ORIGINAL ARTICLE

# Procalcitonin, C-Reactive Protein-to-Mean Platelet Volume Ratio, and Neutrophil-to-Lymphocyte Ratio as Predictors of Secondary Bacterial Infections in COVID-19 Patients

Rizka Humardewayanti Asdie[1,2], Tri Hartati[1,2,3], Eko Budiono[1,2], Faisal Heryono[1], Dhite Bayu Nugroho[1,3]

[1] Department of Internal Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, 55281
[2] Antimicrobial Stewardship Team at Sardjito Hospital, Yogyakarta, Indonesia, 55281.
[3] Clinical Epidemiology and Biostatistics Unit, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, 55281

**ABSTRACT**

**Introduction:** Coronavirus disease 2019 (COVID-19) can lead to secondary bacterial infections, particularly among critically ill patients. Differentiating between viral and bacterial infections is crucial for timely and appropriate antibiotic treatment. This study aimed to assess the predictive value of procalcitonin (PCT), C-reactive protein-to-mean platelet volume ratio (CRP-to-MPV ratio), and neutrophil-to-lymphocyte ratio (NLR) for secondary bacterial infections in COVID-19 patients. **Methods:** A retrospective analysis was conducted on COVID-19 patients admitted to RSUP dr. Sardjito between April 2020 and April 2021. Clinical data, procalcitonin levels, CRP-to-MPV ratio, NLR, culture results, and antibiotic susceptibility tests were analyzed. Statistical tests, including chi-square, t-tests and Mann-Whitney tests, were employed, with significance set at $p<0.05$. Receiver operating characteristic (ROC) analysis was performed to determine optimal cutoff values. Multivariate analysis was performed using logistic regression to ascertain the effects of multiple factors on the likelihood of developing secondary bacterial infections in COVID-19 patients. **Results:** Among 328 COVID-19 patients, 98 met the inclusion criteria. PCT had limited predictive value (AUC=0.535, p=0.638) with a sensitivity of 18.18% and specificity of 97.37% at a cutoff of 3.59. The CRP-to-MPV ratio showed slightly better predictive ability (AUC=0.587, p=0.198) with a sensitivity of 77.27% and specificity of 48.68% at the same cutoff value. The NLR demonstrated a higher predictive value (AUC=0.674, p=0.002) with a sensitivity of 90.91% and specificity of 44.74% at a cutoff of 3.64. Patients with an NLR of ≤3.64 exhibited an 8.01-fold elevated risk in the multivariate model. **Conclusion:** In COVID-19 patients hospitalized for up to seven days, an NLR greater than 3.64 can serve as a predictor of secondary bacterial infections. The use of NLR as a prognostic tool may aid in early identification and appropriate management of bacterial infections in COVID-19 patients.
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**Keywords:** COVID-19, secondary bacterial infections, procalcitonin, CRP-to-MPV ratio, neutrophil-to-lymphocyte ratio

**Corresponding Author:**
Dhite Bayu Nugroho, PhD
Email: dhite@ugm.ac.id
Tel No: +62 822 -255-88822

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection first identified in December 2019 in Wuhan, China. Many individuals infected with COVID-19 may be asymptomatic or present with flu-like symptoms (1). The course of the disease can range from mild to severe (2). The infection is characterized by a substantial inflammatory burden (3), and a subset of patients, roughly 14%, may require hospitalization due to severe disease manifestations. Among these hospitalized individuals, approximately 5% necessitate intensive care.

Bacterial coinfections and secondary infections have also been a concern in COVID-19 patients. Bacterial coinfections were seen in 3.5% of COVID-19 patients, while secondary bacterial infections were found in 14.3% of the patients (4). Notably, the rate of secondary bacterial infections was higher among the critically ill patients. Such infections complicate the clinical scenario since early and accurate identification is critical for appropriate antibiotic administration. Overuse of antibiotics can foster resistance, whereas delay can worsen outcomes. Despite the importance, traditional microbiological assays like blood cultures are time-consuming, underscoring the need for rapid diagnostic markers (5).

