Role of Procalcitonin as a Prognostic Biomarker in Hospitalized COVID-19 Patients: A Comparative Analysis

Biomarker Insights
Volume 20: 1–10
© The Author(s) 2025
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/11772719241296624

Shahin Isha[1*], Lekhya Raavi[1*], Sadhana Jonna[1], Hrishikesh Nataraja[1], Emily C Craver[2], Anna Jenkins[1], Abby J Hanson[1], Prasanth Balasubramanian[3], Arvind Balavenkataraman[3], Aysun Tekin[4], Vikas Bansal[4], Swetha Reddy[1], Sean M Caples[5], Syed Anjum Khan[6], Nitesh K Jain[6], Abigail T LaNou[7], Rahul Kashyap[8], Rodrigo Cartin-Ceba[9], Ricardo Diaz Milian[1], Carla P Venegas[1], Anna B Shapiro[1], Anirban Bhattacharyya[1], Sanjay Chaudhary[1], Sean P Kiley[1], Quintin J Quinones[1], Neal M Patel[1], Pramod K Guru[1], Pablo Moreno Franco[1], Archana Roy[10] and Devang K Sanghavi[1]

[1]Department of Critical Care Medicine, Mayo Clinic in Florida, Jacksonville, FL, USA. [2]Department of Quantitative Health Sciences, Mayo Clinic in Florida, Jacksonville, FL, USA. [3]Department of Pulmonary and Critical Care, Mayo Clinic in Florida, Jacksonville, FL, USA. [4]Department of Critical Care Medicine, Mayo Clinic Rochester, MN, USA. [5]Division of Pulmonary and Critical Care, Mayo Clinic Rochester, MN, USA. [6]Department of Critical Care Medicine, Mayo Clinic Health System in Mankato, Mankato, MN, USA. [7]Emergency Medicine and Critical Care, Mayo Clinic Health System, Eau Claire, WI, USA. [8]Department of Anesthesia and Critical Care Medicine, Mayo Clinic Rochester, MN, USA. [9]Department of Critical Care Medicine, Mayo Clinic Arizona, Phoenix, AZ, USA. [10]Division of Hospital Internal Medicine, Mayo Clinic, Jacksonville, FL, USA.

ABSTRACT

BACKGROUND: Procalcitonin (PCT) is recognized as an inflammatory biomarker, often elevated in COVID-19 pneumonia alongside other biomarkers. Understanding its association with severe outcomes and comparing its predictive ability with other biomarkers is crucial for clinical management.

OBJECTIVES: This retrospective multicenter observational study aimed to investigate the association between PCT levels and adverse outcomes in hospitalized COVID-19 patients. Additionally, it sought to compare the predictive performance of various biomarkers.

DESIGN: The study analyzed data from the Society of Critical Care Medicine (SCCM) Viral Infection and Respiratory Illness Universal Study (VIRUS) registry, comprising COVID-19 patients hospitalized across multiple Mayo Clinic sites between March 2020 and June 2022.

METHODS: A total of 7851 adult COVID-19 patients were included. Patients were categorized into 6 groups based on the worst WHO ordinal scale. Multivariate models were constructed using peak biomarker levels within 72 hours of admission, adjusted for confounders.

RESULTS: Elevated PCT levels were independently associated with increased odds of adverse outcomes, including ICU admission (adjusted odds ratio [aOR] 1.32, 95%CI 1.27-1.38), IMV requirement (aOR 1.35, 95%CI: 1.28-1.42), and in-hospital mortality (aOR 1.30, 95%CI: 1.22-1.37). A 3.48-fold increase in IMV requirement and 3.55 times increase in in-hospital mortality were noted with peak PCT $\geq$ 0.25 ng/ml. Similar associations were observed with other biomarkers like NLR (AUC 0.730), CRP, IL-6, LDH (AUC 0.800), and D-dimer (AUC 0.719). Models incorporating NLR, LDH, D-dimer, and PCT demonstrated the highest predictive accuracy, with a combined model exhibiting an area under the curve (AUC) of 0.826 (95%CI 0.803-0.849).

CONCLUSIONS: Higher PCT levels were significantly linked to worse outcomes in COVID-19 patients, emphasizing its potential as a prognostic marker. Biomarker-based predictive models, particularly those including PCT, showed promising utility for risk assessment and clinical decision-making. Further prospective studies are warranted to validate these findings on a larger scale.

KEYWORDS: COVID-19, procalcitonin, biomarker, predictive model, clinical outcomes

RECEIVED: July 11, 2024. **ACCEPTED:** October 9, 2024.

TYPE: Original Research

CORRESPONDING AUTHOR: Devang K Sanghavi, Department of Critical Care Medicine, Mayo Clinic in Florida, 4500 San Pablo Rd S, Jacksonville, FL, USA. Email: sanghavi.devang@mayo.edu

* Both contributed equally as first authors for the manuscript.

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

Introduction

Severe Acute Respiratory Distress Syndrome–related coronavirus (SARS-CoV-2) affects the upper and lower bronchial epithelium, which triggers regional inflammatory cascades that entail neutrophil recruitment, T lymphocyte trafficking and activation of innate monocytes.[1] The clinical manifestations of such inflammatory process vary from mild symptoms such as fever, dry cough, dyspnea, myalgia, sore throat, and headache, etc., to severe and emergent manifestations, including confusion, chest pain, hypoxemia, pneumonia, and other complications requiring intensive care unit (ICU) admission and invasive mechanical ventilation (MV).[2-4] COVID-19 infection often leads to a hyperinflammatory state, leading to the release of TNF-alpha, interleukin-1, interleukin-6, and other proinflammatory cytokines in extremely high quantities, considerably enhancing the creation of reactive oxygen species, leading to tissue injury and vascular damage.[5] Patients typically affected by such hyperinflammatory responses demonstrate increased disease severity and worse clinical outcomes.[6] In order to improve patient outcomes by potentially curbing this inflammatory response, several treatment options have been included in clinical management, such as systemic corticosteroids, antivirals (such as remdesivir), immunomodulators (such as baricitinib and tocilizumab) which have shown significant benefit in improving patient outcomes.[7-12]

Given the wide range of severity and possible precipitous worsening of COVID-19 symptoms, there is always a need for prompt diagnosis of early danger signs, risk stratification, and appropriate treatment. Challenged by an initial strain on healthcare resources worldwide during the early pandemic, extensive work has been done to create various COVID-19 severity scales, and treatment strategies have evolved over several waves of the COVID-19 pandemic. With an initial focus on pre-existing comorbid factors, studies have explored the prognostic utility of different biomarkers on COVID-19 patients, including C-reactive protein (CRP), Lactate dehydrogenase (LDH), D-dimer, neutrophil-lymphocyte ratio (NLR), etc.[13-15] However, with non-uniform institutional practices, availability issues, varying sample sizes, there remains a need for further research and head-to-head comparison between these biomarkers.

