

COVID-19 Related Acute Respiratory Distress Syndrome versus Classical Acute Respiratory Distress Syndrome Patients: Inflammatory Biomarkers as Predictors of Mortality in Pulmonary Septic Shock

Cosmin Iosif Trebuan^{1,2}, Daian Popa^{3,4}, Florina Buleu^{5,6}, Dumitru Sutoi^{1,5}, Carmen Gabriela Williams³, Iulia Najette Crintea^{1,3}, Raul Daniel Chioibas¹, Aida Iancu⁷, Livia Ciolac⁸, Ovidiu Alexandru Mederle^{1,3}

¹Department of Surgery I, "Victor Babes" University of Medicine and Pharmacy, Timișoara, Romania; ²Emergency County Hospital, Reșița, Romania; ³Emergency Clinical Municipal Hospital, Timișoara, Romania; ⁴"Victor Babes" University of Medicine and Pharmacy, Timișoara, Romania; ⁵Emergency County Hospital "Pius Brinzeu", Timișoara, Romania; ⁶Department of Cardiology "Victor Babes" University of Medicine and Pharmacy, Timișoara, Romania; ⁷Department of Radiology "Victor Babes" University of Medicine and Pharmacy, Timișoara, Romania; ⁸Clinic of Obstetrics and Gynecology, "Pius Brinzeu" County Clinical Emergency Hospital, Timișoara, Romania

Correspondence: Florina Buleu, Email florina.buleu@umft.ro

Introduction and Objectives: Coronavirus disease-2019 (COVID-19)-related severe acute respiratory distress syndrome (ARDS) differs pathophysiologically from other pulmonary septic shock-related ARDS. Thus, we assessed whether all-cause in-hospital mortality differs for severe COVID-19-related and classical severe ARDS and which inflammatory biomarkers can predict mortality among these patients.

Material and Methods: This single-center, retrospective, observational cohort study included pulmonary septic shock patients (n = 114) with COVID-19-related and classical severe ARDS admitted in the Intensive Care Unit.

Results: Patients with a mean age of 73 (IQR 62–82), predominantly male (63%), were divided into two groups based on outcomes: survivors (n = 50) and non-survivors (n = 64). COVID-19-related severe ARDS (n = 48) accounts for 75% of deaths. Present comorbidities like heart disease (p = 0.043), neurologic disorders (p = 0.018), and liver disease (p = 0.038) were associated with in-hospital mortality, as well. Regarding inflammatory biomarkers, the AUC/c-statistic was 0.656 (95% CI: 0.53–0.759) for leukocytes, 0.613 (95% CI: 0.509–0.717) C-reactive protein (CRP) and 0.651 (95% CI: 0.548–0.753) for procalcitonin in predicting all-cause in-hospital mortality among patients with pulmonary septic shock and severe ARDS.

Conclusion: Patients with pulmonary septic shock and with COVID-19-related severe ARDS had a higher incidence of in-hospital mortality than those with classical severe ARDS. The high value of leukocytes, C-reactive protein, and procalcitonin were predictive for all-cause in-hospital mortality in patients with pulmonary septic shock and ARDS. Infection with COVID-19 was an independent predictor of in-hospital mortality in the presence of ARDS.

Keywords: pulmonary septic shock, severe ARDS, inflammatory biomarkers, COVID-19, outcomes

Introduction

Septic shock, as a severe medical problem, has placed a substantial socioeconomic burden on intensive care units (ICUs), affecting both patients and physicians. Several pathophysiological indicators, including hypotension in the absence of hypovolemia, leukocytosis/leukopenia, elevated serum lactate, and hyper/hypothermia, define this life-threatening organ dysfunction caused by a dysregulated host response to infection.¹ Acute respiratory distress syndrome (ARDS) is

a severe complication of septic shock. Both septic shock and ARDS share similar mechanisms, characterized by inflammation and dysfunction of the endothelium. Furthermore, septic shock is the leading cause of ARDS, and individuals with sepsis-induced ARDS have a higher fatality rate compared to those with other risk factors for ARDS.²

Moreover, the pulmonary origin of septic shock (ie, pneumonia) is the most common cause of ARDS.³ Since the first documentation of ARDS, viral pneumonia has also been identified as one of its causes. However, certain strains of viruses that have a higher propensity to induce ARDS surface intermittently. Notable examples include SARS-CoV (2003), H1N1 influenza (2009), MERS-CoV (2012), and most significantly, the SARS-CoV-2 virus (2019) that sparked the global COVID-19 pandemic.⁴ As of the time of this report, the pandemic has tragically claimed the lives of at least 6 million individuals worldwide, with the majority succumbing to ARDS.⁵

The precise prevalence and mortality rate of ARDS in pulmonary septic shock is still uncertain. Disparities on a significant scale have been proposed, with ARDS in Europe purportedly being ten times lower compared to the United States.⁶ A study that included ICUs from fifty different countries discovered that the occurrence of ARDS among ICU admissions was 10.4%.³ It became clear that this syndrome was not receiving the attention it deserved, leading to a significant mortality rate. These findings highlight the necessity for enhancing the care and treatment of patients suffering from ARDS.

