of comorbidities in each age group in the DM with comorbidities group. Several study have indicated that age serves as an independent factor in patients with diabetic polyneuropathy, suggesting a progressive increase in its prevalence with each decade of life. Animal studies have shown that the severity of diabetic neuropathy is associated with nerve conduction velocity. In young rats, no changes in conduction velocity are observed initially, but a subsequent decline occurs over time. With increasing age, there is an accumulation of nerve damage, in which patients with diabetic neuropathy may experience injury to both large and

small nerve fibers, caused by axonal damage and demyelination.[16]

Similarly, with height, we found no statistically significant difference between height and severity of diabetic neuropathy in both groups of DM patients without and with comorbidities. This may also be related to other risk factors such as age and HbA1C variability.[24] The San Luis Valley study also found that height was not associated with the occurrence of diabetic neuropathy.[25] Study by Toeko Matsumoto, *et al* also found that height was not associated with neuropathy. These results differ from a population study in Mauritius where height gave significant results in increasing the risk of diabetic neuropathy. Height is associated with diabetic polyneuropathy due to the length-dependent pattern of the disease, which is related to the length of the nerve fibers. The taller the individual, the longer the segment of axonal tapering and the slower the conduction velocity. In addition, the internodal distance becomes shorter, axonal transport slows down and alterations in cell membrane properties occur.

In this study, there was no statistically significant difference between HbA1C and the severity of diabetic neuropathy in both groups of DM patients without comorbidities and with comorbidities. However, this study found that patients with diabetes mellitus (DM) without comorbidities have higher HbA1C levels compared to those with comorbid conditions. This may be related to age as a risk factor and to the higher level of treatment adherence observed among patients with comorbidities compared to those without. Based on study by Dipika Bansal, *et al*, it was found that high levels of HbA1C were not significantly associated with diabetic polyneuropathy. Increased variability of HbA1C in patients with diabetes mellitus is associated with increased severity of diabetic neuropathy. Study by Caprnda *et al*, was found that there was no association between short-term variability of glycemic levels and micro- and macrovascular complications in type 2 DM.[26] Long-term variability of glycemic levels assessed by HbA1C variability can increase oxidative stress leading to cell and tissue damage.[27]

CONCLUSION

This study found differences in the severity of diabetic neuropathy based on EMG examination between patients with type 2 diabetes mellitus without comorbidities, type 2 diabetes mellitus with comorbid hypertension and type 2 DM with comorbid hypertension and hyperlipidemia. There was also a difference in the severity of diabetic neuropathy between patients with type 2 diabetes mellitus without comorbidities and with comorbid hypertension and hyperlipidemia. However, no significant differences between diabetic neuropathy without comorbidities and comorbid hypertension alone. The more comorbidities in patients with diabetic neuropathy, the greater the severity of diabetic neuropathy. This study found a correlation between distal latency and amplitude in type 2 DM patients without comorbidities and with comorbidities, which shows that diabetic neuropathy can have both components according to severity. When associated with other risk factors such as age, height and HbA1C, there was no significant difference in the severity of diabetic neuropathy in both patients with type 2 DM without comorbid and with comorbid.

Based on this study, the following limitations were found: data collection from medical records where electromyography examination may not be carried out ideally, the number of samples is limited to patients with Diabetes mellitus with 1 type of comorbid, this study does not consider diabetes mellitus therapy obtained by patients and physical activity of patients. Other risk factors such as the onset of type 2 diabetes mellitus cannot be precisely ascertained considering that the data were taken based on medical records. Long-term variability of HbA1C is closely related to the severity of diabetic neuropathy. However, in this study, HbA1C data collection was only done in the short term.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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Original Article

Correlation between Maximal Inspiratory Pressure and the Sit-to-Stand Test in Post-COVID-19 Patients

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Abstract

Background : Coronavirus Disease 2019 (COVID-19) can lead to long-lasting complications such as ongoing respiratory issues and functional impairments. Damage to the alveoli and respiratory muscles, particularly the diaphragm, may result in lower maximal inspiratory pressure (MIP) and decreased physical performance. Although prior studies have examined the connection between MIP and functional tests in various respiratory conditions, research focusing on post-COVID-19 populations, particularly in Indonesia, is scarce.
Aims : To investigate the correlation between Maximal Inspiratory Pressure (MIP) and 30-second Sit-to-Stand (30s STS) test performance in adult post-COVID-19 patients.
Methods : A cross-sectional study was conducted at two tertiary hospitals in Jakarta, Indonesia, involving 40 adults post-COVID-19 patients aged 18–59 years. Participants underwent clinical screening, spirometry, MIP measurement using the MicroRPM device, and the 30s STS test. Pearson correlation analysis was used for normally distributed variables with significance set at $p < 0.05$.
Results : The average MIP was 79.03 ± 26.68 cmH_2O, while the mean score for the 30s STS test was 12.78 ± 2.47 repetitions. Spirometric measurements revealed an average FEV_1 of 2.23 ± 0.57 L, FVC of 2.84 ± 0.69 L, and an FEV_1/FVC ratio of 81.19%. A moderate positive correlation between MIP and 30s STS performance was identified ($r = 0.515$, $p = 0.001$).
Conclusion : There is a significant moderate correlation between MIP and 30s STS performance among post-COVID-19 patients, suggesting that simple functional tests can be effective tools for assessing respiratory muscle strength and informing rehabilitation strategies in clinical environments.

Keywords : COVID-19; Diaphragm; Maximal Inspiratory Pressure; Sit-to-Stand Test

INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), affects not only pulmonary structures but also respiratory muscles, particularly the diaphragm.[1] COVID-19 can induce acute diaphragmatic weakness through direct viral invasion, systemic inflammation, and immobilization during hospitalization. This condition is associated with reduced Maximum Inspiratory Pressure (MIP), a recognized indicator of inspiratory muscle strength, and may influence physical performance, as reflected in functional tests such as the Sit-to-Stand (STS) test.[2,3]

Globally, up to 60–70% of COVID-19 survivors report symptoms such as dyspnea, muscle fatigue, and reduced exercise tolerance several months following recovery, with functional impairment remaining obvious even two years after the infection. In Indonesia, clinical follow-up for COVID-19 survivors remains inconsistent and objective monitoring of respiratory muscle function is rarely conducted in the framework of standard rehabilitation programs. Simple and low-cost measures, such as MIP and STS testing, represent a viable alternative for the early detection of respiratory and functional impairments, especially in resource-poor healthcare systems.[4–8]

Persistent symptoms following COVID-19, including dyspnea and fatigue, are frequently reported and differ from those observed in COPD, as they often occur in individuals without prior respiratory disease and may not follow a chronic, progressive trajectory.[9] In Indonesia, these sequelae have significant clinical implications given the high number of COVID-19 survivors, the relatively younger demographic profile compared to typical COPD populations, and contextual factors such as nutritional status, physical activity patterns, and healthcare accessibility, which may influence recovery.[10] Investigating the correlation between MIP and STS performance in Indonesian COVID-19 survivors is therefore essential to determine whether inspiratory muscle strength serves as a predictor of functional capacity in this population.

SARS-CoV-2 is known to affect multiple organ systems, due to widespread expression of ACE2 receptors, the virus's primary cellular entry point, including in lung tissue and the diaphragm.[11] Pulmonary imaging often reveals ground-glass opacities (GGOs), consolidation, and in some cases, fibrotic changes––particularly in patients who required mechanical ventilation.[12] In addition to alveolar injury, diaphragm involvement has been increasingly recognized. Diaphragmatic weakness, likely mediated by direct viral infiltration and inflammation, can impair respiratory muscle strength and reduce ventilatory efficiency.[13]

Maximal Inspiratory Pressure (MIP) is a well-established metric for evaluating respiratory muscle strength, particularly diaphragmatic function. Studies in post-COVID-19 populations have shown a measurable decline in MIP compared to healthy controls. For instance, Plaza *et al*. reported MIP reductions of 13.5 cmH□O in females and 10.9 cmH□O in males post-COVID-19, suggesting a meaningful loss of inspiratory capacity.[14]

Functional performance assessments such as the Six-Minute Walk Test (6MWT), One-Minute Sit-to-Stand Test (1MSTST), and 30-Second Sit-to-Stand Test (30s STS) have been widely used to evaluate aerobic capacity and lower-limb function in respiratory and rehabilitation contexts. These tests are simple, cost-effective, and informative tools that may indirectly reflect respiratory function and overall endurance.[15]

Recent evidence has increased the understanding that COVID-19 may directly and indirectly impair respiratory muscle function. SARS-CoV-2 can induce diaphragmatic injury by viral infiltration, systemic inflammation, prolonged immobilization, and possible neural involvement, resulting in inspiratory muscle weakness and persistent dyspnea even after recovery.[4,5,16]

Respiratory muscle dysfunction persisted in a substantial number of COVID-19 survivors and most of the time paralleled peripheral muscle weakness and reduced lung function, even two years post-infection. Several functional tests, such as the Six-Minute Step Test (6MST) and the One-Minute Sit-to-Stand Test (1MSTST), have been validated as reliable, low-cost methods for the assessment of exercise capacity in patients following COVID-19, thereby supplying useful guidance for pulmonary rehabilitation programs.[17] More recently, several systematic reviews reported that RMT in patients following COVID-19 induced significant increases in inspiratory and expiratory muscle strength, reduced dyspnea, improved exercise capacity, and quality of life, although the role of targeted respiratory muscle assessment in the same context remains poorly explored.[18,19] These findings emphasize the need for the assessment of respiratory muscle strength as part of post-COVID-19 rehabilitation strategies.

Previous research has identified correlations between MIP and sit-to-stand test performance in patients with chronic respiratory diseases, particularly chronic obstructive pulmonary disease (COPD).[20] While Indonesia has a high number of COVID-19 survivors, it still lacks structured long-COVID rehabilitation services, with respiratory muscle assessment not always implemented in outpatient settings. Thus, information about the relationship between respiratory muscle strength and functional performance in post-COVID-19 patients is still scant, especially in Indonesian settings. These findings highlight the potential of incorporating MIP and 30s STS into early post-COVID screening

protocols, especially in low-resource rehabilitation settings. This study provides locally relevant evidence for integrating respiratory muscle assessment into clinical practice in Indonesia.

This study presents novelty in both its methodological and contextual aspects. Conducted during the COVID-19 pandemic, when access to diagnostic facilities and procedures involving airborne transmission risk was highly restricted, this research offers a practical and safe alternative for evaluating respiratory muscle function and functional capacity using noninvasive measures. The use of Maximum Inspiratory Pressure (MIP) and the 30-second Sit-to-Stand Test (30s STS) provides a simple yet reliable approach to assess post-COVID-19 respiratory performance under limited-resource conditions.

Given the rising number of COVID-19 survivors experiencing prolonged symptoms, evaluating the association between MIP and functional performance is essential for early detection of residual impairments, planning interventions, and guiding pulmonary rehabilitation. Therefore, this study aims to investigate the correlation between MIP and 30s STS performance in post-COVID-19 adults in Indonesia, offering insights relevant for both local clinical practice and the global rehabilitation community.

METHODS

This observational study employed a cross-sectional design to assess the correlation between Maximal Inspiratory Pressure (MIP) and 30-second Sit-to-Stand (30s-STS) test performance among adult patients recovering from COVID-19. Participant recruitment was conducted consecutively to reduce selection bias. The study was carried out in the outpatient physical medicine and rehabilitation clinics of two tertiary referral hospitals in Jakarta, Indonesia: Dr. Cipto Mangunkusumo General Hospital (RSCM) and Persahabatan Hospital (RSP). This study got two ethical clearances, consist of EC Number KET-1339 /UN2.F1/ETIK/PPM.00.02/2023 from RSCM and EC Number 157/KEPK-RSUPP/12/2023 from RSP.

The source population consisted of individuals with a confirmed history of SARS-CoV-2 infection. The study sample comprised patients attending the rehabilitation clinics of the participating hospitals between July 2022 and June 2024. Inclusion criteria were adults aged 18–59 years, confirmed COVID-19 diagnosis by PCR testing at least three months prior to enrollment, ability to follow verbal instructions (Mini-Mental State Examination [MMSE] score ≥25), and provision of written informed consent.

Exclusion criteria included: significant structural postural deformities (e.g., severe scoliosis, kyphosis, lordosis), long-term corticosteroid use, history of mechanical ventilation during ICU admission, severe cardiopulmonary diseases (e.g., advanced COPD, severe asthma, congestive heart failure), balance impairment (Berg Balance Scale score <21), or major motor weakness (Manual Muscle Testing [MMT] score <3).