Procalcitonin (PCT), on the other hand, is a biomarker that is elevated in bacterial infection and is often used to differentiate bacterial infection from viral infection.[16,17] The use of PCT in identifying superimposed bacterial coinfection in COVID-19 disease is controversial and is shown to be a non-specific marker in various studies.[18-20] Instead, an elevation in PCT level has been linked with COVID-19 disease severity, with multiple studies exploring its association with mortality, the need for invasive ventilation, ICU admission, and other patient-centric outcomes.[13,21] Similar to other biomarkers, there is a growing need for further research to fully understand the implications of using PCT as a predictor of severe outcomes in the COVID-19 population. While individual inflammatory biomarkers have been linked to poor outcomes in COVID-19, research on combining them into a single predictive model is limited. This study also attempts to address this gap by developing a multimodal model to predict invasive mechanical ventilation or in-hospital mortality and evaluate biomarker trends across different pandemic waves to inform risk stratification and resource allocation.

Materials and Methods

Ethics: Ethics approval for this study was issued by the Mayo Clinic Institutional Review Board under the exempt category. Access to the multicenter Mayo Clinic data was granted through "Viral Infection and Respiratory Illness Universal Study [VIRUS]: COVID-19 Registry and Validation of C2D2 (Critical Care Data Dictionary)" under IRB ID 20-002610. The need for informed consent was waived by the IRB due to its retrospective design, data anonymity, and non-interventional nature.

Patient population

We screened 8098 COVID-19 patients hospitalized across different Mayo Clinic sites (Florida, Rochester, Arizona, Mankato, and Eu Claire) between March 2020 and June 2022, of which 7851 were included in the final analysis. Patients were excluded if they were less than 18 years of age at admission or had missing demographic/ outcome variables. The study cohort was stratified into 6 groups based on the highest WHO ordinal scale score during hospital stay (WHO Scale 3: Hospitalized, no oxygen therapy; WHO Scale 4: hospitalized, oxygen mask or nasal prongs; WHO Scale 5: hospitalized, noninvasive mechanical ventilation [NIMV] or high-flow nasal cannula [HFNC], WHO Scale 6: hospitalized, intubation and invasive mechanical ventilation [IMV], WHO Scale 7: hospitalized, IMV and with additional support such as pressors or extracorporeal membranous oxygenation [ECMO], WHO Scale 8: deceased).[22]

Data collection

Patients' information about the demographics, comorbidities, immunological, hematological, and laboratory parameters and outcomes were collected via the Society of Critical Care Medicine (SCCM) Viral Infection and Respiratory Illness Universal Study (VIRUS) registry (IRB ID 20-0022610).[23-26] The VIRUS registry is an observational registry collecting cross-sectional data of all eligible patients admitted with COVID-19 at the participating sites. The VIRUS registry contains demographics, comorbidities, patient outcomes, and serial observation data such as daily labs, vital parameters, and therapeutics. We used the worst (highest values) of different inflammatory biomarkers within 72 hours of admission to estimate our primary and secondary outcome models. The primary

composite outcome was in-hospital mortality rate or invasive mechanical ventilation. The secondary outcomes were hospital length of stay, ICU requirement, invasive ventilation, vent-free days, ECMO requirement, and in-hospital mortality.

Statistical analysis

Statistical analysis was performed using R Statistical Software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized as median (Q1, Q3), while ordinal and categorical variables were reported as frequency (percentage). *P*-values were derived from a Kruskal-Wallis test for continuous and ordinal variables or a Fisher's exact test for categorical variables. Logistic regression models were used for binary outcomes, and linear regression models were used for continuous outcomes. Multivariable models were adjusted for age, sex, race, ethnicity, hypertension, diabetes, chronic lung disease, chronic kidney disease/dialysis, and congestive heart failure. Multivariable analysis was not performed for ECMO requirement outcome, given its rare nature. *P*-values $< .006$ are considered statistically significant after applying a Bonferroni correction for multiple testing.

A categorical version of PCT was modeled to predict secondary outcomes of interest. This categorical predictor was determined by the optimal cut-point value (0.25 ng/ml) for PCT and corresponds to the most significant difference in-hospital mortality rates. Multivariable models were adjusted for age, sex, race, ethnicity, hypertension, diabetes, chronic lung disease, chronic kidney disease/dialysis, and congestive heart failure.

We adopted multivariate logistic regression models to explore the utility of various biomarkers in COVID-19 prognostication. Due to distributional skewness, biomarker measurements were considered on the square root or base-2 logarithm scale (Supplemental Table 1). Our outcome variable for these models was a composite of invasive mechanical ventilation or in-hospital mortality. Separate base models were built for individual biomarkers due to differences in sample size. Base model predictors included age, sex, race, ethnicity, hypertension, diabetes, chronic lung disease, chronic kidney disease, and congestive heart failure. Individual biomarker models were built on combining base models with biomarkers of interest.

In an attempt to explore the difference in serial PCT trends across our primary outcome of interest, we plotted the median PCT value over the hospitalization course up to day 10 of hospitalization, beyond which there was a significant drop in sample size. A graphical representation of the biomarker utilization trend was created based on the percentage of patients undergoing testing for each type of biomarker during the respective quarter of the year. The timeline was broken down into 3 waves of COVID-19 (Pre-Delta, Delta, and Omicron) based on a recent publication using a similar methodology.[27] We also performed additional exploratory analyses to identify any differences in patient characteristics or outcomes across 3 different COVID strain predominant waves.

Results

From March 2020 to June 2022, 8098 COVID-19 patients were admitted to the Mayo Clinic. Of these, 7851 patients met the inclusion criteria. The overall cohort was stratified into 6 groups based on the worst WHO ordinal scale: WHO Scale 3 (n = 1584), WHO Scale 4 (n = 3203), WHO Scale 5 (n = 1885), WHO Scale 6 (n = 89), WHO Scale 7 (n = 502) and WHO Scale 8 (n = 588) based on the severity of COVID-19 infection (WHO ordinal scale). The baseline demographics, laboratory parameters, and outcomes are described in Supplemental Tables 2, and 3, respectively. We noted a significant difference in the age distribution across the worst WHO scale categories, with WHO group 8 having the highest median age. Similarly, we noted significant differences across the groups in terms of gender, race, ethnicity, BMI, and prevalence of comorbidities. There were incremental changes in the COVID-19 vaccination rate across the WHO scale groups, with WHO scale 8 having the lowest (14.5%) and scale 3 having the highest rate (55.7%). We also noted an increasing trend in Dexamethasone use across the WHO groups, with WHO scale 8 and WHO scale 5 having the highest use of dexamethasone (76.7% and 76.3%, respectively; Supplemental Table 2). A graded decrease in the lowest PaO2/FiO2 ratio and an increase in the highest sequential organ failure assessment (SOFA) score during hospitalization was noted with a higher WHO scale score. The worst level of each biomarker within 72 hours of admission was also compared across various WHO groups. There was a consistent increase in the median level of each inflammatory marker with a worsening WHO scale score (Supplemental Table 3). Supplemental Table 3 also summarizes the differences in patient outcomes across WHO groups.

