Original Article

The Predictive Factors of Mortality In COVID-19 In The Intensive Care Unit: A Retrospective Study From Universitas Airlangga Hospital Surabaya

Vindy Vanessa Wennas [1], Arief Bakhtiar[2], Mochamad Yusuf [3], Wiwin Is Effendi [2]

[1]Faculty of Medicine, Universitas Airlanga, Surabaya, Indonesia
[2]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[3]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Abstract

Background: Coronavirus disease 2019 (COVID-19) poses a significant global challenge due to its highly transmissible nature and many positive cases and deaths. Myriad factors are known to affect the outcome of COVID-19 patients. Therefore, identifying predictive factors is essential for developing strategies to reduce mortality.

Methods: An analytical observational retrospective study was conducted at Universitas Airlangga Hospital Surabaya from January to June 2021. A total of consecutive sampling was performed on all patients in the intensive care unit. Thirty-one variables were included and analysed using a two-step statistical analysis: univariate and multivariate logistic regression.

Results: The mortality rate among 116 patients was 61.2%. The univariate analysis showed that dyspnoea, hypoxia, hyperglycaemia, and fever at admission were positively correlated with mortality. The multivariate analysis showed that fever (adjusted odds ratio [OR]=5) and hyperglycaemia (adjusted OR=8) at admission were independent predictors of mortality.

Conclusion: Patients with hyperglycaemia or fever at admission face an increased likelihood of dying from COVID-19, with risks elevated by eight times and five times, respectively.

Keywords: COVID-19, ICU, mortality, outcome, predictive

Corresponding Author:
Arief Bakhtiar | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia | arief-b@fk.unair.ac.id

Submitted: October 8th, 2024
Accepted: April 15th, 2025
Published: April 20th, 2025

J Respirol Indones. 2025
Vol. 45 No. 2: 113–20
https://doi.org/10.36497/jri.v45i2.830

INTRODUCTION

On December 31st, 2019, coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China. Declared as a global pandemic on March 15, 2020, COVID-19 led to a dramatic loss of human life worldwide.[1] The spread of COVID-19 prompted significant global changes, including nationwide lockdowns, and placed immense pressure on healthcare systems.[2]

Previous studies have identified various predictors of COVID-19 worldwide. Older age was commonly found as the major predictor of COVID-19 mortality.[3–5] Increased mortality was also predominated among males gender.[6,7] Diverse clinical manifestations among deceased patients have been documented. In Wuhan, China, cough and fever were reported in 87.5% of deceased patients. [8] In Kuwait, shortness of breath (81.7%) and fever (61.7%) were frequently observed among deceased intensive care unit (ICU) patients.[6]

In Florida, hypertension (73.1%) and diabetes (57.7%) were the most common comorbidities.[9] In Papua, hypertension (19.1%), electrolyte imbalance (10.2%), and diabetes (10.0%) are the most prevalent comorbidities.[5] Additionally, hyperglycaemia at admission was linked to a 3.45-fold increase in mortality risk and a 2.09-fold increase in risk of complications and severity of COVID-19.[10]

However, only a few studies have analysed the factors that affect the outcomes of COVID-19 patients in Indonesia, leaving clinicians in a dilemma as disease progression remains unpredictable. Therefore, this research aims to identify and analyse the main predictive factors associated with the

outcomes of ICU patients to provide appropriate preventive measures to mitigate disease progression, reduce mortality, and improve patient prognosis.

METHODS

This study was an analytical observational retrospective study conducted at Universitas Airlangga Hospital, Surabaya, between January and June 2021. Total consecutive sampling was performed on all patients in the ICU aged 18 years and above with a confirmed COVID-19 diagnosis. A positive real-time polymerase chain reaction (RT-PCR) result was used to verify the diagnosis. Patients were admitted to the ICU based on the physician's decision. No further classifications were applied for patients admitted to the ICU.

This study included patients with sufficient medical record data. This study excluded patients who died with a negative RT-PCR result, and individuals who were pregnant or in a post-partum period. The outcomes of COVID-19 were evaluated retrospectively using patients' medical records. No informed consent was required in this study. The Committee of Research Ethics at Universitas Airlangga Hospital granted ethical clearance for this study with reference number 177/KEP/2021 and protocol number UA-02-2179.

