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Cytokine 149 (2022) 155755

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Association and predictive value of biomarkers with severe outcomes in hospitalized patients with SARS-CoV-2 infection

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ARTICLE INFO

Keywords:
COVID-19
Critical care
Growth factors
Cytokines and inflammatory mediators
Inflammation
Intensive care
Mechanical ventilation

ABSTRACT

This study analyzed the levels at admission of biomarkers for their association with and ability to predict risk of severe outcomes, including admission to the ICU, need for invasive mechanical ventilation (IMV), need for vasopressor use (VU), and in-hospital mortality (IHM) in 700 patients hospitalized with COVID-19. Biomarker data split by outcomes was compared using Mann-Whitney U tests; frequencies of biomarker values were compared using Chi-square tests and multivariable logistic regression analysis was performed to look at the impact of biomarkers by outcome. Patients that suffered IHM were more likely to have reduced platelet numbers and high blood urea nitrogen (BUN) levels among patients admitted to the ICU. Risk factors for mortality were related to hyper-coagulability (low platelet count and increased D-dimer) and decreased respiratory (PaO_2/FiO_2 ratio) and kidney function (BUN). Association with risks of other severe outcomes were as follows: ICU with hyper-inflammation (IL-6) and decreased respiratory function; IMV with low platelet count, abnormal neutrophil–lymphocyte ratio with reduced respiratory function, VU with inflammatory markers (IL-6), and low platelet count with respiratory function. Our studies confirmed the association of biomarkers of hematological, inflammatory, coagulation, pulmonary and kidney functions with disease severity. Whether these biomarkers have any mechanistic or causal role in the disease progress requires further investigation.

1. Introduction

The pandemic of Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has already infected over 209 million people and caused over 4.4 million deaths around the world as of 08/19/2021 [1]. COVID-19 has presented substantial clinical challenges, in great part due to its highly heterogenous clinical presentation that can range from asymptomatic or mild to very severe cases [2]. Infected patients may present with any of the following: fever, cough, myalgia, sputum production, headache, hemoptysis, diarrhea, dyspnea and in severe cases, acute respiratory distress syndrome (ARDS), septic shock, acute cardiac injury, multiorgan failure and death [2,3]. The clinical course of the disease can be difficult to predict, with some patients rapidly developing severe symptoms and deadly complications while some others can slowly progress to critical illness. Additionally, after acute infection, many patients exhibit post-acute sequelae of SARS-CoV-2 infection, such as fatigue, dyspnea, anosmia, dysgeusia, cognitive dysfunction, and psychological problems, including anxiety and depression [4].

Approximately a fifth of SARS-CoV-2-infected patients develop a severe disease [5–7]. Among U.S. cases, approximately 14% of patients required admission to a hospital, with 26–32% of them requiring admission to the Intensive Care Unit (ICU) [2,8]. Of those admitted to the ICU, 67–85% developed ARDS. Mortality rates for those admitted to the ICU are high, ranging from 39 to72% depending on patient characteristics [2,7,9]. Therefore, urgent categorization of patients into risk groups following diagnosis is necessary to ensure optimal treatment and resource allocation during surges of infection.

Abbreviations: BNP, Brain natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IHM, in-hospital mortality; IMV, invasive mechanical ventilation; PCT, Procalcitonin; VU, vasopressor use.

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https://doi.org/10.1016/j.cyto.2021.155755
Received 31 May 2021; Received in revised form 24 August 2021; Accepted 27 October 2021
Available online 6 November 2021

Early reports from China at the beginning of the pandemic compared the association of different comorbidities and laboratory data in patients that survived versus those that succumbed to the infection [9]. These reports identified hypertension, diabetes, and coronary heart disease as some of the most significant comorbidities and pointed out the association of abnormalities in hematological, inflammatory, coagulation and organ damage-related biomarkers with an increased risk of death [6,9,10]. These data also shed important information about the pathogenesis of severe manifestations of COVID-19 and identified potential therapeutic targets [11,12]. In addition, the CDC has included cancer, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease (COPD), history of smoking, obesity and pregnancy as conditions that increase risk of severe illness [2].

Considering the multi-system involvement of severe COVID-19, effective patient stratification and disease outcome prediction requires a holistic approach, including hematological and serum biomarkers in tandem with other clinical measures of cardiovascular and pulmonary function, as well as CT imaging data. The identification of laboratory biomarkers able to classify patients based on their risk of severe outcomes is imperative to guarantee early intervention. Many studies have demonstrated that an involvement of inflammatory and coagulation systems, including complement activation, cytokine storms and vascular alterations are responsible for the underlying organ damage in seriously ill patients [12–15]. Reports have consistently found that serum biomarkers associated with these systems are altered and correlate with the severity of disease [12,16]. The aim of this study was to analyze the data from 700 hospitalized COVID-19 patients in the Louisville, KY, area in order to explore the association and predictive value of different biomarkers with severe disease outcomes, including ICU admission, need for invasive mechanical ventilation (IMV), need for vasopressor use (VU), and in-hospital mortality (IHM).

