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# Identification of Risk Factors Predicting Mortality in Patients with Acute Respiratory Distress Syndrome Related to Severe COVID-19

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## Abstract

Acute Respiratory Distress Syndrome (ARDS) is one of the common clinical manifestation of severe COVID-19 and it is also responsible for the high ventilators demand in worldwide. Our study aims to assess the risk factors predicting mortality in patients with ARDS developing as complication of severe COVID -19. We collected clinical data of 289 COVID- 19 related to ARDS patients from 4 hospitals in Baku city, Azerbaijan. The clinical characteristics of the survivors ARDS group and non-survivors ARDS group of COVID-19 patients were clinically, laboratory and radiographically compared.

Results indicated that the median age of non-survivors ARDS patients was 68.4 years old, which was significantly older than those with survivors ARDS by 9,9 years. Male and patients with BMI>30 were more likely to die from ARDS. The prevalence of consolidation (Consolidation\ground glass opacities ratio>1) in lung, secondary bacterial infection, mechanical ventilation and pack of use dexamethasone before intubation were common among non-survivors ARDS.

Carlson index was higher in non-survivors ARDS patients (p=0.001). Among laboratory values most important risk factors predicting death of patients with ARDS were: D-dimer (p=0.0001), creatinine (p<0.009), lymphocytes can't $<0.6 \times 10^9$ ($p \leq 0.045$), procalcitonin (p<0.01), and brain natriuretic peptide (p<0.0001). SOFA score at the time of admission was higher in non survivors ARDS patients (p<0.05). Partial pressure of oxygen to fraction of inspired oxygen ($PaO2/FiO_2$) at the time of admission also was significantly lower compared to survivors ARDS patients (p<0.05) and arterial blood gas analysis values were significantly differ: partial pressure of carbon dioxide ($PaCO_2$) was markedly higher (p=0.023), $PaO_2$ was lower (p=0.026) and acidity of the blood pH was also lower (p=0.02).

We identified predictors of mortality in patients with ARDS related to severe COVID-19. These findings may be helpful for healthcare providers take appropriate measures and impact to clinical outcomes in patients with severe COVID-19 complicated with ARDS.

**Keywords:** Acute respiratory distress syndrome • Severe COVID-19 • Intensive care unit • Patient outcomes • Risk factors • Mortality

## Introduction

Approximately up to 20% of patients hospitalized with moderate to severe coronavirus disease 2019 (COVID-19) are admitted to intensive care unit (ICU) with severe hypoxemia and diffuse lung infiltrates [1] and many of them progression of the disease may require mechanical ventilation(MV) for the acute respiratory distress syndrome (ARDS) [2-4]. Addressing this challenge would be requiring a good understanding of the factors that predict poor clinical outcomes in patients with severe COVID-19 complicated with ARDS.

The severity of hypoxemia, expressed as the $PaO_2/FiO_2$ (P/F) ratio is widely used to startify ARDS into mild, moderate and severe categories according to the Berlin definition [5]. There is large number evidences regarding risk factor predicting mortality in ARDS, however, many of these evidences are conflicting and can`t be used for identification of mortality risk in such patients [6-8]. ARDS complicated of COVID-19 appears to have atypical features compared to other causes of ARDS. In appropriate correlation of dyspnea and hypoxemia is one of most common clinical manifestations of ARDS developed as result of COVID-19 [9,10].

The goal of this study was to identify risk factors predicting mortality in patients with severe COVID-19 complicated with ARDS. We specifically tested the association of these clinical outcomes with the changes in $PaO_2/FiO_2$ ratio (P/F), arterial blood pH the consolidation to ground glass opacities ratio (C/GGO) the Murray lung injury score (MLIS).

## Methods

This retrospective study was approved by The University Review Board with an exemption for informed concert. Data came from five COVID-19 based hospitals and two of them were university hospitals. Persons under investigation registry from August 01, 2021 to December 30, 2021. The study population included all adults (>18 years ) treated in the hospitals ICUs with ARDS and with a confirmed positive real –time polymerase chain reaction test for SARS-CoV-2 on a nasopharengeal swab specimen (RT-SARS-CoV-2). The number of patients in this study was 289.