Sample size was calculated based on correlation analysis, with assumptions of a significance level (α) of 0.05 (Z_a = 1.96), power (1β) of 80% ($Z\beta$ = 0.842), and an expected correlation coefficient (r) of 0.5. The minimum required sample size was 30 participants.

The primary independent variable was MIP (cmH□O), assessed using the MicroRPM device. The primary dependent variable was lower-limb functional performance, measured by the total number of complete repetitions in the 30s-STS test. Potential confounders included age, sex, body weight, and height. Operational definitions for all variables were predefined to ensure consistency. Demographic data were collected from government-issued identification; anthropometric data were measured using calibrated equipment. All assessments were conducted by trained healthcare personnel following standardized procedures.

Eligible participants underwent clinical screening that included history taking, physical examination, and evaluation using the MMSE and Berg Balance Scale. Subjects meeting all inclusion and exclusion criteria then proceeded with pulmonary function testing. MIP was measured in a standing position using the MicroRPM, following standard respiratory muscle strength testing protocols. After a 10-minute rest period, participants performed the 30s-STS test on a standardized armless chair. Throughout testing, vital signs––including oxygen saturation, blood pressure, and perceived exertion (measured using the modified Borg scale)––were recorded pre- and post-test to monitor for adverse effects.

Data were analyzed using IBM SPSS Statistics for Windows, Version 25.0. Descriptive statistics were used to summarize participant characteristics and outcome variables. The Kolmogorov–Smirnov test was applied to assess data normality. For normally distributed variables, Pearson correlation analysis was used to evaluate the association between MIP and 30s-STS performance. If variables were non-normally distributed, Spearman's rank correlation was applied. Additional group comparisons were conducted using the Kruskal–Wallis test when appropriate. A two-tailed *p*-value <0.05 was considered statistically significant. Correlation strength was interpreted using the correlation coefficient (r) along with 95% confidence intervals.

RESULTS

A total of 52 individuals were screened for eligibility at two research sites. Of these, 12 participants were excluded: 10 due to difficulties completing the assessment procedures and 2 due to a history of knee arthritis. The remaining 40 subjects met the inclusion

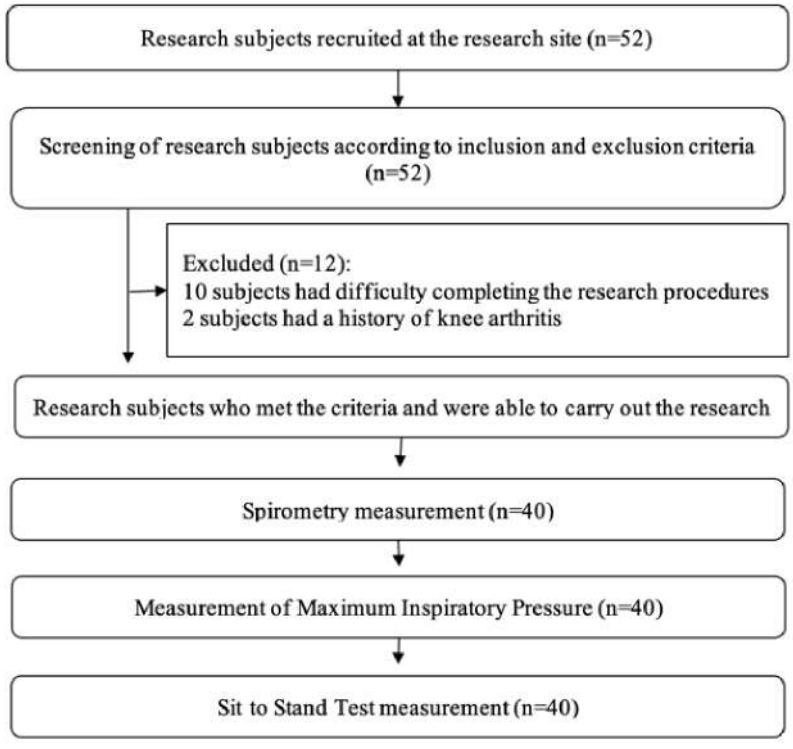

Figure 1. Research Sample Recruitment Flow

criteria and completed the study protocol, which included spirometry, maximal inspiratory pressure (MIP) measurement, and the 30-second sit-to-stand (30s-STS) test. The study received ethical approval.

Among the 40 participants, 15 were male (37.5%) and 25 were female (62.5%). The mean age was 38.80 ± 11.23 years. Nutritional status based on Asia-Pacific BMI classification revealed 2.5% underweight, 20% normal weight, 27.5% overweight at risk, 32.5% obesity class I, and 17.5% obesity class II. Regarding educational background, 72.5% of participants had completed higher education (D1–S2), and 27.5% had completed high school.

Based on time since COVID-19 infection, 5% had recovered within the last year, 47.5% within 1–2 years, and 47.5% more than 2 years prior to the study. Spirometry results indicated normal lung function in 60% of participants, with 25% showing obstructive, 12.5% restrictive, and 2.5% mixed patterns.

The average FEV□ was 2.23 ± 0.57 L, and the mean FVC was 2.84 ± 0.69 L. The mean FEV□/FVC ratio was 81.19%, ranging from 49% to 95%.

The mean 30s-STS score for all subjects was 12.78 ± 2.47 repetitions. Males performed an average of 13 (11–15) repetitions, while females averaged 12 (range 8–20). Participants with a COVID-19 onset <1 year prior achieved the highest average score (13 repetitions), while those with restrictive lung function recorded the highest mean score (14 repetitions) across pulmonary subgroups.

The mean MIP for all subjects was 79 cmH□O (range 60–100). Males exhibited higher mean values 95 cmH□O (range 80–110) cmH□O compared to females 64 cmH□O (range 41–144). The highest average MIP was recorded in the group with COVID-19 onset under 1 year 111 cmH□O (range 91–130). Among pulmonary function groups, the mixed-type group had the highest mean MIP at 91 cmH□O.

Pearson's correlation analysis revealed a statistically significant moderate positive correlation between MIP and 30s-STS test performance ($r = 0.515$, $p = 0.001$). This indicates that individuals with higher inspiratory pressure tended to perform better on the functional sit-to-stand assessment.

DISCUSSION

The mean score for the 30-second sit-to-stand (30s STS) test in this study was 12.78 repetitions, which is substantially lower than the established cutoff of 29 repetitions for detecting functional impairment in patients with mild post-COVID-19 conditions. This finding suggests the presence of residual functional limitations, even among individuals who may not exhibit overt clinical symptoms. Given its simplicity, low cost, and minimal equipment requirements, the 30s STS test serves as a practical screening tool to identify patients who may benefit from targeted rehabilitation interventions during the recovery phase. Study by

TABLE 1
Participant Characteristics

Variable	Subjects (n = 40)
Age (years)	38.80 ± 11.23
Sex, n (%)	
Male	15 (37.5%)
Female	25 (62.5%)
Body Weight (kg)	64.5 (43–116)
Height (cm)	158.83 ± 8.875
Nutritional Status/BMI, n (%)	
Underweight	1 (2.5%)
Normal Weight	8 (20%)
Overweight	11 (27.5%)
Obesity I	13 (32.5%)
Obesity grade II	7 (17.5%)
Education, n (%)	
High School Graduate	11 (27.5%)
College Graduate (D1–S2)	29 (72.5%)
COVID-19 Onset, n (%)	
Less than 1 year	2 (5%)
1–2 years	19 (47.5%)
More than 2 years	19 (47.5%)
Lung Function, n (%)	
Normal	24 (60%)
Obstructive	10 (25%)
Restrictive	5 (12.5%)
Mixed	1 (2.5%)

Amput., *et al* (2025) show results that the 1-min-STST demonstrated outstanding test–retest reliability in post-COVID-19 patients. Lower limb muscular endurance and its contribution to functional ability are assessed using the 1-min-STST. These mechanisms show how well post-COVID-19 patients respond to rehabilitation regimens and carry out daily tasks.[17]

The Sit-to-Stand test has gained increasing attention as a safe and sensitive measure of physical performance in post-COVID-19 patients. In the prospective cohort study by Faria *et al.* (2023), post-COVID-19 patients presented with significantly lower heart rate response and oxygen saturation at the end of the 1MSTST and reduced repetition number compared to recovered patients without post-COVID symptoms. The threshold value below which HRend/HRmax ratio was suggestive of post-COVID-19 condition was established as less than 62.65%, which underlines that STS test is able to unmask subtle exercise intolerance and autonomic dysregulation even when overt pulmonary function abnormalities are absent.[7]

These findings support the inclusion of functional tests, such as STS, in standard post-COVID evaluations, given the potential early impairments of cardiovascular and muscular responses to exercise. Added to MIP, a direct indicator of inspiratory muscle strength, clinicians are able to better describe the relationship between respiratory and systemic limits. Our study indicates that even young, well-educated patients with increased body mass index are showing significant impairment of both

TABLE 2
Spirometry Results

Variable	Value (n=40)
FEV1 (L)	2.23 ± 0.57
FVC (L)	2.84 ± 0.69
FEV1/FVC (%)	81.19 (49 – 95)

TABLE 3
30s Sit-to-Stand Test Results

Variable	Sit to Stand Test (times)
Sex	
Male	13 (11–15)
Female	12 (8–20)
COVID-19 Onset	
Under 1 year	13 (11–15)
1–2 years	13 (11–15)
> 2 years	13 (11–15)
Lung Function	
Normal	13 (11–15)
Obstructive	12 (10–14)
Restrictive	14 (12–16)
Mixed	11

STS performance and MIP values post-COVID-19, reinforcing the concern that post-COVID sequelae are not limited to severe cases or aged individuals. This emphasizes the importance of early, personalized rehabilitation protocols, particularly those utilizing RMT, to enhance ventilatory efficiency, reestablish functional capacity, and prevent long-term deconditioning among all post-COVID-19 survivors, whatever baseline risk.[7]

The average maximal inspiratory pressure (MIP) in this study was 79.03 cmH□O (males 94.6 cmH□O, females 64 cmH□O), which is substantially lower than normative values for healthy young adults, typically exceeding 128 cmH□O in males and 97 cmH□O in females. This reduction reflects persistent inspiratory muscle weakness likely related to post-COVID-19 sequelae such as diaphragmatic or intercostal dysfunction, deconditioning, or direct viral muscle injury, consistent with previous reports showing lingering MIP deficits in recovered patients.[6,21] Similar reductions in MIP have been reported in recent studies showing persistent respiratory muscle weakness months to years after COVID-19 recovery, with inspiratory pressures in the lower range in about 40% of survivors and impaired diffusion capacity.[4,5] Numerous interconnected mechanisms, such as systemic inflammation, microvascular damage, and critical illness-related myopathy, are probably responsible for the reported decrease in respiratory muscle strength. Further factors that may impair muscular contractility and endurance include oxidative stress and ventilator-induced diaphragmatic dysfunction. According to a study by Verduri *et al*. (2024), the use of noninvasive ventilation (NIV), which seems to serve as an independent risk factor, was linked to both MIP and MEP dysfunction. Long-term inspiratory muscle performance may deteriorate because to diaphragmatic deconditioning brought on by prolonged NIV exposure. Overall, these results imply that the cumulative effects of supportive respiratory therapies during the acute phase as well as the direct impacts of the infection itself are reflected in post-COVID-19 respiratory muscle dysfunction.[4] In this respect, direct diaphragmatic

TABLE 4
Maximal Inspiratory Pressure Results

Variable	Maximal Inspiratory Pressure (cmH□O), Median (IQR)
Sex	
Male	95 (80–110)
Female	64 (41–144)
COVID-19 Onset	
Under 1 year	111 (91–130)
1–2 years	75 (60–90)
> 2 years	79 (60–100)
Lung Function	
Normal	74 (41–144)
Obstructive	74 (60–90)
Restrictive	76 (60–95)
Mixed	91

TABLE 5
Correlation Between Maximal Inspiratory Pressure and 30s Sit-to-Stand Test

Variable	Mean ± SD	Correlation Coefficient (r)	*p*-value
Sit to Stand Test	12.78 ± 2.47	0.515	0.001
Maximal Inspiratory Pressure	79.03 ± 26.68		

involvement, as well as systemic myopathy, is likely to be responsible for muscle weakness.[16]