Percentages were used to present descriptive statistics for categorical variables. The relationship between patients' demographic data, symptoms, laboratory results at hospital admission, comorbidities, nutritional status, lifestyle, IMPROVE-DD Risk Assessment Model (RAM) for venous thromboembolism (VTE) score, length of ICU stay, and patient outcomes was determined using the Chi-square test. Statistical significance was defined with a value of $P<0.05$. One of the symptoms included in this study is dyspnoea and hypoxia. Dyspnoea is defined as a respiratory rate outside the normal range, specifically below 12 or above 20 breaths per minute. Hypoxia is characterized by a measured peripheral oxygen saturation of less than 95%.

Factors associated with mortality were evaluated in a two-step statistical analysis: univariate and multivariate logistic regression. The univariate analysis used crude odds ratios (ORs) and 95% confidence intervals (95% CI) to examine the strength of factors associated with COVID-19 mortality. Results with a value of $P<0.10$ were included in the multivariate logistic regression. Adjusted OR and 95% CI were used to assess whether significant factors act as independent predictors. Variables with a value of $P<0.05$ from the multivariate analysis were deemed determinants of COVID-19 mortality. Microsoft Excel 2016 was used for data management, and IBM SPSS Statistics software version 26 was used for statistical analysis.

RESULTS

Out of the 116 patients, seventy-one (61.2%) died from COVID-19 in the ICU. Patients aged 18 to 60 years are mostly deceased (60.6%) and are mostly male (56.3%). However, no significant differences were found between age or sex to COVID-19 mortality. Eight symptoms at hospital admission were noted in this study. Among these, dyspnoea (94.4%) and hypoxia (87.3%) were significantly associated with higher mortality, independent of sex and age. Diabetes was the most prevalent comorbidity, observed in 46 deceased patients (64.8%), followed by hypertension in 37 deceased patients (52.1%). Malignancy was the least common comorbidity (4.2%); however, all patients with malignancy at admission died.

Based on the nutritional status, a higher proportion of deceased patients were obese (23.9%) compared to those who were malnourished (1.4%). Laboratory results indicated that deceased patients commonly presented with lymphopenia (93%) and an increase in neutrophil-to-lymphocyte ratio (NLR) (90.1%). No significant difference was found between lymphopenia and increased NLR in this study. Additionally, 74.7% of deceased patients had elevated random blood glucose (RBG) at admission, with a significant association with mortality ($P=0.016$).

Table 1. Characteristics of the study

Characteristics	Discharged	Deceased	*P*
Patients Demography			
Age			
18-60 years old	30 (66.7%)	43 (60.6%)	0.641
>60 years old	15 (33.3%)	28 (39.4%)	
Sex			
Male	28 (62.2%)	40 (56.3%)	0.665
Female	17 (37.8%)	31 (43.7%)	
Symptoms Upon Admission			
Dyspnoea	36 (80.0%)	67 (94.4%)	0.037
Hypoxia	31 (68.9%)	62 (87.3%)	0.029
Fever	13 (28.9%)	35 (49.3%)	0.048
Cough	36 (80.0%)	55 (77.5%)	0.927
Fatigue	25 (55.6%)	55 (35.2%)	0.050
Anosmia	8 (17.8%)	4 (5.6%)	0.075
Diarrhoea	6 (13.3%)	8 (11.3%)	0.968
Vomiting	7 (15.6%)	8 (11.3%)	0.699
Laboratory Results			
Leukopenia (<4x10^9/L)	11 (24.4%)	11 (15.5%)	0.339
Lymphopenia (<1.0x10^9/L)	39 (86.7%)	66 (93.0%)	0.423
PLR (>180)	29 (64.4%)	49 (69.0%)	0.758
NLR (≥3.13)	37 (82.2%)	64 (90.1%)	0.340
eGFR			
60 mL/min/1.73m^2	19 (42.2%)	31 (43.7%)	
60–90 mL/min/1.73m^2	14 (31.1%)	20 (28.2%)	0.943
>90 mL/min/1.73m^2	12 (26.7%)	20 (28.2%)	
AST (>40 U/L)	27 (60.0%)	51 (71.8%)	0.263
ALT (>33 U/L)	29 (64.4%)	42 (59.2%)	0.708
Hypoalbuminemia (<35g/L)	12 (26.7%)	28 (39.4%)	0.226
RBG (>7.77 mmol/L)	23 (51.1%)	53 (74.7%)	0.016
Comorbidities			
CVD	5 (11.1%)	13 (18.3%)	0.435
CKD	2 (4.4%)	11 (15.5%)	0.125
Malignancy	0 (0.0%)	3 (4.2%)	0.426
Hypertension	27 (60.0%)	37 (52.1%)	0.522
Diabetes	21 (46.7%)	46 (64.8%)	0.083
Nutritional Status			
Obesity	8 (17.8%)	17 (23.9%)	0.579
Malnourished	2 (4.4%)	1 (1.4%)	0.687
Lifestyle			
Smoking	4 (8.9%)	1 (1.4%)	0.143
IMPROVE-DD RAM for VTE Score			
Low Risk	4 (8.9%)	6 (8.5%)	
Moderate Risk	23 (51.1%)	32 (45.1%)	0.786
High Risk	18 (40.0%)	33 (46.5%)	
Length of ICU Stay (> 7 days)	31 (68.9%)	28 (39.4%)	0.004