The study outcomes were in-hospital mortality in the first 28 days after ICU

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admission. Patients were considered survivors if they were discharged alive from the hospital at the time of data analysis.

Demographics major comorbidities, vital signs and laboratory values were assessed at ED admission. Arterial Blood Gas (ABG) variables included PH, partial pressure of oxygen ($PaO_2$), and partial pressure of carbon dioxide ($PaCO_2$).

We calculated the multivariable MLIS with a modified radiographic scoring method [11], as follows 3 thoracic radiologists scored the geographical extent of parenchymal lung infiltrates or consolidation in each lung separately on 0-4 scull (0= no involvement, 1=<25%, 2=26-50%, 3=51-75%, 4=>75% involvement). For each patient, the mean scores for the right and left lung were added together, divided by 2, and rounded to the nearest integer [12].

The mean value of each score (SOFA,MLIS, Cons/GGO ratio and P/F ratio) during days 1 to 4, 5 to 8, 9 to 12 and 13 to 16 of ICU admission were calculated separately, and referred to as early and late time points, respectively, as described in results section.

Group comparisons of categorical variables in frequencies and percentages were performed using the $X^2$ test or Fisher exact test. The temporal differences in clinical variables between survivor and non-survivor groups were compared using a t-test. The associations between clinical variables and mortality were evaluated using logistic regression with odds ratios (ORs). Logistic regressions were adjusted for age, gender and the presence of comorbidities, measured by Carlson index. For all analyses, a P value of <0.05 was considered to be statistically significant.

## Results

The study size consisted of 289 COVID-19 positive patients admitted to intensive care unit (ICU) of university and non-university hospitals, of Baku city. Mortality was 41.9%. The demographics, comorbidity, vital signs, ABG and other laboratory values at admission to the ICUs have demonstrated on Table 1. Patients in the survivors group were younger compared to non-survivor group (p<0.0001) and less male (p<0.05).

Among comorbidities obesity (BMI> 30 kg/m²), chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD) were common in non-survivor group (p=.001; =.02; =.003; respectively). Carlson index also was higher in non-survivor group. (p=0.001)

In non-survivor patients group also had slightly lower value of MAP (p=.042) and markedly lower value of oxygen saturation (p=0.007) and respiratory rate (p=0.006). Among laboratory values notable differences were fixed accordingly higher serum levels of creatinine, bilirubin, brain natriuretic peptide (BNP), d-dimer, and procalcitonin (PCT) in non-survivor group, as shown in Table 2. In non-survivor group also had slightly lower level of thrombocytes and lymphocytes (p=0. 044 and 0.045; respectively)

Non-survivor $PaCO_2$ was significantly higher (p=0.23) and pH values also were lower (p=0.20) at the time of ICU admission.

The values of assessing scores (MLIS, Cons/GGO ratio, P/F ratio and SOFA) were changed differently. Among non-survivor group these scores were getting worsening by time, and in contrary to these among survivor all these scores were getting better and to the end of the 16-th were near normal ranges.

Based on these observations, we grouped the data into early ( days 1-4) and late (days 13-16) time points and expressed them as value changes between early and late time points ("temporal changes"). The temporal changes in MLIS and Cons/GGO ratio differed between survivors and non-survivors, showing an increase in non-survivors and decline in survivors and to the end of 16-th days of observation the difference in MLIS score between survivors and non-survivors was significantly higher (OR 1.2 [0.09-1.54] 95% CI; *vs*. 3.9 [3.4-4.0] 95% CI: p=0.001) The similar changes we have observed by assessment of Cons/GGO score. However, in contrary to MLIS score in Cons/GGO score was differed at the time admission to the ICU (p<0.05), and further observation above these data showed significantly decline of this score in survivors and an increase in non-survivors and to the end of 16-th day this score was markedly higher in non-survivor group (OR 2.4 [1.1-3.3] 95% CI; *vs*. 0.39 [0.31-0.63] 95% CI; p=0.001)