Procalcitonin (PCT) levels, one of the inflammatory markers, can be evaluated to predict survival depending on the pathogen in sepsis patients.⁷ Additionally, procalcitonin levels of sepsis patients who do not survive are higher than those who survive.⁸ On the other hand, inflammatory findings such as procalcitonin, C-reactive protein (CRP), and ferritin are also associated with the severity of the disease in COVID-19 patients. Monitoring these inflammatory findings may help predict prognosis and treat COVID-19.^{9,10}

Therefore, we aimed to investigate several more crucial aspects of ARDS. The main goal was to assess all-cause in-hospital mortality in patients with pulmonary septic shock and severe ARDS, considering the presence or absence of SARS-CoV-2 infection and the second one sought to determine the ability of these factors to predict in-hospital mortality.

Material and Methods

Study Population, Inclusion, and Exclusion Criteria

For the present study, we reviewed all electronic and paper medical records covering admission to the ICU hospitalization, including administered treatments of consecutive patients aged 18 years or older with pulmonary septic shock and ARDS ($n = 229$), to analyze the medical reports, ventilation modes, and outcomes. All patients from this study were hospitalized at the County Emergency Hospital Resita, Romania, between 1 November 2021 and 31 October 2022.

Patients included in the study were those with septic shock resulting from pulmonary infections. The diagnosis of septic shock¹¹ was determined by the need for a vasopressor to maintain a mean arterial pressure (MAP) of ≥ 65 mmHg, an elevated serum lactate level above two mmol/L, and procalcitonin levels higher than 0.5 ng/dL.

One hundred fourteen patients admitted with ARDS in the ICU from our hospital who met the inclusion criteria were selected. The patient's choice were made based on the following inclusion criteria even from the ICU admission: age 18 years or older, diagnosis of pulmonary septic shock and severe ARDS supported by Berlin-definition criteria¹² ($\text{PaO}_2/\text{FiO}_2 < 100$ mmHg), and severe lung lesions ($>60\%$ on chest computed tomography or radiography). Patients were excluded for insufficient data available regarding analyzed data, therapy, and outcome, as well as the patients with septic shock caused by another source than the lungs, severe renal (Creatinine clearance <30 mL/min), and liver failure ($>5\times$ normal transaminase levels) and major COVID-19 complications as acute myocardial infarction (AMI), pulmonary embolism and ICU length of stay. The baseline data of all patients was collected first at admission in the ICU and second at 30 days, following up in-hospital mortality. The pulmonary septic shock patients were divided into two groups based on death outcome in survivors ($n = 50$, 56% of patients with COVID-19-related severe ARDS patients) and non-survivors ($n = 64$, 75% of patients with COVID-19-related severe ARDS).

SARS-CoV-2 infection was confirmed by positive detection of viral RNA in nasopharyngeal secretions using a specific real-time reverse transcriptase–polymerase chain reaction (PCR) test. A consistent clinical history, epidemiological contact, and a positive SARS-CoV-2 test confirmed COVID-19 illness.¹³ COVID-19-related severe ARDS was

diagnosed when someone with confirmed COVID-19 infection meets the Berlin 2012 ARDS diagnostic criteria.¹² These criteria use the arterial oxygen partial pressure ratio to inspired oxygen fraction (PaO₂/FiO₂) to categorize the severity of the condition.

For comparisons with COVID-19 ARDS, we included patients admitted to our department who, during hospitalization, met the diagnostic criteria for ARDS. To ensure the homogeneity of comparison groups about ARDS, we excluded patients with ARDS attributable to coinfection with viral and bacterial pulmonary pathogens. Based on available clinical and microbiological studies, we included only patients with ARDS secondary to direct lung injury from viral, bacterial, or culture-negative pneumonia.

Lung protective mechanical ventilation was part of the management of patients with ARDS. The patients were intubated with endotracheal intubation (ETI) in case of severe hypoxemia with PaO₂/FiO₂ <150 mmHg and a breathing rate above 25–30 per min despite maximal noninvasive support.¹⁴

Data Collection

The following patient data were collected, including their demographics (age, sex, smoking status), length of ICU stay, use of anticoagulant or antiplatelet therapy, presence of comorbidities (COVID-19, heart failure, chronic obstructive pulmonary disease, chronic venous insufficiency, chronic kidney disease, liver cirrhosis, neurological disorders, active cancer, hematological diseases), laboratory analysis results (complete blood count, C-reactive protein, serum creatinine, procalcitonin, international standard ratio, fibrinogen), vital signs (SpO₂, heart rate, blood pressure) and arterial blood gases (pH, PaO₂, FiO₂, PaCO₂, lactate).