2. Materials and methods

2.1. Study design, subjects, and setting

This was a retrospective multicenter study including patients with a diagnosis of SARS-CoV-2 and biomarker data, who were hospitalized in any of the eight adult hospitals in the city of Louisville, KY. The study group was part of a larger study of hospitalized COVID-19 patients and included patients hospitalized between March 5th, 2020, and ended on July 1st, 2020. The demographic and clinical characteristics of these patients have been previously reported [17].

2.2. Human subjects protection

The study was approved by the Institutional Review Board (IRB) at the University of Louisville Human Subjects Research Protection Program Office (IRB number 20.0257) and by the research offices at each participating hospital. The study was exempt from informed consent.

2.3. Data collection

Data were extracted from hospital electronic medical records. Collected data included patient age; sex; race/ethnicity; body mass index; medical and social history; physical examination findings; laboratory findings, including blood type, chest radiographs and chest CT findings; medications; ICU admission; need for IMV; VU; and IHM. Race was categorized as White, Black, Asian and other; and ethnicity was categorized as Hispanic and non-Hispanic.

2.4. Study definitions

SARS-CoV-2 infection: A patient hospitalized with a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal swab or other respiratory sample.

Clinical outcomes: Binary outcomes evaluated included admission to ICU, need for IMV, need for continuous (>6h) vasopressor use (Norepinephrine only or Norepinephrine and additional pressor agent/s), and in-hospital death.

Laboratory results: Laboratory data included in this study were the first recorded results obtained within the first 24 h of hospital admission. Laboratory tests included hematology data (WBC, neutrophil to lymphocyte ratio [N/L], platelet counts and erythrocyte sedimentation rate [ESR]), immunological and biochemical inflammatory markers (IL-6, C-reactive protein [CRP], ferritin, procalcitonin, D-dimer, brain natriuretic peptide [BNP], blood urea nitrogen [BUN]), and oxygenation data (PaO_2/FiO_2). Biomarker results were categorized according to cut-points representing established normal versus abnormal levels, with the exceptions of IL-6 and the PaO2/FiO2 ratio. Based on several studies looking at IL-6 levels and COVID-19 disease severity, we used the cut-point of 37.65 pg/mL, reported by Zhang et al. (18) to be highly predictive of intra-hospital mortality; while we used a PaO_2/FiO_2 ratio of 200, as it represents a moderate to severe respiratory dysfunction.

2.5. Statistical analysis

Continuous variables were reported as medians and interquartile ranges; categorical variables were reported as frequencies and percentages. Unadjusted comparison tests for biomarkers split by outcomes were conducted using Mann-Whitney U tests, and box plots were produced. Spearman correlations were calculated for each pair of biomarkers, and a correlation heatmap was produced. Biomarkers were categorized by cut-points and frequency distributions between different outcome groups and compared using Chi-squared tests. To assess the impact of biomarkers on outcomes, multivariable logistic regression analysis was performed using categorized laboratory values for the neutrophil to lymphocyte ratio, platelet count, IL-6, D-dimer, PaO_2/FiO_2, and BUN. A clinical model, using significant results from the multivariable logistic regression for in-hospital mortality, was produced to show the estimated mortality based on biomarker cut points. P-values <0.05 were used to denote significance for all tests conducted. Statistical analysis was performed using R Studio Version 3.6.1.

3. Results

3.1. Demographics, outcomes and laboratory values

A total of 700 patients met the inclusion criteria for analysis. Patient demographic characteristics and outcomes are shown in Table 1. The median age of the overall population was 61 years [IQR: 45–73], and 55% of the patients were female. Overall, the patient population identified as 55% White, 31% Black, 4% Asian and 10% as Other. Twelve percent of patients identified themselves as Hispanic. For the recorded clinical outcomes, 259 (37%) of the patients were admitted to the ICU, 159 (23%) required IMV, 119 (17%) required VU, and 108 (15%) died while in the hospital. There was considerable overlap among the outcome groups, with all patients requiring IMV or VU also being admitted to the ICU (the only exception was a patient that received IMV in the Emergency Room) and 87/108 of the IHM cases having also been admitted to the ICU. Laboratory values are described in Table 1, including the number of available results for each laboratory test in the general patient population.