**Table 1.** Baseline characteristics of survivors and non-survivors patients with moderate-to-severe ARDS.

| Characteristics | Survivors (n=168) | Non-survivors (n=121) | P value |
|---|---|---|---|
| Age, median | 58.5 (42.0-68.0) | 68.4 (58.0-80.0) | <0.001 |
| Male | 73 (43%) | 79 (65%) | <0.05 |
| Comorbidities hypertension | 86 (51%) | 72 (59%) | 0.088 |
| Diabetes obesity (BMI >30) | 34 (20%) | 56 (46%) | 0.001 |
| Bronchiectasis | 7 (4%) | 6 (5%) | 0.598 |
| Asthma | 6 (3%) | 5 (4%) | 0.614 |
| Chronic obstructive pulmonary disease | 12 (7%) | 21 (17%) | 0.02 |
| Coronary artery disease | 28 (16%) | 33 (27%) | 0.003 |
| Immunosuppression | 16 (9%) | 11 (10%) | 0.729 |
| Cancer | 9 (5%) | 11 (9%) | 0.211 |
| Chronic Kidney disease | 19 (11%) | 24 (19%) | 0.094 |
| Carlson index | 3 ± 1 | 5 ± 1 | 0.001 |
| Alanineaminotransferase | 41 (20-68) | 43 (22-70) | 0.624 |
| Creatinine | 1.1 (0.7-1.6) | 1.5 (0.9-2.9) | 0.002 |
| Bilirubin | 1.6 (1.0-2.1) | 2.3 (1.6-5.9) | 0.001 |
| Thrombocytes | 154 (108-204) | 123 (86-169) | 0.042 |
| Lymphocytes | 10 (7-15) | 7 (5-12) | 0.045 |
| Bicarbonate | 24 (21-28) | 16 (12-22) | 0.044 |
| C-reactive protein | 15 (5-22) | 19 (7-28) | 0.042 |
| Lactate dehydrogenase | 421 (296-614) | 502 (340-708) | <0.01 |
| Brain natriuretic peptide | 168 (62-801) | 814 (327-3244) | <0.0001 |
| D-dimer | 421 (201-607) | 724 (403-1821) | 0.0001 |
| Ferritin | 785 (300-1726) | 896 (324-1819) | 0.421 |
| Troponin | 0.01 (0.01-0.01) | 0.02 (0.01-0.07) | 0.014 |
| Procalcitonin | 0.3 (0.1-0.7) | 0.6 (0.3-1.2) | <0.01 |
| Sodium | 134 (131-138) | 136 (132-140) | 0.126 |
| **Vital signs at admission** | | | |
| Mean arterial pressure | 105 (80-125) | 85 (60-98) | 0.042 |
| Heart rate | 92 (81-108) | 94 (84-110) | 0.72 |
| Oxygen saturation | 92 (90-95) | 89 (86-91) | 0.007 |
| Respiratory rate | 23 (19-28) | 26 (22-30) | 0.006 |
| **Ventilatory support** | | | |
| Non-invasive ventilation | 76 (46%) | 10 (9%) | 0.001 |
| Invasive mechanical ventilation | 92 (54%) | 111 (91%) | 0.001 |
| Use of dexamethasone before intubation | 134 (80%) | 56 (46%) | <0.02 |
| **Arterial blood gas at admission** | | | |
| $HCO_3$ | 34 (21-28) | 16 (12-22) | 0.044 |
| Pa $CO_2$ | 41 (35-52) | 58 (38-70) | 0.023 |
| Pa $O_2$ | 72 (60-83) | 62 (51-75) | 0.026 |
| pH | 7.35 (7.25-7.43) | 7.28 (7.20-7.34) | 0.02" |

P/F ratio was differed at the time of ICU admission between survivors and non-survivors (p<0.05), however, this differences have been increasing by time and to the end of time frame was significantly lower in non-survivor group (88.0 [0.54-114.2] *vs*. 355.4 [299.3-412.2] p=0.001), that was indicated significantly worsening of respiratory failure as result of progressing of consolidation in lung tissue.