Accumulating evidence indicates that COVID-19 impairs respiratory muscles through a combination of direct viral and secondary systemic mechanisms. SARS-CoV-2 may infect diaphragmatic myofibers via ACE2 receptors, provoking inflammatory and fibrotic remodeling that compromises contractility. In concert, systemic inflammation, microvascular injury, protracted immobilization, and ventilator-associated diaphragm dysfunction promote muscle atrophy and weakness. Additional neural involvement, including phrenic neuropathy and possible injury to central respiratory control pathways, may further contribute to persistent dysfunction. The interaction between these factors yields continued inspiratory muscle weakness, decreased ventilatory efficiency, and chronic exertional dyspnea even in individuals with spared pulmonary parenchyma. Recognition of these mechanisms underlines the clinical relevance of routine respiratory muscle assessment and specific rehabilitation during follow-up care after COVID-19.[16]

Systematic reviews also suggest that RMT significantly improves MIP and MEP and reduces dyspnea and enhances exercise performance in post-COVID-19 patients. These findings support the clinical applicability of inspiratory training as a core component of rehabilitation programs.[19] These findings align with randomized controlled trial evidence demonstrating that structured inspiratory muscle training (IMT) can significantly improve respiratory muscle strength and alleviate breathlessness in long-COVID patients. Collectively, these data underline the reality of sustained inspiratory muscle impairment after COVID-19 and the clinically meaningful benefits of integrating IMT into rehabilitation protocols to restore ventilatory function and reduce exertional dyspnea.[22]

RMT, both inspiratory (IMT) and combined inspiratory-expiratory modality, has emerged as an effective rehabilitation intervention in COVID-19 survivors with persistent dyspnea, fatigue, and reduced exercise capacity. Post-COVID-19 respiratory muscle weakness is multifactorial, resulting from diaphragmatic dysfunction, systemic inflammation, microvascular

injury, and prolonged inactivity. RMT directly addresses these mechanisms by applying targeted resistance to breathing, thus stimulating adaptive remodeling of the diaphragm and accessory inspiratory muscles. These adaptations result in enhanced strength, endurance, and ventilatory efficiency through physiological mechanisms similar to skeletal muscle training. Randomized controlled trials and systematic reviews report significant gains in maximal inspiratory and expiratory pressures (MIP and MEP), inspiratory endurance, and functional capacity following a structured RMT program.[19,23,24]

Recent studies further confirm that moderate-intensity, individualized RMT improves respiratory performance and patient self-reported outcomes without untoward effects. Supervised training for six to eight weeks has been shown to enhance inspiratory muscle strength and endurance, decrease perceived breathlessness, and enhance the dyspnea component of quality-of-life instruments such as the Chronic Respiratory Disease Questionnaire. Strengthened inspiratory and expiratory muscles reduce the proportion of maximal effort required during daily activities, decreasing respiratory drive and neural activation and translating to lower dyspnea intensity. Combined inspiratoryexpiratory protocols yield greater improvements in expiratory flow and airway clearance, key components for restoring effective ventilation and reducing respiratory effort during exertion.[19,23,24]

Besides physiological recovery, RMT significantly contributes to functional restoration and the regain of general health in patients post-COVID-19. Participants receiving RMT demonstrate significant improvement in six-minute walk distance, a reduction in exertional dyspnea, and improved health-related quality of life. While spirometric parameters such as FEV□ and FVC usually remain unaltered, these functional and perceptual improvements reflect improved respiratory efficiency and oxygen utilization. Importantly, RMT provided in home-based or telerehabilitation formats has shown excellent adherence and safety, supporting its feasibility in long-term recovery programs. Altogether, these data suggest that RMT is a safe, evidence-based, widely available intervention to promote respiratory muscle reconditioning and reduce dyspnea, thus facilitating the resumption of daily activities in patients with persistent post-COVID-19 sequelae.[19,23,24]

A statistically significant moderate positive correlation was observed between MIP and 30s STS performance ($r = 0.515$, $p = 0.001$), indicating that individuals with greater inspiratory strength tended to demonstrate better lower-limb functional capacity. This relationship aligns with previous studies showing a strong association between respiratory muscle strength and functional performance in post-COVID-19 populations. Motta *et al*. reported that more than half of long-COVID patients presented with maximal inspiratory pressures below 80% of predicted values, which were significantly correlated with reduced six-minute walk distance, thereby underscoring the impact of inspiratory weakness on exercise tolerance.[6,25,26] Clinically, this suggests that the 30s STS test may serve as a surrogate marker for inspiratory muscle strength, particularly in resource-limited settings where direct MIP measurement is not feasible. The Sit-to-Stand (STS) test can serve as a functional surrogate because it reflects lower limb strength, endurance, and indirectly respiratory muscle performance. This is based on the physiological link: inspiratory muscles contribute significantly to trunk stabilization during STS movements, and reduced respiratory muscle strength has been shown to correlate with poorer STS performance in post-COVID and chronic respiratory disease patients. Such a surrogate could enhance early identification of patients requiring respiratory rehabilitation.

The combined use of 30s STS and MIP measurements provides a comprehensive yet accessible method for monitoring physical recovery in post-COVID-19 patients. These tools offer valuable insights into both systemic muscle function and respiratory capacity, enabling clinicians to tailor rehabilitation programs according to individual needs. Notably, our study population included younger individuals with relatively high education levels and increased BMI, yet still demonstrated significant reductions in functional and respiratory parameters. This reinforces the need for proactive rehabilitation strategies, even in populations perceived to be at lower risk of severe post-COVID sequelae.[8]

Despite these findings, several limitations must be acknowledged. The sample size was relatively small, and classification of participants based on the severity of initial COVID-19 infection was not performed, limiting generalizability. Moreover, no imaging studies (e.g., chest radiographs or CT scans) were conducted to objectively assess pulmonary pathology, which may have influenced respiratory performance outcomes. The study also faced challenges in participant recruitment, partly due to the evolving public perception of COVID-19 as a commonplace illness. Lastly, a subset of participants initially demonstrated difficulty performing the test procedures correctly; however, this was mitigated through standardized instruction and demonstration by trained assessors. Given the limited access to specialized pulmonary rehabilitation centers in Indonesia, the adoption of MIP and STS assessments in primary care settings could improve early identification of post-COVID functional impairment. Future research is recommended to employ larger, multicenter cohort designs to improve generalizability and allow stratification of participants by the severity of their initial COVID-19 infection. Outcome measures may include maximal inspiratory pressure, sit-to-stand performance,

six-minute walk distance, diaphragm excursion, and patient-reported assessments of dyspnea and fatigue. Study populations should encompass post-COVID patients across varying degrees of disease severity, from those managed in the community to ICU survivors, along with healthy control groups, to strengthen external validity.

CONCLUSION

This study demonstrated a moderate but statistically significant correlation between maximal inspiratory pressure (MIP) and 30-second sit-to-stand (30s STS) performance among post-COVID-19 patients, indicating that respiratory muscle strength is closely linked to functional capacity in this population. Although spirometric parameters were generally within normal limits, both inspiratory strength and lower-limb functional performance were notably reduced, suggesting residual respiratory and peripheral muscle dysfunction despite apparent pulmonary recovery. These findings support the clinical utility of the 30s STS test as a simple, reliable, and low-cost surrogate for evaluating inspiratory muscle strength, particularly in settings where direct measurement of MIP is not feasible.

The persistence of respiratory muscle weakness underlines the multifactorial consequences of COVID-19: direct involvement of the diaphragm, systemic inflammation, deconditioning, and potential neural impairment. Thus, the integration of respiratory muscle assessment and targeted interventions, such as respiratory muscle training or inspiratory muscle training, in post-COVID rehabilitation programs may be an important requisite for restoring ventilatory efficiency and reducing exertional dyspnea and improving exercise tolerance. Functional performance tests coupled with respiratory strength measures can provide a more comprehensive approach to monitoring recovery, guiding individualized rehabilitation, and enhancing the quality of life among COVID-19 survivors.

Besides the clinical applications, this study further underscores the need for community-oriented rehabilitation approaches that would enable patients to engage more actively in their own process of recovery. A promotion of self-monitoring of breathing effort and progressive physical reconditioning could lead to even better post-COVID outcomes in daily life.

Future studies should explore longitudinal changes in MIP and STS performance following structured respiratory rehabilitation to determine the extent of reversibility of inspiratory muscle weakness. Establishing normative recovery trajectories could guide the timing and intensity of therapeutic interventions, ultimately improving outcomes for COVID-19 survivors.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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Original Article

In Vitro Testing of the Antibacterial Activity of Ethanol Extract of Lontar Leaves *(Borassus flabellifer)* Against *Staphylococcus aureus*

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Abstract

Background : *Staphylococcus aureus* is a bacterium that frequently causes infections and often develops resistance to antibiotics. Efforts to identify alternative treatments using herbal remedies are increasing. In Indonesia, a country rich in biodiversity, lontar leaves *(Borassus flabellifer)* have been traditionally used and show potential antibacterial activity. The aims of this study was to evaluate the antibacterial activity of ethanol extract of lontar leaves against *Staphylococcus aureus* in vitro.
Methods : This experimental study employed a post-test-only control group design. Antibacterial activity was tested using the well diffusion method. Extracts were obtained through maceration with 96% ethanol and tested at 75%, 50%, and 25% concentrations. Ciprofloxacin was used as the positive control, and 10% DMSO as the negative control.
Results : The inhibition zone diameters were 21.86 mm (75%), 19.64 mm (50%), and 18.37 mm (25%). The positive control (ciprofloxacin) measured 24.43 mm, while the negative control (DMSO) showed 0 mm.
Conclusion : The 96% ethanol extract of lontar leaves demonstrated antibacterial activity against *Staphylococcus aureus*, with higher concentrations yielding stronger inhibition.

Keywords : *Borassus flabellifer*, antibacterial activity, *Staphylococcus aureus*, herbal extract, in vitro study

INTRODUCTION

Staphylococcus aureus is one of the most commonly ncountered bacteria of clinical significance due to its diverse clinical manifestations.[1] It is part of the normal human microbiota, with 60% of healthy individuals having *S. aureus* colonized on their skin, particularly in moist areas.[2–4] Although *S. aureus* is a normal component of human microbiota, it can become pathogenic and infect humans.[4] Transmission of *S. aureus* primarily occurs via direct skin-to-skin contact rather than through the air, leading to various conditions ranging from minor skin infections to life-threatening diseases such as meningitis.[2,4] Local skin infections caused by *S. aureus* include impetigo, folliculitis, abscesses, and cellulitis.[5]

Treatment of *Staphylococcus aureus* infections presents a challenging issue due to the bacterium's ability to rapidly adapt to antibiotic treatments, leading to the emergence of resistant strains such as MRSA *(methicillin-resistant Staphylococcus aureus)*. According to the WHO, MRSA is a pathogen that requires special attention in its treatment.[6] Epidemiological studies over the past two decades have shown a significant increase in MRSA prevalence in the United States, reaching up to 40%. In Asia, MRSA incidence is reported to be the highest in the world. Data from the Asian Network for Surveillance of Resistant Pathogens (ANSORP) indicate that in Southeast Asia, particularly Indonesia, MRSA prevalence is approximately 28%.[7–9]

Due to this bacterium's increasing prevalence and antibiotic resistance, researchers are investigating alternative antibiotics. This necessitates the exploration of other substances that could serve as alternative antibiotics to inhibit or eliminate the growth of *Staphylococcus aureus*, such as herbal plants.[10]

In Indonesia, particularly in South Sulawesi, there is a plant that serves as a botanical symbol of the region: the lontar palm. Every part of the lontar plant from its roots to its leaves is utilized for various purposes. It is used in daily activities such as construction, traditional ceremonies, and herbal remedies. The lontar plant is utilized as a herbal medicine due to its pharmacological activities in its flowers, fruit, leaves, roots, and seeds, including antioxidant, antibacterial, antifungal, anti-arthritis, anti-infland immunomodulatory effects.[11]

Lontar fruit extract demonstrated antibacterial effects against *Staphylococcus aureus*. This is attributed to compounds in the fruit that exhibit antibacterial properties, including alkaloids, flavonoids, tannins, triterpenoids, and saponins.[12] Additionally, phytochemical analysis of lontar leaves revealed a similar profile of compounds, including flavonoids, glycosides, tannins, proteins, steroids, triterpenoids, carbohydrates, fats, and oils.[10] These compounds in the lontar leaves have potential antibacterial activity. Supporting this, one study demonstrated the broad-spectrum antimicrobial potential of *Borassus flabellifer* extract, including activity against several Gram-negative bacteria. Although the study focused on multiple pathogens, the findings support the plant's potential role in inhibiting *Vibrio cholerae* growth in vitro due to its rich phytochemical profile.[11]

Unfortunately, studies investigating the antibacterial properties of *Borassus flabellifer* (lontar) leaf extract remain limited. To date, no substantial research has been conducted to explore its activity against *Staphylococcus aureus*, a Gram-positive bacterium commonly associated with antibiotic resistance. Further investigation using resistant bacterial strains is needed to uncover the potential of plant-based therapeutics in addressing antimicrobial resistance. Based on this gap, the current study aims to evaluate whether ethanol extract of lontar leaves exhibits inhibitory effects on the growth of *Staphylococcus aureus*.