3.2. Biomarker levels and outcomes

Fig. 1 depicts box plots of the levels of different biomarkers by outcomes. Unadjusted comparisons stratified by severity showed that most biomarker levels were significantly different in populations with severe outcomes compared to populations without those outcomes. For the hematological biomarkers, WBC and N/L ratios were consistently and significantly higher for patients who experienced all four outcomes.

Table 1
Patient Characteristics, Outcomes and Laboratory values.

Patient Characteristics	Value*	Laboratory Values	Value**
Total Population	700	Hematology	
Demographics		White blood cells x1000/mL[a]	6.5 [4.6–9.0]
Age, median [IQR]	61 [45–73]	Neutrophil-Lymphocyte Ratio[a]	4.6 [2.8–7.6]
Sex, n (%)		Platelets x1000/mL[a]	195 [157–246]
Female	384 (55)	Erythrocyte sediment rate, mm/hr[b]	49 [30–76]
Male	316 (45)	Inflammatory markers	
Race, n (%)		IL-6, pg/mL[c]	58.1 [29.2–130.6]
White	383 (55)	C-reactive protein, mg/L[d]	76 [35–169]
Black	220 (31)	Ferritin, ng/mL[e]	386 [156–830]
Asian	27 (4)	Procalcitonin, μg/L[f]	0.12 [0.05–0.43]
Other	72 (10)	D-dimer, ngFEU/mL[g]	792 [400–1589]
Ethnicity, n (%)		Brain natriuretic peptide, pg/mL[h]	159 [42–1188]
Hispanic	81 (12)	Kidney function markers	
Non-Hispanic	619 (88)	Blood urea nitrogen, mg/dL[a]	17 [11–27]
Outcomes, n (%)		Respiratory markers	
ICU admission	259 (37)	PaO_2 / FiO_2[i]	248 [144–352]
Need for IMV	159 (23)		
Vasopressor use	119 (17)		
In-hospital mortality	108 (15)		

*Number (percentage); **Median [IQR];[a] n = 700, [b] n = 142, [c] n = 201. [d] n = 459, [e] n = 457, [f] n = 523, [g] n = 465, [h] n = 238, [i] n = 246.

There were no statistically significant differences in platelet counts with the exception of significantly lower platelet numbers in patients who died versus those who did not.

The ESR was significantly higher in patients admitted to the ICU and those requiring VU, but not for the other two outcomes. For the inflammatory biomarkers (IL-6, CRP, ferritin, PCT and BNP), as well as D-dimer and BUN, levels in patients who experienced all four severe outcomes were significantly different (elevated) compared to those patients who did not experience such outcomes. Finally, patients who experienced all four different outcomes had significantly different (lower) PaO_2/FiO_2 ratios compared to those that did not. As expected from the interrelationship of the potential pathogenic mechanisms in severe COVID-19, including hematologic/immune alterations, inflammation, coagulation and resulting organ dysfunction, many of these biomarkers were correlated. The correlations among biomarkers and their significance are depicted in Supplemental Fig. 1.

3.3. Biomarker distribution based on outcomes

The distribution of biomarker results in the overall patient population and those patients who experienced severe outcomes, as determined on the cut-points defined in *Materials and Methods*, are shown in Table 2. In general, the percentage of patients with "abnormal" biomarker values increased in the patients who experienced severe outcomes compared to the overall hospitalized population. Leukocytosis (WBC > 11,000/μl) was present in only 16% of patients in the overall population, but this proportion was almost twice as high in patients who experienced severe outcomes, reaching 35% in those who died in the hospital. A low platelet count (<150,000/μl) was more prevalent in patients in need of VU and those who died in the hospital. While neutrophil/lymphocyte ratios ≥ 3.5 were observed in 65% of the overall population, this biomarker was even more prevalent (77–81%) in patients who experienced severe outcomes. Abnormal ESRs (≥30 mm/hr) were found to be more prevalent in patients with severe outcomes, particularly in patients that needed VU (28 vs. 15% in the overall population). A similar picture emerged for inflammatory markers, including IL-6, CRP and ferritin, where the prevalence of patients with "abnormal" values was higher than in the overall population. The proportions of patients with above-cut-point values (abnormal) for PCT and BNP were also consistently higher for those who experienced severe outcomes, particularly in those who died. D-dimer levels > 500 pg/mL were detected in 45% of the overall patient population, but this figure increased to 58–64% in patients who experienced severe outcomes. While low (<200) PaO_2/FiO_2 ratios (evidence of respiratory dysfunction) were observed in 14% of the overall population, they were more than twice as prevalent in patients who experienced severe outcomes, and the highest in patients who died (39%). Finally, although high (>20 mg/dL) BUN levels were registered in almost half (48%) of the overall population, the prevalence increased in patients with severe outcomes, particularly in those who died in the hospital (75%). A comparison of the ICU group versus the overall patient population showed that the proportions of patients with "abnormal" biomarker results were significantly higher ($p < 0.001$) for most biomarkers with the exception of platelet counts and BUN in patients that required ICU admission. No statistically significant differences with the ICU group were found in the proportions of patients with abnormal biomarker results in the IMV and VU severe outcome groups, with exception of higher numbers of patients with abnormal ferritin levels in the VU group ($p = 0.042$). However, a comparison of the ICU group versus the IHM group showed that patients who died in the hospital were significantly more likely to have low platelet numbers ($p = 0.008$) and higher BUN ($p < 0.0001$), PCT ($p = 0.031$) and BNP levels ($p = 0.026$).