In the realm of diagnostic markers, NLR has emerged as a potent indicator of inflammation in various diseases, from inflammatory bowel disease (6), diabetes mellitus (7), gastrointestinal problem (8) and cardiac conditions (9), irritable bowel syndrome (10), thyroiditis (11) to SARS-CoV-2 infections (12). Moreover, MPV and CRP are well-established markers linked with inflammation in myriad conditions such as type 2 DM (13), diabetic nephropathy (14), hypothyroidism (15), infections (16), nasal polyps (17), vertebral discopathies (18), rheumatoid arthritis (13), and in ICU patients (21). Similarly, CRP based inflammatory markers have been reported to be associated with various inflammatory conditions such as diabetic nephropathy (22), thyroiditis (23), diabetic neuropathy (24) and hepatitis (25)

Against this background, the potential of indicators such as PCT, CRP-to-MPV ratio, and NLR becomes increasingly evident in forecasting secondary bacterial infections in patients with COVID-19. The significance of examining these markers is accentuated by their linkage with inflammation, especially considering the intense inflammatory response characterizing COVID-19. There exists a compelling rationale to delve deeper into these markers, evaluating their diagnostic and prognostic capacities in relation to secondary bacterial infections in patients afflicted with COVID-19.

## MATERIALS AND METHODS

### Study Design

This study employed a retrospective approach, reviewing the medical records of COVID-19 patients admitted to the hospital from April 2020 to April 2021. Patients were consistently chosen using a consecutive sampling technique, ensuring every eligible individual during the stated period was considered.

To enhance the robustness of our study, we determined the minimum sample size required for each variable. Drawing from the research by Langford BJ et al. (4), which identified a 14.3% proportion of COVID-19 patients with secondary infections, we applied the diagnostic test formula. Using a one-sided hypothesis with a type I error of 5%, the calculation followed as:
Za = 1.64 (for 5% alpha),
P = 0.14 (14.3% secondary infection rate),
Q = 0.86,
d = 0.06 (6% absolute error).

Applying the formula,
$n = (1.64^2 \times 0.14 \times 0.86) / 0.06^2$
yields a required sample size of approximately 90 participants.

### Inclusion and Exclusion Criteria

Inclusion criteria for this study were as follows: patients with confirmed COVID-19 diagnoses, with or without secondary bacterial infections identified through bacterial culture examinations, no history of shock other than septic shock, no hematological malignancies or solid tumors, and no steroid or immunosuppressive therapy received within seven days prior to COVID-19 diagnosis. Exclusion criteria were incomplete data records.

### Data Collection

Demographic data and clinical data were collected from the medical records. Clinical data included COVID-19 clinical manifestations and severity, PCT levels, CRP levels, MPV, NLR, bacterial culture results, and antibiotic susceptibility tests. All samples were procured within 24 hours of admission for uniformity, while flow cytometry and the Sysmex XN 1000 were used for precise leukocyte and hematological evaluations, respectively, and the Cobas pro instrument was employed for accurate quantification of biomarkers like CRP and PCT.

### Data Analysis

Before any further statistical analysis, the data's normality was assessed using the Kolmogorov-Smirnov test. Data that passed the normality test ($p>0.05$ in the Kolmogorov-Smirnov) were considered to follow a normal distribution. Based on the results of this normality analysis, differences between groups were assessed using t-tests for normally distributed data. For data that did not adhere to a normal distribution, Mann-Whitney tests were employed.

The significance threshold for statistical significance was set at $p<0.05$ with a 95% confidence interval. The optimal cut-off values for predicting secondary bacterial infections in COVID-19 patients were determined using receiver operating characteristic (ROC) curve and area under the curve (AUC) analyses. The significance level for the ROC/AUC analyses was also set at $p<0.05$.

Multivariate analysis was performed using logistic regression to ascertain the effects of multiple factors on the likelihood of developing secondary bacterial infections in COVID-19 patients

### Ethical Clearance

This study was approved by the Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, with the reference number KE/FK/0651/EC/2021.

## RESULTS

328 COVID-19 patient records were obtained during the study period; however, only 98 patient records with comprehensive data that met the inclusion and exclusion criteria were analyzed. The Kolmogorov-Smirnov normality test revealed that all variables, with the exception of the lymphocyte count, were not normally distributed. Table I displays the baseline characteristics of the study subjects.