Note: PLR=platelet-to-lymphocyte ratio; NLR=neutrophil-to-lymphocyte ratio; eGFR=estimated glomerular filtration rate; AST=aspartate aminotransferase; ALT=alanine transaminase; RBG=random blood glucose; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease; CKD=chronic kidney disease

The majority of deceased patients (69.9%) spent less than eight days in the ICU. A stay longer than seven days in the ICU was significantly linked to increased mortality (*P*=0.004). Further details about the study characteristics are mentioned in Table 1.

The univariate analysis was performed in the first statistical phase, which included all 31 independent variables of this study. Patients with dyspnoea at hospital admission had the greatest risk of mortality (*P*=0.024; OR=4.187; 95% CI=1.205-14.550) compared to other presenting symptoms. Deceased patients with dyspnoea had a history of malignancy (100%), chronic kidney disease (81.8%), or diabetes (71.4%).

Similarly, deceased patients with hypoxia independent of dyspnoea at hospital admissions had comorbidities of malignancy (100%), CKD (90%), and cardiovascular disease (CVD) (73.3%). Patients who presented with comorbidities of CKD, CVD, or malignancy demonstrated an increased risk of mortality, although these associations were not statistically significant. Elevated RBG at hospital admission was noted in 76 patients with an increased risk of mortality (*P*=0.010; OR=2.816; 95% CI=1.275-6.219). Results of the univariate analysis are mentioned in Table 2.

The multivariate analysis included dyspnoea, hypoxia, fever, fatigue, anosmia, elevated RBG, CKD, diabetes, smoking, and length of ICU stay. Fever (*P*=0.005; adjusted OR=5.336; 95% CI=1.654-17.218) and elevated RBG (*P*=0.001; adjusted OR=7.531; 95% CI=2.384-23.794) at hospital admission were identified as statistically significant independent predictors of COVID-19 mortality. Results of the multivariate analysis for independent predictors of COVID-19 mortality are mentioned in Table 3.

Table 3. Multivariate logistic regression analysis for independent predictors of COVID-19 mortality

Parameters	Adjusted OR	*P*	95% C.I.
Dyspnoea	3.983	0.065	0.915-17.337
Fever	5.336	0.005	1.654-17.218
Fatigue	0.165	0.001	0.054-0.502
Anosmia	0.068	0.004	0.011-0.418
RBG (>7.77mmol/L)	7.531	0.001	2.384-23.794
Smoking	0.089	0.109	0.005-1.713
Length of ICU Stay (> 7 days)	0.094	0.000	0.029-0.300

Note: OR=Odds Ratio; CI=Confidence Interval; RBG=random blood glucose; ICU=Intensive Care Unit

Table 2. Univariate logistic regression analysis on the mortality of COVID-19 patients