Statistical Analysis

All statistical analysis was performed using Statistical Package for Social Sciences software (SPSS v28.0.1.1., IBM Corporation, Armonk, NY, USA). Patients were divided, according to their evolution, into survivors and non-survivors. They were characterized using descriptive statistics [percentage, median, range of quarters]. The analytical Kolmogorov–Smirnov test was performed to evaluate the normality of distribution. All numerical variables displayed non-normal distribution, plotted as median (25th and 75th IQR), and the Kruskal–Wallis test was used for intergroup comparison. Categorical variables were plotted as numerical and percentile values. They were compared using the Chi-squared test. The Spearman rank correlation coefficient (*r*) was used to evaluate the relationships between several clinical and biological parameters and mortality. In addition, binary logistic regression was performed to assess factors associated with mortality among the study population. Furthermore, a receiver operating characteristic (ROC) curve was plotted to evaluate the predictive value of inflammatory biomarkers about patient mortality across the entire study population. A two-tailed *p*-value <0.05 was considered statistically significant.

Ethics

This study follows the Declaration of Helsinki and was performed according to the Ethics Committees of the Resita County Emergency Hospital (1424/30.01.19).

Results

Descriptive Statistics

The entire study formed 114 patients, who, according to their evolution, were divided into two groups: survivors (*n* = 50) and non-survivors (*n* = 64). These patients' demographic, clinical, and biological parameters are summarized in Table 1. Fifty-six percent (*n* = 28) of survivors and 75% (*n* = 48) of non-survivors were positive for SARS-COV-2. There were no significant differences about age and gender between the two groups. (Table 1)

Regarding blood analyses, we noticed a trend toward lower blood pH and hemoglobin among non-survivors, although not reaching statistical significance (*p* = 0.120 and *p* = 0.889, respectively). Lactic acid was also higher in non-survivors (median 3.30 mmol/L, IQR: 1.95–5.10), although not reaching statistical significance (*p* = 0.074).

Table 1 Descriptive Statistics for the Studied Groups (n = 114)

Variable	Survivors (n= 50)	Non-survivors (n= 64)	p value
Age (years)	72 (62, 81.2)	74.5 (63.2, 82)	0.419
Male, % (n)	66 (33)	60.9 (39)	0.578
Smoker,% (n)	16 (8)	14.1 (9)	0.796
Heart failure, % (n)	20 (10)	37.5 (24)	0.043
CVI, % (n)	2 (1)	12.5 (8)	0.075
COVID, % (n)	56 (28)	75 (48)	0.033
COPD, % (n)	22 (11)	17.2 (11)	0.518
CKD, % (n)	10 (5)	15.6 (10)	0.418
Neurologic disorder, % (n)	16 (8)	35.9 (23)	0.018
Hepatic disorder, % (n)	18 (9)	35.9 (23)	0.038
Psychiatric disorder, % (n)	4 (2)	1.6 (1)	0.581
Oncologic disorder, % (n)	14 (7)	6.3 (4)	0.208
Hematological disorder, % (n)	38 (19)	31.3 (20)	0.451
Chronic ischemic heart disease, % (n)	34 (17)	39.1 (25)	0.578
Plasma exchange, % (n)	16 (8)	37.5 (24)	0.020
CVVHDF % (n)	36 (18)	46.9 (30)	0.243
Antiplatelet treatment, % (n)	54 (27)	54.7 (35)	0.942
Anticoagulant treatment, % (n)	88 (44)	85.9 (55)	0.746
HFNC, % (n)	66 (33)	64.1 (41)	0.830
CPAP, % (n)	52 (26)	59.4 (38)	0.431
Oral intubation, % (n)	56 (28)	64.1 (41)	0.382
ICU stay, (days)	7.5 (6, 10.2)	6 (4.2, 10)	0.090
SpO2 at admission, %	81.5 (74, 87)	78.5 (74, 87.7)	0.258
PaO2 in ICU 1 hour from admission, %	57 (49, 62.5)	54 (47, 62.7)	0.404
FiO2, %	1 (0.9, 1)	1 (0.9, 1)	1
PaO2/FiO2,%	57 (49, 75.5)	54 (47, 71.1)	0.380
PaCO2,%	35.3 (29.1, 38.4)	36 (29, 43.5)	0.631
pH	7.42 (7.34, 7.45)	7.37 (7.27, 7.45)	0.120
Hb, g/dL	13.5 (11.1, 14.7)	12.9 (11.2, 14.7)	0.889
Lactic acid, mmol/L	2.45 (1.75, 3.50)	3.30 (1.95, 5.10)	0.074
WBC x109/mm3	14.99 (9.38, 19.41)	18.97 (14.79, 25.03)	0.004
PLT x 103/mm3	238 (164, 388)	242 (156, 382)	0.713
CRP, mg/L	106 (61.2, 154.7)	139.5 (67.7, 207.7)	0.038
Procalcitonin ng/mL	3.40 (1.50, 8.22)	6.65 (3.09, 10.50)	0.006
Fibrinogen, mg/dL	424 (275, 563)	475 (285, 623)	0.406
Creatinine, mg/dL	1.34 (0.84, 2.13)	1.54 (1.09, 2.14)	0.286
INR	1.39 (1.14, 1.83)	1.36 (1.13, 1.70)	0.551

Note: Significant differences are represented in bold.