3.4. Multivariate logistic regression analysis

To explore the impact of specific biomarkers on the four outcomes, multivariable logistic regression analysis was performed with selected biomarkers representing leukocyte populations (N/L ratios), platelet numbers, inflammatory (IL-6) and coagulation (D-dimer), as well as respiratory (PaO_2/FiO_2 ratios) and kidney (BUN) function; results are shown in Fig. 2. The PaO_2/FiO_2 ratio was the only marker to show significant association with all four outcomes. Low platelet numbers were significantly associated with need of IMV, VU and mortality; high IL-6 levels were significantly associated with risk of ICU admission and VU; abnormal neutrophil/lymphocyte ratios were associated with need of IMV; and high levels of both D-dimer and BUN were significantly associated with mortality.

3.5. Clinical model

Fig. 3 presents an algorithm showing a flowchart including the biomarkers identified in the multivariate logistic regression analysis to be significantly associated with in-hospital mortality (low platelet numbers, BUN, PaO2/FiO2 ratio and D-dimer levels) along with the observed distribution and predicted mortality.

4. Discussion

Our study demonstrates the importance of biomarkers in the management of SARS-CoV-2 infection as a means to guide early intervention. Given its significant variability in presentation and unpredictable course, severe COVID-19 presents substantial clinical challenges, particularly for hospitalized patients, for whom risk stratification, accurate prognosis and optimal treatment and use of resources are essential. By incorporating biomarkers into initial assessments, early treatment to prevent adverse clinical outcomes can be instituted. We undertook this study with the purpose of evaluating the association and predictive value of a panel of biomarkers associated with COVID-19 pathogenesis with four clinical outcomes in hospitalized patients. For this study, the first laboratory values obtained at hospital admission were analyzed and compared. Our data confirmed the association of biomarkers related to hematological and inflammatory abnormalities,

