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Association Between Insulin Resistance and Disease Severity in Patients with Chronic Obstructive Pulmonary Disease: A Cross-Sectional Study

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ABSTRACT: Chronic obstructive pulmonary disease is a chronic inflammatory disorder accompanied by abnormalities including insulin resistance. Evidence suggests insulin resistance may contribute to progression, but its relationship with severity remains unclear in Southeast Asian populations. Study investigated associations with severity, pulmonary function, symptom burden, and exacerbation risk. In 77 chronic obstructive pulmonary disease patients, insulin resistance was assessed using the Homeostatic Model Assessment for Insulin Resistance. Severity included GOLD grades, Group ABE classification, pulmonary function, Modified Medical Research Council scale, COPD Assessment Test, and exacerbation history. Associations used Fisher–Freeman–Halton exact, Kruskal–Wallis, and Spearman's rank correlation tests. High or very high insulin resistance (HOMA-IR ≥ 3.0) was identified in 45.5% of participants. Higher HOMA-IR categories were significantly associated with advanced GOLD spirometry grades, Group ABE classification, and exacerbation risk (all $p < 0.001$). HOMA-IR was negatively correlated with predicted FEV₁ ($\rho = -0.634$) and FEV₁/FVC ($\rho = -0.602$), while positive correlations were observed with mMRC score ($\rho = 0.728$), CAT score ($\rho = 0.680$), and exacerbation frequency ($\rho = 0.702$) (all $p < 0.001$). Fasting insulin concentrations and HOMA-IR increased progressively across GOLD spirometry grades, accompanied by a smaller but statistically significant increase in fasting plasma glucose ($p < 0.001$). Insulin resistance is associated with greater disease severity, obstructive pulmonary, increased symptom burden, and higher exacerbation risk in chronic obstructive pulmonary disease, supporting HOMA-IR as a biomarker of disease severity.

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressively worsening respiratory condition characterized by persistent airflow limitation. This limitation results from chronic airway inflammation, structural alterations, and alveolar damage, culminating in a permanent reduction in lung function [1,2]. COPD remains a major global public health concern, accounting for approximately 3.5 million deaths in 2021 and ranking among the leading causes of mortality worldwide [3,4]. The global prevalence of COPD among individuals aged 40 and above is estimated at 10.6%. Projections suggest that the number of affected individuals could approach 600 million by 2050, driven by an aging population and ongoing exposure to environmental

risk factors [5]. Beyond respiratory complications, COPD is increasingly recognized as a systemic inflammatory disorder associated with various comorbidities, which significantly worsen clinical outcomes and elevate the healthcare burden [6,7].

Insulin resistance (IR) represents a significant metabolic concern commonly observed in individuals with chronic obstructive pulmonary disease (COPD) and constitutes a critical component of metabolic syndrome [8,9]. The development of IR in COPD is associated with factors such as chronic systemic inflammation, oxidative stress, tissue hypoxia, physical inactivity, and corticosteroid administration. These factors contribute to the disruption of insulin signalling pathways, which are affected by inflammatory cytokines, including tumour necrosis factor- α (TNF- α) and interleukin-6 (IL-6) [10,11]. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) is a validated measure for assessing insulin sensitivity and is widely employed in clinical research [12–14]. Previous studies have demonstrated that insulin resistance is present in 30–60% of COPD patients, with elevated HOMA-IR values being associated with diminished lung function, endothelial dysfunction, increased cardiovascular risk, and a deterioration in clinical status [15].

Evidence increasingly suggests that insulin resistance may contribute to the progression of disease by exacerbating systemic inflammation, accelerating the decline in lung function, and increasing the frequency of exacerbations in patients with COPD [16,17]. Nevertheless, the association between insulin resistance and COPD severity is not consistently reported across various studies, and there is a paucity of data from Southeast Asian populations, particularly in Indonesia [18,19]. Furthermore, no previous research has comprehensively investigated the relationship between HOMA-IR and disease severity, as classified by spirometry GOLD criteria, symptom burden, and exacerbation history in COPD patients at Dr. Wahidin Sudirohusodo Hospital and its affiliated centres. Therefore, this study aimed to investigate the relationship between insulin resistance and COPD severity, as well as its association with clinical symptoms and exacerbation history.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This observational analytical study employed a cross-sectional design to investigate the association between insulin resistance and disease severity in individuals with chronic obstructive pulmonary disease. During the study period, clinical evaluations, spirometry, symptom assessments, and laboratory tests were conducted. Participants were recruited from Dr. Wahidin Sudirohusodo Hospital in Makassar and teaching hospitals affiliated with the Department of Pulmonology and Respiratory Medicine at the Faculty of Medicine, Hasanuddin University.