In light of this evidence gap, the present study aimed to evaluate the in vitro antibacterial activity of ethanol extract of lontar leaves against the Gram-positive bacterium *Staphylococcus aureus*.

METHODS

This study employed a true experimental design using a post-test-only control group approach to evaluate the antibacterial activity of lontar leaf extract *(Borassus flabellifer)* against *Staphylococcus aureus*. The research was conducted from September to November 2023 at the Microbiology Laboratory and the Natural Pharmaceutical Materials Laboratory of the Pharmacy Undergraduate Program, Universitas Muslim Indonesia. Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Makassar, under the number 378/UM.PKE/VIIII/45/2023.

The samples used in this study consisted of lontar leaf extract and *Staphylococcus aureus* ATCC 25923, which were cultured on Nutrient Agar and incubated at 37°C for 24 hours. The inclusion criteria required the use of uncontaminated and viable *S. aureus* colonies, while the exclusion criteria involved the removal of non-growing bacterial cultures. Dried lontar leaves were subjected to maceration using 96% ethanol for approximately three days to obtain the crude extract. The filtrate was then evaporated to remove the solvent, and the resulting extract was analyzed through phytochemical screening to identify active compounds such as tannins, steroids, flavonoids, and saponins.

Following extraction, the crude extract was diluted using 10% DMSO to obtain the concentrations of 25%, 50%, and 75%. Ciprofloxacin was used as the positive control, and 10% DMSO served as the negative control. The antibacterial activity was evaluated using the well diffusion method. A standardized suspension of

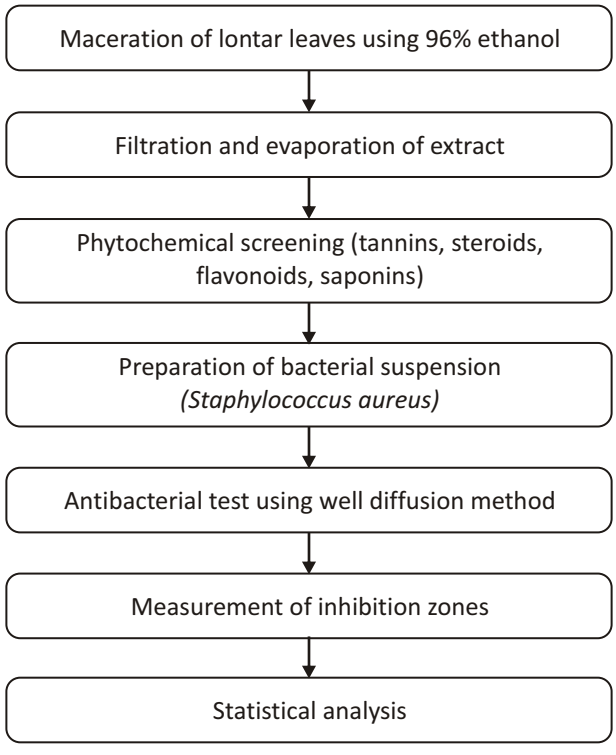

Figure 1. The Flowchart Of The Data Collection

Staphylococcus aureus was evenly spread on Nutrient Agar plates, and wells were created using a sterile cylinder. Each well was filled with 100 µL of the respective extract concentrations, positive control, and negative control. The plates were then incubated at 37°C for 24 hours. Zones of inhibition were measured using a digital caliper, and their diameters were interpreted based on the Greenwood classification: inhibition zones greater than 20 mm were considered strong, 16–20 mm moderate, 10–15 mm weak, and less than 10 mm indicated no inhibition.

Data obtained from the five groups was analyzed using SPSS software. The normality of the data distribution was tested using the Shapiro-Wilk test due to the sample size being fewer than 50. Homogeneity of variances was tested using Levene's test. Since the data was normally distributed and homogenous, parametric testing was conducted using one-way ANOVA, followed by the LSD post hoc test to determine specific group differences. A p-value of less than 0.05 was considered statistically significant at a 95% confidence interval.

The instruments used in this study included a rotary evaporator, incubator, autoclave, digital caliper, analytical balance, micropipettes, petri dishes, and sterile cotton swabs. The materials used consisted of lontar leaves, 96% ethanol, Nutrient Agar (Oxoid), *Staphylococcus aureus* ATCC 25923, ciprofloxacin, and 10% DMSO.

RESULTS

In the antibacterial activity test, ethanol extract of lontar leaves *(Borassus flabellifer L.)* was used at 25%, 50%, and 75%. Ciprofloxacin was the positive control, while 10% DMSO was the negative control. The results are presented in the Tabel 1.

To conduct the One-Way ANOVA hypothesis test, normality testing using the Shapiro-Wilk test and homogeneity testing using Levene's test were performed, with *p*-values >0.05. Since the results of both normality and homogeneity tests met the criteria, parametric testing using One-Way ANOVA was conducted. The ANOVA test yielded a *p*-value <0.001, indicating significant differences among the five treatment groups. To further determine if there are significant differences between specific treatment groups, a post-hoc LSD test will be conducted.

DISCUSSION

In this study, the ethanol extract of lontar leaves was prepared using the maceration method with 96% ethanol as the solvent. Maceration is a simple extraction technique that does not involve heating, thus preserving the secondary metabolites in the plant. Ethanol is considered a universal solvent capable of extracting both polar and non-polar compounds. It is less toxic compared to other solvents, such as methanol and water, allowing

TABLE 1
Results of the Diameter Measurement of Inhibition Zones for Various Concentrations of 96% Ethanol Extract of Lontar Leaves Against Staphylococcus aureus Growth

Extract Concentration	Diameter of inhibition zone (mm)					Average	Description	*P* Value**
	1*	2*	3*	4*	5*			
K1	18.35	18.35	18.33	18.63	18.21	18.37	Moderate	<0.001
K2	19.65	19.89	19.33	19.85	19.51	19.64	Moderate	
K3	21.95	21.68	21.96	22.01	21.73	21.86	Strong	
K (+)	24.28	23.99	24.45	24.69	24.76	24.43	Strong	
K (-)	0	0	0	0	0	0	Not Inhibit	

Note :
K1 : Group with 25% concentration of ethanol extract of lontar leaves
K2 : Group with 50% concentration of ethanol extract of lontar leaves
K3 : Group with 75% concentration of ethanol extract of lontar leaves
K(+) : Positive control (Ciprofloxacin)
K(-) : Negative control (10% DMSO)
* : Replicate
** : One-Way ANOVA test (significant if $p < 0.05$)

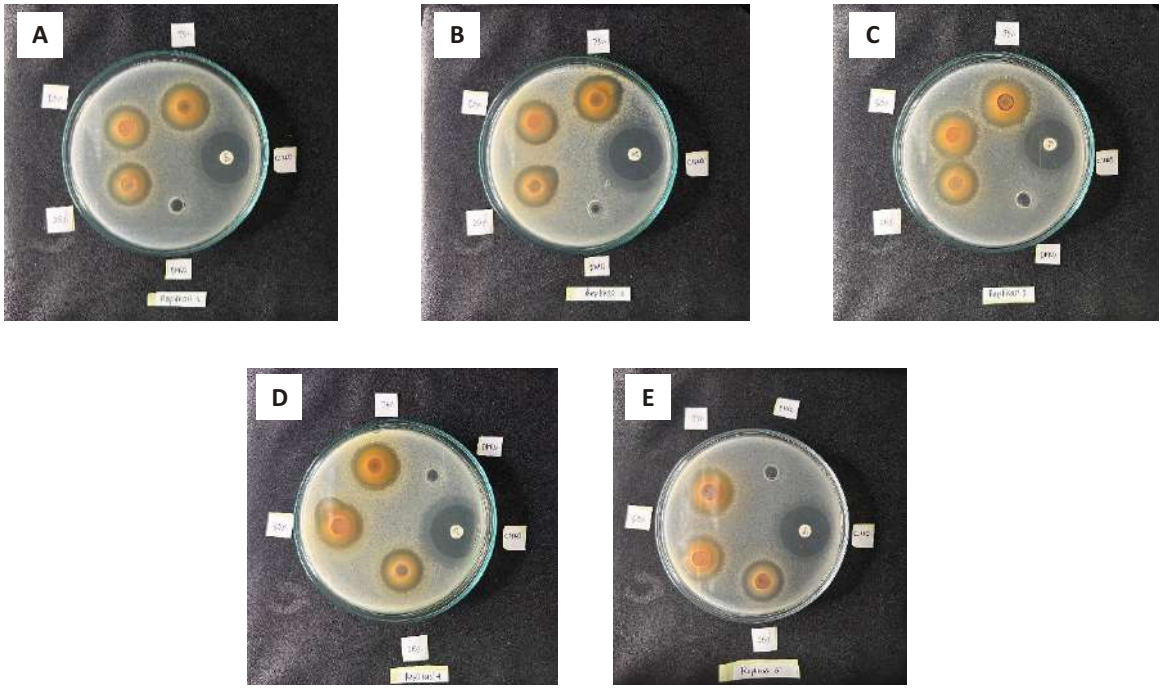

Figure 2. Replication (A. Replication 1, B. Replication 2, C. Replication 3, D. Replication 4, E. Replication 5)

for a higher yield of metabolites.[13]

Several previous studies have assessed the effect of ethanol concentration on the extraction of bioactive compounds. One study found that 96% ethanol extracted a higher flavonoid content from red dragon fruit peel than 70% ethanol.[14] While previous studies reported better results using 70% ethanol for flavonoid extraction from *Centella asiatica* and *Sargassum polycystum*.[13,15] In contrast, 96% ethanol has also been shown to be effective in extracting terpenoids and tannins from red ginger

TABLE 2
Results of the Post-Hoc Least Significant Difference (LSD) Test

Treatment		Differences Average	Confidence Interval 95%		*P* Value**
I	II		Min	Max	
K1	K2	-1.27200*	-1.6703	-0.8737	<0.001
	K3	-3.49200*	-3.8903	-3.0937	<0.001
	K+	-6.06000*	-6.4583	-5.6617	<0.001
	K-	18.37400*	17.9757	18.7723	<0.001
K2	75%	-2.22000*	-2.6183	-1.8217	<0.001
	K+	-4.78800*	-5.1863	-4.3897	<0.001
	K-	19.64600*	19.2477	20.0443	<0.001
K+	K+	-2.56800*	-2.9663	-2.1697	<0.001
	K-	21.86600*	21.4677	22.2643	<0.001
K (+)	K (-)	24.43400*	24.0357	24.8323	<0.001

Note :
K1 : Group with 25% ethanol extract of lontar leaves
K2 : Group with 50% ethanol extract of lontar leaves
K3 : Group with 75% ethanol extract of lontar leaves
K (+) : Positive control (Ciprofloxacin)
K (-) : Negative control (10% DMSO)
P : Significant if $p < 0.05$

residue.[16] These findings highlight that optimal ethanol concentration may vary depending on the polarity of the target compounds and the plant matrix.

Phytochemical screening of the ethanol extract of lontar leaves was performed to identify the presence of compounds both qualitatively and quantitatively. The results indicated that the extract contained tannins and steroids, but saponins and flavonoids were undetected. This differs from previous studies that reported flavonoid presence,[10] which could be attributed to environmental or methodological variations.

The antibacterial activity of the lontar leaf extract *(Borassus flabellifer)* against *Staphylococcus aureus* was assessed using the well diffusion method. The extract exhibited moderate to strong antibacterial activity, as evidenced by the formation of inhibition zones around the wells in the medium after a 24-hour incubation period. The inhibition zone diameter was directly proportional to extract concentration, confirming a dose-response relationship.

This finding is consistent with a previous study, which demonstrated that 80% ethanol extract of lontar leaves produced an inhibition zone of 18.37 mm against *Vibrio cholerae*.[13] Although *Vibrio cholerae* is Gram-negative, the comparable results support the extract's potential as a broad-spectrum antibacterial.

