

## Original Article



# Association of hematological, coagulation and biochemical with respiratory insufficiency and mortality in severe COVID-19 patients: A prospective observational study

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### Abstract

**Introduction:** Some changes in the peripheral blood and arterial blood gas (ABG) parameters will occur in patients with severe COVID-19 infections. These changes have the potential to provide clues or guidance for the diagnosis, treatment, and prognosis of COVID-19 patients. The aim of this study was to evaluate the association of hemodynamic, peripheral blood markers and arterial blood gas parameters with respiratory insufficiency and mortality rate in severe COVID-19 patients.

**Methods:** This single-center, prospective observational study was conducted on severe COVID-19 patients admitted to the general ICU of a university affiliated hospital in the northwest of Iran. Hemodynamic, hematological, coagulation, biochemical and ABG parameters were compared between survivors and non-survivors and also between patients with mild to moderate and severe respiratory insufficiency. Unadjusted and adjusted binary logistic regression analyses were employed to identify risk factors related to the respiratory insufficiency and mortality.

**Results:** In adjusted binary logistic regression, low oxygen saturation (odds ratio [OR]: 0.763, 95% CI: 0.037-0.990,  $P=0.008$ ), elevated polymorphonuclear leukocyte (PMN)/lymphocyte ratio (OR: 1.999, 95% CI: 1.224-3.008,  $P=0.008$ ), elevated lactate dehydrogenase [LDH] (OR: 1.711, 95% CI: 1.222-2.051,  $P=0.045$ ), elevated creatine phosphokinase [CPK] (OR: 1.712, 95% CI: 1.323-2.004,  $P=0.038$ ), high level of [FiO<sub>2</sub>] (OR: 1.736, 95% CI: 1.419-2.052,  $P<0.001$ ) and low level of partial pressure of oxygen (PaO<sub>2</sub>)/FiO<sub>2</sub> ratio (OR: 0.894, 95% CI: 0.387-1,  $P=0.047$ ) had increased risk of ICU mortality.

**Conclusion:** The potential risk factors of high LDH, CPK, PMN/lymphocyte ratio, FiO<sub>2</sub>, low SpO<sub>2</sub> and PaO<sub>2</sub>/FiO<sub>2</sub> ratio could help clinicians identify patients at high risk of death early in the ICU admission.

### Introduction

The world has been experiencing pandemic caused by SARS-CoV-2 for three years, the virus that causes COVID-19.<sup>1-3</sup> To date, COVID-19 has infected over 430 million people and more than 5.9 million deaths worldwide.<sup>4</sup> COVID-19 patients are characterized by pneumonia symptoms, radiographic evidence of pneumonia, respiratory symptoms, and other symptoms such as fever, sore throat, cough, headache, fatigue, anosmia, and diarrhea.<sup>5</sup> Symptoms of COVID-19 can vary from person to person and can lead to clinical manifestations of the disease from asymptomatic infection to mild-moderate or severe infection.<sup>6</sup> Severe cases are

associated with acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, coagulation dysfunction, and multiple organ failure, which ultimately results in approximately 54% mortality in these patients.<sup>7-10</sup> This condition is life-threatening for patients with severe COVID-19 and requires admission to the intensive care unit (ICU). Therefore, immediate identification of acute respiratory insufficiency and prediction of mortality in severe COVID-19 patients are essential for accurate allocation of health care resources and the possibility of earlier clinical intervention and monitoring to improve clinical outcomes.