Upon exploring the association between the procalcitonin level of individual outcomes of interest, we noted that with each unit increase in the log of highest PCT, there was 1.32 times increase in ICU admission risk (aOR 1.32, 95% 1.27-1.38), 1.35 times increase in IMV requirement (aOR 1.35, 95CI: 1.28-1.42), and 1.30 times increase of in-hospital mortality (aOR 1.30, 95%CI: 1.22-1.37; Table 1). Table 1 also demonstrates the comparison of patient outcomes across an optimum cutoff of 0.25 ng/ml. We noted a 3.48-fold increase in IMV requirement and 3.55 times increase in in-hospital mortality with peak PCT $\geq$ 0.25 ng/ml. Figure 1 illustrates the serial PCT trends over the period of hospitalization. The median PCT value for patients who required IMV or had in-hospital mortality was consistently higher over the hospitalization days compared to patients who did not have the composite outcome.

While evaluating the association of PCT and other biomarkers with the risk of intubation or in-hospital mortality, we performed multivariate analyses, adjusting for confounders like

Table 1. Association of peak Procalcitonin level (highest level within 72 hours of admission) with patient outcomes.

PROCALCITONIN ASSOCIATION WITH PATIENT OUTCOMES- CONTINUOUS PREDICTOR						
	MEDIAN (MIN, MAX) OR NO. (%)		UNADJUSTED ANALYSIS		MULTIVARIABLE ANALYSIS	
OUTCOME	TOTAL (N = 3491)	ASSOCIATION MEASURE	ESTIMATE (95%CI)	*P*-VALUE	ESTIMATE (95%CI)	*P*-VALUE
IMV requirement	410 (11.7%)	Odds ratio	1.33 (1.27, 1.39)	<.001	1.35 (1.28, 1.42)	<.001
Hospital mortality	257 (7.4%)	Odds ratio	1.29 (1.22, 1.36)	<.001	1.30 (1.22, 1.37)	<.001
ICU admission	888 (25.4%)	Odds ratio	1.32 (1.27, 1.37)	<.001	1.32 (1.27, 1.38)	<.001
Hospital length of stay (days)	5.8 (0.2, 209.0)	Regression coefficient	0.15 (0.13, 0.17)	<.001	0.15 (0.13, 0.17)	<.001
ECMO requirement	52 (1.5%)	Odds ratio	1.26 (1.13, 1.40)	<.001	N/A	N/A
PROCALCITONIN ASSOCIATION WITH PATIENT OUTCOMES- CATEGORICAL PREDICTOR						
OUTCOME	PCT < 0.25 NG/ML (N = 2212)	PCT ⩾ 0.25 NG/ML (N = 1279)	ESTIMATE (95%CI)	*P*-VALUE	ESTIMATE (95%CI)	*P*-VALUE
IMV requirement	152 (6.9%)	258 (20.2%)	3.42 (2.77, 4.25)	<.001	3.48 (2.79, 4.35)	<.001
Hospital mortality	89 (4.0%)	168 (13.1%)	3.61 (2.77, 4.73)	<.001	3.55 (2.70, 4.69)	<.001
ICU admission	403 (18.2%)	485 (37.9%)	2.74 (2.35, 3.21)	<.001	2.74 (2.33, 3.22)	<.001
Hospital length of stay (days)	5.0 (0.7, 194.6)	7.3 (0.2, 209.0)	0.58 (0.51, 0.66)	<.001	0.57 (0.49, 0.65)	<.001
ECMO requirement	15 (0.7%)	37 (2.9%)	4.36 (2.43, 8.23)	<.001	N/A	N/A

Abbreviation: CI, confidence interval.
Logistic regression models were used for binary outcomes (IMV requirement, hospital mortality, ICU admission, and ECMO requirement). Hospital length of stay was evaluated using linear regression models. Due to distributional skewness, procalcitonin and hospital length of stay were considered on the base-2 logarithm scale. Multivariable models were adjusted for age, sex, race, ethnicity, hypertension, diabetes, chronic lung disease, chronic kidney disease/dialysis, and congestive heart failure. Multivariable analysis was not performed for ECMO requirement outcome, given its rare nature.
The optimal cutpoint was calculated using the hospital mortality outcome. The cut-off value of 0.25 ng/ml corresponds to the most significant difference in-hospital mortality.

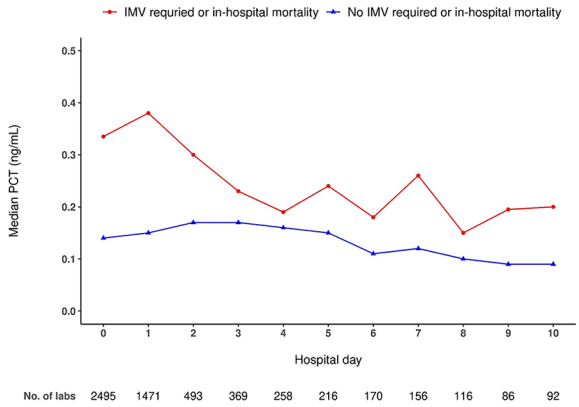

Figure 1. Comparison of PCT trends during hospital stay by composite outcome groups.

age, gender, race, ethnicity, and comorbidities. We observed that with every 1-unit increase in the log of the highest PCT value, the odds of having a composite outcome increased by 1.36 times (adjusted OR 1.36, 95%CI 1.30-1.42, $P < .001$; Table 2). The correlation with worse hospital outcomes was noticed with most other biomarkers, such as CRP (Adjusted OR 1.16, 95%CI 1.14-1.18), IL-6 (Adjusted OR 1.36, 95% 1.28-1.45), LDH (Adjusted OR 5.99, 95%CI 5.03-7.17), Ferritin (Adjusted OR 1.43, 95%CI 1.37-1.51), D-dimer (Adjusted OR 1.43, 95%CI 1.37-1.51), but not with Fibrinogen (Adjusted OR 1.00, 95%CI .98-1.02; Table 2). We also evaluated the performance of various predictive models built using individual biomarkers combined with a base model (demographics and comorbidities). There was significant improvement in model performance with the addition of each biomarker except for fibrinogen. The biomarker models that showed the highest AUROC were: NLR-model (AUROC 0.730), PCT-model (AUROC 0.710), LDH-model (AUROC 0.800), and D-dimer model (AUROC 0.719). A combined model utilizing NLR, PCT, LDH, and D-dimer was built that showed an AUROC of 0.826 (Table 2).