**Table I: Characteristics of the Study Subjects**

| Variable | n (%) | Mean ± SD |
|---|---|---|
| Age (years) | | 46.44 ± 12.713 |
| Gender | | |
| - Male | 56 (57.1%) | |
| - Female | 42 (42.9%) | |
| COVID-19 severity | | |
| - Moderate | 27 (27.6%) | |
| - Severe | 41 (41.8%) | |
| - No information available | 30 (30.6%) | |
| Secondary infection | | |
| - With secondary infection | 22 (22.4%) | |
| - Without secondary infection | 76 (77.6%) | |
| Discharge status | | |
| - Alive | 81 (82.7%) | |
| - Died | 17 (17.3%) | |
| Leukocyte count | | 8.8675 ± 4.50095 |
| Neutrophil count | | 74.3064 ± 12.17198 |
| Lymphocyte count | | 17.0153 ± 8.52977 |
| C-reactive protein level | | 107.2041 ± 368.5369 |
| Mean platelet volume | | 8.5878 ± 3.47976 |
| Procalcitonin level | | 1.1259 ± 4.08127 |
| Neutrophil-to-lymphocyte ratio | | 6.2523 ± 4.86220 |
| C-reactive protein-to-mean platelet volume ratio | | 8.8878 ± 14.20010 |

In this study, the mean age of COVID-19 patients was 46.44 12.713, and 56 (57.1%) of the cases were male. The most prevalent severity of COVID-19 in this study was severe, with 41 (41.8%) cases, as the study hospital was the leading referral center for patients with severe and critical conditions. In addition, the majority of patients (77, or 77.6%) did not have confirmed secondary bacterial infections.

Several factors may explain why COVID-19 patients lack confirmed secondary infections. Patients referred to the study hospital may have previously received antibiotics, resulting in negative blood culture results at the study hospital. Alternately, the virulence of the COVID-19 infection in certain patients may have precluded the collection of blood cultures.

### ROC Curve of Procalcitonin

The ROC AUC analysis of PCT (Figure 1A) yielded an AUC of 0.535 with a p-value of 0.638 (statistically not significant). Youden's Index analysis revealed that a PCT value above 3.59 resulted in a sensitivity of 18.18% and a specificity of 97.37% for predicting secondary bacterial infections in COVID-19 patients.

### ROC Curve of CRP to MPV Ratio

The ROC AUC analysis of the CRP to MPV ratio (Figure 1B) yielded an AUC of 0.587 with a p-value of 0.198 (statistically not significant). Youden's Index analysis revealed that a CRP to MPV ratio above 3.59 resulted in a sensitivity of 77.27% and a specificity of 48.68% for predicting secondary bacterial infections in COVID-19 patients.

### ROC Curve of Neutrophil to Lymphocyte Ratio

The ROC AUC analysis of the neutrophil to lymphocyte ratio resulted in an AUC of 0.674 with a p-value of 0.002. Youden's Index analysis revealed that a neutrophil to lymphocyte ratio above 3.64 provided a sensitivity of 90.91% and a specificity of 44.74% for predicting secondary bacterial infections in COVID-19 patients (Figure 1C).

Except for the neutrophil count, lymphocyte count, and neutrophil to lymphocyte ratio, Table II shows that there were no significant differences between the groups with and without secondary bacterial infections. In bacterial infections, an elevated white blood cell count and a leftward shift in the differential count are frequently observed.

Using the Chi-square test, the bivariate analysis of Table III revealed that only the neutrophil-to-lymphocyte ratio