SOFA score as predictor of severity sepsis was higher in non-survivors at the time of admission (p<0.5) and an increased by time and achieved to the peak data to the end of 16$^{th}$ day (p=0.001). The SOFA score was declined in survivors group that is indicated about lack of secondary bacterial infection in survivors (31/18%). In contrary to this in non-survivor group the prevalence of secondary bacterial infection was significantly higher (85/70%; P>0.001) and

**Table 2.** Continues variables and risk of mortality in patients with moderate to severe ARDS related to COVID-19.

| Variables | | Survivors (n=168) | Non-survivors (n=121) | P value |
|---|---|---|---|---|
| Murray lung injury score | Days 1-4 | 3.2 (2.5-3.8) | 3.3 (2.5-3.9) | 0.52 |
| | Days 5-8 | 2.6 (1.9-3.0) | 3.5 (2.7-3.9) | 0.041 |
| | Dats 9-12 | 1.9 (1.2-2.2) | 3.7 (2.9-4.0) | 0.01 |
| | Days 13-16 | 1.2 (0.69-1.54) | 3.9 (3.4-4.0) | 0.01 |
| Cons/GGO ratio | Days 1-4 | 0.74 (0.55-1.4) | 1.11 (0.61-1.3) | <0.05 |
| | Days 5-8 | 0.68 (0.51-1.0) | 1.3 (0.78-1.8) | 0.03 |
| | Days 9-12 | 0.42 (0.39-0.74) | 1.8 (0.89-2.2) | 0.01 |
| | Days 13-16 | 0.39 (0.31-0.63) | 2.4 (1.1-3.3) | 0.001 |
| P/F ratio | Days 1-4 | 198.6 (156.4-254.6) | 164.1 (95.0-228.2) | <0.05 |
| | Days 5-8 | 224.1 (180.4-295.3) | 142.6 (75.0-184.3) | <0.01 |
| | Days 9-12 | 288.4 (200.3- 320.6) | 104.9 (63.0-141.6) | 0.001 |
| | Days 13-16 | 355.4 (299.3-412.2) | 88.0 (54.0-114.2) | 0.001 |
| SOFA score | Days 1-4 | 8 ± 2 | 9 ± 2 | <0.05 |
| | Days 5-8 | 6 ± 1 | 10 ± 2 | 0.01 |
| | Days 9-12 | 4 ± 1 | 11 ± 2 | 0.0003 |
| | Days 13-16 | 2 ± 1 | 13 ± 2 | 0.0001 |