Finally, a graphical representation of biomarker testing and utilization trends over the 3 waves of COVID-19 (Pre-Delta, Delta, and Omicron) is in Figure 2. A stable trend was noted with the utilization of traditional inflammatory markers such as NLR and CRP over the 3 waves. However, an initial rise followed by a declining trend was noted with ferritin, PCT,

Table 2. Associations between COVID-19 biomarkers and risk of IMV or in-hospital mortality.

BIOMARKER	N	UNADJUSTED ANALYSIS		MULTIVARIABLE ANALYSIS		AUC (95%CI)	
		OR (95%CI)	*P*-VALUE	OR (95%CI)	*P*-VALUE	BASE MODEL	BIOMARKER MODEL
NLR	7325	1.81 (1.71, 1.92)	<.001	1.82 (1.72, 1.93)	<.001	0.587 (0.568, 0.606)	0.730 (0.714, 0.745)
CRP	6960	1.17 (1.15, 1.19)	<.001	1.16 (1.14, 1.18)	<.001	0.594 (0.575, 0.614)	0.693 (0.677, 0.709)
IL-6	2028	1.35 (1.27, 1.43)	<.001	1.36 (1.28, 1.45)	<.001	0.605 (0.572, 0.638)	0.689 (0.657, 0.720)
Procalcitonin	3491	1.35 (1.29, 1.41)	<.001	1.36 (1.30, 1.42)	<.001	0.597 (0.570, 0.623)	0.710 (0.686, 0.732)
LDH	3858	5.42 (4.60, 6.42)	<.001	5.99 (5.03, 7.17)	<.001	0.588 (0.561, 0.615)	0.800 (0.780, 0.821)
Ferritin	6096	1.44 (1.37, 1.50)	<.001	1.43 (1.37, 1.51)	<.001	0.597 (0.576, 0.616)	0.678 (0.659, 0.697)
Fibrinogen	2727	1.01 (0.99, 1.04)	.22	1.00 (0.98, 1.02)	.91	0.617 (0.592, 0.642)	0.617 (0.592, 0.643)
D-dimer	6765	1.52 (1.47, 1.58)	<.001	1.53 (1.47, 1.59)	<.001	0.593 (0.574, 0.612)	0.719 (0.702, 0.736)
Combination biomarker model (NLR + PCT + LDH + D-dimer) (N = 2750)						0.594 (0.564, 0.623)	0.826 (0.803, 0.849)

Abbreviations: CI, confidence interval; OR, odds ratio.
ORs, 95%CIs, and *P*-values result from logistic regression models. Due to distributional skewness, biomarker measurements were considered on the square root or base-2 logarithm scale. Multivariable models were adjusted for age, sex, race, ethnicity, hypertension, diabetes, chronic lung disease, chronic kidney disease/dialysis, and congestive heart failure. *P*-values < .006 are considered as statistically significant after applying a Bonferroni correction for multiple testing.
Base model predictors: age + sex + race + ethnicity + hypertension + diabetes + chronic lung disease + chronic kidney disease/dialysis + congestive heart failure.
Biomarker model predictors: Base model predictors + biomarker(s) of interest.
Due to distributional skewness, biomarker measurements were considered on the square root or base-2 logarithm scale.

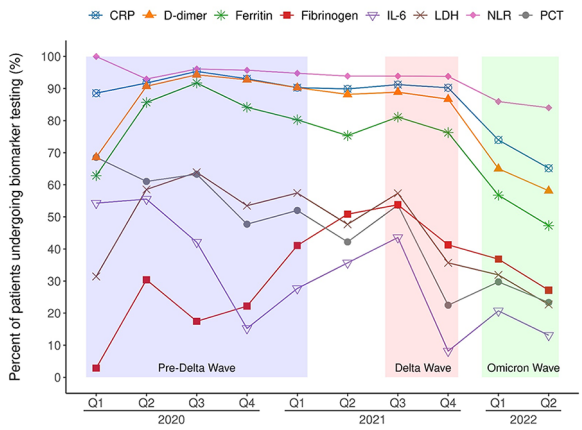

Figure 2. Comparison of biomarker testing during COVID waves.

LDH, D-dimer, and Fibrinogen. IL-6 utilization level fluctuated over the 3 waves, with an initial drop, followed by a rise during the Delta wave and a further drop during the Omicron wave. There was a gradual decline in using all biomarkers toward the end of the study period (Omicron wave).

In our exploratory analysis, where we compared patient characteristics or outcomes across 3 different COVID strain predominant waves, we noted patients in the Delta-predominant wave were more likely to be young, Caucasian, and unvaccinated compared to pre-Delta or Omicron waves. However, patients in the pre-Delta wave were more likely to have pre-existing hypertension or diabetes mellitus compared to Delta and Omicron waves. On the other hand, patients in the Omicron wave were more likely to be obese and had a higher median BMI (Supplemental Table 4). Median levels for most inflammatory markers (NLR, IL-6, LDH, Ferritin, and Fibrinogen) were higher during the Delta wave except for CRP and D-dimer, which were higher during the Omicron wave. Interestingly, the median procalcitonin level did not vary across the 3 waves (Supplemental Table 5). The incidence of steroid (dexamethasone) administration was higher during the Delta-predominant wave, with relatively more patients being treated with high-dose dexamethasone during this wave (Supplemental Table 4). Upon comparing the hospitalization outcomes across the 3 waves, we noted worse outcomes during the Delta-predominant wave (higher ICU requirement, longer length of stay in the hospital and ICU, higher invasive/non-invasive ventilation usage, ECMO support, and in-hospital mortality rates). Outcomes during the Omicron waves were generally better than pre-delta and delta waves (Supplemental Table 5).

Supplemental Tables 6 and 7 describe the difference in baseline patient characteristics, laboratory parameters, and outcomes across primary outcomes of interest (IMV or mortality). In general, patients who underwent IMV support or died during hospitalization were more likely to be males, obese, and had pre-existing hypertension or diabetes mellitus but were less likely to be vaccinated. These patients also had higher levels of inflammatory markers and higher incidence of dexamethasone administration, although suffering from worse hospitalization outcomes.

