Original Article

International Journal of Integrated Health Sciences (IIJHS)
ISSN Print: 2302-1381; ISSN Online: 2338-4506

Differential White Blood Cell Count and COVID-19 Hospital Length of Stay: A Post-hoc Analysis

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Article History

Received: April 16, 2024
Accepted: September 27, 2024
Published: October 4, 2024

DOI: 10.15850/ijihs.v12.n2.3915
IJIHS. 2024;12(1):125–132

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Abstract

Objective: To explore the association between differential white blood cell count and hospital length of stay (LOS) in COVID-19 patients.

Methods: This study is a post-hoc analysis of two prospective cohort studies involving hospitalized COVID-19 patients who received standard therapy, including antiviral and supportive treatments at Persahabatan Hospital, Jakarta, Indonesia, during the Delta and Omicron dominant pandemic periods. Baseline differential white blood cell count before initiation of therapy were documented. LOS was categorized as ≤10 days and >10 days.

Result: Data from 463 subjects were included with most subjects were males (62.2%) with a median age of 54 (14–93) years. The average LOS for subjects was 12.7 (12.1–13.4) days. Bivariate tests showed that lymphocytes, neutrophils, monocytes, neutrophil-lymphocyte ratio (NLR), and neutrophil-monocyte ratio (NMR) had significant association ($p < 0.05$) to LOS. Logistic regression showed that higher monocyte counts were associated with shorter LOS (adjusted OR 0.89; 95% CI 0.840–0.943; $p<0.001$). ROC curve showed that higher monocyte counts (>8.35×10^3/μL) at admission may predict shorter hospitalization (<10 days).

Conclusion: Monocyte count may serve as a potential marker for length of stay in COVID-19 patients, offering key insights for optimizing patient management and resource allocation.

Keywords: COVID-19, length of stay, monocyte, neutrophil, risk factor

Introduction

The global pandemic of Coronavirus disease 2019 (COVID-19) posed one of the most significant threats to public health worldwide. The rapid transmission characteristics of SARS-CoV-2 led to a surge in patients, significantly increasing the demand for healthcare resources beyond their capacity.[1] Indonesia was one of the countries that experienced a dramatic rise in COVID-19 cases, particularly during the first quarter of 2021, the subsequent third and fourth quarters of 2021, and the first and second quarters of 2022, with various virus variants (i.e., Delta, Omicron).[1,2]

The COVID-19 pandemic resulted in increased demands for screening and testing of suspected cases, contact monitoring, patient isolation, and intensive care unit (ICU) management of severe cases.[2] However, the overwhelming number of Omicron cases led to a significant rise in hospitalizations worldwide. Patients infected with the Omicron variant

were less likely to develop severe disease compared to those who contracted previous variants.[3]Research also suggests that patients admitted to hospitals during the mixed Omicron/Delta variant period had shorter hospital stays than those admitted during the Delta variant period. This finding contradicts the hospitalization rates observed.[4]

Hypoxemia is the most common reason for hospitalization in COVID-19 patients and varies in severity. Mild cases are managed with oxygen therapy, while severe cases may progress to Acute Respiratory Distress Syndrome (ARDS) and require mechanical ventilation. The underlying mechanism of hypoxemia in COVID-19 is thought to involve ventilation/perfusion (V/Q) mismatch due to vascular pathology in the lungs. This mismatch is driven by an intense inflammatory response, which increases lung permeability and disrupts pulmonary perfusion regulation. Additionally, an imbalance in procoagulant and fibrinolytic activity contributes to microthrombi formation, further worsening the vascular pathology.[5–7]the causative agent of coronavirus disease 2019 (COVID-19

A study in India showed that white blood cell differential counts are associated with the severity of COVID-19 infection. Indicators of disease severity include neutrophilia, lymphopenia, monocytopenia, a high neutrophil-lymphocyte ratio (NLR), and a high neutrophil-monocyte ratio (NMR).[8] Several laboratory parameters associated with infection and inflammatory processes have been identified as potential predictors of severity and length of stay (LOS) among patients inflicted with COVID-19.[9,10] This study aimed to investigate the relationship between infection markers, specifically differential white blood cell counts, and the LOS in COVID-19 patients during two dominant pandemic waves in Indonesia.

Methods

Post hoc analysis was conducted on datasets from two previous cohort studies in Jakarta.[11] The first cohort study, the REMISI Study, evaluated the safety and effectiveness of antiviral drugs (Remdesivir and Favipiravir) in COVID-19 patients following Emergency Use Authorization (EUA) in Indonesia during the Delta wave (April-August 2021).[12] The second study, the MEGACRON Study, was a prospective cohort study that compared the effects of antiviral therapy on PCR conversion in hospitalized COVID-19 patients during the Omicron wave in Jakarta (January–February 2022).