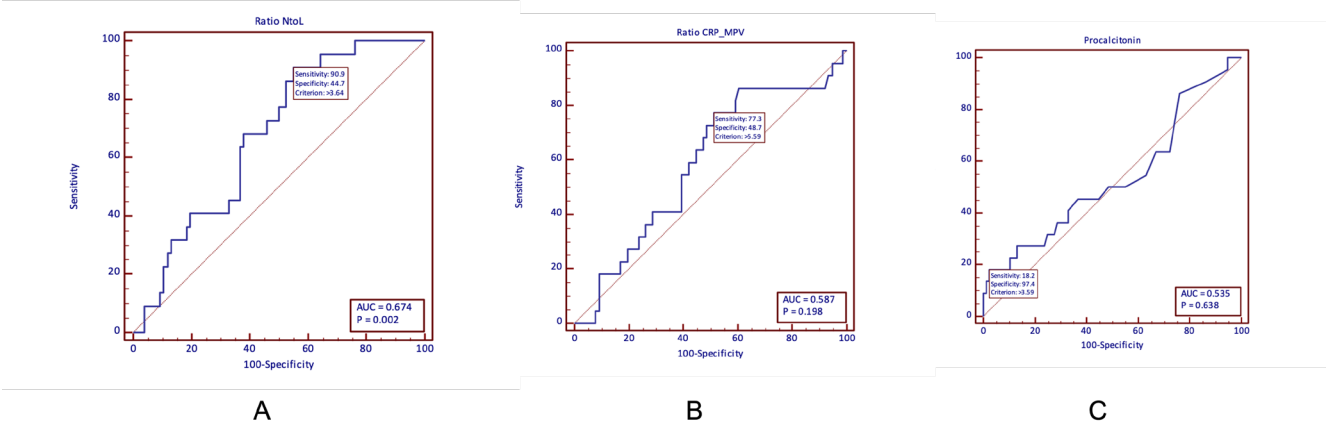


**Figure 1: ROC curve for Procalcitonin, CRP to MVP ratio and NLR**

**Table II: Comparison of Study Subjects' Characteristics with and without Secondary Infection**

| Variable | With Secondary Infection (n=22) | Without Secondary Infection (n=77) | p-value |
|---|---|---|---|
| Age (years) | 48.00 | 49.93 | 0.779 |
| Age (in years, n) | | | |
| - <55 | 47 | 13 | 0.816 |
| - >55 | 29 | 9 | |
| Gender (n)* | | | 0.093 |
| - Male | 16 | 40 | |
| - Female | 6 | 36 | |
| COVID-19 severity* | | | - |
| - Moderate | 5 | 36 | |
| - Severe | 11 | 16 | |
| - No information available | 6 | 24 | |
| Discharge status* | | | 0.907 |
| - Alive | 18 | 63 | |
| - Died | 4 | 13 | |
| Leukocyte count | 55.66 | 47.72 | 0.249 |
| Neutrophil count | 63.57 | 45.43 | 0.008 |
| Lymphocyte count** | 13.0636 ± 5.47205 | 18.1592 ± 8.93355 | 0.013 |
| C-reactive protein | 56.52 | 47.47 | 0.188 |
| Mean platelet volume | 46.73 | 50.30 | 0.603 |
| Procalcitonin | 52.16 | 48.73 | 0.618 |
| Neutrophil-to-lymphocyte ratio | 62.73 | 45.67 | 0.013 |
| C-reactive protein-to-mean platelet volume ratio | 56.09 | 47.59 | 0.217 |

Note: *Analyzed using Fisher exact test, **Analyzed using T-test.

**Table III: Characteristics of Study Subjects by Presence or Absence of Secondary Infection**

| Variable | Without Secondary Infection (n=77) | With Secondary Infection (n=22) | p-value |
|---|---|---|---|
| Age (in years, n) | | | |
| - <55 | 47 | 13 | 0.816 |
| - >55 | 29 | 9 | |
| Gender (n)* | | | 0.093 |
| - Female | 36 | 6 | |
| - Male | 4 | 16 | |
| Neutrophil-to-lymphocyte ratio* | | | 0.03 |
| - <3.64 | 33 | 2 | |
| - >3.64 | 43 | 20 | |
| C-reactive protein | | | 0.05 |
| - <49 | 35 | 5 | |
| - >49 | 41 | 17 | |
| Mean platelet volume | | | 0.272 |
| - <11.2 | 66 | 17 | |
| - >11.2 | 10 | 5 | |
| C-reactive protein-to-mean platelet volume ratio* | | | 0.039 |
| - <3.45 | 29 | 3 | |
| - >3.45 | 47 | 19 | |
| Procalcitonin* | | | 0.073 |
| - <3.59 | 74 | 19 | |
| - >3.59 | 2 | 3 | |

Note: *Analyzed using Fisher exact test.

and CRP levels were substantially different between COVID-19 patients with and without secondary bacterial infections.