Characteristics	n (%)	*P*	Crudes OR	95% CI
Patients Demography				
Age				
18-60 years old	73 (62.9%)	0.508	0.768	0.351-1.678
>60 years old	43 (37.1%)	Ref	Ref	Ref
Sex				
Male	68 (58.6%)	0.531	0.783	0.365-1.681
Female	48 (41.4%)	Ref	Ref	Ref
Symptoms Upon Admission				
Dyspnoea	103 (88.8%)	0.024	4.187	1.205-14.550
Hypoxia	93 (80.2%)	0.018	3.111	1.213-7.979
Fever	48 (41.4%)	0.031	2.393	1.081-5.299
Cough	91 (78.4%)	0.746	0.859	0.343-2.153
Fatigue	50 (43.1%)	0.033	0.435	0.203-0.933
Anosmia	12 (10.3%)	0.046	0.192	0.078-0.979
Diarrhoea	14 (12.1%)	0.740	0.825	0.266-2.559
Vomiting	15 (12.9%)	0.504	0.689	0.231-2.053
Laboratory Results				
Leukopenia (<4 x10^9/L)	22 (19.0%)	0.234	0.567	0.222-1.444
Lymphopenia (<1.0 x 10^9/L)	105 (90.5%)	0.267	2.031	0.581-7.096
PLR (>180)	78 (67.2%)	0.610	1.229	0.557-2.710
NLR (≥3.13)	101 (87.1%)	0.221	1.977	0.663-5.892
eGFR				
60 mL/min/1.73 m2	50 (43.1%)	0.943	Ref	Ref
60–90 mL/min/1.73m^2	34 (29.3%)	0.964	0.979	0.392-2.445
>90 mL/min/1.73m^2	32 (27.6%)	0.760	0.857	0.319-2.305
AST (>40 U/L)	78 (67.2%)	0.188	1.700	0.772-3.743
ALT (>33 U/L)	71 (61.2%)	0.569	0.799	0.369-1.730
Hypoalbuminemia (<35g/L)	40 (34.5%)	0.161	1.791	0.793-4.043
RBG (>7.77 mmol/L)	76 (65.5%)	0.010	2.816	1.275-6.219
Comorbidities				
CVD	18 (15.5%)	0.301	1.793	0.593-5.426
CKD	13 (11.2%)	0.084	3.942	0.831-18.696
Malignancy	3 (2.6%)	0.999	1.096	0.000-0.000
Hypertension	64 (55.2%)	0.406	0.725	0.340-1.546
Diabetes	67 (57.8%)	0.056	2.103	0.982-4.504
Nutritional Status				
Obesity	25 (21.6%)	0.433	1.456	0.570-3.722
Malnourished	3 (2.6%)	0.341	0.307	0.027-3.490
Lifestyle				
Smoking	5 (4.3%)	0.091	0.146	0.016-1.355
IMPROVE-DD RAM for VTE Score				
Low Risk	10 (8.6%)	0.787	Ref	Ref
Moderate Risk	55 (47.4%)	0.777	0.818	0.204-3.283
High Risk	51 (44.0%)	0.491	0.759	0.346-1.665
Length of ICU Stay (> 7 days)	59 (50.9%)	0.002	0.294	0.133-0.648

Note: PLR=platelet-to-lymphocyte ratio; NLR=neutrophil-to-lymphocyte ratio; eGFR=estimated glomerular filtration rate; AST=aspartate aminotransferase; ALT=alanine transaminase; RBG=random blood glucose; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease; CKD=chronic kidney disease; OR=Odds Ratio; CI=Confidence Interval

DISCUSSION

COVID-19 patients present with varying levels of severity at hospital admission, leading to different hospital care requirements. To our knowledge, few studies have investigated the predictors of COVID-19 mortality among ICU patients in Indonesia. This study found that hyperglycaemia and fever at hospital admission were significant predictors of COVID-19 mortality in the ICU. Additionally, patients with

dyspnoea and hypoxia at admission were observed with increased mortality risk.