The post hoc analysis was conducted at Persahabatan General Hospital in Jakarta from January to March 2024, following the completion of two prior cohort studies. MID and FAR coordinated to obtain permission from the data custodians of each study to conduct additional analyses on the existing datasets. Each dataset from the two previous studies contains masked patient identity data to protect the confidentiality of the subjects, along with clinical baseline data and initial laboratory results collected at the time of hospital admission. GFG, DAN, and MID carried out the data screening and cleaning process.

The workflow of each study is illustrated in Fig. 1. In order to achieve a homogeneous subject population, only adult and adolescent subjects >13 years old confirmed with COVID-19 who were hospitalized and received standard COVID-19 therapy according to national guidelines (antivirals and supportive therapy) were included in the analysis. The exclusion criteria for this analysis included incomplete data (absence of admission or discharge dates) or if the patient had died.

The data collected for this study includes demographic information about the subjects, body mass index, presence of comorbidities, and length of hospital stay. The laboratory data analyzed consists of initial lab results obtained on the first day subjects were admitted to the hospital, before receiving antiviral medication. The initial laboratory results included differential white blood cell counts, which were reviewed by the attending physician and are part of the patient care program (not solely for research purposes). The laboratory automatically calculated the neutrophil-lymphocyte ratio as part of routine infection markers. The lymphocyte-monocyte ratio and neutrophil-monocyte ratio were calculated manually by the researchers (GFG, DAN, and MID) under the supervision of EBN, with consultation from a clinical pathologist.
The treatment duration is calculated from when the patient first entered the emergency department (for non-referred cases) or the isolation room (for referred cases). In this analysis, the researcher categorized the length of stay using a 10-day cut-off, where a stay of 10 days or more is considered prolonged. The selection of the 10-day cut-off is based on literature indicating that the average length of stay for COVID-19 patients ranges from 4 to 10 days,[13,14] and for patients with community-acquired pneumonia, the range is between 5

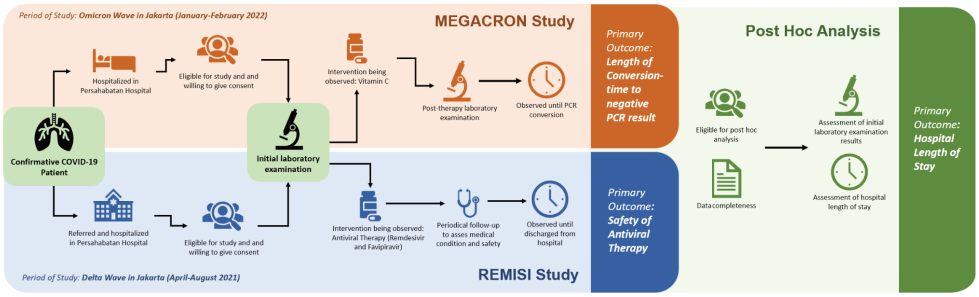

Fig. 1 Subject Recruitment Flow and Post-hoc Analysis

and 9.8 days.[15,16]

In this study, no sample size calculation was conducted; the authors used a convenience sample derived from the available cohort based on specific inclusion criteria. Participant characteristics were summarized using median and interquartile ranges to represent central tendency and variability, particularly for non-normally distributed data. A bivariate analysis was performed to compare leukocyte differential counts between two groups (<10 days and ≥10 days) using an unpaired T-test to identify significant differences. Variables with a p-value <0.25 were further analyzed using logistic regression to explore relationships between multiple variables and treatment duration, adjusting for age, gender, BMI, and comorbidities. The optimal cut-off values for each variable were determined through receiver operating characteristic (ROC) analysis with a 95% confidence interval, which helped assess the sensitivity and specificity of the variables in predicting treatment duration. All statistical analyses were performed using SPSS version 25, with a significance level set at $p<0.05$ to ensure the reliability of the findings.

The ethical review and informed consent process for this post hoc analysis adhered

Table 1 Subject Characteristics

Parameter	Delta wave Period (n = 415)	Omicron wave Period (n = 48)	p-value
Demographic characteristics			
Age [median (IQR), year]	54.5 (20–93)	49.5 (14–75)	<0.001
Gender, n(%) Female Male	 153 (63.1) 262 (36.9)	 22 (45.8) 26 (54.2)	0.225
BMI [median (IQR), kg/m^2]	25.71 (15.56–51.65)	22.63 (16.04–38.57)	<0.001
Presence of comorbidity n (%) Yes No	 374 (90.1) 41 (9.9)	 36 (75) 12 (25)	0.002
Clinical characteristics			
Length of stay (days)	12 (2–47)	7 (1–12)	<0.001
Neutrophil (10^3/µL)	78.95 (10.7–96.2)	69.65 (29–92.3)	<0.001
Lymphocyte (10^3/µL)	13.4 (1.3–86.3)	19.1 (4–58.4)	<0.001
Monocyte (10^3/µL)	7.1 (0.8–22.1)	8.3 (3.5–14.5)	0.002
NLR (%)	5.91 (0.12–73.46)	3.49 (0.5–23.08)	<0.001
LMR (%)	2.01 (0.16–50.76)	2.35 (0.60–8.37)	0.496
NMR (%)	10.96 (2.16–120.25)	8.01 (2.64–26.37)	<0.001