Table IV offers a detailed comparison between univariate and multivariate models regarding various predictors linked to secondary infections in COVID-19 patients. In the multivariate model, females demonstrated a notable increase in risk, with a 4.3-fold higher likelihood of secondary infections compared to males, substantiated by an odds ratio of 4.3 and a p-value of 0.022. Similarly, patients with a NLR of ≤3.64 exhibited an 8.01-fold elevated risk, a slight increase from the univariate analysis. On the other hand, while the C-reactive protein-to-mean platelet volume ratio showed a 3.09-fold increase in risk in the multivariate context, it wasn't statistically significant. Procalcitonin, despite a 2.65-fold elevated risk in the multivariate model, lacked overall statistical significance.

Other parameters, such as the severity of COVID -19 and conditions like hypertension and diabetes mellitus, were evaluated but didn't demonstrate statistically significant variations in risk. Thus, the multivariate regression analysis highlights the importance of gender and NLR in predicting secondary infections in COVID-19 patients, suggesting the need for clinicians to consider these markers for a thorough risk assessment.

## DISCUSSION

This study hasn't confirmed PCT's role in differentiating between solely viral and secondary bacterial infections in COVID-19 patients. PCT is produced via: 1) the classical pathway from thyroid gland, lungs, and small intestine cells; and 2) the alternative pathway, influenced by endotoxins and potentially by cytokine storms in COVID-19, leading to high PCT levels without bacterial endotoxin triggers (26).

PCT levels vary due to factors like systemic infections, fungal infections, malaria, trauma, neonates' early life, and conditions like cardiogenic shock and severe pancreatitis (27,28). Conversely, low PCT doesn't always exclude bacterial/fungal infections, as early or localized infections might yield false negatives (28). The study couldn't account for all influencing factors, affecting its conclusions on PCT's diagnostic value in COVID-19 patients.

C-reactive protein has not yet been demonstrated in this study as a distinguishing marker between viral

**Table IV: Multivariate analysis**

| Variable | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR[1] | 95% CI[1] | p-value | OR1 | 95% CI[1] | p-value |
| Gender | | | | | | |
| Male | — | — | | — | — | |
| Female | 2.4 | 0.88, 7.29 | 0.1 | 4.3 | 1.31, 16.5 | 0.022 |
| Age (years) | | | | | | |
| <55 | — | — | | — | — | |
| ≥ 55 | 1.12 | 0.42, 2.94 | 0.8 | 1.14 | 0.34, 3.76 | 0.8 |
| Neutrophil-to-lymphocyte ratio | | | | | | |
| <3,64 | — | — | | — | — | |
| ≥ 3.64 | 7.67 | 2.04, 50.2 | 0.009 | 8.01 | 1.82, 59.0 | 0.015 |
| C-reactive protein-to-mean platelet volume ratio | | | | | | |
| < 3.45 | — | — | | — | — | |
| ≥ 3.45 | 3.91 | 1.20, 17.7 | 0.04 | 3.09 | 0.76, 16.1 | 0.14 |
| Procalcitonin | | | | | | |
| <3,59 | — | — | | — | — | |
| ≥ 3,59 | 1.43 | 0.54, 3.74 | 0.5 | 2.65 | 0.79, 9.66 | 0.12 |
| Covid-19 severity | | | | | | |
| Moderate | — | | — | — | | |
| Severe-critical | 0.87, 6.32 | 0.1 | 2.16 | 0.71, 7.03 | 0.2 | |
| Comorbidity | | | | | | |
| No | — | — | | — | — | |
| Yes | 1.8 | 0.28, 35.0 | 0.6 | 4.82 | 0.45, 125 | 0.2 |
| Hypertension | | | | | | |
| No | — | — | | — | — | |
| Yes | 1.5 | 0.51, 4.18 | 0.4 | 1.7 | 0.46, 6.32 | 0.4 |
| Diabetes Mellitus | | | | | | |
| No | — | — | | — | — | |
| Yes | 0.83 | 0.22, 2.62 | 0.8 | 0.46 | 0.10, 1.81 | 0.3 |