Abbreviations: CVI, chronic venous insufficiency; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CVVHDF, continuous veno-venous hemodiafiltration; HFNC, high flow nasal cannula; CPAP, continuous positive airway pressure; ICU, intensive care unit; SpO2, oxygen saturation on pulse oximeter; PaO2, partial pressure of oxygen in arterial blood; FIO2, fraction of inspired oxygen; PaCO2, partial pressure of carbon dioxide in arterial blood; pH, potential of hydrogen; Hb, hemoglobin; WBC, white blood cell; PLT, platelets; CRP, C-reactive protein; INR, international normalized ratio.

Furthermore, non-survivors displayed higher levels of inflammatory biomarkers: WBC ($p = 0.004$), C-reactive protein ($p = 0.038$), and procalcitonin ($p = 0.006$). These differences are also depicted in [Figure 1](#).

Factors Correlated with Mortality Across the Entire Lot

As can be seen in [Table 2](#), there was a significant positive correlation between mortality and COVID-19 infection, heart failure, chronic venous insufficiency, neurologic disorders, and hepatic disorders.

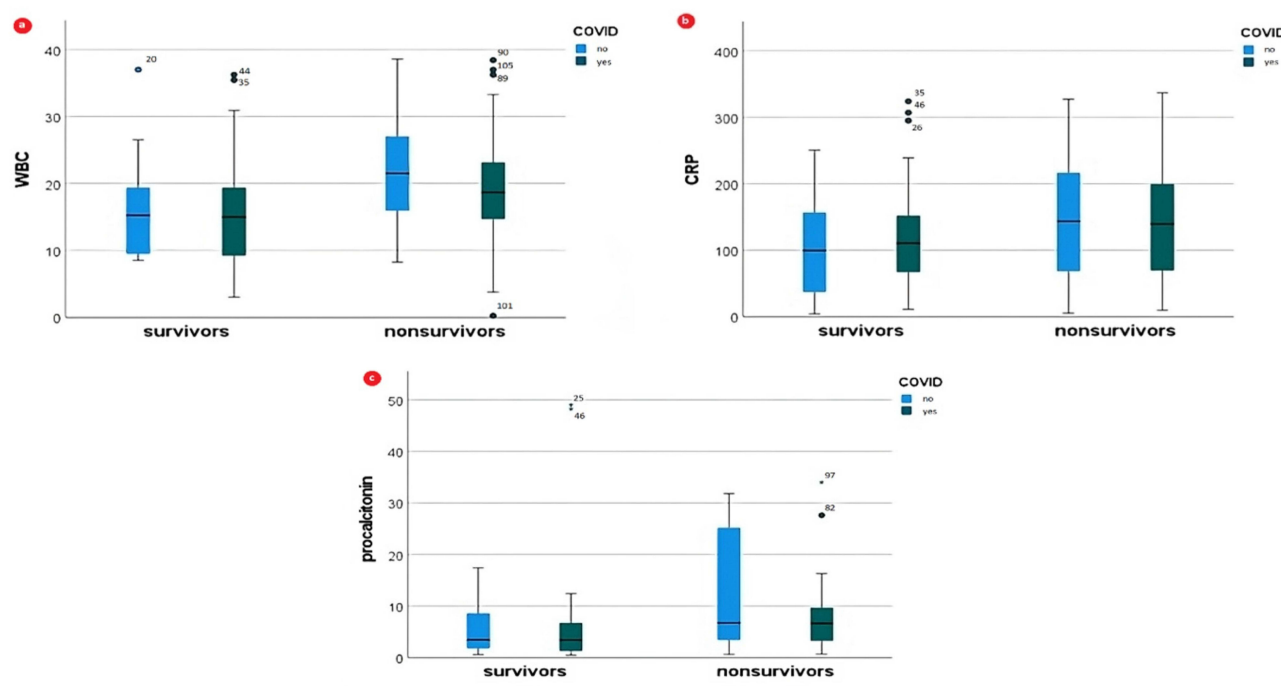


Figure 1 Comparison of inflammatory biomarkers between pulmonary septic shock patients with ARDS who survived and those who did not survive (a) WBC, (b) CRP, and (c) procalcitonin.

In addition, inflammatory biomarkers, WBC, CRP, and procalcitonin, were also positively correlated with mortality (Table 2, Figure 2).

Factors Associated with Mortality Across the Study Population

In addition, we performed binary logistic regression analysis to verify the association of COVID-19 infection, inflammatory biomarkers, and ventilation modes with patient mortality in severe ARDS patients. As seen in Table 3, COVID-19 infection, WBC, and plasma exchange appeared as independent factors associated with mortality of ARDS patients ($p = 0.026$, $p = 0.027$, and $p = 0.015$, respectively).