Furthermore, lontar fruit extract has also been shown to exhibit antibacterial activity against *Staphylococcus aureus*, suggesting that various parts of the plant contain bioactive compounds with antibacterial effects.[12]

The mechanism of action is believed to be due to the presence of tannins and steroids. Tannins interfere with polypeptide synthesis required for bacterial cell wall construction, while steroids reduce membrane integrity, leading to leakage of cell contents and eventual bacterial cell death.

These results underline the potential of lontar leaf extract as a natural antibacterial agent, particularly in response to the growing resistance of *Staphylococcus aureus* to conventional antibiotics such as MRSA strains. While ciprofloxacin showed higher inhibition, the plant-based extract demonstrated promising activity and could be explored further in topical formulations or as an adjunct treatment.

Future research should aim at isolating specific bioactive compounds, standardizing extraction processes, and testing broader bacterial strains. In vivo studies and toxicity profiling would also be necessary before clinical application.

CONCLUSION

The 96% ethanol extract of lontar leaves contains bioactive compounds, specifically tannins and steroids, that exhibit antibacterial potential. This study demonstrated that the extract produced measurable antibacterial activity against Staphylococcus aureus, with inhibition zone diameters increasing proportionally to the concentration of the extract.

These findings suggest that lontar leaf extract could serve as a promising alternative antibacterial agent, especially in the context of rising antibiotic resistance such as MRSA. While its efficacy did not surpass that of ciprofloxacin, the extract's natural origin and local availability provide valuable prospects for future development.

Further research is recommended to explore its application in pharmaceutical formulations, conduct in vivo studies, and evaluate the toxicity to assess its safety and clinical potential.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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Case Report

S1 Dorsal Root Ganglion And Inferior Hypogastric Plexus Pulsed Radiofrequency Neuromodulation May Improve Type III Coccydynia Pain: a Case Report

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Abstract

Introduction : Coccygeal pain occurs in 1% to 2.7% of people without a clear coccygeal origin, unless provoked by prolonged sitting or anatomical changes found incidentally during surgery. Pain transmission blocked by pulsed radiofrequency (PRF) neuromodulation of the inferior hypogastric plexus (IHP) and dorsal root ganglion (DRG) can improve both nociceptive and neuropathic pain.
Methods : A 16-year-old female with a one-month history of coccydynia, coccygeal numbness radiating to the heels, and normal motor, micturition and voiding functions. The CSK 15 needle was inserted through both S1 neuroforamens to reach the DRG, then pulsed radiofrequency (PRF) 42°C for 2 minutes using the Cosman G4 device, followed by triamcinolone 20mg 1mL also administered contralaterally. Thus, PRF was also performed on both sides of the IHP anterior to the sacrum through the S2 neuroforamen approach.
Results : Improvement was observed after one month (NRS 0-1), whereas coccygeal numbness improved gradually. The combination analgesic (paracetamol 300mg, diazepam 2mg, diclofenac sodium 12.5mg) or pregabalin 50mg is administered as required, while vitamin B12 50 mcg/ 12h is continued.
Discussion : The pelvic sympathetic trunk (PSN) lies extraperitoneally anterior to the sacral and anteromedial to the anterior sacral neuroforamen with four or five interconnected ganglia. It rise to the lumbar sympathetic trunk (above) and the impar ganglion (below), which involved in transmitting sympathetic nociceptive from the perineum, distal rectum, distal vagina, distal urethra and anus. The parasympathetic afferent cells within the S2-S4 DRGs associated with pelvic splanchnic and somatic nerves.
Conclusion : Neuromodulation treatment for coccydynia has good results in DRG and IHP.

Keywords : coccydynia, pain, nociceptive, neuropathic, dorsal root ganglion, inferior hypogastric

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INTRODUCTION

The clinical complaint of coccygeal pain is commonly known as "coccydynia" or tail bone pain and was first described by Simpson in 1858. The pain is felt in the coccyx, buttocks and sometimes in the lower back. About 1% to 2.7% of people complain of coccygeal pain during theuraptic treatments, but few of them fail to identify the site of the lesion from the coccyx. Neurological examinations are not clear enough to describe these disorders, unless the worsening pain is mainly aggravated by prolonged sitting. Meanwhile, the anatomical changes can be seen incidentally during surgery under C-arm fluoroscopy. In addition, there are few important underlying conditions to rule out, such as soft tissue abscess or osteomyelitis, both of which are malignant and serious problems. Direct vertical trauma to the coccyx can result in a variety of outcomes, ranging from contusion to fracture-dislocation. Excessive flexion or extension of the coccyx also plays a role in increasing pain.[1] The coccyx is the terminal segment of the spine and gets its name from the Greek word for 'cuckoo bird's beak'. Consisting of three to five fused segments, the first of these is known as the coccygeal cornua and articulates with the sacral cornua. The lower part of the filum terminale and the coccygeal ligament are attached to this segment. A clinical examination may reveal tenderness or pain around the coccyx, which could indicate a fracture, inflammation or infection. If there is no tenderness, the pain may originate in the pelvis or lower back. The examination may also reveal erythema, swelling, a rash, discharge, fistulas, or skin breakdown, which could suggest cellulitis or osteomyelitis. The coccyx has several important functions, including supporting the anus.[2] It can classified as 6 types. *Type I:* gentle ventral curvature with caudally pointed apex of the coccyx (> 50%); *Type II:* more prominent of ventral curvature with apex pointing anteriorly (8–32%); *Type III:* acute anterior angulation without subluxation (4–16%); *Type IV:* subluxation at sacro-coccygeal or inter-coccygeal Joint (1–9%); *Type V:* retroverted with posteriorly angulated apex (1–11%); *Type VI:* scoliotic or laterally subluxated coccyx (1–6%).[3]

Coccydynia, or coccyx pain, may not be thought of as the cause of persistent chronic pain. Instead, the sign and symptom as clear as increased pain when sitting and localised pain known as coccydynia or coccygodynia. This is typically aggravated by pressure over the coccyx or prolonged sitting and is most common in people with abnormal coccygeal mobility. Although male and female with similarities of prevalence but like five folds more common in women with an average age of 40 years.[4]

The risk factors for developing coccydynia, such as obesity and being female (five times more common than male), are so common in teenagers and adults that rapid weight loss can cause the mechanical cushion to be lost. The underlying causes include falls, dislocation or ligament laxity, fracture, infection (osteomyelitis) and neoplasm (such as chordoma). Internal trauma is most commonly associated with the birth of a child during labour, particularly in the setting of a difficult or instrumented delivery.[5] In addition to articulating with the sacrum, the coccyx is connected to various structures via five main ligaments. The anterior longitudinal ligament originates at the front of the sacrum and extends to the front of the coccyx. The superficial division begins at the edge of the sacral hiatus and attaches to the dorsal surface of the coccyx. The deep division begins at the posterior orifice of the fifth sacral segment, inside the sacral canal, and extends down to the dorsal surface of the coccyx, beneath the superficial division. The lateral sacrococcygeal ligaments connect the lower lateral part of the sacrum to the transverse processes of the coccyx on the same side, as well as to the ischial spines of the ipsilateral sacrum and coccyx. The sacrotuberous ligament connects the ischial tuberosity to the sacrum and coccyx. The coccygeus, gluteus maximus, external anal sphincter, and two levator ani muscles (pubococcygeus and iliococcygeus) all attach to the coccyx. Somatic nerves and the sympathetic ganglion impar carry nociceptive signals from the coccygeal plexus, formed by the fourth and fifth sacral nerves and the coccygeal nerve. The two sacral sympathetic chains converge to form the terminal end of the sympathetic trunk, known as the ganglion impar. This is located close to the midline of the anterior aspect of the coccyx, below the sacrococcygeal joint. The ganglion provides nociceptive and sympathetic innervation to the coccygeal region. This includes afferent innervation from the perineum, distal rectum, anus, distal urethra and lower vagina.[6] Non-traumatic coccydynia is caused by degeneration, laxity or hypermobility of the ligaments of the sacrococcygeal joint, infection, etc. Pain may radiate into the toes and may be confused with sciatica. Comprehensive treatment is required, and patients may have to suffer; correct ergonomic posture is essential, physical manipulation of the levator ani muscles, anti-inflammatory prescriptions, nerve block, steroid or single local anaesthetic or dextrose 5% prolotherapy ganglion impar block may improve in some patients. And few patients need repeat injections. Implantable spinal cord stimulation (SCS) can provide a satisfactory cure, but cost may be an issue. However, coccygectomy is not recommended by many surgeons as the benefits are not worth the risk.[7]

DRG neuromodulation by RF is a promising treatment for coccydynia and may avoid surgical treatment. Steroid blocks are an effective short-term temporary treatment.[8] Injection treatment may be useful for diagnostic prediction and treatment, although the site of injection is controversial. There is a need for more adequate studies of sacrococcygeal and intercoccygeal joint, tender point or ganglion impar injection. Ganglion

impar blocks have been shown to result in approximately 75% improvement at 6 months, while neuromodulation using SCS in the conus region from L2–S2 has also shown improvement in severe perineal pain.[3] Meanwhile, the point entry approach to reach the impar ganglion is challenging as in the case presented a Type III coccyx. We therefore performed a bilateral inferior hypogastric plexus (IHP) block at the S2 segment, which connects to the impar ganglion and the S1 dorsal root ganglion (DRG). The DRG is a key structure in sensory transduction, modulation and pain transmission. Many studies suggest that targeting the DRG can treat both nociceptive and neuropathic pain syndromes.[10,11] Despite the potential complications and adverse effects that accompany it, long-term analgesic medication remains a viable option for managing coccydinia syndrome. Therefore, we hypothesised that nerve root and sympathetic blockades might lead to a better outcome.

METHODS

A 16-year-old female complained of coccydynia for more than 1 month, which. The symptoms occurred after a felt sit down during sport. The motor function, micturation and defecation are normal, tingling or numbness in the perianal area and in both feet. Conservative and medical physiotherapy management has been undertaken, but the symptoms are still experienced as bothersome. The pain is particularly severe with prolonged sitting and can even feel like a burning sensation. Magnetic resonance imaging (MRI) results revealed a Type III coccyx fracture and interventional radiofrequency pain management under local anaesthesia was planned. Radiofrequency (RF) neuromodulation procedures are performed by consultant pain and minimally invasive neurologists who are trained and experienced in complex pain interventions since 2012.

Surgical preparation to operating room standards, emergency equipment, 0.9% normal saline infusion 20 drops per minute, premedicated cefazolin 1 gram antibiotic, C-arm fluoroscopic guidance, Cosman G4 radiofrequency generator, and aseptic and antiseptic measures in the surgical area (regions L4–5 to S1–2). The patient is placed on the operating table in a pronated position with the C-arm fluoroscope in the postero-anterior (PA) position, visualising the L4–5 and S1–2 regions. At the landmark point on the left S2, the posterior neuroforamen was aligned under C-arm fluoroscopy and the CSK 15 RF electrode needle was inserted in a gentle pass through the neuroforamen after 2 mL of lidocaine 2% injection. The depth of the needle could be monitored by switching the C-arm fluoroscope to a lateral view. When inserting the needle inline at the S2–3 articulation, the direction can be maintained. The tip should be stopped when it reaches approximately 0.5 cm anterior to the sacrum, just anterior to the S2 foramen. Confirm the position by injecting 1 mL of Iopamiro 370 dye contrast and it will appear to form a thickened line anterior to the sacrum, indicating that it corresponds to the inferior hypogastric plexus. The C-arm fluoroscope is positioned in PA view to confirm that the needle position is in line with the area of the inferior hypogastric plexus. Sensory stimulation with the Cosman G4 RF device provided a tingling sensation if the readings were above 1.00Hz, followed by motor stimulation to ensure that no nearby viscera were involved. Pulsed RF (PRF) 42°C for 2 minutes followed by injection of triamcinolone 20mg 1ml to prevent neuritis. Similar procedures were performed at the S2 neuroforamen on the right side. Sensory stimulation should not exceed 1.00Hz and motor stimulation should not be used to induce visceral contraction. After confirmation of the stimulated response, pulsed RF at 42°C was applied for 2 minutes and the same procedure was repeated on the opposite side. The PA was viewed at the left S1 neuroforamen, which was the next targeted anatomical landmark for DRG-selective nerve roots. After RF CSK15 electrode needle insertion and the tio is around the DRG, so the 1 mL of dye contrast injected for confirmation. Sensory and motor stimulation was performed to confirm that the RF electrode needle was just around the DRG. Pulsed RF neuromodulation was then performed with the same settings and duration. Postoperative medical therapy included levofloxacin 500 mg/ 24h for 4 days and vitamin B12 50 mcg/ 12h. Analgesics were given in the form of a combination capsule (paracetamol 300mg, diazepam 2mg and diclofenac sodium 12.5mg) and pregabalin 50mg for persistent pain. RF technology provides better pain relief than steroid ganglion block or open surgical treatments.[1]

It is so widely used in the treatment of coccydynia by ganglion impar block because it can reach the nociceptive and sympathetic fibres simultaneously. According to a recent study, it can provide long-term pain relief with minimal risk, except when caution is required regarding neuritis or inadvertent injection from the use of neurolytic agents. In patients with unusual coccyx anatomy, such as in this study of Type III coccyx fractures, difficulties have been observed in approaching the fracture. Therefore, we need an optional approach technique by treating the IHG and S1 DRG. This study adds S1 DRG level for interruption of pain transmission as this may be clinically relevant for chronic intractable pain.[12]

RESULTS

After one month of follow-up, we found that the intensity of the pain had decreased (NRS 0–1), although the hypesthesia around the coccyx could come and go. The analgesic drugs with dose reduced, except when the pain occurs spontaneously. The neurotrophic drugs vitamin

B12 50 mcg/ 12h, the analgesic (paracetamol 300mg, diazepam 2mg and diclofenac sodium 12.5mg) or pregabalin 50mg could be administered if the pain persisted. Overall, she felt much better than before, accompanied by personal treatment while sleeping on the bed with knees bent, then swinging from side to side in a relaxed manner (3–4 times a day). She also avoided sitting for long periods, squatting or sitting in a low position, or sitting on her back.