Discussion

In our retrospective study, we observed that the PCT levels increased with the severity of the disease. After adjusting for

confounders, we have observed that the rise in the PCT levels is associated with the increased rate of ICU admission, IMV requirement, hospital LOS, and mortality, indicating that PCT can be used as a potential biomarker to predict the outcomes in the COVID-19 pneumonia patients. A similar trend was noted with other inflammatory biomarkers like NLR, CRP, IL-9, LDH, D-dimer, and ferritin, but not with fibrinogen. A predictive model comprising baseline comorbidities and 4 -different biomarkers (NLR, PCT, LDH, and D-dimer) demonstrated high accuracy in predicting composite outcome (IMV or mortality) with an AUROC of 0.826. Upon exploring the utilization rates of different biomarkers during the pandemic, we noted a fluctuating trend for most biomarkers with a gradual decline through the omicron wave. Such findings corroborate several past studies yet offer some novel perspectives.

In a retrospective study on 27 154 COVID-19-positive US veterans with post-infection PCT, laboratory test data demonstrated that an elevated serum PCT level (>0.20 ng/ml) was linked with mechanical ventilation (MV) progression and severity (adjusted HR, 1.80, 95%CI: 1.67-1.94) and in-hospital death (adjusted HR, 1.76, 95%CI: 1.66-1.87).[28] Our study results align well with their findings and some other prior works on this topic.[28-32] We also explored the association of PCT level with a composite outcome of invasive ventilation or mortality, as they are both particularly important from a resource allocation perspective. Procalcitonin (PCT) synthesis is enhanced by various cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha).[33] Since hyperinflammation plays a crucial role in the progression of COVID-19 infections, the dysregulated immune response may also stimulate PCT production and explain such association with worse outcomes.[18] On the other hand, immunomodulatory treatments like systemic corticosteroids, antivirals, and IL-6 antagonists (eg, tocilizumab), which have shown significant mortality and morbidity benefits in COVID-19, have also been found to decrease the level of PCT and other inflammatory biomarkers in some prior[7,12,34-36] studies. This demonstrates the interplay of biomarkers with COVID-19 outcomes and may also affect the predictive performance of such biomarkers in the presence of immunomodulatory therapy.

COVID-19 disease not only predisposes the affected patients to hyperinflammatory response but there is also always a tendency toward weakened immunity and risk of superimposed bacterial or fungal infections.[37-39] PCT has previously been established as a marker of bacterial infection in studies based on critically ill non-COVID and COVID patients, including its role in antibiotic stewardship.[16,17,40] However, based on extensive work done subsequently on the role of PCT in bacterial co-infection among COVID-19 patients, conflicting pieces of evidence have come up, with the majority reporting a poor correlation of elevated PCT with bacterial co-infection.[20,41,42] With the advent of immunomodulatory therapy in COVID-19 management, such poor association was considerably noted, even after the cessation of immunosuppressive therapy.[36] Our prior work based on data from the same cohort demonstrated that procalcitonin has limited sensitivity and specificity for bacterial coinfections in COVID-19 pneumonia, a PCT cutoff of 0.25 ng/ml showed 47.9% sensitivity, 59.8% specificity, positive predictive value of 21.5%, and negative predictive value of 83.3% in predicting culture-proven bacterial infection.[19] Our prior work also demonstrated no difference in the incidence of culture-proven bacterial infection across a PCT cutoff of 0.25 ng/ml. Studies have also shown that initial PCT value may not always be a valid prognostic sign as preexisting comorbidities like CKD and congestive heart failure may have an impact on PCT readings, causing baseline values to be high.[43] Our study demonstrates that PCT can serve as a reliable biomarker in predicting the disease severity in COVID-19 pneumonia patients, even after adjusting for the comorbidities.

In prior studies in COVID-19 hospitalized patients, unfavorable outcomes have been linked with alteration in the levels of inflammatory biomarkers, such as CRP, CK, PCT, D-dimer, LDH, ALT, AST, etc.[21] In our multivariate biomarker models, we noted similar findings, with the most predictive biomarkers being NLR, PCT, LDH, and D-dimer. Both neutrophilia and lymphopenia have been shown to carry poor prognostic implications in COVID-19 disease, with a dose-response increase in neutrophil level being observed with non-severe to severe progression of COVID-19 disease.[44,45] Therefore, an elevation of NLR, as found in our work, has been linked with COVID-19 disease severity in prior studies.[46-49] LDH is known to be a marker of cardiac injury, which is often elevated during infective processes in response to cytokine-mediated injury to the tissues.[50] COVID-19-related inflammatory response induces injury to lung tissues as well as end-organ systems. Elevated LDH levels have, therefore, been shown to be associated with worse clinical outcomes in a large number of studies.[51-54] D-dimer, on the other hand, is thought to be an indicator of the thromboembolic process, another common finding in the COVID-19 disease process. An increased level of D-dimer can be an indicator of venous or pulmonary thrombosis, while a steady increase in its level is shown to be associated with COVID-19 disease progression and mortality.[55-57]

Although there are multiple studies exploring individual biomarker performance in COVID-19 prognostication, there is a dearth of literature focusing on the comparison and combination of those different biomarkers. Among the existing studies that presented combination models, a relatively lower sample size is one of the limiting factors.[58,59] Nguyen et al employed a machine learning-based model to predict the likelihood of worsening the severe COVID-19 disease. They identified 2 different sets of biomarkers (D-dimer, IL-6, and ferritin; and CRP, D-dimer, and IL-6) for the assessment of disease severity and prognosis but did not incorporate PCT in their analysis. In this study, we present a combination biomarker model based on the highest individual AUC comprising 4 biomarkers (NLR, PCT, LDH, and D-dimer) along

with baseline demographic and comorbidities (age, sex, race, ethnicity, hypertension, diabetes, chronic lung disease, chronic kidney disease, and congestive heart failure) which was found to have a very high predictive value (AUC 0.826, 95%CI: 0.803-0.849).

Biomarkers serve as a valuable tool for diagnosing and monitoring disease severity by non-invasive means. Considering the variable presentation of COVID-19 pneumonia symptoms, incorporating PCT early in the evaluation can guide physicians in monitoring disease progression and providing appropriate treatment promptly to prevent adverse outcomes. In resource-limited setups where invasive life support systems are limited, it can also help in early anticipation of resource scarcity, patient triaging, and strategic planning. This multicentric retrospective study provides further evidence of the need to adopt a multimodal approach toward any future pandemic-like situation.

In our study, we note the trend in utilization rates of various biomarkers in hospitalized COVID-19 patients. With the onset of the COVID-19 pandemic, extensive research efforts were going on all over the world, leading to the publication of newer evidence over time in an attempt to understand the disease process fully.[15] Moreover, changes were noted in the pathogenicity, infectivity, and outcomes of various COVID-19 strains across the different waves of COVID-19, which warranted re-exploration of existing evidence. Therefore, the fluctuation in the trends of various biomarker utilization over different COVID-19 waves could be a reflection of this. Although the management guidelines for hospitalized COVID-19 patients changed parallelly, the recommendations regarding the incorporation of biomarkers in clinical decision-making were often variable across institutions or clinical preferences. The differences were even more apparent when global trends were considered. A more inclusive approach with a combination of pre-existing and newer biomarkers to develop risk scores could be helpful in the future. In our future work, we intend to validate our current four-biomarker model in a different cohort and explore the possibility of developing a simplified scoring system that could add to the growing evidence.