Table 2 Correlation Analysis of Factors Associated with Mortality Across the Entire Lot

Risk factor	p value	R
COVID -19	0.033	0.200
Heart failure	0.043	0.190
CVI % (n)	0.039	0.193
Neurologic disorder	0.017	0.222
Chronic kidney disease	0.382	0.083
Chronic obstructive pulmonary disease	0.522	-0.061
Oncological disease	0.167	-0.130
Hematological disease	0.455	-0.071
Hepatic disease	0.035	0.198
Plasma exchange	0.013	0.233
WBC	0.004	0.268
CRP	0.038	0.195
Procalcitonin	0.005	0.259

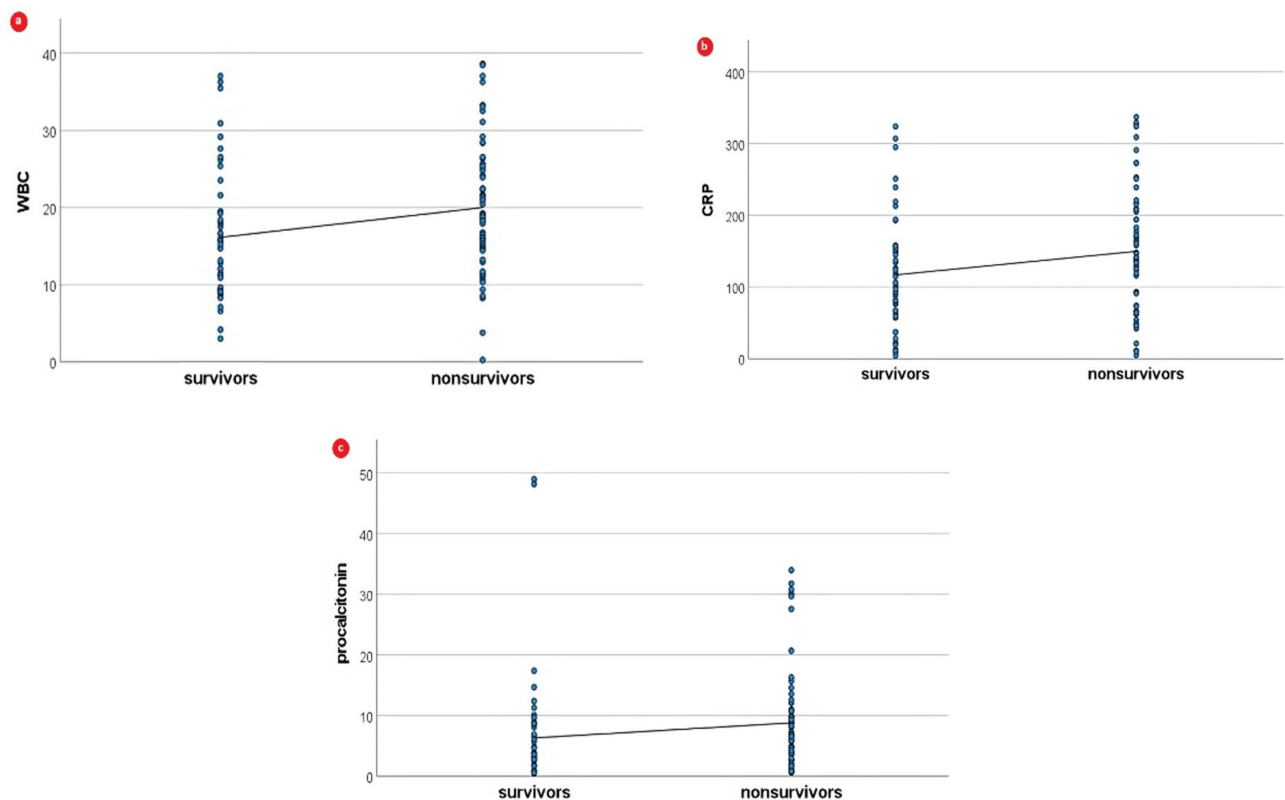


Figure 2 Correlation analysis of inflammatory biomarkers in survivors and non-survivors: (a) WBC, (b) CRP, and (c) procalcitonin.

Moreover, using ROC analysis, we evaluated the discriminatory performance of several inflammatory biomarkers in predicting mortality among severe ARDS patients, as summarized in [Figure 3](#) and [Table 4](#).

Among the evaluated biomarkers, WBC had an AUC/*c*-statistic of 0.656 (95% CI: 0.53–0.759), CPR had an AUC/*c*-statistic of 0.613 (95% CI: 0.509–0.717) in predicting mortality and procalcitonin had an AUC/*c*-statistic of 0.651 (95% CI: 0.548–0.753) in predicting mortality among those with pulmonary septic shock and severe ARDS.