DISCUSSION

In women, pelvic pain syndromes can be a serious problem as there are many possible causes. These include: urogynaecological (ovarian cysts, endometriosis, premenstrual syndrome), gastrointestinal (mesenteric adhesions, irritable bowel syndrome), neuromusculoskeletal (nerve root compression, fibromyalgia), interstitial cystitis or psychosomatic.[13] Determining which tissue is the source of pain in people with LBP requires a comprehensive assessment and analysis based on clinical examination and imaging. Pain types and syndromes can help to focus on the main problems. The pain experienced by people with LBP is caused by structural abnormalities of the muscles, bones, joints, ligaments, vasculature or nerve fibre units involved. For example, sciatic nerve entrapment is characterised by electrical, radiating pain in the foot, cluneal nerve entrapment manifests as buttock pain, or coccydinia in women may be related to visceral organs. Similarly, the patient who had pain manifested as aggravation with prolonged sitting without radiating pain. As branches S1 to S4, forming the cluneal nerve, innervate the skin of the buttock close to the sacrum and coccyx, this nerve may have been injured after spinal surgery or felt while sitting.[14] The sacral nerves are divided into lateral and medial branches which appear to pass originally through the dorsal sacral neuroforamens. The lateral branches pass posteriorly to the sacrotuberous ligament (STL) and then to the posterior sacrococcygeal plexus (PSCP) or posterior sacral plexus. The adjacent tissue, the posterior sacroiliac ligament, could become entrapped and cause low back pain (LBP). This may be of greater concern if the patient is over 76 years of age. The medial branches contribute from S1 to coccyx on 5 sides (50%) and from S1 to S5 (30%), whereas at S3–S4 and S4–S5 these branches do not contribute. The sacral dorsal rami from S1-S2 formed the LT in 37.5%, S1–S3 in 12.5%, S1–S4 in 31.3% and S2–S4 in 18.8%.[15] The inferior hypogastric plexus (IHP) lies anterior to the sacrum and ventromedial to the sacral foramina S2, S3 and S4. It receives efferent sympathetic fibres from the hypogastric and pelvic splanchnic nerves, preganglionic parasympathetic fibres from the pelvic splanchnic nerves and visceral afferent fibres from the pelvic viscera.[13]

Pain blocks are usually performed on the superior hypogastric plexus (SHP), but this does not provide optimal pain relief. The lower pelvic organs are innervated by the IHP, although this is rarely used for pelvic pain management with effective and safe for improving on chronic pelvic pain. Recently, intrarectal manipulation has been used to adjust the coccygeal joints, which influences the intercoccygeal and sacrococcygeal joints. This increases the coccyx's range of motion by at least 50% and typically provides pain relief within six months. However, patients were not satisfied with this approach in terms of pain relief.[6] Another approach involves injecting glucose to trigger acute inflammation and promote the repair and regeneration of damaged tissue. It has been observed that a low concentration of 5% dextrose reduces pain by influencing sensory peptidergic nerves. Reinjection can improve neural sensation and terminate neuropathic pain. One of our studies revealed that a 5% dextrose solution increases the expression of angiogenic factors, including vascular endothelial growth factor A (VEGF-A), platelet-derived growth factors A and B (PDGF-A and PDGF-B), and insulin-like growth factor I (IGF-I). The study also demonstrated an increase in apoptotic factors, such as caspases 3 and 8, in cultures of adult fibroblasts.[16] Then, inject a solution containing 15% dextrose and 40 mg of lidocaine into the lesion site on the coccyx. This is followed by two injections: the first is given caudally, followed by cranially. Both are administered at a volume of 23 cc. A second set of caudal and cranial injections using a solution containing 20% dextrose and 40 mg of lidocaine at a volume of 4 cc are administered 24 weeks later. These procedures aim to tighten loose tendons, ligaments and joint capsules by multiplying and activating the fibroblasts associated with the pathological structures. The pain score decreased gradually from 8 to 4 and then to 01 by the end of the four-week procedure. If pain relief is not satisfactory, the procedure may be repeated.[17] Surgical treatment, such as amputating a coccyx fragment just above the sacrococcygeal junction, carries a risk of complications and is not always an effective way of relieving pain. For this reason, this procedure is generally not recommended.[18]

Spinal cord stimulation (SCS) technology involves implanting an electrode into the sacral epidural space to interrupt the transmission of pain impulses to the dorsal horn. This neuromodulation technique can provide long-term pain relief by reducing levels of excitatory amino acids and preventing antidromic modulation of the gamma-aminobutyric acid (GABA) and adenosine-dependent systems. SCS covers the S1–S4 anterior and posterior rami, which form the sacral plexus and supply the gluteal, sciatic, posterior cutaneous and pudendal nerves. The posterior rami of the S5 and coccygeal nerves supply sensory innervation to the coccyx region and join with a branch of the anterior ramus of S4 to form the coccygeal plexus and the anococcygeal nerves. These

nerves innervate the sacrotuberous ligament on the dorsal aspect of the coccyx –– the site of pain in coccydynia.[19,20] Another clinician with experience in this field performed the SCS procedure, placing electrodes on the bilateral L1 dorsal root ganglia (DRGs). Positive outcomes were reported in terms of pain relief and reduced requirements for opioid medication.[18] However, proper electrode placement, therapy costs and routine evaluation of electrode implantation must be considered.

Fluoroscopic guidance may be helpful in approaching the dorsal foramen S2, which is usually chosen because it is better visualised than others. Care must be taken when blocking the SHP because of its proximity to the bladder, bowel and common iliac artery, with the potential risk of nerve injury, paraesthesia, haematoma, vascular injury and rectal puncture. The study found that the L1–S3 anterior sacral nerve roots can even be affected by IHP blocks through the S2 neuroforamen level.[13] Approach to the blocked IHP through the S2 foramen appears to extend to the upper (S1) and lower (S3) levels, as recently observed with a success rate of approximately 73% of patients achieving analgesia. Bilateral blocks performed close to the midline and by advancing the drug volume would also increase the success rate of analgesia with this technique.[21] The autonomic fibres from the L4 to S1 segments, corresponding to the T12 and L1 vertebrae. The pelvic spinal nerves (PSNs) separate from the spinal nerves as they exit the sacral foramina and then enter the presacral tissues as a highly intertwined bundle of fibres. The sacral hypogastric fascia gives rise to the sacral nerve roots S1–S4, while the PSNs arise from S2 to S4. They run anterolaterally into the inferior hypogastric plexus (IHP) to supply the pelvic viscera. They also lie superolaterally within the presacral tissue. This IHP is essential for autonomic function, in particular supplying the cervix, the vaginal fornix and the posterior aspect of the bladder and ligaments, either the coccyx or the sacrum. This means that afferent somatic or autonomic fibres from the coccyx area continue proximally to the brain, passing through the sacral DRGs and also the IHP.[11] The autonomic nervous system (ANS) also plays an important role in chronic pain due to clinical and traumatic entities. Sacral fractures and spinal cord injuries can affect the peripheral nervous system (PNS) and the ANS. The coccygeal attachments to the sacrotuberous ligaments are anatomically related to the dural sac and anatomically related to the filum terminale. If the altered structures cause tension or strain on the muscles and tendons that make up the pelvic floor, complaints of low back or coccygeal pain will result. Traumatic sitting can cause changes in the sacrococcygeal angle as the protective mechanisms change. This can lead to instability, hypermobility and hyperflexion of the coccygeal segments in excess of 25 degrees.[22]

The pelvic sympathetic trunk lies extraperitoneally anterior to the sacral bone and anteromedial to the anterior sacral foramen with four or five interconnected ganglia. Above, it continues into the lumbar sympathetic trunk; below, the two trunks converge into a single small ganglion, the impar ganglion, which lies close to the sacrococcygeal joint and the coccygeal apex. The ganglion thus plays an important role in the development of pelvic and coccygeal pain by transmitting sympathetic efferent signals to nociceptive afferent signals from various areas including the perineum, distal rectum, distal vagina, distal urethra and anus.[1] The electrical impulses from the DRG are involved in the expression of pain due to peripheral nerve damage. Pelvic innervation plays an important role in understanding coccydynia and pelvic pain. The cell bodies of the parasympathetic afferents lie within the S2–S4 DRGs and then run together with the pelvic splanchnic and somatic nerves. DRG neuromodulation appears to be a good option for blocking pain transmission or using neuromodulation technology such as radiofrequency or SCS implantation. This may prove that by treating the DRGs, good results can be observed in both nociceptive and neuropathic pain syndromes, which are thought to play a role in chronic coccydynia.[23] Radiofrequency treatment setups are classified as either continuous (CRF) or pulsed (PRF). The applications of these differ depending on temperature, cycle time and the number of repetitions. CRF relies on the thermal energy produced when temperatures are in the range of 60–90 °C. This commonly results in the ablating of tissue and irreversible changes to the targeted nerves. In contrast, PRF is delivered at temperatures below 42°C and neuromodulates pain transmission from the targeted nerves.[24] A combination of superior hypogastric plexus (SHP) treatment and pulsed radiofrequency (PRF) of the sacral roots (S2, S3 and S4) was found to be slightly more effective at relieving chronic pelvic and perineal pain than SHP treatment alone. Following the second procedure, the effectiveness rate ranged from 62% to 72%, demonstrating that sacral neuromodulation can effectively treat pelvic pain. Sacral nerve stimulation may also reduce pain severity and improve quality of life. It is thought that the analgesic effect of PRF is due to electromagnetic waves inducing neuroplastic changes rather than thermal destruction. Furthermore, PRF may alter noradrenergic and serotonergic descending pain inhibitory pathways, as well as reducing tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in neural tissues. Additionally, c-Fos expression increases in laminae I and II of the dorsal horn, while microglia activity is suppressed at the lesion site.[25]

CONCLUSION

Neuromodulation for coccydynia produces good results when treating the sacral dorsal root ganglion (DRG) and

inferior hypogastric plexus (IHP). It also provides easier access to the impar ganglion than the transarticular approach, provided the needle is inserted correctly. However, the anterior angulation of the coccyx can present an obstacle that requires skill to overcome.

CONFLICTS OF INTEREST

We have no conflicts of interest or funding support in relation to this study.

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Case Report

Dengue Virus Infection in Pregnancy: A Case Series

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Abstract

Background : Indonesia is an endemic country for dengue virus infections, particularly in several regions. Dengue virus infection is a disease caused by the dengue virus and transmitted through the bite of the Aedes aegypti mosquito. In pregnancy, dengue virus infection increases the risk of dengue shock syndrome, pre-eclampsia, fetal distress, preterm delivery, cesarean section and maternal death. Despite the abundance of reports on dengue infection in pregnancy, data from Indonesia remain limited, particularly regarding clinical presentation, management decisions, and outcomes in resource-limited settings. This case series aims to contribute practical insights into clinical management, decision-making during the critical phase, and maternal-fetal outcomes in dengue-infected pregnancies.