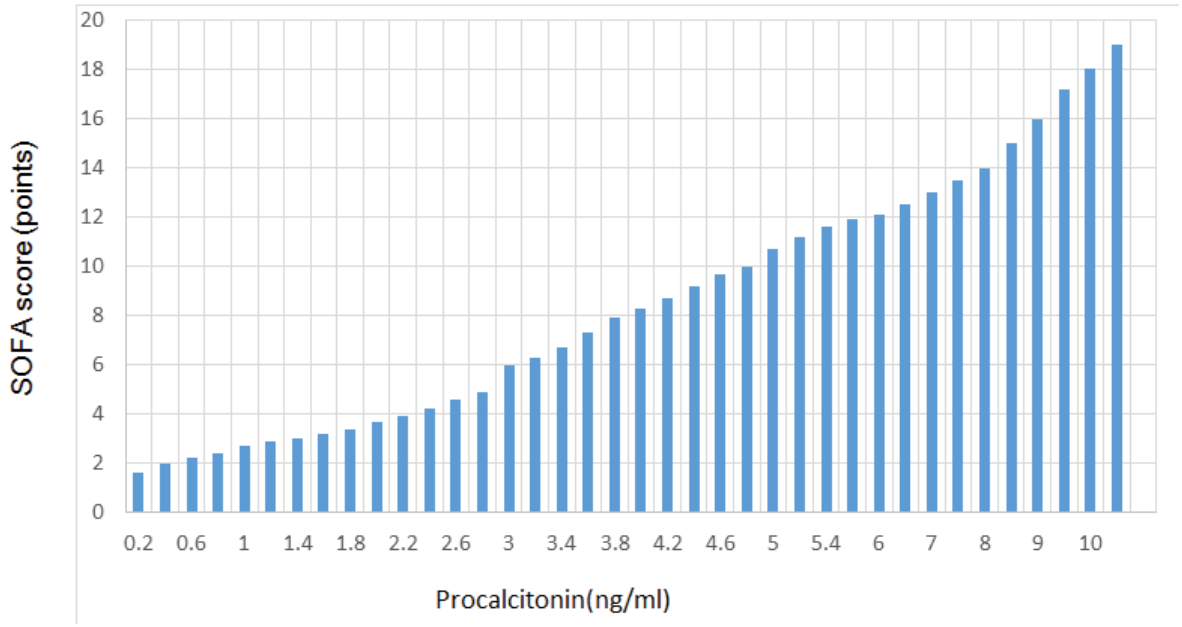


**Figure 1.** The correlation between SOFA score and procalcitonin levels in non-survivor COVID-19 related ARDS patients.

was positively correlated with intubation rate among non-survivors (p=0.002) Common pathogens separated from sputum, endotracheal aspirate and broncho-alveolar lavage fluid (BALF) were: *Klebsiella pneumonia* (29/34%); *Pseudomonas aeruginosa* (24/28%); *Staphylococcus aureus* (19\22%) and *Acinobacteri baumanii* (11/13%). The rate of multidrug –resistant pathogens (MDR) was higher among non-survivors (OR 5.64 [1.54-7.22] 95%CI; p= 0.001/and was positively correlated with mortality rate (p=0.0001)

## Discussion

In this retrospective study, severe COVID-19 patients complicated with ARDS, we explored the relationship between mortality and the changes of MLIS, Cons/GGO, P/F ratio and SOFA score values during the 16 days of ICU admission. Our findings were:

(I) After day 4 of ICU admission, the $FiO_2$ in non-survivors began to increase compared to survivors, and these was differences in $PaO_2$ at the time of admission between groups. That is, compared to survivors, non -survivors required a substantially greater rate and prolonged time of mechanical ventilation to sustain the same level of oxygenation. The P/F ratio improved in survivors, however, its value was lower at the time of admission in non-survivor group, since improved in survivors, worsened in non survivors to the day of 16th.

Prior reports of ARDS in non-COVID-19 patients have shown that PIF ratio is variably and only weakly associated with mortality, with ORs ranging from 1.0 to 1.8, while clinical factors such as age, organ failure scores, and active malignancy are more strongly predictive of mortality[11]. This supports the postulate that death from non-COVID related ARDS is closely related to non-pulmonary organ failure and not closely relate to gas exchange failure parse [12].

In contrast, a recent cohort study of COVID-19 patients found that pulmonary dysfunction itself was the primary cause of death in 56% of COVID-19 patients compared to 22% of those with respiratory failure of other causes [13]. Our results once again evidenced and widened these findings, showing that in COVID related ARDS worsening PIF ratio after 4 days of ICV admission and MV is itself strongly and independently associated with higher mortality.

(II) We observed that the higher MLIS which was similar at the time of admission to ICU between groups at the later time points was strongly associated with mortality in non-survivors (OR-3.9). The current

scoring systems for critically ill patients are widely used clinically, such as the acute physiology chronic health evaluation II (APACHE II) and the Murray lung injury score (MLIS), which have been proved to be related to patient outcomes [14]. However, the scoring systems are often subjective, and they cannot effectively predict the prognosis or death risks of patients with specific diseases [15]. For example, APACHE II is not specific at distinguishing sepsis, ARDS, or acute kidney injury. Another study showed that there was no difference in the APACHE II scores between ARDS survivors and non-survivors [16]. Therefore, the further development of the ARDS mortality predictors will have a great clinical value for clinical treatment optimization and patient prognosis. Though we have explored our patients to the more accurate predictor for mortality as MLIS. Our study showed the higher MLIS is associated with higher mortality rate and independent risk factor of mortality in non survivors COVID-19 related ARDS patients. An increase of extension of lung injury (MLIS) by time and achieved peak scores to the end day of 16-th predicts mortality in non-survivors.