2.2 Study Population

The study targeted adult patients diagnosed with chronic obstructive pulmonary disease (COPD) who either attended outpatient clinics or were hospitalized at the participating centres during the research period. Eligible participants were recruited consecutively upon providing written informed consent. To be included, patients were required to be at least 40 years old and have a confirmed diagnosis, as evidenced by post-bronchodilator spirometry indicating a forced expiratory volume in one second/forced vital capacity ratio of less than 0.70. Furthermore, participants were required to undergo fasting blood tests for laboratory evaluation.

Exclusion criteria included a prior diagnosis of diabetes mellitus or other endocrine disorders affecting glucose metabolism, such as thyroid disease and hypercortisolism. Additional exclusion criteria encompassed severe systemic conditions, including heart failure, chronic kidney disease, liver failure, active autoimmune diseases, cancer, or the inability to fast for 8–12 hours prior to blood sampling.

2.3 Sample Size and Sampling Technique

The minimum number of participants required was calculated using a formula for comparing two proportions, considering the expected prevalence of metabolic abnormalities among patients with different levels of disease severity. This calculation determined that each comparison group should consist of at least 30 participants, leading to a total requirement of at least 60 participants for the study. A consecutive sampling method was utilized, enrolling all eligible patients who presented during the recruitment period until the necessary sample size was achieved.

2.4 Clinical Assessment

Demographic and clinical baseline characteristics, including age, gender, body mass index, smoking habits, corticosteroid usage, and relevant comorbidities, were collected using a standardized case report form and a review of medical records. Airflow limitation was confirmed through post-bronchodilator spirometry, adhering to the Global Initiative for Chronic Obstructive Lung Disease guidelines. Disease severity was classified into GOLD 1–4 based on the percentage of predicted forced expiratory volume in one second. Clinical grouping was determined using the Group ABE classification, which integrates symptom burden with exacerbation history. The severity of dyspnoea was assessed using the Modified Medical Research Council scale, while the disease's impact on health status was evaluated with the COPD Assessment Test. Exacerbation history, encompassing emergency department visits, systemic corticosteroid or antibiotic treatments, and hospitalizations during the observation period, was obtained through structured interviews and corroborated with medical records.

2.5 Laboratory Measurements

Venous blood samples were collected after an overnight fast of 8–12 hours. The hospital's clinical laboratory utilized standard procedures to measure fasting plasma glucose and fasting serum insulin levels. Insulin resistance was calculated using the Homeostatic Model Assessment for Insulin Resistance, according to the following equation:

$$\text{HOMA-IR} = [\text{Fasting insulin } (\mu\text{U/mL}) \times \text{Fasting plasma glucose (mg/dL)}] / 405$$

Participants were subsequently categorized according to HOMA-IR values as normal (<2.0), increased risk (2.0 – 2.9), high insulin resistance (3.0 – 3.9), and very high insulin resistance (≥ 4.0).

2.6 Outcome Measures

The primary outcome concentrated on the association between insulin resistance and the severity of COPD, as evaluated by spirometry GOLD grades and the Group ABE classification. Secondary outcomes investigated the relationships between HOMA-IR and symptom burden, lung function metrics, historical exacerbation frequency, and hospital admissions due to exacerbations.

2.7 Statistical Analysis

Data management and statistical analyses were performed using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed via the Shapiro–Wilk test, and these variables are presented as either mean $\pm$ standard deviation or median (range), contingent upon their suitability. Categorical variables are expressed as counts and percentages. For the comparison of categorical variables, the chi-square test, Fisher's exact test, or the Fisher–Freeman–Halton exact test was employed, as appropriate. For continuous variables, the independent-samples *t* test was applied to data with a normal distribution, whereas the Mann–Whitney *U* test was utilized for data lacking a normal distribution. The Kruskal–Wallis test was used to evaluate differences in fasting plasma glucose, fasting insulin, and HOMA-IR across GOLD spirometry grades. Spearman's rank correlation coefficient was employed to investigate the relationships between HOMA-IR and pulmonary function parameters, symptom scores, and exacerbation frequency. All statistical tests were two-tailed, with a *p* value of less than 0.05 considered indicative of statistical significance.