1 OR = Odds Ratio, CI = Confidence Interval

infections and secondary bacterial infections in patients with COVID-19 viral infections due to the presence of numerous uncontrolled factors that can increase CRP levels in the absence of infection. Tang et al. (2018) report that baseline serum hs-CRP levels increase with age and are substantially higher in men than in healthy women (29). Smokers have substantially elevated concentrations of circulating inflammatory markers such as CRP, IL-6, and fibrinogen compared to nonsmokers (30). Patients with cirrhosis devoid of infection have elevated circulating IL-6 concentrations and TNF receptor expression, resulting in elevated basal CRP levels (31). Pro-inflammatory cytokines, such as IL-6, are among the newly discovered compounds expressed in human adipose tissue, causing a positive correlation between increasing adipose tissue and basal CRP levels (32). According to research, CRP levels rise in 27.6% of the sample population. Overweight individuals (body mass index [BMI] 25-29.9 kg/m2) and those with obesity (BMI >30 kg/m2) are more likely to have elevated CRP levels than normal-weight individuals (BMI 25) (32).

MPV denotes average platelet size in blood, with a typical range of 7.2 to 11.7 fL. It's influenced by cytokines like thrombopoietin, IL-6, and IL-3, which control megakaryocyte ploidy and platelet size. Larger, younger platelets emerge from heightened platelet activation and MPV reflects their production rate (33). Various factors, such as age, certain diseases, and medications, can influence platelet indices. The study couldn't control all these factors, affecting its conclusions on MPV's role in distinguishing viral from bacterial infections.

The link between COVID-19 and platelet indices is ambiguous. The SARS-CoV-2 virus might affect hematopoietic cells, causing thrombocytopenia. Histological data from COVID-19 patients show significant inflammatory reactions, which might lead to DIC and thrombosis. Lung inflammation and extended oxygen therapy can also hinder platelet generation (34). Increased platelet use and diminished production can result in thrombocytopenia (35). A fall in platelet count triggers the body to produce larger platelets, elevating MPV, and resulting in varied platelet sizes (33). In COVID-19 patients, rapid viral replication triggers inflammation, causing lung tissue damage and a possible cytokine storm (35). Certain cytokines influence megakaryocyte ploidy, potentially increasing MPV. This widespread inflammation can lead to Acute Respiratory Distress Syndrome, multiorgan failure, and even death (35).

The neutrophil-to-lymphocyte ratio was particularly notable as a significant predictor, especially in the multivariate model. Inflammation involves the recruitment of various inflammatory cells to eliminate pathogens (36). Neutrophils also produce extracellular traps (NETs) in response to bacteria, which have antimicrobial properties and play a vital role in combating bacterial infections (37). They recognize opsonized pathogens, facilitating phagocytosis and eliminating them using antimicrobial molecules (36).

Apoptosis in sepsis is clinically relevant, especially in lymphocytes. Several studies have emphasized the correlation between lymphocyte apoptosis and sepsis severity (38,39). Moreover, delayed neutrophil apoptosis can lead to tissue injury and increase mortality in sepsis patients. Persistently activated neutrophils can cause damage to tissues, and a high neutrophil-to-lymphocyte ratio can help distinguish between secondary bacterial and solitary viral infections in patients (40).

In light of the multifaceted inflammatory response and platelet activation related to COVID-19, this study offers insights that could refine clinical choices by elucidating the implications of altered NLR indices. These patterns might facilitate early detection of secondary bacterial infections, optimizing antibiotic treatments and potentially enhancing patient outcomes. Nevertheless, our single-center research carries inherent limitations, emphasizing the need for multi-center studies to obtain more generalizable results.

Comparing our findings with prior research reveals varying outcomes, underscoring the importance of ongoing research in understanding COVID-19's relationship with bacterial pathogens. Implementing our results in clinical settings could enable more precise patient care, particularly in differentiating between viral and bacterial infections. Such insights can promote targeted therapies, curb unnecessary antibiotic usage, and bolster patient recovery.

However, the study's research question remains inconclusive. Potential reasons include a possibly inadequate sample size of 98 subjects and prior antibiotic treatments received by hospitalized COVID-19 patients. The inclusion of patients with mixed infections and undefined timing of blood culture collections post-antibiotic administration might have influenced the observed results. Future studies should consider these factors for more accurate outcomes.

## CONCLUSION

In conclusion, our research indicates that an NLR of 3.64 or higher serves as a reliable predictor for the emergence of secondary bacterial infections within a week in COVID-19 patients. To enhance the validity of these findings and mitigate the limitations of this study, we recommend undertaking a prospective cohort study for a more rigorous research design and to reduce potential biases.

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