Several previous studies found that the hematological,

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coagulation and arterial blood gas (ABG) parameters were related to the severity and prognosis of patients, and could be used to predict the severity and prognosis of patients with COVID-19.<sup>11-17</sup> The relation of certain hematological parameters, including hemoglobin (Hb) and red cell distribution width (RDW), within COVID-19 patients has been demonstrated in earlier studies.<sup>18,19</sup> A pooled analysis and review study by Henry et al,<sup>20</sup> found that the elevated C-reactive protein (CRP), procalcitonin (PCT), and lactate dehydrogenase (LDH) in mild to severe pediatric COVID-19 patients. In a study by Velavan and Meyer,<sup>21</sup> laboratory markers were compared in patients with severe and mild COVID-19 disease and the authors stated that the lymphopenia, ferritin, D-dimer, CRP, cardiac troponin, and LDH were significant parameters with predictive value. A retrospective cohort study by Liu et al,<sup>22</sup> demonstrated that CRP and interleukin-6 (IL-6) levels increased in severe stages of the disease, and CRP > 41.8 (mg/L) may be an independent risk factor for progression in the early stage patients with COVID-19. In a retrospective study by Wang,<sup>23</sup> revealed that the elevated CRP accompanies lung lesions and therefore reflects the severity of disease.

These findings suggest that some changes in the peripheral blood will occur in patients with SARS-CoV-2 infections. These changes have the potential to provide clues or guidance for the diagnosis, treatment, and prognosis of COVID-19 patients. It is evident from the studies in the literature that various blood parameters are used in determining the severity of COVID-19 infection. However, the parameters that are effective in determining respiratory insufficiency and mortality in severe COVID-19 patients should be clearly revealed. On the other hand, a comprehensive and complete study in this field in the Middle East population with COVID-19 has not been performed to date to measure all these parameters. Therefore, we conducted this study to prospectively analyze the association of hemodynamic, hematological, coagulation, biochemical and ABG parameters with respiratory insufficiency and mortality in severe COVID-19 patients

## Methods

### Study design

This single-center, prospective observational study was conducted on patients with severe COVID-19, to evaluate the association of hemodynamic, hematological, coagulation, biochemical and arterial blood gas parameters with respiratory insufficiency and mortality rate. The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association.<sup>24</sup> The study protocol was reviewed in accordance with the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.<sup>25</sup> Written informed consent was obtained from all patients or their legal representatives if they were

unable to provide consent

### Study population

All patients admitted to the general ICU of Imam Reza Hospital of Tabriz University of Medical Sciences in Tabriz, Iran between January and December, 2021 were included in the study if they met the following inclusion criteria: (a) aged 18 years and over, (b) diagnosed as having severe COVID-19 according to the Guidelines for the Diagnosis and Treatment of Corona Virus Disease,<sup>26</sup> to receive this diagnosis patients had one or more of the following: respiratory distress with respiratory rate > 30 breaths/min, oxygen saturation ( $SpO_2$ ) < 93% on room air, or arterial oxygen index (arterial partial pressure of oxygen/fraction of inspired oxygen,  $PaO_2/FiO_2$ ) < 300 mm Hg. Laboratory confirmation of COVID-19 which includes positive result on a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of a specimen collected on a nasopharyngeal swab.<sup>27</sup> Patients were excluded if an alternative medical diagnosis explained their clinical presentations or had missing outcome and baseline information.

### Data collection

Data were collected on (a) demographics (age, gender), (b) comorbidities (diabetes mellitus [DM], hypertension [HTN], hyperlipidemia [HLP] and end-stage renal disease [ESRD]); (c) severity of illness on first day of ICU admission based on Acute Physiology and Chronic Health Evaluation (APACHE) IV and Sequential Organ Failure Assessment (SOFA); (d) respiratory status on first day of admission (conventional O<sub>2</sub> therapy, non-invasive mechanical ventilation or invasive mechanical ventilation); (e) respiratory insufficiency that was diagnosed and defined according to the Berlin definition,<sup>28</sup> (based on degree of hypoxemia; mild to moderate [ $100 \text{ mm Hg} < PaO_2/FiO_2 \leq 300 \text{ mm Hg}$ ] and severe [ $PaO_2/FiO_2 \leq 100 \text{ mm Hg}$ ] and four ancillary variables for severe cases: radiographic severity, respiratory system compliance [ $\leq 40 \text{ mL/cm H}_2\text{O}$ ], positive end-expiratory pressure [ $\geq 10 \text{ cm H}_2\text{O}$ ], and corrected expired volume per minute [ $\geq 10 \text{ L/min}$ ], (f) hemodynamic parameters; pulse rate (PR) beats per minute (BPM), respiratory rate (RR per minute), systolic blood pressure (SBP-mm Hg), diastolic blood pressure (DBP-mm Hg), oxygen saturation ( $SpO_2$ -%) and body temperature; (g) hematological parameters includes white blood cell (WBC-cells  $\times 10^9/L$ ), polymorphonuclear leukocyte (PMN) (PMN-%), lymphocytes count (cells  $\times 10^9/L$ ), PMN/lymphocyte ratio, hemoglobin (Hb-g/dL), and Platelet (Plt- cells  $\times 10^3/L$ ); (h) coagulation parameters includes partial thromboplastin time (PTT-seconds), international normalized ratio (INR) and D-dimer (ng/mL); (i) biochemical parameters includes blood urea nitrogen (BUN-mg/dL), blood sugar (mg/dL), creatinine (Cr-mg/dL), lactic acid dehydrogenase (LDH-U/L),