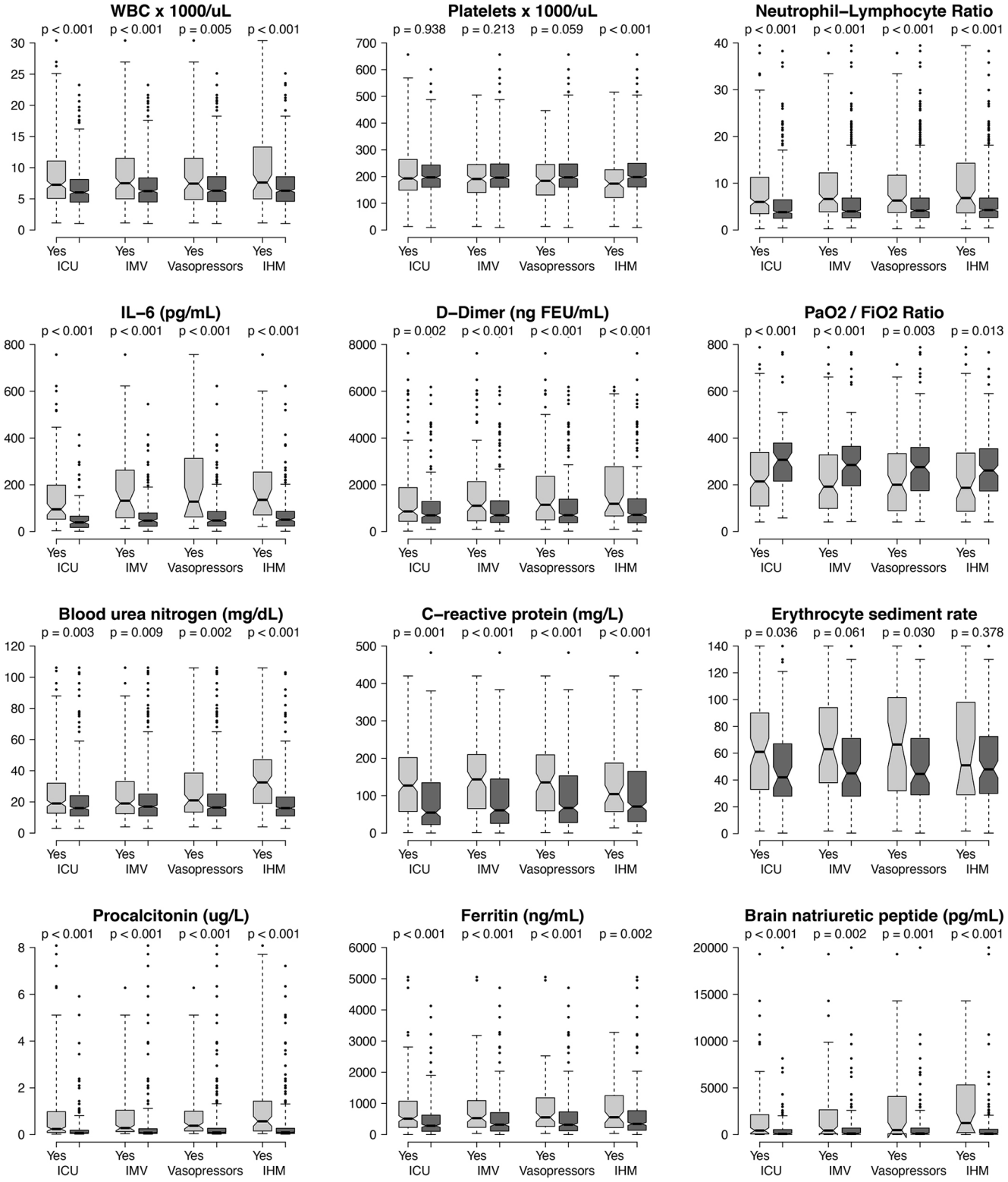

Fig. 1. Biomarker levels and severe outcomes. Box plots of biomarker levels in each of the four different severe outcomes, including ICU admission, need for IMV, need for VU and IHM. Unadjusted levels in the population with the severe outcome (indicated by Yes) were compared to those that did not registered it using a Mann-Whitney *U* test. Narrowing in the box plots represent the median value. *p*-values are indicated at the top of each box.

activation of coagulation, organ damage and worsened oxygenation with severity of COVID-19 [12,16]. When comparing groups of patients who experienced a particular outcome versus those who did not, there were significant differences in almost every biomarker. Consistently, the frequencies of patients with "abnormal" levels of most biomarkers were significantly increased when comparing patients who experienced severe outcomes to the overall hospitalized patient population. Low platelets, abnormal D-dimer, low PaO_2/FiO_2 ratio, and increased BUN levels at admission were independently associated with in-hospital mortality (IHM).

Table 2
Distribution of Biomarker values according to cut-points and outcome.

Biomarkers (cut-points)	Distribution Overall (%)	Distribution ICU (%)	Distribution IMV (%)	Distribution VU (%)	Distribution IHM (%)
WBC					
<11,000/μL	84	73	71	71	65
≥11,000/μL	16	27*	29	29	35
Platelets					
<150,000/μL	22	25	28	32	39***
150,000–400,000/μL	75	71	69	66	57
≥400,000/μL	3	4	3	3	4
N/L ratio					
0.8–3.5	35	23	19	21	20
≥3.5	65	77*	81	79	80
ESR					
<30 mm/hr	85	77	74	72	79
≥30 mm/hr	15	23*	26	28	21
IL-6					
<37.65 pg/mL	81	70	72	68	69
≥37.65 pg/mL	19	30*	28	32	31
CRP					
<10 mg/mL	39	25	24	22	31
≥10 mg/mL	61	75*	76	78	69
Ferritin					
<336 ng/mL	65	49	45	38	48
≥336 ng/mL	35	51*	55	62*	52
PCT					
<0.5 ng/mL	83	69	65	61	57
≥0.5 ng/mL	17	31*	35	39	43**
BNP					
<100 pg/mL	79	66	64	62	54
≥100 pg/mL	21	34*	36	38	46**
D-dimer					
<500 pg/mL	65	42	38	36	38
≥500 pg/mL	45	58*	62	64	62
PaO_2/FiO_2					
≥200	86	69	62	63	61
<200	14	31*	38	37	39
BUN					
<20 mg/dL	52	50	48	44	25
≥20 mg/dL	48	50	52	56	75***

Values represent the percentages of patients with biomarker levels above/below defined cut-points in the overall patient population and for those with the four different outcomes. N (overall: 700; ICU: 259; IMV: 159; VU: 119; IHM: 108). *ICU significantly different from Overall ($p < 0.01$); **significantly different from ICU ($p < 0.05$); ***significantly different from ICU ($p < 0.01$).