3. RESULTS AND DISCUSSION

3.1 Baseline Characteristics of the Study Population

A total of 77 patients with COPD were included in the final analysis after meeting the eligibility criteria and completing clinical, spirometry, and laboratory assessments. Most participants were aged ≥ 60 years (64.9%), male (59.7%), and had a current or previous smoking history (57.1%). Normal body weight was the most common nutritional status (37.7%), although overweight (35.1%) and obesity (27.3%) were also frequently observed. Post-bronchodilator spirometry confirmed persistent airflow obstruction in all participants, with a mean FEV₁/FVC ratio of $55.8 \pm 10.7\%$ and a mean predicted FEV₁ of $55.9 \pm 22.1\%$. The baseline demographic, clinical, and spirometry characteristics are summarized in Table 1.

Table 1. Baseline demographic, clinical, and spirometric characteristics of the study population

Variable	Value
Age group, n (%)	
40–49 years	7 (9.1)
50–59 years	20 (26.0)
60–69 years	23 (29.9)
≥70 years	27 (35.1)
Sex, n (%)	
Male	46 (59.7)
Female	31 (40.3)
Body mass index, n (%)	
Underweight	0 (0.0)
Normal weight	29 (37.7)
Overweight	27 (35.1)
Obesity	21 (27.3)
Smoking status, n (%)	
Never smoker	33 (42.9)
Current/former smoker	44 (57.1)
Spirometric parameters	
Post-bronchodilator FEV ₁ /FVC (%)	55.8 ± 10.7; median 59.0 (32.0–69.0)
Predicted FEV ₁ (%)	55.9 ± 22.1; median 57.9 (17.0–93.8)

3.2 Distribution of COPD Severity, Insulin Resistance, and Clinical Outcomes

According to the GOLD spirometry classification, GOLD 2 was the most frequent stage (45.5%), while 55.8% of patients were categorized as Group E, indicating a high exacerbation risk. The mean fasting plasma glucose, fasting insulin, and HOMA-IR values were 99.49 ± 11.93 mg/dL, 11.16 ± 4.72 μ IU/mL, and 2.82 ± 1.36 , respectively. High or very high insulin resistance (HOMA-IR ≥ 3.0) was identified in 35 patients (45.5%). Most participants had a high symptom burden (87.0%), whereas 60 patients (77.9%) experienced at least one exacerbation and 38 (49.4%) required hospitalization during the observation period. The distribution of disease severity is presented in **Table 2**, whereas metabolic characteristics and clinical outcomes are summarized in **Table 3**.

Table 2. Distribution of COPD severity according to GOLD grade and GOLD ABE classification

Variable	Value
GOLD spirometric grade, n (%)	
GOLD 1 (FEV ₁ $\geq 80\%$ predicted)	14 (18.2)
GOLD 2 (FEV ₁ 50–79% predicted)	35 (45.5)
GOLD 3 (FEV ₁ 30–49% predicted)	14 (18.2)
GOLD 4 (FEV ₁ $<30\%$ predicted)	14 (18.2)
GOLD ABE classification, n (%)	
Group A (low symptoms, low exacerbation risk)	8 (10.4)
Group B (high symptoms, low exacerbation risk)	26 (33.8)
Group E (high exacerbation risk)	43 (55.8)

3.3 Association Between Insulin Resistance and COPD Severity

A significant association was observed between HOMA-IR category and COPD severity. Patients with low HOMA-IR (<2.0) were predominantly classified as GOLD 1–2 (100%), whereas those with HOMA-IR ≥ 3.0 were mainly distributed across GOLD 3–4 (69.3% and 68.2%, respectively; $p < 0.001$). Likewise, higher HOMA-IR categories were strongly associated with more severe Group ABE classification, with 92.3% of patients in the HOMA-IR 3.0–3.9 category and 86.4% of those with HOMA-IR ≥ 4.0 classified as Group E ($p < 0.001$). These findings indicate a close relationship between insulin resistance and increasing disease severity (Tables 4 and 5).