C-reactive protein (CRP-mg/L), ferritin ( $\mu\text{g/L}$ ), creatinine phosphokinase (CPK- $\mu\text{g/L}$ ), erythrocyte sedimentation rate (ESR-mm/h), aspartate aminotransferase (AST-U/L) and alanine aminotransferase (ALT-U/L), and alkaline phosphatase (ALP- IU/L); (j) ABG parameters includes blood PH, partial pressure of carbon dioxide ( $\text{PCO}_2$ -mm Hg), bicarbonate ( $\text{HCO}_3^-$ - mEq/L), partial pressure of oxygen ( $\text{PaO}_2$ -mm Hg), fraction of inspired oxygen ( $\text{FiO}_2$ ), and  $\text{PaO}_2/\text{FiO}_2$  ratio (mm Hg). All the laboratory data including complete blood count (BC-6900, Mindray, Shenzhen, China), serum biochemistry (AU5800, Beckman Coulter, CA, USA), and coagulation tests (ACL TOP 700, Werfen, Barcelona, Spain), were collected from the laboratory information system (LIS). Clinical outcomes including ICU length of stay (LOS), mechanical ventilation (MV), MV duration, and mortality rate were monitored for each patient until deceased or discharged from the ICU.

### Statistical analysis

All statistical analysis was done by SPSS software (ver.21) (SPSS Inc. IL, Chicago, USA). The normally distributed of numeric variables was checked by Kolmogorov-Smirnov and Shapiro-Wilk and tests. Normal distributed data were reported as mean and standard deviation (SD) or percentage (%) for continuous and categorical variables, respectively. While non-normal distributed continuous data were reported as median and interquartile range (IQR). To compare the differences in terms of demographic characteristics, clinical data, outcomes, hemodynamic, hematological, coagulation, biochemical and ABG parameters between survivors and non-survivors, and in the patients with different severity of respiratory insufficiency (mild to moderate vs, severe) the Mann-Whitney U test and t-test were used for non-normal distributed and normal distributed continuous variables, respectively, and  $\chi^2$  test or Fisher's exact test for categorical variables. Unadjusted and adjusted binary logistic regression models were used to explore the risk factors associated with sufficient respiratory and mortality, associations were reported using the odds ratio (OR) and 95% confidence intervals (CI). In adjusted analysis, according to conditional logistic regression, variables with a  $P$  value  $< 0.05$  in the unadjusted analyses were proposed for entry into the model and adjusting was done based on confounding factors including age, gender, comorbidities, severity of illness (APACHE and SOFA scores) and MV. GraphPad Prism 9<sup>®</sup> (GraphPad Software Inc., La Jolla, CA) was used for forest plot of adjusted binary logistic regression analysis to show the association of parameters with the risk of respiratory sufficiently and mortality. In all analyses,  $P$ -values less than 0.05 were considered as significant.