Since there was considerable overlap between the four different severe outcome groups (the ICU group included most of the patients in the IVM and VU groups and 80% of the patients who died), we compared the frequency distribution of abnormal biomarker levels in the IVM, VU and IHM groups to the ICU group to investigate whether there were differences that could help predict which patients in the ICU were more likely to suffer the other severe outcomes. This analysis indicated that among patients admitted to the ICU, patients who died (IHM) were more likely to have low platelets, increased BUN and increased PCT and BNP levels.

Neutrophil/lymphocyte ratios have been associated with COVID-19 severity and mortality in COVID-19 in several reports [12,19,20]. This association is likely the result of neutrophilia coupled to lymphocytopenia in severe COVID-19. The increase in the neutrophil count also appears to be associated with increased neutrophil activation and is likely the result of high levels of pro-inflammatory cytokines, particularly IL-6 and IL-8 [12,21]. The causes of lymphocytopenia in COVID-19 patients are not completely clear, but they may involve several lymphocyte subsets, including memory T helper cells, cytotoxic lymphocytes (CTLs) and regulatory T cells [22]. In our study, patients presenting with each of the four severe outcomes had higher neutrophil/lymphocyte ratios. However, after adjusting for other inflammatory markers in the logistic regression analysis, the only significant association was with need of IMV.

The severity of COVID-19 has also been associated with an acute hyper-inflammatory reaction by the immune system, or "cytokine storm", leading to immunological abnormalities, hypotension, and organ damage [23,24]. Many reports have suggested that the levels of several cytokines, particularly IL-6, as well as the levels of acute-phase proteins such as C-reactive protein and ferritin, could be considered indicators of disease severity in COVID-19 [12,25,26]. Our results showed significantly higher levels of IL-6 for patients who experienced any of the four outcomes, which is consistent with disease severity and many previous reports on the association of this cytokine with COVID-19 severity [14–18]. Moreover, the adjusted logistic regression analysis demonstrated an over three-fold increase in odds of ICU admission and need of VU for higher levels of IL-6. However, there was not a statistically significant association with need of IMV or with mortality after adjusting for other markers.

Severe COVID-19 has also been associated with reduced platelet numbers, possibly due to increased consumption due to platelet activation, aggregation, and subsequent clotting [27,28]. Unsurprisingly, microthrombi formation is responsible for many of the pulmonary, cardiac and other organ dysfunction seen in severe COVID-19 patients [29,30], and postmortem studies of COVID-19 cases have indicated that micro-thrombosis is the main causal pathology [31]. Consistent with these studies, our study showed that platelet counts were significantly lower in patients who died compared to those survived. In the adjusted logistic regression analysis, a low platelet count was predictive of IMV, VU and a three-fold increase in odds of mortality.

D-dimer level, an indicator of the activation of the coagulation system, has also been reported to correlate with the clinical severity of COVID-19 [12,32,33]. Severe COVID-19 is associated with hypercoagulability and microthrombi formation in various organs, such as the lung, heart, kidneys and brain, accounting for damage to these organs