Table 3. Metabolic, Clinical, and Outcome Characteristics of the Study Population (n = 77)

Variable	Value
Laboratory findings	
Fasting plasma glucose (mg/dL)	99.49 $\pm$ 11.93; median 99.00 (78.00–124.00)
Fasting insulin (μ U/mL)	11.16 $\pm$ 4.72; median 10.57 (1.69–20.13)
HOMA-IR	2.82 $\pm$ 1.36; median 2.83 (0.40–5.12)
HOMA-IR category, n (%)	
Normal/low (<2.0)	26 (33.8)
Increased risk (2.0–2.9)	16 (20.8)
High insulin resistance (3.0–3.9)	13 (16.9)
Very high insulin resistance (≥ 4.0)	22 (28.6)
Symptom burden, n (%)	
Low symptoms (mMRC 0–1 and CAT <10)	10 (13.0)
High symptoms (mMRC ≥ 2 and/or CAT ≥ 10)	67 (87.0)
Clinical Outcomes, n (%)	
Exacerbation during observation	60 (77.9)
No exacerbation	17 (22.1)
Hospitalization due to exacerbation	38 (49.4)
No hospitalization	39 (50.6)

Table 4. Association Between HOMA-IR Category and GOLD Spirometric Grade

HOMA-IR Category	GOLD 1 n (%)	GOLD 2 n (%)	GOLD 3 n (%)	GOLD 4 n (%)	Total	p-value
<2.0	9 (34.6)	17 (65.4)	0 (0.0)	0 (0.0)	26	<0.001
2.0–2.9	5 (31.3)	7 (43.8)	2 (12.5)	2 (12.5)	16	
3.0–3.9	0 (0.0)	4 (30.8)	5 (38.5)	4 (30.8)	13	
≥ 4.0	0 (0.0)	7 (31.8)	7 (31.8)	8 (36.4)	22	
Total	14 (18.2)	35 (45.5)	14 (18.2)	14 (18.2)	77	

Data are presented as n (%). P values were calculated using the **Fisher–Freeman–Halton exact test**.

Table 5. Association Between HOMA-IR Category and GOLD ABE Classification

HOMA-IR Category	Group A n (%)	Group B n (%)	Group E n (%)	Total	<i>p</i> -value
<2.0	5 (19.2)	15 (57.7)	6 (23.1)	26	<0.001
2.0–2.9	3 (18.8)	7 (43.8)	6 (37.5)	16	
3.0–3.9	0 (0.0)	1 (7.7)	12 (92.3)	13	
≥4.0	0 (0.0)	3 (13.6)	19 (86.4)	22	
Total	8 (10.4)	26 (33.8)	43 (55.8)	77	

*P values were calculated using the Fisher–Freeman–Halton exact test.

3.4 Relationship Between HOMA-IR and Pulmonary Function

HOMA-IR demonstrated significant inverse correlations with pulmonary function, including predicted FEV₁ ($\rho = -0.634$, $p < 0.001$) and FEV₁/FVC ratio ($\rho = -0.602$, $p < 0.001$). In contrast, positive correlations were observed between HOMA-IR and mMRC score ($\rho = 0.728$), CAT score ($\rho = 0.680$), and exacerbation frequency ($\rho = 0.702$), all of which were statistically significant ($p < 0.001$). These findings indicate that increasing insulin resistance is associated with worsening airflow limitation, greater symptom burden, and more frequent exacerbations (Table 6).

Comparison across GOLD spirometry grades further demonstrated progressive increases in fasting insulin and HOMA-IR with increasing disease severity. Median HOMA-IR increased from 1.45 in GOLD 1 to 4.14 in GOLD 4, while median fasting insulin increased from 6.4 to 16.1 μ IU/mL (both $p < 0.001$). Fasting plasma glucose also differed significantly across GOLD grades, although the magnitude of change was less pronounced than that observed for insulin and HOMA-IR (Table 7).