Table 3 Binary Logistic Regression Analysis of Risk Factors Associated with Mortality in Severe ARDS

Variable	OR	95% CI for OR		Sig.
		LL	UL	
COVID –19	0.2719	1.125	6.574	0.026
WBC (x10 ³ /mm3)	0.1067	1.007	1.130	0.027
Procalcitonin (ng/mL)	1.009	0.954	1.068	0.746
Plasma exchange	3.407	1.274	9.114	0.015
HFNC	1.244	0.499	3.100	0.639
CPAP	1.334	0.562	3.169	0.514
Oral intubation	1.072	0.451	2.546	0.875

Note: Significant differences are represented in bold.
Abbreviations: OR, odds ratio; 95% CI, 95% Confidence Interval; LL, lower limit; UL, upper limit; WBC, white blood cells; HFNC, high-flow nasal cannula; CPAP, continuous positive airway pressure.

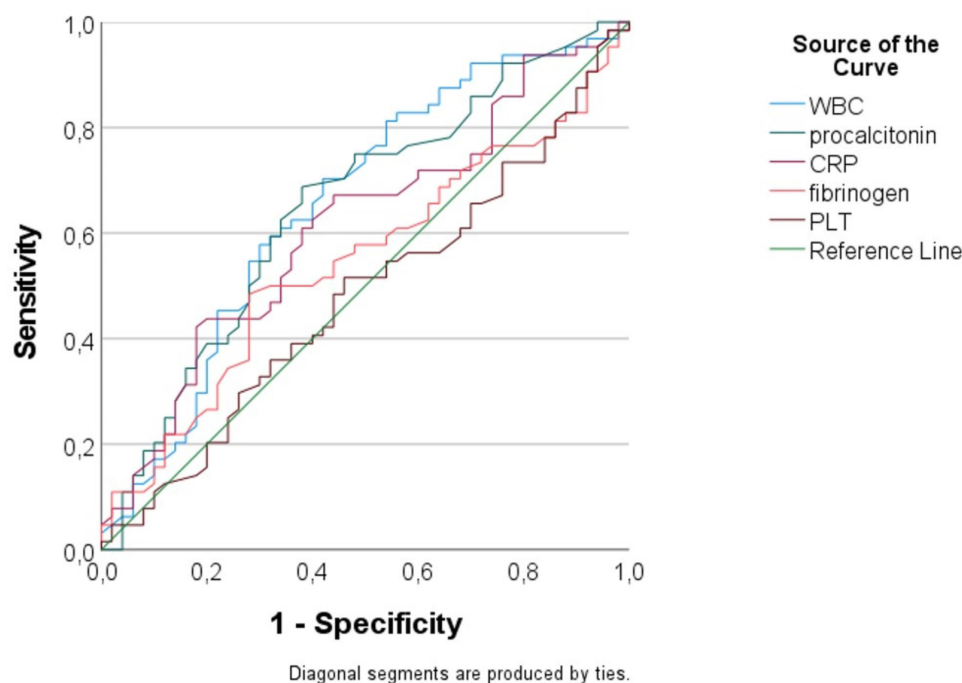


Figure 3 Discriminatory performance of various inflammatory biomarkers in predicting mortality among patients with pulmonary septic shock and severe ARDS; ROC, receiver operating characteristic.

Discussion

Our study found that the prevalence of non-surviving patients with pulmonary septic shock and ARDS was 56.14% ($n = 64$). These findings are different from another previous study conducted in America, which included the VALID cohort (Validating Acute Lung Injury markers for Diagnosis; $n = 337$) and Berlin criteria defined the ARDS, where the attributable mortality of ARDS was 37% (CI 10%, 51%). It should be mentioned that this study included hospitalized patients before the onset of the COVID-19 pandemic.¹⁵ However, another study, Field 12 from China, with a similar design to ours, was employed to examine the mortality rates of COVID-19 and non-COVID-19 ARDS in the Asian population in 2021. This study focused on patients who needed invasive mechanical ventilation. The findings revealed that the all-cause in-hospital mortality rate for all patients was 38 (38%), and there were no significant differences between COVID-19 and non-COVID-19-related ARDS (17 [34%] vs 21 [42%], $p = 0.410$). It is important to note that this study included only unvaccinated patients and highlighted that the two potential risk factors for patients with ARDS are immunocompromised status and progression to severe ARDS. COVID-19 itself was not identified as a risk factor for mortality. Similar to our study, high in-hospital mortality was also reported by other studies that included patients with

Table 4 Discriminative Ability Comparison of Analysis in Predicting Death Outcomes in Patients with Pulmonary Septic Shock and Severe ARDS

	AUC	SE	95% CI	Sensitivity	Specificity	Cut-Off	p-value
WBC ($\times 10^3/\text{mm}^3$)	0.656	0.053	0.53–0.759	0.656	0.600	16.05	0.004
Platelets ($\times 10^9/\text{mm}^3$)	0.480	0.054	0.373–0.587	0.453	0.560	259	0.713
CRP (mg/L)	0.613	0.053	0.509–0.717	0.609	0.600	125.5	0.038
Procalcitonin (ng/mL)	0.651	0.052	0.548–0.753	0.641	0.640	4.75	0.006
Fibrinogen (mg/dL)	0.545	0.054	0.373–0.587	0.516	0.560	448	0.406

Note: Significant differences are represented in bold.