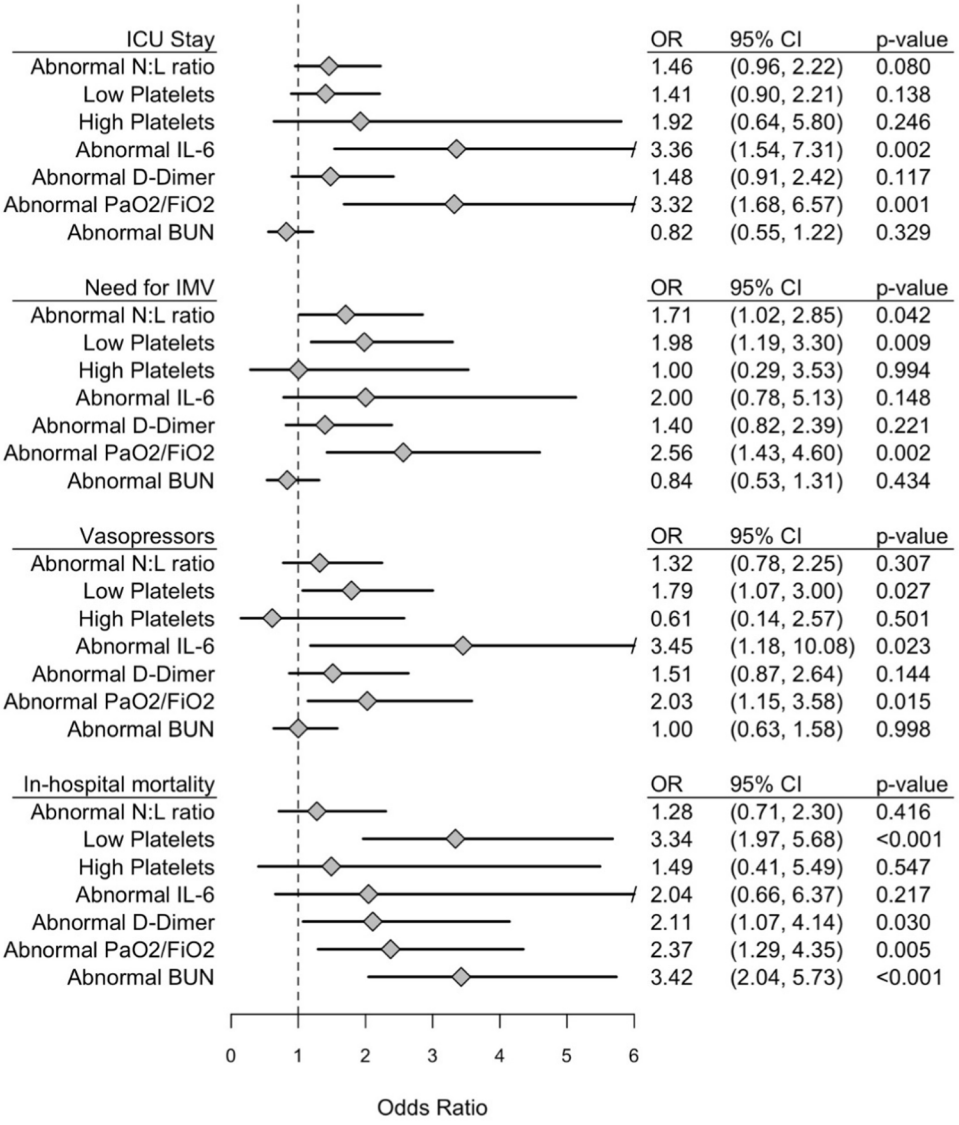

Fig. 2. Multivariable logistic regression results. Forest plots of the multivariable logistic regression results for the indicated biomarkers, showing odds ratios (OR) with confidence intervals and *p*-values.

[31,33]. Our data showed that similarly to IL-6, significantly higher D-dimer levels were found in patients who experienced any of the four high-severity outcomes, and the adjusted logistic regression analysis indicated a two-fold increase in odds of mortality.

The PaO_2/FiO_2 ratio is a marker of respiratory distress and compromised oxygen exchange, common manifestations of moderate to severe COVID-19 [33]. Interestingly, a recent study of critically ill COVID-19 patients showed a positive linear correlation between the PaO_2/FiO_2 ratio before intubation and platelet count [34]. Low PaO_2/FiO_2 is often associated with need for supplemental oxygen and mechanical ventilation. Unsurprisingly, the PaO_2/FiO_2 ratio was significantly lower in patients who experienced all four high severity outcomes. It was the only biomarker that was independently associated with every outcome in the adjusted logistic regression analysis, with two- to three-fold increased odds of adverse outcomes.

An association between BUN, an indicator of kidney function, and disease severity has also been reported in COVID-19, indicating potential kidney insufficiency [35–37]. Moreover, the BUN/Creatinine ratio has also been suggested as an even better predictor of COVID-19 disease severity and mortality [38]. Results from our study showed higher median BUN levels for patients suffering any of the four high severity outcomes. The adjusted logistic regression analysis showed a three-fold increase in odds of mortality among patients with elevated BUN levels.

This study has several limitations. Although our sample included 700 hospitalized patients, not all laboratory values were available for all patients within 24 h of admission, the only exceptions being hematological markers (neutrophil/lymphocyte ratios and platelet counts) and BUN. Because all laboratory values were taken as standard of care, the varying clinical presentation, comorbid conditions, and demographic characteristics of patients may have biased collection of these laboratory values. For example, it is likely that the patients whose arterial blood gases were assessed were expected to have oxygenation problems; this might have led to selection bias. In adjusted logistic regression analysis, patients who were missing laboratory values were given their own factor level to account for this limitation. No groups with missing laboratory values were found to be statistically significantly different than their normal level counterparts. No imputations were done for missing values.