Our study is a large, multicenter retrospective study of hospitalized COVID-19 pneumonia patients. With one of the largest sample sizes to date, we aim to provide significant contributions to the existing literature while improving the generalizability, rigor, and external validity of our findings. Unlike many previous studies that focused on specific waves or subsets of COVID-19 patients, our research encompasses data from all waves of the pandemic. This comprehensive approach ensures that we can observe potential changes in the behavior of the virus and patient outcomes over time. While the prognostic significance of individual inflammatory biomarkers in COVID-19 has been extensively studied, there is limited research on integrating multiple biomarkers into a single predictive model that can reliably forecast clinical outcomes. Such an approach is crucial for enhancing risk stratification and guiding treatment decisions in a rapidly evolving pandemic scenario. This study aims to address this gap by evaluating a multimodal biomarker model, incorporating neutrophil-to-lymphocyte ratio (NLR), procalcitonin (PCT), lactate dehydrogenase (LDH), and D-dimer, alongside baseline comorbidities, to predict adverse outcomes in hospitalized COVID-19 patients. By facilitating early identification of high-risk patients, our model could enable more efficient allocation of limited resources, such as ICU beds or mechanical ventilation, which remains a global concern. We also explore the impact of evolving viral variants and treatment strategies on their clinical utility by examining biomarker trends across different pandemic waves.This comprehensive analysis not only adds to existing knowledge but also provides a practical tool for early identification of high-risk patients, optimizing clinical management, and resource allocation in diverse healthcare settings.

There are several potential limitations to our study. First, the retrospective nature of the study prevents us from establishing causality and avoiding unexplored confounders, such as a difference in care at the provider level. Most of our data is derived from tertiary care centers, where the overall patient population and level of care might be different from the general population. Thirdly, missing data due to the retrospective nature of the study may have reduced statistical power. However, further large and prospective studies are necessary to validate our findings and explore the possibility of utilizing a procalcitonin-based biomarker model in the clinical decision-making process.

Conclusions

Our study indicates that elevated PCT levels are correlated with unfavorable outcomes in patients with COVID-19 pneumonia. A procalcitonin-based biomarker model can be useful as a prognostic tool for guiding patient care. Further large-scale and prospective studies are needed to fully explore its utility.

Abbreviations

COVID-19: Coronavirus disease 19
SARS-CoV-2: Severe Acute Respiratory Distress Syndrome-related coronavirus
ICU: Intensive care unit
MV: Mechanical ventilation
CRP: C-reactive protein
LDH: Lactate Dehydrogenase
NLR: Neutrophil-lymphocyte ratio
IL-6: Interleukin 6
PCT: Procalcitonin
VIRUS: Viral Infection and Respiratory Illness Universal Study
SCCM: Society of Critical Care Medicine
WHO: World Health Organization
NIMV: Noninvasive mechanical ventilation
HFNC: High-flow nasal cannula
IMV: Invasive mechanical ventilation

ECMO: Extracorporeal membranous oxygenation
CI: Confidence interval
OR: Odds ratio
aOR: Adjusted odd ratio
AUROC: Area under receiver operating curve
BMI: Body mass index
LOS: Length of stay
HR: Hazard ratio
CKD: Chronic kidney disease
BP: Blood pressure
SOFA: Sequential organ failure assessment
BUN: Blood urea nitrogen

Declarations

Ethics Approval and Consent to Participate

Ethics: Ethics approval for this study was issued by the Mayo Clinic Institutional Review Board under the exempt category. Access to the multicenter Mayo Clinic data was granted through "Viral Infection and Respiratory Illness Universal Study [VIRUS]: COVID-19 Registry and Validation of C2D2 (Critical Care Data Dictionary)" under IRB ID 20-002610.

Consent: The need for informed consent was waived by the IRB due to its retrospective design, data anonymity, and non-interventional nature.

Consent for Publication

All authors approved the manuscript and gave consent for publication.

Author Contributions

Shahin Isha, M.D.: Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data curation, Writing – Original draft, Writing – Review and editing ; Lekhya Raavi M.B.B.S.: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Data curation, Visualization, Writing – Original draft, Writing – Review and editing; Sadhana Jonna, M.B.B.S.: Methodology, Writing – Original draft, Writing – Review and editing; Hrishikesh Nataraja M.B.B.S.: Methodology, Writing – Original draft, Writing – Review and editing; Anna Jenkins B.S.: Project administration, Writing – Review and editing; Abby J. Hanson, B.S.: Methodology, Writing – Original draft, Writing – Review and editing; Emily C. Craver: Software, Formal Analysis, Investigation; Prasanth Balasubramanian, M.D.: Investigation, Methodology, Writing – Original draft, Writing – Review and editing; Arvind Bala Venkataraman, M.B.B.S.: Investigation, Methodology, Writing – Original draft, Writing – Review and editing; Aysun Tekin, M.D.: Investigation, Supervision, Writing – Original draft, Writing – Review and editing; Vikas Bansal, M.B.B.S., M.B.A.: Investigation, Methodology, Writing – Original draft, Writing – Review and editing; Swetha Reddy, M.B.B.S., M.D.: Conceptualization, Supervision, Writing – Original draft, Writing – Review and editing; Sean M. Caples, D.O., M.S.: Conceptualization, Supervision, Writing – Original draft, Writing – Review and editing; Syed Anjum Khan, M.D.: Conceptualization, Supervision, Writing – Original draft, Writing – Review and editing; Nitesh K. Jain, M.B.B.S.: Data curation, Writing – Original draft, Writing – Review and editing; Abigail T. LaNou, M.D.: Investigation, Writing – Original draft, Writing – Review and editing; Rahul Kashyap, M.B.B.S., M.B.A.: Conceptualization, Methodology, Resources, Supervision, Writing- Original draft, Writing – Review and editing; Rodrigo Cartin-Ceba, M.D.: Resources, Writing – Original draft, Writing – Review and editing; Ricardo Diaz Milian, M.D.: Conceptualization, Methodology, Supervision, Writing – Review and editing; Carla P. Venegas, M.D.: Conceptualization, Supervision, Writing – Review and editing; Anna B. Shapiro, M.D.: Conceptualization, Supervision, Writing – Review and editing; Anirban Bhattacharyya, M.D.: Conceptualization, Supervision, Writing – Review and editing; Sanjay Chaudhary, M.B.B.S., M.D.: Conceptualization, Supervision, Writing – Review and editing; Sean P. Kiley, M.D.: Conceptualization, Writing – Original Draft, Writing – Review and editing; Quintin J Quinones, M.D.: Writing – Original Draft, Writing – Review and editing; Neal M. Patel, M.D., M.P.H.: Conceptualization, Validation, Visualization, Writing – Review and editing; Pramod K. Guru, M.D.: Conceptualization, Supervision, Writing – Original Draft, Writing – Review and editing; Pablo Moreno Franco, M.D.: Conceptualization, Supervision, Writing – Original Draft, Writing – Review and editing; Archana Roy, M.D.: Conceptualization, Methodology, Project administration, Supervision, Validation, Resources, Writing – Original draft, Writing – Review and editing; Devang K. Sanghavi, M.B.B.S., M.D.: Conceptualization, Methodology, Project administration, Supervision, Validation, Resources, Writing – Original draft, Writing – Review and editing.