Abbreviations: AUC, Area under the curve; SE- Standard Error; 95% CI, 95% Confidence Interval; WBC, white blood cells; CRP, C-reactive protein.

ARDS. The one conducted by Khandelwal et al¹⁶ reported a mortality of 68% higher among patients who received rescue therapy compared with patients treated conventionally, or the one performed by Schuijt et al, which had a primary end-point 28-day mortality and which observed a mortality of 44% in patients with severe ARDS and COVID-19. Differences in these studies' results may be from differences in disease severity. For example, in our study, we included patients with pulmonary septic shock and severe ARDS. In addition, variations in study populations (eg, comorbidities, age, sex) may also affect study results.

To assess the significance of risk factors in 60-day mortality, a study examined the interaction between disease groups (Sepsis, ARDS, or COVID-19) using logistic regression models. The study included a total of 32,501 adult ICU patients. Notably, the model analyzing 60-day mortality in sepsis and COVID-19 revealed significant interactions with disease groups for age, sex, and asthma. Similarly, the model investigating 60-day mortality in ARDS and COVID-19 identified significant interactions with cohorts for acute disease severity, age, and chronic renal failure.¹⁷ In our study, the risk factors for in-hospital mortality were the presence of COVID-19 infection, heart failure, chronic venous insufficiency, neurologic disorders, and hepatic disorders. When all-cause in-hospital mortality was analyzed in a recent study where a 1:1 propensity score matching was performed to correct potential confounders by age, obesity or not, and ARDS severity for all included patients ($n = 100$), this was 38 (38%), with no significant differences found between COVID-19 ($n = 50$) and non-COVID-19 ($n = 50$) ARDS ($p = 0.410$). Both groups analyzed had no statistically significant differences regarding length of hospitalization (30.0 [20.0–46.0] vs 27.0 [13.0–45.0] days, $p = 0.312$) and length of ICU hospitalization (19.0 [13.0–35.0] vs 16.0 [10.0–32.0] days, $p = 0.312$). Immunocompromised status (Hazard ratio: 3.63; 95% CI: 1.51–8.74, $p = 0.004$) and progression to severe ARDS (Hazard ratio: 2.92; 95% CI: 1.18–7.22, $p = 0.020$) were significant predictors related to in-hospital mortality.¹⁸ Another study enrolled 63 patients with moderate to severe primary ARDS, including 38% ($n = 24$) of patients with confirmed SARS-CoV-2 infection and 62% ($n = 39$) of patients with other causes of ARDS (including six cases associated with a flu diagnosis). The median age was 61 years (IQR, 51–69). There were statistically significant differences in the COVID group, as they were older ($P = 0.02$) and had a higher incidence of obesity ($P = 0.04$) and diabetes ($P = 0.03$). The prevalence of immunodeficiency was significantly higher in the non-COVID-19 group ($P = 0.004$). The median time (IQR) between symptom onset and orotracheal intubation was longer in the COVID-19 group (ten vs five days; $P = 0.0001$). On discharge from the ICU, the survival rate was 46% in the non-COVID-19 group and 42% in the COVID-19 group ($p = 0.80$).¹⁹ In a similar study, overall hospital mortality was 59% ($n = 108$), with high in-hospital mortality for patients with severe ARDS. Still, over 80% of study patients discharged alive survived the mid-term observation period. Non-survivors were at a median of 68 years (IQR 63–75) and significantly older than survivors (IQR 58–70).²⁰

In our study, most patients were between 50 and 80 years old, with 35% from the 70–80 age decade. Two young patients, ages 21 and 30 years, were also included, of whom one died. This is concordant with other studies that concluded that elderly patients were at the highest risk of developing a severe form of COVID-19; however, although rarely seen, young patients can also be affected.²¹