In conclusion, our studies confirmed the association of biomarkers of hematological, inflammatory, coagulation, pulmonary and kidney function with disease severity and high severity outcomes of COVID-19. For mortality, the most substantial risk factors were related to decreased platelet count, increased D-dimer, decreased oxygenation (PaO_2/FiO_2

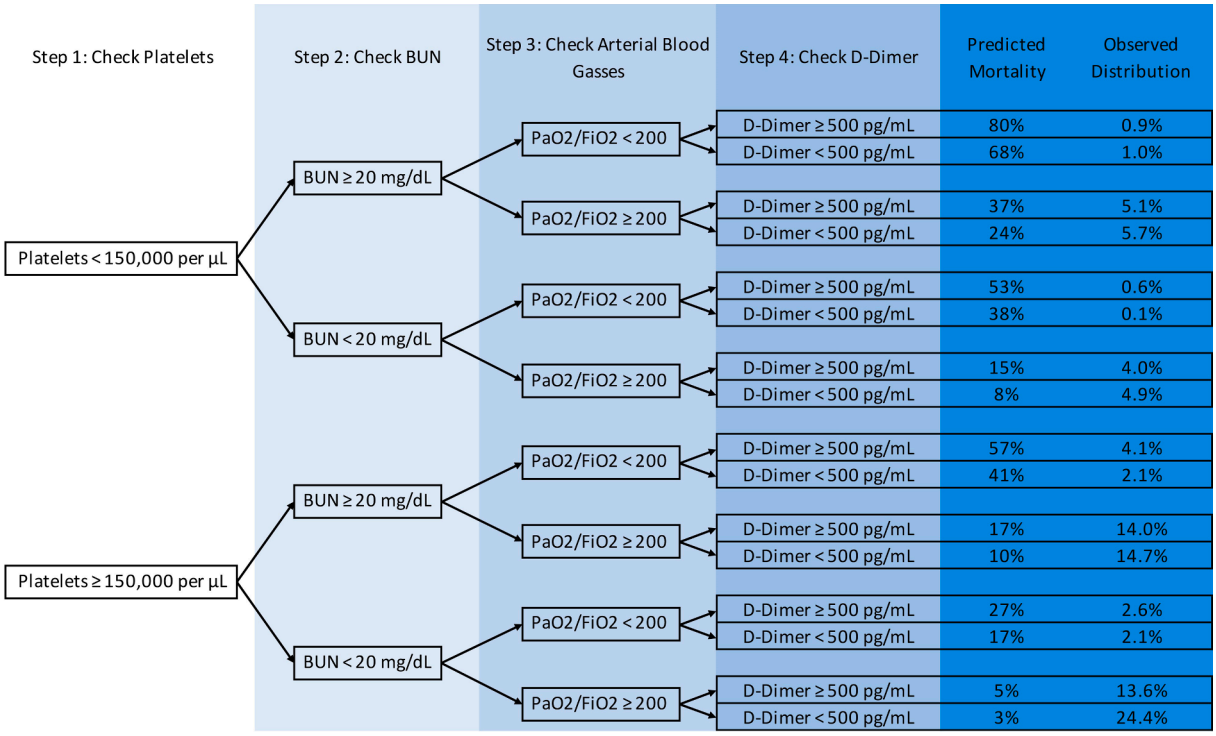

Fig. 3. Clinical model showing an algorithm including biomarkers associated with IHM.

ratio), and increased BUN. In contrast, the risk of ICU admission was significantly associated with hyper-inflammation (IL-6) and decreased oxygenation. Low platelet count, abnormal neutrophil–lymphocyte ratio, and reduced oxygenation were significantly associated with risk of requiring IMV; inflammatory markers (IL-6), low platelet count and low oxygenation were significantly associated with risk of requiring VU. Future studies should evaluate the potential mechanistic and causal roles of these biomarkers in predicting poor outcomes, and post-acute sequelae of SARS-CoV-2 infection, particularly in patients who were hospitalized and experienced more severe disease.

CRediT authorship contribution statement

Rafael Fernandez-Botran: Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Project administration. **Stephen Furmanek:** Formal analysis, Data curation, Writing – review & editing, Visualization. **Raghava Sekhar Ambadapoodi:** Validation, Investigation, Writing – original draft. **Evelyn Expósito González:** Validation, Writing – original draft. **Meredith Cahill:** Formal analysis. **Ruth Carrico:** Conceptualization, Resources, Funding acquisition. **Ozan Akca:** Writing – review & editing. **Julio A. Ramírez:** Conceptualization, Resources, Writing – review & editing, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are indebted to Mr. Alex Glynn, M.A. for his editorial expertise in the preparation of this manuscript.

Funding

This work was funded by the Center of Excellence for Research in Infectious Diseases (CERID) of the University of Louisville.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author (RFB), upon reasonable request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2021.155755.

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