Table 2 Bivariate Analysis of Differential White Blood Cell Counts to Length of Stay

Parameter	Unit	Length of Stay		*p-value*
		Less than 10 days Median (min-max)	10 days or more Median (min-max)	
Lymphocyte	10^3/µL	16.20 (1.3-58.4)	13.00 (1.9-86.3)	0.001
Monocyte	10^3/µL	8.00 (1.3-22.1)	6.80 (0.8-19.7)	0.001
Neutrophil	10^3/µL	74.35 (29.0-95.7)	79.5 (10.7-96.2)	<0.001
Neutrophil-Lymphocyte Ratio (NLR)	%	4.50 (0.5-73.5)	6.20 (0.1-50.4)	<0.001
Lymphocyte-Monocyte Ratio (LMR)	%	2.13 (0.16–8.21)	2.02 (0.25–50.76)	0.659
Neutrophil-Monocyte Ratio (NMR)	%	9.31 (2.39–72.31)	11.23 (2.16–120.25)	0.014

to the protocols established in two previous cohort studies: the REMISI Study and the MEGACRON Study. Both studies received ethical clearance from the Research Ethics Committee of Persahabatan Hospital (64/KEPK-RSUPP/06/2021 for REMISI and 03/KEPK-RSUPP/01/2022 for MEGACRON). All participants in these cohort studies provided informed consent for their involvement in the research.

Result

This study included hospitalized individuals from standard inpatient and intensive care units infected with COVID-19 during the surge in cases caused by the Delta and Omicron variants. The analysis involved data from 463 patients who met the study criteria. The majority of the participants were male, comprising 62.2% of the total. The median age of the participants was 54 years, with a range from 14 to 93 years. Subject characteristics are presented in Table 1.

The LOS was categorized with a cut-off of 10 days. Bivariate tests revealed a significant association between lymphocytes, neutrophils, monocytes, NLR, and NMR and LOS (Table 2).

Logistic regression was performed with adjustment to age, gender, BMI, and comorbidity. The analysis revealed a significant association between monocyte count and length of stay (adjusted OR 0.899; 95% CI 0.840–0.943; p<0.001).

ROC analysis was further performed to evaluate the role of monocyte count as a marker for LOS. The area under the curve (AUC) was found to be 0.595, which suggested that monocyte count is a very poor marker of LOS. A cut-off monocyte count of 8.35 (10^3/µL) demonstrated a sensitivity of 44.8% and a specificity of 69.4% in predicting a patient LOS of less than 10 days. This suggests that lower monocyte counts are associated with longer LOS (Fig. 2).

Table 3 Logistic Regression of Differential White Blood Cell Counts to Length of Stay Adjusted With Age, gender, BMI, and Comorbidity

Variables	OR	95% CI	p-value
Neutrophil	1.009	0.988–1.030	0.406
Lymphocyte	1.032	0.930–1.145	0.555
Monocyte	0.8909	0.840–0.943	<0.001*
NLR	0.980	0.951–1.011	0.204
NMR	0.992	0.968–1.017	0.552