Gender distribution displayed a male prevalence (63% male ($n = 72$)). This is concordant with general observations and studies, which state higher risks for males regarding severe forms of COVID-19.²² The mortality for male patients was slightly higher (61% vs 59%) than female patients. The smaller total number of female patients can explain this insignificant statistical difference. It is already known that the number of chronic comorbidities is increasing the risk of severe disease in COVID-19,²³ which was also observed in this study. Patients from the survivor's group ($n = 50$) had a mean of 3.2 ± 0.6 comorbidities, while the non-survivor patients' group ($n = 64$) had a mean of 3.33 ± 1.49 comorbidities. Only one patient from the non-survivor's group did not present any comorbidity, showing a significant risk for a severe form of COVID-19 due to comorbidities. In terms of the gender comparison, we observed that male patients had more often hepatic, cardiac, and pulmonary diseases, which could be because men in Romania drink alcohol more frequently and in higher quantities than women and, therefore, have a higher risk for chronic diseases.^{24,25} The same is shown for smoking and working in hazardous conditions as etiological factors for pulmonary diseases, from which men are more often affected.²⁶ Unlike males, female patients in this study have a BMI $> 30 \text{ kg/m}^2$ than male patients (56% vs 37%). This is also concordant with the PREDATOR study of Popa et al on 2681 subjects aged 20–79 years from Romania, where they observed that women

were more likely to be obese than men.²⁷ This would also explain why female patients in this study have a higher prevalence of diabetes mellitus, as obesity is a significant risk factor for it.

To evaluate which factors are associated with mortality across the patients with pulmonary septic shock and severe ARDS included in our study, we performed binary logistic regression analysis. Concerning the inflammatory biomarkers analyzed (CRP, lactic acid, procalcitonin, and leukocytes), significantly more significant increases were found for routine markers (CRP, WBC, and procalcitonin) in patients with worse evolution. This test revealed that in our study population, the inflammatory biomarkers upon admission, such as WBC, CRP, and procalcitonin, were the most critical factors associated with patients' mortality, as opposed to age, gender, oxygenation at admission/during the first hour in the ICU and ventilation modes, which were similar between the two groups. A single-center prospective cohort study of patients diagnosed with COVID-19 ($n = 60$) showed a link to mortality in these patients for CRP, lactate dehydrogenase, ferritin, and IL-6, not just COVID-19 severity. In fatal patients, these parameters were statistically increased.²⁸

As our results show, the discriminatory performance of different inflammatory biomarkers in predicting mortality among patients with pulmonary septic shock and severe ARDS was as follows: the WBC had an AUC/c statistic of 0.656 (95% CI: 0.53–0.759), CPR had an AUC/c-statistic of 0.613 (95% CI: 0.509–0.717) in predicting mortality and procalcitonin had an AUC/c-statistic of 0.651 (95% CI: 0.548–0.753). These biomarkers are still a diagnostic tool for differentiating between favorable outcomes and mortality in patients with severe ARDS. Contrary to our results, the study of Schupp et al that investigates the diagnostic and prognostic value of C-reactive protein and procalcitonin in patients with sepsis and septic shock shows that CRP and procalcitonin have a poor predictive value about 30-day all-cause mortality.²⁹ Therefore, the present study highlights the need to further evaluate inflammatory biomarkers in patients with pulmonary septic shock and severe ARDS.

Limits of Study

There are a few limitations to consider in our study. Firstly, being a retrospective observational cohort study, selection bias is possible due to other prognostic variables. However, we took measures to minimize this bias by including participants from both groups who were diagnosed with pulmonary septic shock and severe ARDS and admitted to the same hospital simultaneously, thus reducing potential confounders. Secondly, the sample size in our study was small due to inclusion criteria (severe ARDS), which means that the clinical results only represent patients with pulmonary septic shock and severe ARDS from a single regional hospital. Although we used propensity score matching to address extreme values and adjusted for known confounders, we may have missed other variables. Thirdly, it is essential to note that only a tiny part of our study's patients with COVID-19-related severe ARDS were vaccinated. This is due to several factors, such as vaccination policies, incomplete information, and individual choices in 2021. Therefore, the study primarily shows the results of unvaccinated patients. Fourthly, our study mainly included patients with an average PaO₂/FiO₂ ratio of 55 mmHg, as we had limited ICU beds available. This limitation hindered our ability to fully assess the effectiveness of noninvasive mechanical ventilation, as these patients would have benefited more from endotracheal intubation. Furthermore, it made it challenging to compare our results with other studies that used different criteria for defining ARDS or did not analyze patients based on ARDS severity. Additionally, the absence of specialized equipment such as ECMO restricted the extent of therapy we could provide.

Conclusion

Patients with pulmonary septic shock and with COVID-19-related severe ARDS had a higher incidence of in-hospital mortality than those with classical severe ARDS. The high value of leukocytes, C-reactive protein, and procalcitonin were predictive for all-cause in-hospital mortality in patients with pulmonary septic shock and ARDS. Infection with COVID-19 was an independent predictor of in-hospital mortality in the presence of ARDS. Furthermore, the importance of these inflammatory biomarkers in predicting mortality needs to be noted and further investigated. Therefore, routine laboratory markers CRP, WBC, and procalcitonin can distinguish patients who develop severe ARDS in terms of an unfavorable outcome.

Institutional Review Board Statement

The study was conducted following the Declaration of Helsinki and approved by the Ethics Committee of Emergency Clinical Hospital Resita (approval number: 1424/30.01.2019).

Data Sharing Statement

The datasets are private, but de-identified data may be provided upon request from Popa Daian.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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