Cases : We report three cases of dengue virus infection during pregnancies. All three patients presented with acute fever and thrombocytopenia. Two of the three exhibited elevated in transaminase enzymes. One patient tested positive for NS1 antigen, while the other two tested positive for anti-dengue IgM and IgG. Blood component transfusions were administered to two patients during treatment. Two cases underwent termination of pregnancy via cesarean section due to indications of maternal and fetal distress. One neonate initially presented with an abnormal outcome but showed clinical improvement after intensive treatment. All three cases had normal maternal outcomes.

Discussion : Pregnancy involves various physiological changes related to the cardiovascular, respiratory, and hematological systems. In these three cases, acute fever and thrombocytopenia (first and second cases) were observed, and there was no increase in hematocrit exceeding 20% of the baseline data, thus leading to a diagnosis of dengue fever. The WHO states that there is no difference in the amount and rate of intravenous fluid administration for pregnant and non-pregnant women, but recommends using pre-pregnancy body weight for fluid calculations. During the critical phase, termination of pregnancy should be performed only if the mother's life is threatened or if the patient experiences spontaneous labor. Timely multidisciplinary decision-making is crucial to optimize maternal and fetal outcomes, as fetal complications such as distress or preterm delivery may occur. In the first case,

termination of pregnancy by cesarean section during the critical phase was performed due to induction failure and fetal distress. The neonate initially suffered moderate asphyxia but experienced clinical improvement after intensive care.

Conclusion : Dengue virus infection in pregnancy increases the risk of morbidity and mortality for both mother and fetus. Therefore, strict monitoring and evaluation are needed, as well as management involving a multidisciplinary team that considers aspects of maternal and fetal safety.

Keywords : dengue virus infection, pregnancy, maternal and fetal outcome

INTRODUCTION

Indonesia is an endemic country for dengue virus infections, particularly in several regions.[1,2] Dengue virus infection is a disease caused by the dengue virus which is transmitted through the bite of the *Aedes aegypti* mosquito.[3] In 2021, Indonesian Ministry of Health reported 73,518 cases of dengue virus infection with 705 fatalities.[1,4] This number increased sharply in 2022 to 143,266 cases and 1,237 deaths. In 2023, there were 114,720 infections and 894 deaths.[1,4]

Dengue virus infection during pregnancy presents significant health risks for both mothers and their infants, with a range of potential complications and adverse outcomes.[5–7] It increases the risk of dengue shock syndrome, pre-eclampsia, fetal distress, preterm delivery, cesarean delivery and maternal death.[5–8]

Although dengue virus infection in pregnancy has been reported globally, data from Indonesia are still scarce, especially regarding how clinical management is adapted in real- world hospital settings with limited access to molecular diagnostics such as RT-PCR.[7,15,31] This case series aims to describe three cases of dengue virus infection during pregnancy, focusing on clinical presentation, management decisions, and outcomes. By presenting these cases, this report contributes to a better understanding of how dengue infection affects pregnancy and highlights the importance of individualized management strategies in endemic, resource- limited contexts.[2,14,27]

CASE ILLUSTRATION

Case 1

A 26-year-old female, G2P0A1 at 38 weeks of pregnancy presented with complaints of fever for 5 days, retro-orbital pain, muscle pain, a sudden gush of watery fluid from vagina since 12 hours prior to hospital admission and infrequent contraction. On physical examination, the patient was hemodynamically stable with a temperature of 37.0°C. Laboratory examination revealed hemoglobin 16g/dL, hematocrit 45.5%, leukocytes 11,000/µL, thrombocytopenia 48,000/µL, AST 71 U/L, ALT 25 U/L, prolonged coagulation study (aPTT/Control 36.9 seconds/25.9 seconds), anti-dengue IgM (-), anti-dengue IgG (+). During treatment, the patients received crystalloids therapy according to guidelines. On the second day of treatment, the patient underwent termination of pregnancy by cesarean section due to indications of failed induction and fetal distress. A baby girl was born weighing 3495 grams, with an APGAR score 5-6-7, necessitating treatment in the Neonatal Intensive Care Unit (NICU), where CPAP therapy was administered for 3 days due to respiratory distress. The total NICU length of stay was 8 days.

After delivery, vaginal bleeding of 800 mL occurred. Transfusion of one unit of whole blood and one unit fresh frozen plasma was administered. During treatment, the patient received management for Premature Rupture of Membranes (PROM) according to the Obstetrics and Gynecology Clinical Practice Guidelines which included prophylactic antibiotics (ampicillin 2 grams intravenous, followed by erythromycin 500 mg/6 hours orally for 5 days). Diuresis remained >0.5 mL/kg/hour. On the fifth day of treatment, the patient was clinically and hemodynamically stable, afebrile for >24 hours without antipyretics, platelets increased to 136,000/µL, and transaminase enzymes returned to normal, the patient was allowedto be outpatient. The mother was discharged in stable condition and advised to return for postpartum evaluation within one week.

During the NICU stay, the infant showed gradual improvement, with no signs of long- term complications such as seizures, feeding intolerance, or abnormal neurological reflexes. Breastfeeding was successfully initiated after respiratory support was discontinued, and maternal-infant bonding was supported in the latter part of the NICU stay. Upon outpatient follow-up, the mother remained clinically stable with no signs of infection or bleeding, and the infant showed appropriate weight gain, adequate feeding, and no further respiratory symptoms.

Case 2

A 26-year-old female, G2P1A0 at 35 weeks of pregnancy, presented with fever for 5 days and muscle pain. The patient's neighbor had dengue infection. On physical examination, hemodynamics were stable. Laboratory

examination revealed hemoglobin 12.6 g/dL, hematocrit 39.3%, leukocytes 6,700/µL, thrombocytopenia 31,000/µL, AST 62 U/L, ALT 34 U/L, and coagulation profile within normal limits, with positive anti-dengue IgM, anti-dengue IgG. During treatment, patients received crystalloids and antipyretic therapy according to guidelines. Serial routine blood monitoring and blood clotting time every 8–12 hours, revealed a reduction in platelets to 20,000 without bleeding. The patient received 4 unit thrombocyte concentrate transfusions. During treatment, diuresis remained >0.5 mL/kg/hour. On the fifth day of treatment, patient was clinically and hemodynamically stable, afebrile for >24 hours without antipyretics, platelets increased to 96,000/µL, transaminase enzymes improved, the patient was then discharged for outpatient. Following hospital discharge, the patient has continued routine antenatal care and reports no new symptoms.

Case 3

A 29-year-old female, G3P2A0 at 37 weeks of pregnancy, was admitted to the hospital with fever for 3 days, muscle pain and nausea. The patient's husband previously had a dengue infection. On physical examination, the temperature was 38.9°C. Laboratory examination revealed moderate microcytic hypochromic anemia (hemoglobin 8.8 g/dL), hematocrit 28.3%, leukocytes 5,000/µL, platelets 215,000/µL, AST 28 U/L, ALT 37 U/L, and a positive NS1 antigen. The patient received

TABLE 1
Summary of clinical and laboratory characteristics of serial case study

Clinical and laboratory characteristics	Case 1	Case 2	Case 3
Age (years)	26	26	29
Gestasional age (weeks)	38	35	37
Presenting complaints	Fever for 5 days, retro-orbital pain, muscle pain, sudden gush of watery fluid from vagina and infrequent contraction. Vaginal bleeding of 800 mL after delivery	Fever for 5 days and muscle painafter delivery	Fever for 3 days, muscle pain and nausea
Delivery method	CS	–	CS
Transfusion of blood components	WB, FFP	TC	PRC
Hemoglobin (g/dL) (Highest)	16.0	13.8	9.7
Hemoglobin (g/dL) (Lowest)	9.6	11.9	7.9
Hematocrit (%) (Highest)	46.2	42.5	29.9
Platelet (10^3/µL) (Lowest)	32	20	133
AST/ALT (U/L) (Highest)	102/71	62/34	28/37
NS1 Antigen	N/A	N/A	NS1 (+)
Anti–Dengue IgM/IgG	IgM (–)	IgM (+)	N/A
	IgG (+)	IgG (+)	
RT–PCR/DENV maternal	N/A	N/A	N/A
RT–PCR umbilical cord	N/A	N/A	N/A
Maternal outcome	Normal	Normal	Normal
Neonatal clinical characteristics	3.495g	–	2.710g
	Apgar Score: 5/6/7		Apgar Score: 9/9/10
	Moderate asphyxia		Normal vitality

N/A : not available; CS : cesarean section; PRC : packed red cell; WB : whole blood; TC : thrombocyte concentrate; FFP: fresh frozen plasma

crystalloids and antipyretics therapy according to the guidelines. On the third day of treatment, the patient underwent cesarean section due to indication of placenta previa totalis and a history of previous cesarean section. Baby boy was born weighing 2710 grams, clinically fit. During treatment, diuresis remained >0.5 mL/kg/hour. On the fifth day of treatment, the patient was clinically and hemodynamically stable, afebrile for >24 hours without antipyretics, and platelets were 133,000/µL. Both the patient and the baby were then discharged from hospital. The mother was advised to undergo a postpartum follow-up visit within 7 to 10 days after discharge to evaluate clinical recovery, monitor wound healing from cesarean section, and assess for any signs of secondary infection or delayed complications associated with dengue infection. The newborn, who was clinically fit at birth, was scheduled for routine neonatal follow-up within one week of discharge to monitor weight gain, feeding adequacy, and overall development. The mother reported no complications during thepostpartum period following hospital discharge. At the post-discharge visit, the baby had gained appropriate weight and showed normal developmental progress.

DISCUSSION

Dengue virus infection is characterized by fever for 2–7 days, retro-orbital pain, arthralgia, myalgia, bleeding manifestations, leukopenia, and thrombocytopenia.[2,3] Dengue fever is differentiated from dengue hemorrhagic fever based on the absence of plasma leakage.[3] In pregnancy, various physiological changes related to the cardiovascular, respiratory and hematological systems.[6,32] At the end of the third trimester, plasma volume increases by approximately 40%, resulting in dilutional anemia, thereby obscuring the hemoconcentration that occurs in the critical phase.[6] It is important to monitor diuresis in addition to hemodynamics to ensure adequate fluid requirements, especially during the critical phase.[3]

The World Health Organization (WHO) states that there is no difference in the amount and rate of intravenous fluid administration for pregnant women and non-pregnant women. Forfluid calculations, the pre-pregnancy body weight should be used.[3] In the three cases presented, patients experienced acute fever, thrombocytopenia (first and second cases) and there was no increase in hematocrit of more than 20% of the baseline data, thus leading to the diagnosis of dengue fever.

In the clinical evaluation of febrile illness during pregnancy, especially in dengue- endemic regions, it is important to consider several differential diagnoses that may present with similar clinical and laboratory features. These include malaria, typhoid fever, leptospirosis, chikungunya, COVID-19, urinary tract infection, and HELLP syndrome. All of these conditions can manifest with fever, thrombocytopenia, and elevated liver enzymes, overlapping with dengue presentations.[16–18] However, in all three cases presented, the diagnosis of dengue was supported by compatible clinical features, epidemiological exposure, and positive dengue- specific serological markers (NS1 antigen or anti-dengue IgM/IgG).[15,31] The absence of other signs such as hemolysis, bacterial infection markers, or specific exposure history helped to rule out these alternative diagnoses and supported the working diagnosis of dengue infection.[16,17]

Both the first and second cases indicated secondary dengue infection, while the third case was diagnosed with dengue based on a positive NS1 antigen result.[15,31] Diuresis was monitored every 4 hours and adequate diuresis (>0.5 mL/kg/hour) in all three patients during treatment.