Table 6. Correlation Between HOMA-IR and Pulmonary Function, Symptom Burden, and Exacerbation Frequency

Variable	HOMA-IR				ρ	<i>p</i> -value
	<2.0	2.0–2.9	3.0–3.9	≥4.0		
Predicted FEV ₁ (%)	69.1 (53.1–92.4)	65.8 (18.2–93.8)	38.0 (17.0–73.7)	35.1 (18.8–75.2)	−0.634	<0.001
FEV ₁ /FVC (%)	64.0 (53.0–69.0)	62.0 (35.0–68.0)	50.0 (38.0–67.0)	50.0 (32.0–63.0)	−0.602	<0.001
mMRC score	1 (0–3)	2 (0–4)	3 (2–4)	3 (2–4)	0.728	<0.001
CAT score	12.5 (4–22)	13.5 (5–35)	23.0 (16–32)	23.5 (14–35)	0.680	<0.001
Exacerbation frequency	0 (0–2)	1 (0–3)	2 (1–3)	3 (1–3)	0.702	<0.001

Values are presented as median (range). Correlations were assessed using Spearman's rank correlation coefficient.

Table 7. Comparison of Metabolic Parameters Across GOLD Spirometric Grades

Parameter	GOLD 1	GOLD 2	GOLD 3	GOLD 4	<i>p</i> -value
Fasting plasma glucose (mg/dL)	93.0 (78.0–107.0)	96.0 (78.0–118.0)	108.5 (90.0–124.0)	107.0 (93.0–123.0)	<0.001
Fasting insulin (μ IU/mL)	6.4 (2.9–10.1)	9.1 (1.7–18.4)	15.1 (10.4–18.1)	16.1 (10.9–20.1)	<0.001
HOMA-IR	1.45 (0.60–2.40)	2.10 (0.40–4.79)	3.86 (2.83–5.12)	4.14 (2.93–5.12)	<0.001

Values are presented as median (range). *P* values were calculated using the **Kruskal–Wallis test**.

3.5 Association Between Insulin Resistance and Exacerbation Risk

Higher HOMA-IR categories were significantly associated with an increased risk of COPD exacerbations ($p < 0.001$). Exacerbations occurred in only 46.2% of patients with HOMA-IR < 2.0 but increased to 81.3% among those with HOMA-IR 2.0–2.9. Notably, all patients with HOMA-IR values ≥ 3.0 experienced at least one exacerbation during the observation period, demonstrating a clear dose-response relationship between insulin resistance and clinical deterioration (Table 8).

Table 8. Association Between HOMA-IR Categories and the Risk of COPD Exacerbations

HOMA-IR Category	No Exacerbation, n (%)	Exacerbation, n (%)	p-value
< 2.0	14 (53.8%)	12 (46.2%)	
2.0–2.9	3 (18.8%)	13 (81.3%)	
3.0–3.9	0 (0.0%)	13 (100.0%)	
≥ 4.0	0 (0.0%)	22 (100.0%)	< 0.001

* *P* values were calculated using the Fisher–Freeman–Halton exact test.

3.6 Discussion

The present study identified a significant association between insulin resistance and the severity of COPD. Patients with more severe airflow limitation, increased symptom burden, and more frequent exacerbations demonstrated progressively higher HOMA-IR values. Furthermore, elevated HOMA-IR levels were consistently associated with advanced GOLD spirometry grades and the Group ABE classification. These findings suggest that insulin resistance is not merely a metabolic comorbidity but also a systemic manifestation closely linked to the progression of COPD.

The association between HOMA-IR and disease severity is consistent with previous studies. Kiran et al. (2015) demonstrated that insulin resistance was significantly more prevalent in COPD patients than in healthy individuals and was correlated with increased airflow restriction [1]. Similarly, Vaz et al. (2016) reported that elevated HOMA-IR levels were linked to diminished lung function and poorer clinical outcomes [10]. Furthermore, Kim et al. (2019) found that insulin resistance was associated with a more rapid decline in lung function within a community-based cohort [20]. Collectively, these findings support the hypothesis that metabolic disturbances contribute to the progression of COPD, extending beyond the effects of lung inflammation alone.

Several biological mechanisms may explain these findings. Persistent systemic inflammation induces the production of pro-inflammatory cytokines, including tumour necrosis factor- α and interleukin-6. These cytokines impair insulin signalling by promoting serine phosphorylation of insulin receptor substrate proteins, consequently reducing glucose uptake in skeletal muscle and adipose tissue. Furthermore, chronic hypoxemia, oxidative stress, mitochondrial dysfunction, and physical inactivity may further aggravate insulin resistance by disrupting cellular energy metabolism. These processes establish a harmful cycle in which declining pulmonary function results in metabolic disturbances, while insulin resistance exacerbates systemic inflammation and accelerates disease progression.