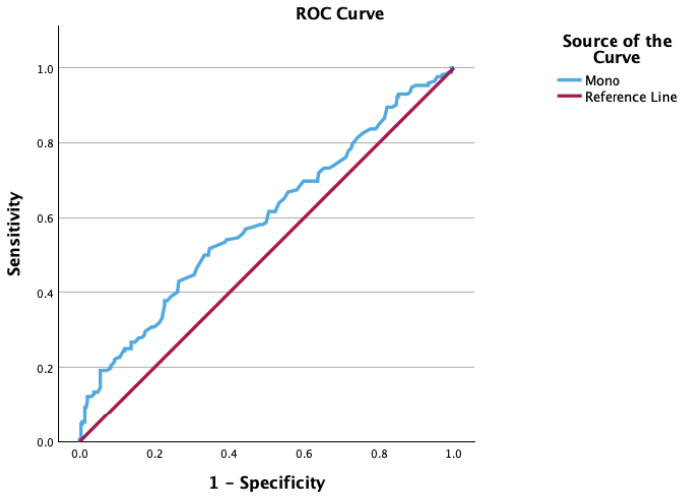

Fig. 2 ROC Curve of Monocyte Count As A Marker of Shorter LOS

Discussion

In this study, a post hoc evaluation was performed on 463 patients with SARS-CoV-2 infection at a national COVID-19 referral hospital. All patients included in this study were confirmed to have SARS-CoV-2 based on a positive RT-PCR assay. The guidelines for hematological laboratory testing in hospitalized COVID-19 cases in Indonesia are crucial tools for disease management and prognosis assessment.[17,18] This study demonstrated a notable relationship between differential white blood cell counts and the LOS in COVID-19 patients. Analysis revealed that lymphocyte, neutrophil, and monocyte counts, as well as the neutrophil-lymphocyte ratio, were significantly associated with a prolonged LOS exceeding 10 days. In particular, monocyte counts higher than 8.35 × 10^3/µL were identified as a predictor of hospital stays of less than 10 days.

Several studies have indicated a correlation between lymphopenia and prolonged hospitalization among COVID-19 patients. A meta-analysis by Tan *et al*. found that lymphopenia was associated with disease severity and could serve as a predictor of prolonged hospital stays.[19] Additionally, a retrospective cohort study by Zhou *et al*. demonstrated that lymphopenia was a common feature among hospitalized COVID-19 patients, with lower lymphocyte counts observed in those with severe illness and longer hospital stays.[20] Similarly, this bivariate tests revealed a significant association between lymphocyte levels and hospital stays longer than 10 days, with patients exhibiting lower median lymphocyte counts. This association between lymphopenia and prolonged hospitalization underscores the importance of monitoring lymphocyte levels as a prognostic indicator for disease severity and patient outcomes in COVID-19 cases.

On the other hand, the relationship between monocyte levels and length of hospital stay in COVID-19 patients has been less extensively studied. Emerging evidence suggests that monocyte alterations may also affect disease progression and outcomes. Several studies, including those by Zhao *et al*. and Liu *et al*., have shown that monocytopenia is associated with a shorter length of hospital stay. Patients with lower monocyte counts upon admission experience milder disease and shorter hospitalizations compared to those with normal monocyte levels,[21,22] which were different to the findings in this study. However, another study conducted by Kilercik *et al*. reported a complex relationship between monocyte count and COVID-19. In severe cases, there may be a depletion of monocyte counts, possibly due to selective recruitment of monocytes during the development of acute respiratory distress syndrome (ARDS) and the presence of microbial superinfections. This leads to a "shift-to-the-left" process in white blood cell production and alterations in myeloid cell homeostasis.[23,24] Although it should be highlighted that the AUC in this

study was poor, the use of monocytes as a marker should be interpreted cautiously, and other markers (i.e., differential white blood cell counts and inflammatory markers) may be beneficial as adjuncts.

Elevated neutrophil counts and an increased NLR have been identified as potential indicators of prolonged hospitalization among COVID-19 patients.[25] Neutrophilia, characterized by elevated neutrophil levels, is associated with severe COVID-19 disease and adverse outcomes. Studies, such as the one conducted by Liu *et al*., have reported that higher neutrophil counts are significantly correlated with disease severity and prolonged hospital stays in COVID-19 patients.[20] Additionally, research by Lagunas-Rangel emphasized the prognostic value of NLR, indicating that elevated NLR levels can predict disease severity and unfavorable clinical outcomes in COVID-19 cases.[26] The NLR reflects the balance between pro-inflammatory neutrophils and lymphocytes involved in the immune response, and its elevation may signify dysregulation of the immune system and heightened inflammation, leading to a more severe disease course and extended hospitalization periods. This study similarly revealed a significant association between neutrophil levels and NLR with LOS, showing that patients with an LOS greater than 10 days had higher median neutrophil and NLR values.

This study has several limitations. First, as an observational study conducted at a single research center, the findings may not be readily generalizable to other settings, particularly where patient characteristics differ significantly, thereby impacting external validity. Additionally, there is a potential for selection bias, as the sample was chosen based on the completeness of available data, which may have been more pronounced during the Omicron wave of COVID-19. The analysis was performed comprehensively without any subset analysis to mitigate this concern and preserve data validity,

In summary, this study found that monocyte counts may serve as a potential marker for the length of stay in COVID-19 patients. These findings could provide valuable insights for optimizing patient care and resource allocation during the pandemic.

Acknowledgment

We would like to express our sincere appreciation to the MEGACRON and REMISI study teams for their exceptional work and for granting permission to conduct further analysis of the data from both studies. We also extend our gratitude to Dr. Dean Handimulya, MD, from the Department of Clinical Pathology at the Faculty of Medicine, Universitas Indonesia, for kindly providing valuable consultation during the data processing stage.

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