This study emphasizes that hyperglycaemia at hospital admission was an independent risk factor for COVID-19 mortality. Hyperglycaemia increased the likelihood of mortality by 7.53 times regardless of the patient's age, sex, and prior diabetic status. The cut-off value of hyperglycaemia was RBG ≥140 mg/dl or RBG >7.77 mmol/L at hospital admission. Despite an extensive literature review, research on hyperglycaemia as a predictor of COVID-19 mortality remains scarce. A meta-analysis by Lazarus et al reported an increased susceptibility to poorer outcomes for hyperglycaemic COVID-19 patients at admission, irrespective of age and sex.[11] This also corresponds with the results of a systematic review and meta-analysis done in Nanjing, China, where a greater increase in blood glucose was reported in severe COVID-19 infection compared to mild COVID-19.[12]

The relationship between hyperglycaemia and COVID-19 is postulated to be bidirectional. A hyperglycaemic state may indicate a stress or inflammatory condition contributing to adverse metabolic responses to infection. Acute hyperglycaemia in COVID-19 is caused by several mechanisms. The interaction between SARS-CoV-2 and ACE receptors damages the pancreatic islets, impairing insulin production. Additionally, the infectious state alters the body's metabolism and triggers the release of pro-inflammatory cytokines, leading to insulin resistance.[11,12]

Hyperglycaemia can also result from physiological stress, which activates counterregulatory hormones that increase hepatic gluconeogenesis while decreasing glucose deposition. This ultimately leads to a relative insulin deficiency. Furthermore, stress hyperglycaemia was associated with elevated pro-inflammatory cytokines (C-reactive protein (CRP), interferon-gamma, interleukin-6) and free fatty acids that exacerbate insulin resistance. This chain of events causes adverse reactions in the body, namely immune dysregulation, generation of reactive oxygen species, and advanced glycation end-product generation that may have detrimental effects on patient outcomes.[13]

This study found that fever at hospital admissions increases the likelihood of mortality by five times, regardless of the clinical state. Fever is a temporary rise in the body's temperature. In this study, fever was defined as measured axillary temperature ≥38ºC. Fever is typically observed during the first week of COVID-19 infection, as a response of the immune system to combat the virus. Nonetheless, if replication continues unabated during this phase, it may lead to complications such as cytokine storm, which manifests as unremitting fever in patients. Fever can further promote inflammation and immune activation, potentially harming the patient.[14] Our findings were consistent with a multi-center registry study in Turkey by Kokturk et al, which found that fever was related to a twenty-two-fold increased risk of mortality.[15]

Dyspnoea is a marker of underlying disease that requires prompt diagnosis and treatment to decrease mortality.[16] This study classified patients with a respiratory rate of greater than twenty or less than twelve breaths per minute as having dyspnoea. We found that dyspnoea at hospital admission led to a fourfold higher risk of mortality.

Dyspnoea was also more prevalent in deceased patients, with a mortality rate of 57.7%. This observation aligns with a study in Turkey, which reported a higher prevalence of dyspnoea among nonsurvivors, with a mortality rate of 77.6% and a sevenfold increased risk of mortality.[15] Furthermore, a study conducted in the emergency department (ED) by Safwenberg et al found that dyspnoea, in the absence of a history of asthma and wheezing on physical examination, increased the risk of mortality by one-fold over ten years compared to the general population.[17]

Dyspnoea can contribute to mortality due to impaired lung function. Inflammation and oedema from SARS-CoV-2 infection hinder gas diffusion by increasing the distance between capillaries and alveoli. Additionally, the virus activates the coagulation cascades and damages the endothelium, creating a prothrombotic state. Fibrin deposition

reduces perfusion by increasing functional dead space in the alveoli. Formation of thrombus and microclots disrupts ventilation/perfusion, limiting carbon dioxide elimination, leading to hypercapnia.[18]

Patients with hypoxia, indicated by a peripheral oxygen saturation SpO_2 <90%, faced a higher risk of COVID-19 mortality. Hypoxia results from insufficient oxygen at the tissue level to maintain homeostasis. SARS-CoV-2 infection induces acute inflammation of lung tissues. This inflammation is associated with increased levels of inflammatory markers, including elevated neutrophil counts, d-dimer, CRP, and white blood cell count, which may contribute to severe pulmonary damage and result in persistent hypoxemia.[19] It may cause accumulation of oxygen-free radicals, lactic acid, electrolyte changes, and intracellular pH changes, all of which may further exacerbate cellular damage.[20]

Interestingly, this study found that there were eight percent of deceased patients who presented with dyspnoea did not exhibit hypoxia upon hospital admissions. This discrepancy may be due to the variations in the definitions of dyspnoea and hypoxia used in the study. Additionally, dyspnoea is a subjective sensation influenced by psychological factors such as anxiety[16], which can increase the respiratory rate without a corresponding decline in peripheral oxygen levels.