During the critical phase, vaginal delivery or cesarean section should be performed only if the mother's life is threatened or the patient experiences spontaneous labor.[8] The American College of Obstetrics and Gynecology (ACOG) recommends platelet transfusion with a target platelet count of more than 50,000/µL before major surgery.[9] The Italian Society of Transfusion Medicine and Immunohaematology (SIMTI) recommends that prophylactic platelet transfusions be administered if platelets are less than 20,000/µL in a febrile patients without bleeding,[10] whereas the British Committee for Standards in haematology recommends platelet transfusions if platelets are less than 10,000/µL without bleeding.[11] Additional guidelines emphasize clinical judgment and institutional protocols.[12,13]

In all three cases, the timing and indication for cesarean section were clearly presented; however, a more detailed discussion of the risk-benefit considerations and adherence to clinical guidelines is essential, particularly regarding performing delivery during the febrile or critical phase of dengue infection.[8,20,33]

In the first case, termination of pregnancy by cesarean section was performed on the second day of hospitalization during the critical phase, with thrombocytopenia (48,000/µL), prolonged aPTT, and a background of secondary dengue infection (IgG positive).[5,9] The procedure was indicated due to failed induction and signs of fetal distress, both of which constituted obstetric emergencies.[8,21] Although the timing was not ideal in terms of dengue phase, the decision was made to prioritize fetal survival and avoid further deterioration.[8] The risk of hemorrhagic complications was mitigated by preoperative evaluation, availability of blood products, and close monitoring.[9,12,13] Postoperatively, the maternal condition remained stable, platelets increased to 136,000/µL, and she was discharged on day five.[8,22] The neonate, who suffered moderate asphyxia, required intensive care but showed clinical improvement with NICU support.[25] Alternative

management approaches such as delaying delivery until the recovery phase were considered; however, they were not feasible due to the obstetricemergency. This deviation from standard dengue management was justified by the need to address failed induction and fetal distress, which posed immediate risks to both mother and fetus.[8,21]

In the second case, although the patient had severe thrombocytopenia with a nadir of 20,000/μL during the critical phase,[9,10] there was no obstetric indication for delivery. Accordingly, the medical team followed a conservative approach, adhering to clinical guidelines that recommend delaying elective delivery during the febrile or critical phase of dengue unless maternal or fetal complications arise.[8,20,33] The patient received four units of platelet concentrate,[9,12] and her condition improved without requiring delivery. On day five, with platelets rising to 94,000/μL and clinical stabilization, the patient was discharged and continued routine antenatal care without further complications.[8,22] This case illustrates appropriate risk-benefit consideration and compliance with dengue management protocols in pregnancy.[8,20]

In the third case, cesarean section was performed during the febrile phase due to a clear obstetric indication––placenta previa totalis combined with a history of previous cesarean section––which carries a high risk of massive hemorrhage and maternal morbidity if not addressed promptly.[8,23] Although the patient was still febrile (38.9°C) on admission, her platelet count was within normal limits (215,000/μL), and liver enzymes were only mildly elevated.[3] Given the high obstetric risk and acceptable hematological parameters, the benefit of timely delivery outweighed the risks associated with dengue.[8,20] Both maternal and neonatal outcomes were favorable, and the patient was discharged on the fifth day.[22,25]

These cases emphasize the importance of individualized decision-making in managing dengue-infected pregnancies.[8,33] While elective delivery is generally deferred during the critical phase of dengue due to increased bleeding risk,[3] emergency obstetric indications may necessitate surgical intervention regardless of the dengue phase.[8,23] In such situations, careful perioperative planning, availability of blood products, and multidisciplinary collaboration are critical for optimizing outcomes.[8,33] Highlighting these justifications supports clinical relevance and reflects real-world complexity in managing dengue during pregnancy.[20,33]

Recent literature has reported that dengue infection during pregnancy may be associated with a higher incidence of preterm delivery, intrauterine growth restriction, and stillbirth compared to non-infected pregnancies.[5,19,29,30] The findings in this case series align with prior studies showing that most maternal outcomes are favorable with timely fluid management and close monitoring, but fetal complications such as distress and asphyxia remain possible during the critical phase.[5,19,25]

The management observed in these cases supports the growing consensus that multidisciplinary collaboration is essential to optimize outcomes.[24,33] The cases also underscore the importance of conservative management whenever possible and the need for precise decision-making regarding delivery timing, especially in the presence of fetal distress or obstetric emergencies.[8,33]

Clinically, this case series illustrates that while serological confirmation (NS1, IgM, IgG) remains the most practical diagnostic approach in endemic settings, access to RT-PCR could improve diagnostic accuracy and epidemiological understanding.[15,21,31] Future case management and reporting should integrate molecular

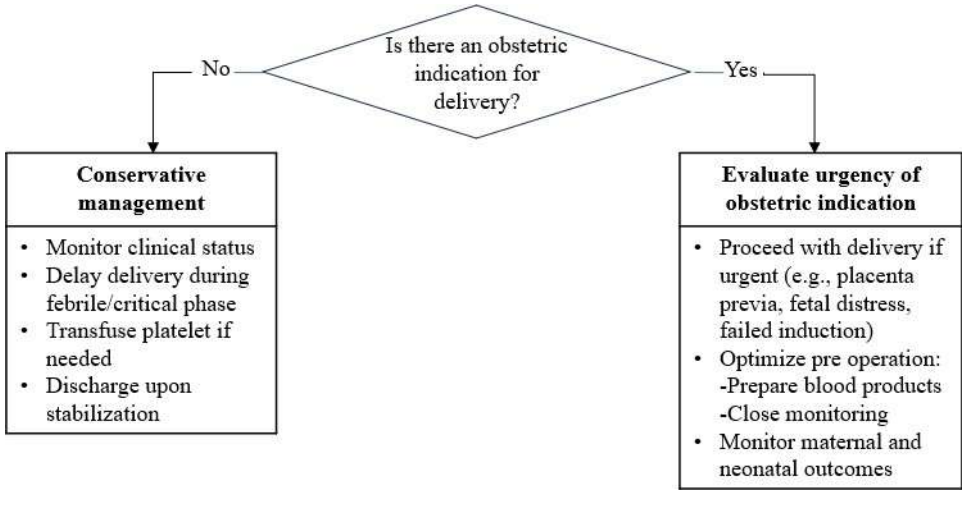

Figure 1. Decision Flowchart: Delivery Management in Pregnant Patient with Dengue Virus Infecion[3,8,9,33]

confirmation and dengue serotype identification, as these factors may correlate with the severity of maternal and neonatal outcomes.[21,26]

From a public health perspective, these findings reinforce the need for enhanced surveillance of dengue in pregnancy and the inclusion of pregnancy-specific management protocols in national dengue control programs.[1,4,27,28]

A limitation of this case series is that the marker for plasma leakage was based solely on the hematocrit value, without the use Chest X-ray or abdominal ultrasound to rule out pleural effusion or ascites.[3] In all three reported cases, the diagnosis of dengue infection was based on clinical features, epidemiological exposure, and serological testing, including NS1 antigen and/or anti-dengue IgM/IgG assays. These tests are relatively inexpensive than reverse transcriptase polymerase chain reaction (RT-PCR) and can be performed at the point of care, making them suitable for resource-limited settings. However, RT-PCR, the current gold standard for confirming dengue virus infection and determining the viral serotype, was not performed. PCR testing requires specialized laboratory equipment and trained personnel, which may not be readily available in all hospitals, particularly in particularly in low- and middle- income countries (LMICs).[15,31]

In real-world clinical practice, particularly during outbreaks or in endemic areas, serological testing combined with clinical and epidemiological findings is often sufficient to initiate appropriate management.[3,15,31] In these cases, all patients presented during pregnancy with typical symptoms of dengue, supported by positive NS1 antigen or anti-dengue IgM/IgG results,[15,31] and responded to dengue-targeted supportive therapy as outlined in current clinical guidelines.[3,8,14]

While the use of RT-PCR could have strengthened diagnostic confirmation and enabled serotype identification––potentially providing more insight into the risk of severe dengue or secondary infection––its omission did not alter the overall management or clinical outcomes inthese cases.[15,21,31] Nevertheless, the authors acknowledge that future cases would benefit from RT-PCR testing where available, particularly for research, surveillance, and epidemiological tracking of dengue virus serotypes in pregnant populations.

CONCLUSION

Dengue virus infection in pregnancy increases the risk of morbidity and mortality for both mother and fetus. Therefore strict monitoring and evaluation are needed as well as management involving a multidisciplinary team that considers aspects of maternal and fetal safety.

INFORMED CONSENT

Written informed consent was obtained from the patients for the publication of this case series and any accompanying data. All identifying details have been omitted to protect patient confidentiality, and the report complies with ethical publication standards.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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

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

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

Methods :
1. Explains research design, settings and time
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3. For clinical trial, explains randomization and conceal allocation, and Kappa test if conducted and detailed investment
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1. Is presented in a logical sequence
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3. Explains subjects who drop out and the reasons. If possible, provides consort diagram
4. Maximum 3-4 tables
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2. Is compared with previous study findings.
3. Mentions research strengths/weaknesses and its impact on findings.

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2. Should be based on research findings, not quotation
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References :
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2. Contains no abbreviation unless standard

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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
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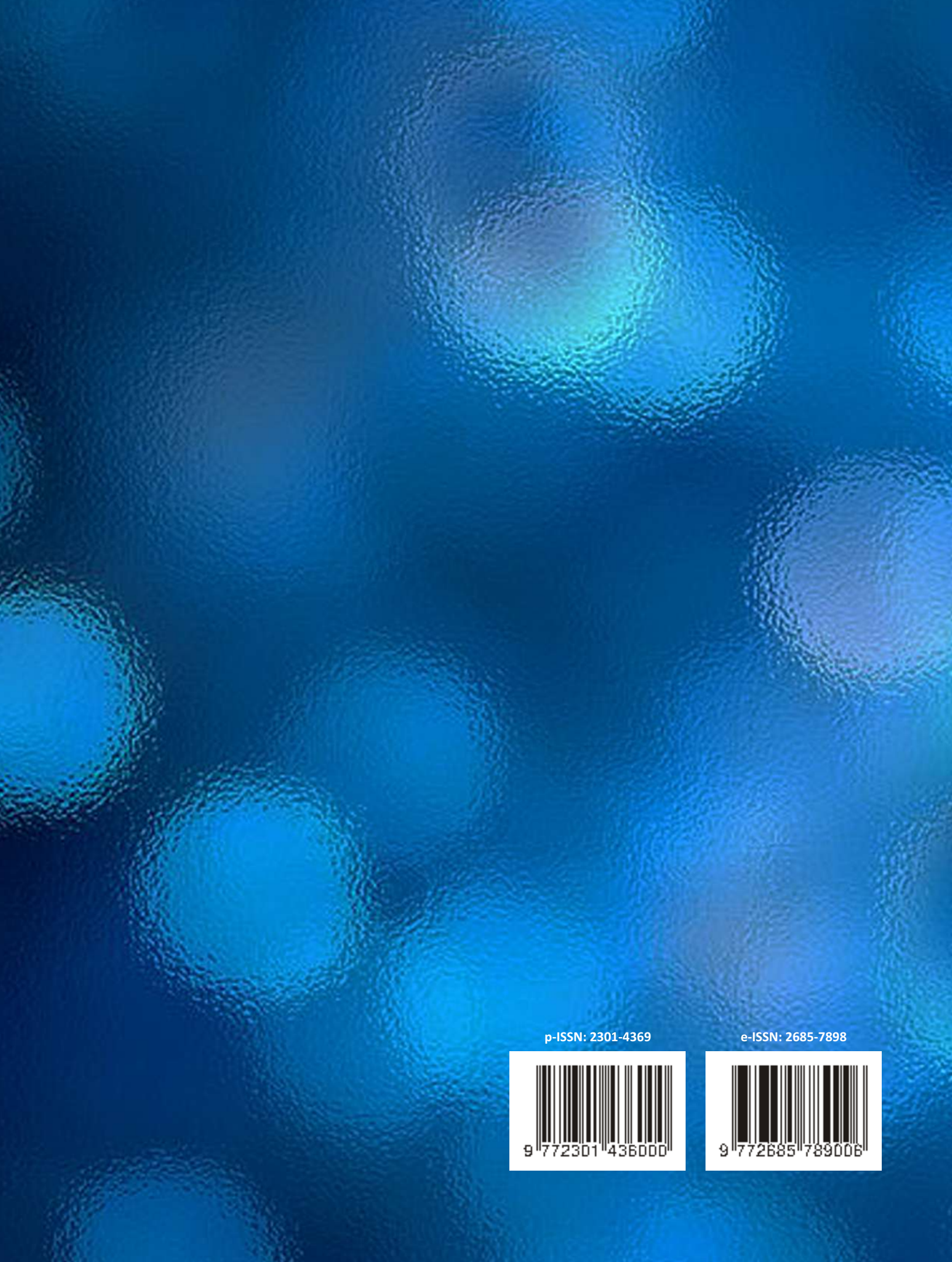

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