## Results

### Demographic and clinical characteristics

We enrolled 210 patients with severe COVID-19

including 118 (56.2%) males and 92 (43.8%) females with a mean age of  $62.98 \pm 16.49$  years. According to respiratory insufficiency patients were divided into mild to moderate cases ( $n=32$ , 15.2%) and severe cases ( $n=178$ , 84.8%). There was no significant difference in terms of age ( $P=0.135$ ) and gender ( $P=0.435$ ) between the two groups. However, the mean of APACHE IV score ( $P=0.029$ ) and the median score of SOFA ( $P=0.045$ ) was significantly higher in the patients with severe respiratory insufficiency than patients with mild to moderate respiratory insufficiency. More patients with severe respiratory failure underwent MV than patients with mild to moderate respiratory failure (85.4% vs. 68.8%,  $P=0.021$ ). Also the mortality rate was significantly higher in the patients with severe respiratory insufficiency than the patients with mild to moderate respiratory insufficiency (72.5% vs. 46.9%,  $P=0.004$ ) (Table 1).

Of these 210 severe COVID-19 patients, 66 (31.4%) patients survived, and 144 (68.6%) patients did not survive. A comparison of demographic characteristics and clinical data in the survivors and non-survivors groups is presented in Table 1. Compared with survivors, non-survivors were more likely to be older ( $67.33 \pm 14.61$  vs.  $53.50 \pm 16.49$ ,  $P<0.001$ ) and had the comorbidities (79.2% vs. 62.1%,  $P=0.009$ ). Non-survivors had higher APACHE IV and SOFA than survivors ( $P<0.001$ ). The majority of non-survivors (99.3%) used MV and the MV duration was significantly higher in these patients than the survivors (7 days vs. 1 day,  $P<0.001$ ).

### Hemodynamic, hematological and coagulation parameters

Comparison of hemodynamic, hematological and coagulation parameters in COVID-19 patients with different severity of respiratory insufficiency and in survivors and non-survivors groups is presented in Table 2. According to the result the  $\text{SpO}_2$  level was significantly lower in the patients with severe respiratory insufficiency than those with mild to moderate respiratory insufficiency (85.5% vs. 91%,  $P=0.005$ ). There were no significant differences in terms of hematological and coagulation parameters between severe group and mild-moderate groups with respiratory failure ( $P>0.05$ ). PMN (80.8% vs. 74.7%,  $P=0.016$ ), PMN/ lymphocyte ratio (16.5 vs. 10.1,  $P=0.001$ ) and INR (1.3 vs. 1.2,  $P=0.002$ ), D-dimer (1910 ng/mL vs. 903 ng/mL,  $P=0.005$ ) levels in non-survivors were significantly higher than the survivors. However, the levels of  $\text{SpO}_2$  (78.9% vs. 87.3%,  $P=0.001$ ) and lymphocyte ( $0.87 \times 10^9/\text{L}$  vs.  $1.14 \times 10^9/\text{L}$ ,  $P=0.002$ ) were significantly lower than the survivors.

### Biochemical parameters

Comparison of biochemical parameters in COVID-19 patients with different severity of respiratory insufficiency and in survivors and non-survivors groups is shown in Table 3. There were no significant differences in

**Table 1.** Comparison of demographic characteristics and clinical data in patients with different severity of respiratory insufficiency and in survivors and non-survivors groups