Comorbidities such as CKD, CVD, or malignancy increase the risk of mortality and are prevalent among deceased patients. SARS-CoV-2 infects the ACE 2 receptors in the renal epithelium, triggering pathological events, including mitochondrial impairment, tubular necrosis, glomerulopathy, and ultimately leading to renal injury and impairment. Similar results were observed in Kuwait, where 65% of ICU non-survivors had kidney injury, compared to 4.5% of ICU survivors.[5]

SARS-CoV-2 also infects myocytes, causing injury and vascular inflammation, which contributes to microangiopathic thrombi, arrhythmias, acute coronary syndrome, myocarditis, heart failure, and death.[19] Likewise, cancer patients are highly susceptible to infection. The disease itself, treatment, and progression alter immune function, further worsening outcomes. A study in Turkey found that malignancy increased the mortality risk by 10.5 times.[15]

The relationship between laboratory results and mortality has been investigated. Most deceased patients had elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. SARS-CoV-2 binds to ACE2 receptors on hepatocytes, increasing liver enzyme breakdown.[21] Liver injury in most COVID-19 patients was reportedly mild and transient.[20] Our findings align with a study in Wuhan, which observed higher AST and ALT levels in non-survivors compared to survivors.[8]

Lymphopenia was the most prevalent laboratory abnormality among deceased patients. A study in Kuwait reported similar findings, with lymphopenia more prevalent and severe in ICU non-survivors than ICU survivors.[6] During an infection, lymphopenia primarily affects CD4+ T cells and, to a lesser extent, some CD8+ cells. Changes in these levels disrupt the innate and adaptive immune responses, delaying viral clearance and leading to the hyperactivation of neutrophils and macrophages.[20] Lymphopenia is linked to increased mortality as it is postulated that IL-6, a proinflammatory cytokine, utilizes lymphocytes, leading to their depletion.[22]

The length of ICU stay cut-off in this study was based on a systematic review by Rees et al. Similar trends were observed with patients who had longer ICU stays, who were more likely to be discharged alive. Hospital stay duration is influenced by factors such as age, gender, and comorbidities, which impact disease outcomes.[23] This study found that most patients who died within seven days had cardiovascular disease or fever.

A previous study stated that critically ill COVID-19 patients admitted to the ICU have been strongly associated with an increased risk of VTE. The IMPROVE-DD RAM for VTE stratifies patients into low, moderate, and high-risk categories. A low-risk classification corresponds to a score of 0-1 points, moderate risk to 2-3 points, and high risk to 4-12 points. The scoring includes the following: a prior episode of VTE (3 points), thrombophilia (2 points),

paralysis of the lower extremities during hospitalization (2 points), cancer (2 points), a maximal D-dimer level exceeding three times the upper limit of normal (2 points) immobilization for at least seven days (1 point), ICU admission (1 point) and over the age of 60 years (1 point).[24] Majority of patients in this study were classified as moderate or high risk, but VTE occurrence was not examined.

LIMITATION

A single-centre study in the referral hospital for neighbouring healthcare facilities limits the generalizability of our results. This study also does not further classify patients in the ICU, such as the usage of high-flow nasal cannula or a ventilator.

CONCLUSION

This study highlights that elevated RBG at hospital admission was an independent predictor of COVID-19 mortality in the ICU. Patients with hyperglycaemia and fever at admission face an increased likelihood of dying from COVID-19, with risks elevated by eight times and five times, respectively. These finding underscores the necessity for tight monitoring of RBG levels or body temperature to prevent disease progression, complications, and reduce mortality. Patients admitted with symptoms of dyspnoea or hypoxia were also associated with mortality. Recognizing these warning signs enables early intervention and facilitates communication between the patient's family and physicians regarding illness progression and treatment plans.

ACKNOWLEDGMENTS

We express our gratitude to the staff of the Committee of Research Ethics for their invaluable guidance during data collection and for ensuring the ethical conduct of this study.

CONFLICT OF INTEREST

No conflicts of interest to declare.

FUNDING

No financial support was received for this study.

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