Acknowledgments

The authors would like to thank all the members of Acute Care Research Consortium Team for the successful conduction of this study.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Competing Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Rahul Kashyap: Grant and contracts - Gordan and Betty Moore Foundation, Jenssen and Jenssen

LLC; all payments made to the institution. No conflict of interest related to this manuscript. Rest other authors declare that they have no competing interests.

Availability of Data and Materials

Due to institutional data privacy policy, data cannot be shared publicly but is available upon reasonable request addressed to the corresponding author.

Preprint Server disclosure

No preprint.

ORCID iDs

Vikas Bansal https://orcid.org/0000-0001-6047-5559
Ricardo Diaz Milian https://orcid.org/0000-0003-1253-0343
Sanjay Chaudhary https://orcid.org/0000-0003-4127-5572
Archana Roy https://orcid.org/0000-0001-9010-5153

Supplemental Material

Supplemental material for this article is available online.

REFERENCES

1. Yang JM, Koh HY, Moon SY, et al. Allergic disorders and susceptibility to and severity of COVID-19: a nationwide cohort study. *J Allergy Clin Immunol*. 2020;146:790-798.
2. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of Coronavirus Disease 2019 in China. *New Engl J Med*. 2020;382:1708-1720.
3. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team null. The epidemiological characteristics of an outbreak of 2019 novel Coronavirus Diseases (COVID-19) - China, 2020. *China CDC weekly*. 2020;2:113-122.
4. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and multiorgan response. *Curr Probl Cardiol*. 2020;45:100618.
5. Słomka A, Martucci G, Raffa GM, et al. Immunological and hematological response in COVID-19. *Adv Exp Med Biol*. 2021;1352:73-86.
6. Silva MJA, Ribeiro LR, Gouveia MIM, et al. Hyperinflammatory response in COVID-19: a systematic review. *Viruses*. 2023;15:553.
7. RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021;384:693-704.
8. Chokkalingam AP, Hayden J, Goldman JD, et al. Association of Remdesivir Treatment with mortality among hospitalized adults with COVID-19 in the United States. *JAMA Netw Open*. 2022;5:e2244505.
9. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of covid-19—final report. *N Engl J Med*. 2020;383:1813-1826.
10. Selvaraj V, Finn A, Lal A, et al. Baricitinib in hospitalised patients with COVID-19: a meta-analysis of randomised controlled trials. *med*. 2022;49:101489.
11. Abani O, Abbas A, Abbas F, et al. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;9:1419-1426.
12. The REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med*. 2021;385:1147-1149.
13. Hariyanto TI, Japar KV, Kwenandar F, et al. Inflammatory and hematologic markers as predictors of severe outcomes in COVID-19 infection: A systematic review and meta-analysis. *Am J Emerg Med*. 2021;41:110-119.
14. Gallo Marin B, Aghagoli G, Lavine K, et al. Predictors of COVID-19 severity: a literature review. *Rev Med Virol*. 2021;31:1-10.
15. Semiz S. COVID19 biomarkers: What did we learn from systematic reviews? *Front Cell Infect Microbiol*. 2022;12:1038908.
16. Becker KL, Snider R, Nylen ES. Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. *Crit Care Med*. 2008;36:941-952.
17. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet*. 2010;375:463-474.
18. Gautam S, Cohen AJ, Stahl Y, et al. Severe respiratory viral infection induces procalcitonin in the absence of bacterial pneumonia. *Thorax*. 2020;75:974-981.
19. Isha S, Satashia P, Raavi L, et al. Procalcitonin levels and bacterial coinfection in hospitalized patients with COVID-19. *CHEST Crit Care*. 2024;2:100035.
20. Heer RS, Mandal AK, Kho J, et al. Elevated procalcitonin concentrations in severe Covid-19 may not reflect bacterial co-infection. *Ann Clin Biochem*. 2021;58:520-527.
21. Malik P, Patel U, Mehta D, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. *Evid Based Med*. 2021;26:107-108.
22. Rubio-Rivas M, Mora-Luján JM, Formiga F, et al. WHO ordinal scale and inflammation risk categories in COVID-19. Comparative study of the severity scales. *J Gen Intern Med*. 2022;37:1980-1987.
23. Walkey AJ, Kumar VK, Harhay MO, et al. The Viral Infection and Respiratory Illness Universal Study (VIRUS): an International Registry of Coronavirus 2019-Related Critical Illness. *Critical Care Explor*. 2020;2:e0113.
24. Walkey AJ, Sheldrick RC, Kashyap R, et al. Guiding Principles for the conduct of observational critical care research for coronavirus disease 2019 pandemics and beyond: the Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study Registry. *Crit Care Med*. 2020;48:e1038-e1044.
25. Domecq JP, Lal A, Sheldrick CR, et al. Outcomes of patients with coronavirus disease 2019 receiving organ support therapies: the international viral infection and Respiratory Illness Universal Study Registry. *Crit Care Med*. 2021;49:437-448.
26. Turek JR, Bansal V, Tekin A, et al. Lessons from a rapid project management exercise in the time of pandemic: methodology for a global COVID-19 VIRUS Registry Database. *JMIR Res Protoc*. 2022;11:e27921.
27. Johnson PW, Kunze KL, Senefeld JW, et al. Association of neutralizing antispike monoclonal antibody treatment with coronavirus disease 2019 hospitalization and assessment of the monoclonal antibody screening score. *Mayo Clin Proc Innov Qual Outcomes*. 2023;7:109-121.
28. Jeyapalina S, Wei G, Stoddard GJ, et al. Serum procalcitonin level is independently associated with mechanical ventilation and case-fatality in hospitalized COVID-19-positive US veterans - a potential marker for disease severity. *PLoS One*. 2023;18:e0284520.
29. Heidari-Beni F, Vahedian-Azimi A, Shojaei S, et al. The level of procalcitonin in severe COVID-19 patients: a systematic review and meta-analysis. *Adv Exp Med Biol*. 2021;1321:277-286.
30. Krause M, Douin DJ, Tran TT, et al. Association between procalcitonin levels and duration of mechanical ventilation in COVID-19 patients. *PLoS One*. 2020;15:e0239174.
31. Liu ZM, Li JP, Wang SP, et al. Association of procalcitonin levels with the progression and prognosis of hospitalized patients with COVID-19. *Int J Med Sci*. 2020;17:2468-2476.
32. Tong-Minh K, van der Does Y, Engelen S, et al. High procalcitonin levels associated with increased intensive care unit admission and mortality in patients with a COVID-19 infection in the emergency department. *BMC Infect Dis*. 2022;22:165.
33. Manson JJ, Crooks C, Naja M, et al. COVID-19-associated hyperinflammation and escalation of patient care: a retrospective longitudinal cohort study. *Lancet Rheumatol*. 2020;2:e594-e602.
34. Singh AK, Oks M, Husk G, et al. Impact of timing of tocilizumab use in hospitalized patients with SARS-CoV-2 infection. *Respir Care*. 2022;67:629-630.
35. Ivan Hariyanto T, Kurniawan A. Tocilizumab administration is associated with the reduction in biomarkers of coronavirus disease 2019 infection. *J Med Virol*. 2021;93:1832-1836.
36. Kooistra EJ, van Berkel M, van Kempen NF, et al. Dexamethasone and tocilizumab treatment considerably reduces the value of C-reactive protein and procalcitonin to detect secondary bacterial infections in COVID-19 patients. *Crit Care*. 2021;25:281.
37. Pickens CO, Gao CA, Cuttica MJ, et al. Bacterial superinfection pneumonia in patients mechanically ventilated for COVID-19 pneumonia. *Am J Respir Crit Care Med*. 2021;204:921-932.
38. Al-Tawfiq JA, Alhumaid S, Alshukairi AN, et al. COVID-19 and mucormycosis superinfection: the perfect storm. *Infection*. 2021;49:833-853.
39. Miao Q, Ma Y, Ling Y, et al. Evaluation of superinfection, antimicrobial usage, and airway microbiome with metagenomic sequencing in COVID-19 patients: a cohort study in Shanghai. *J Microbiol Immunol*. 2021;54:808-815.
40. van Berkel M, Kox M, Frenzel T, et al.; on behalf of the RCI-COVID-19 Study Group. Biomarkers for antimicrobial stewardship: a reappraisal in COVID-19 times? *Crit Care*. 2020;24:600.
41. Vanhomwegen C, Veliziotis I, Malinverni S, et al. Procalcitonin accurately predicts mortality but not bacterial infection in COVID-19 patients admitted to intensive care unit. *Ir J Med Sci*. 2021;190:1649-1652.
42. May M, Chang M, Dietz D, et al. Limited utility of procalcitonin in identifying community-associated bacterial infections in patients presenting with coronavirus disease 2019. *Antimicrob Agents Chemother*. 2021;65:e02167-20.
43. Yunus I, Fasih A, Wang Y. The use of procalcitonin in the determination of severity of sepsis, patient outcomes and infection characteristics. *PLoS One*. 2018;13:e0206527.