The study identified a significant association between HOMA-IR and the risk of exacerbations. Patients in higher HOMA-IR categories experienced a markedly increased number of exacerbations, with all individuals in the high and very high insulin resistance groups encountering at least one exacerbation during the study period. These findings are consistent with those of Vaz et al. (2015), who reported a correlation between insulin resistance and a higher frequency of exacerbations, and Marino et al. (2017), who demonstrated that repeated exacerbations increase the risk of metabolic dysfunction and type 2 diabetes mellitus [10,21]. Collectively, these results suggest a bidirectional interaction in which recurrent exacerbations exacerbate metabolic impairment, while insulin resistance may increase susceptibility to future exacerbations due to persistent inflammation and impaired immune responses.

The present study identified a progressive increase in fasting insulin levels and HOMA-IR across various GOLD spirometry stages, while fasting plasma glucose levels remained relatively stable. This pattern suggests that compensatory hyperinsulinemia

precedes any significant disturbances in glucose regulation, indicating that insulin resistance may emerge in the early stages of metabolic dysfunction. Similar findings have been reported in metabolic research, demonstrating that fasting glucose often remains within normal ranges even as insulin sensitivity declines, due to the initial compensatory increase in insulin production by pancreatic β -cells. Collectively, these findings reinforce the concept of COPD as a multisystem disease, characterized by complex interactions between pulmonary inflammation and metabolic imbalance. Clinically, assessing HOMA-IR could facilitate the early identification of patients at elevated risk for severe illness and frequent exacerbations, thereby providing an opportunity for more comprehensive management strategies that address both respiratory and metabolic concerns.

Several limitations of this study must be acknowledged. Firstly, the cross-sectional design precludes the establishment of a causal relationship between insulin resistance and the severity of COPD. Secondly, as participants were recruited from tertiary referral centres, the results may not be generalizable to the broader COPD population. Thirdly, although HOMA-IR is a widely validated surrogate for insulin resistance, it lacks the precision of the hyperinsulinemia-euglycemic clamp technique. Nevertheless, HOMA-IR offers a practical and reliable method for assessing insulin resistance in clinical research and has demonstrated consistent correlations with clinically significant indicators of disease severity in this cohort. Future prospective longitudinal studies are required to clarify the temporal relationships between insulin resistance, disease progression, and exacerbation risk, as well as to evaluate whether addressing metabolic dysfunction can improve long-term clinical outcomes for COPD patients.

4. CONCLUSION

This study demonstrates that insulin resistance is a prevalent metabolic abnormality among patients with COPD, closely linked to increased disease severity and a heightened risk of exacerbations. An increase in HOMA-IR consistently correlates with worsened airflow limitation, a greater symptom burden, more frequent exacerbations, and a more advanced clinical classification. It remains an independent predictor of severe disease after adjusting for potential confounders. These findings underscore the systemic nature of COPD, suggesting that metabolic dysfunction is not merely a comorbid condition but an integral component of disease progression. Although the cross-sectional design limits causal inference, the results indicate the potential clinical utility of HOMA-IR as a straightforward and accessible biomarker for identifying patients at elevated risk of severe disease and adverse clinical outcomes, warranting further validation in prospective longitudinal studies.

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AUTHOR CONTRIBUTIONS

PN conceived and designed the study, collected the data, performed the statistical analyses, interpreted the results, and drafted the manuscript. MI and HAP supervised the study, contributed to the study design, critically revised the manuscript, and approved the final version. EA, NL, and SN contributed to data interpretation, manuscript revision, and approval of the final manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ETHICS STATEMENT

The study complied with the Declaration of Helsinki and received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine at Hasanuddin University (Approval No. 484/UN4.6.4.5.31/PP36/2026). Furthermore, permission to conduct the research at Dr. Wahidin Sudirohusodo Hospital was obtained (Permit No. DP.04.3/D.XVIII.2/7984/2026). All participants provided written informed consent prior to their involvement, and the data collected were anonymized to ensure confidentiality.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

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