(III) In our study the lung involvement on chest CT was presented with mixed radiological pattern (consolidation and ground glass opacities), however, depending on superiority of presenting components and changing of their ratio to the extension of consolidation there were observed different clinical features and mortality rate between survivors and non-survivors. Our finding was consist of the extent lung involvement with prevalence of consolidation (Cons/GGO>1) above GGO are associated with more severe disease course, severe respiratory failure requiring MV and mortality risk. When there is lung involvement, chest CT in the first five days after symptoms most commonly reveals GGO or mixed GGO and consolidation in a peripheral and sub pleural distribution [17-19] with a peak in acute CT findings around day 10. The extent of lung involvement in the acute phase of infection is associated with the degree of underlying systemic inflammation and portends worse outcomes [20,21]. In spite of the prevalence of lung involvement in acute COVID-19 and the recognition of characteristic patterns, these patterns in acute disease are nonspecific. However, in our investigation we have found the relationship between extent consolidation and risk of mortality in COVID-19 related ARDS patients and cons/GGO ratio >1 was independently associated with mortality in non- survivors.

(IV) The sequential organ failure assessment (SOFA) score is one of the recording systems used to evaluate organ failure and can predict severity and outcome the disease [22]. The SOFA scoring system was launched in 1996, and its performance is based on the evaluation of the following 6 major organ functions; circulation, respiration, liver renal function, central nervous system and coagulation function. The score of each organ is between 0 and 4, it is easy to use tool for systemically and continuously evaluating organ functions during hospitalization [23]. Raschke study showed that SOFA scores are not good discriminator for probably mortality in patients with COVID-19 pneumonia requiring MV because the study was conducted in critically ill patients admitted to the ICU for treatment and requiring MV [24]. However our retrospective study was conducted to evaluate the accuracy of the SOFA score in predicting the severity and prognosis in COVID -19 related ARDS patients. The results of our study showed that high SOFA score is associated with higher rate of mortality in COVID-19 related ARDS patients and was independent risk factor predicting mortality in non- survivors. High SOFA score in non survivors also was associated with higher rate of secondary bacterial infection with prevalence of MDR pathogens and high non changeable or progressing level of procalcitonin (p=0.0001) The correlation between SOFA score and procalcitonin levels in non-survivor COVID-19 related ARDS patients have demonstrated in Figure 1.

## Limitations

Our study had some limitations. First, this was retrospective cohort study and as such potentially important factors which could be associated with mortality rate may have been overlooked. We included 4 variables to significantly impact mortality in COVID -19 related ARDS: MLIS, Cons/GGO ratio, P/F ratio and SOFA score. These were the 4 variables that in our data demonstrated the greatest individual ORs. Second, a study of this size may have had insufficient power to detect real difference in the associations of outcomes with P/F ratio of other parameters. Third, data were obtained from a four ICU of hospitals COVID -19 database, that are may not be insufficient for general assessment of results other hospital settings.

## Conclusion

We evaluated 4 variables included Murray lung Injury score, consolidation/GGO ratio, PaO2/FiO2 ratio and SOFA score in COVID-19 related ARDS patients over the 16 days of ICU admission. The temporal changes these variables of these variables clearly differentiated survivors from non- survivors. A worsening these values after day of 4 of ICU admission may have value as a marker of poor outcome in ARDS due to COVID -19.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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## Ethical Approval

Not applicable, because this article does not contain any studies with human and animal subjects.

## Informed Consent

Not applicable, because this article does not contain any studies with human and animal subjects.

## Trial Registration

Not applicable, because this article does not contain any clinical trials.

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