44. Chua PEY, Shah SU, Gui H, et al. Epidemiological and clinical characteristics of non-severe and severe pediatric and adult COVID-19 patients across different geographical regions in the early phase of pandemic: a systematic review and meta-analysis of observational studies. *J Investig Med*. 2021;69:1287-1296.
45. Lim AYH, Goh JL, Chua MCW, et al. Temporal changes of haematological and radiological findings of the COVID-19 infection-a review of literature. *BMC Pulm Med*. 2021;21:37.
46. Li X, Liu C, Mao Z, et al. Predictive values of neutrophil-to-lymphocyte ratio on disease severity and mortality in COVID-19 patients: a systematic review and meta-analysis. *Crit Care*. 2020;24:647.
47. Kumar A, Sarkar PG, Pant P, Kumar J. Does Neutrophil-to-lymphocyte ratio at admission predict severity and mortality in COVID-19 patients? A systematic review and meta-analysis. *Indian J Crit Care Med*. 2022;26:361-375.
48. Parthasarathi A, Padukudru S, Arunachal S, et al. The ole of neutrophil-to-lymphocyte ratio in risk stratification and prognostication of COVID-19: a systematic review and meta-analysis. *Vaccines*. 2022;10:1233.
49. Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: a retrospective study. *Chin Med J*. 2020;133:1261-1267.
50. Martinez-Outschoorn UE, Prisco M, Ertel A, et al. Ketones and lactate increase cancer cell "stemness," driving recurrence, metastasis and poor clinical outcome in breast cancer: achieving personalized medicine via Metabolo-Genomics. *Cell Cycle*. 2011;10:1271-1286.
51. Alnor A, Sandberg MB, Gils C, Vinholt PJ. Laboratory tests and outcome for patients with Coronavirus Disease 2019: a systematic review and meta-analysis. *J Appl Lab Med*. 2020;5:1038-1049.
52. Li X, Pan X, Li Y, et al. Cardiac injury associated with severe disease or ICU admission and death in hospitalized patients with COVID-19: a meta-analysis and systematic review. *Crit Care*. 2020;24:468.
53. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. *J Infect*. 2020;81:e16-e25.
54. Zhang ZL, Hou YL, Li DT, Li FZ. Laboratory findings of COVID-19: a systematic review and meta-analysis. *Scand J Clin Lab Invest*. 2020;80:441-447.
55. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. *Ther Adv Respir Dis*. 2020;14:175346662093717.
56. Lima WG, Barra A, Brito JCM, Nizer WSC. d-Dimer serum levels as a biomarker associated for the lethality in patients with coronavirus disease 2019: a meta-analysis. *Blood Coagul Fibrinolysis*. 2020;31:335-338.
57. Sakka M, Connors JM, Hékimian G, et al. Association between D-Dimer levels and mortality in patients with coronavirus disease 2019 (COVID-19): a systematic review and pooled analysis. *J Méd Vasc*. 2020;45:268-274.
58. Nguyen HTT, Le-Quy V, Ho SV, et al. Outcome prediction model and prognostic biomarkers for COVID-19 patients in Vietnam. *ERJ Open Res*. 2023;9:00481-02022.
59. Qi J, He D, Yang D, et al. Severity-associated markers and assessment model for predicting the severity of COVID-19: a retrospective study in Hangzhou, China. *BMC Infect Dis*. 2021;21:774.