| Variables                             |                          | All patients<br>(n=210)      | Patients with mild to<br>moderate respiratory<br>insufficiency (n=32) | Patients with<br>severe respiratory<br>insufficiency (n=178) | P-value | Survivors<br>(n=66)          | Non-survivors<br>(n=144)     | P value |
|---------------------------------------|--------------------------|------------------------------|-----------------------------------------------------------------------|--------------------------------------------------------------|---------|------------------------------|------------------------------|---------|
| Gender                                | Male (%)                 | 118 (56.2)                   | 20 (62.5)                                                             | 98 (55.1)                                                    | 0.435   | 37 (56.1)                    | 81 (56.3)                    | 0.980   |
|                                       | Female (%)               | 92 (43.8)                    | 12 (37.5)                                                             | 80 (44.9)                                                    |         | 29 (43.9)                    | 63 (43.8)                    |         |
| Age (year)                            | Mean $\pm$ SD<br>(Range) | 62.98 $\pm$ 16.49<br>(21-96) | 58.97 $\pm$ 21.344<br>(21-96)                                         | 63.70 $\pm$ 15.43<br>(25-96)                                 | 0.135   | 53.50 $\pm$ 16.49<br>(21-89) | 67.33 $\pm$ 14.61<br>(29-96) | <0.001* |
| Comorbidities                         | Yes (%)                  | 155 (73.8)                   | 22 (68.8)                                                             | 133 (74.7)                                                   | 0.480   | 41 (62.1)                    | 114 (79.2)                   | 0.009*  |
|                                       | No (%)                   | 55 (26.2)                    | 10 (31.3)                                                             | 45 (25.3)                                                    |         | 25 (37.9)                    | 30 (20.8)                    |         |
| Comorbidity<br>types                  | DM (%)                   | 54 (25.7)                    | 6 (18.8)                                                              | 48 (27)                                                      | 0.328   | 16 (24.2)                    | 38 (26.4)                    | 0.741   |
|                                       | HTN (%)                  | 77 (36.7)                    | 13 (40.6)                                                             | 64 (36)                                                      | 0.614   | 21 (31.8)                    | 56 (38.9)                    | 0.324   |
|                                       | HLP (%)                  | 8 (3.8)                      | 2 (6.3)                                                               | 6 (3.4)                                                      | 0.433   | 2 (3)                        | 6 (4.2)                      | 0.690   |
|                                       | ESRD (%)                 | 4 (1.9)                      | 0                                                                     | 4 (2.2)                                                      | 0.398   | 0                            | 4 (2.8)                      | 0.172   |
|                                       | Others (%)               | 88 (41.9)                    | 16 (50)                                                               | 72 (40.4)                                                    | 0.313   | 21 (31.8)                    | 67 (46.5)                    | 0.045*  |
| APACHE IV                             | Mean $\pm$ SD (Range)    | 14.88 $\pm$ 6.64<br>(1-36)   | 12.53 $\pm$ 5.224<br>(4-24)                                           | 15.30 $\pm$ 6.790<br>(1-36)                                  | 0.029*  | 11.17 $\pm$ 5.38<br>(1-26)   | 16.58 $\pm$ 6.47<br>(3-36)   | <0.001* |
| SOFA                                  | Median (IQR)             | 5 (3-7)                      | 4 (2-6)                                                               | 5 (3-7)                                                      | 0.045*  | 3 (1-5)                      | 6 (4-7)                      | <0.001* |
| Respiratory<br>status<br>on admission | Mask O <sub>2</sub> (%)  | 85 (40.5)                    | 22 (68.8)                                                             | 63 (35.4)                                                    | 0.002*  | 43 (65.2)                    | 42 (29.2)                    | <0.001* |
|                                       | Non-invasive MV (%)      | 27 (12.9)                    | 2 (6.3)                                                               | 25 (14)                                                      |         | 14 (21.2)                    | 13 (9)                       |         |
|                                       | Invasive MV (%)          | 98 (46.7)                    | 8 (25)                                                                | 90 (50.6)                                                    |         | 9 (13.6)                     | 86 (61.8)                    |         |
| ICU LOS                               | Median (IQR)             | 8 (5-13)                     | 7 (4-10)                                                              | 8 (5-13)                                                     | 0.351   | 8.5 (6-12)                   | 8 (4-13)                     | 0.507   |
| MV                                    | Yes (%)                  | 174 (82.9)                   | 22 (68.8)                                                             | 152 (85.4)                                                   | 0.021*  | 31 (47)                      | 143 (99.3)                   | <0.001* |
|                                       | No (%)                   | 36 (17.1)                    | 10 (31.3)                                                             | 26 (14.6)                                                    |         | 35 (53)                      | 1 (0.7)                      |         |
| MV duration                           | Median (IQR)             | 7 (1-11)                     | 4 (1-8)                                                               | 5 (1-10)                                                     | 0.115   | 1 (0-7)                      | 7 (3-11)                     | <0.001* |
| Mortality                             | Yes                      | 144 (68.6)                   | 15 (46.9)                                                             | 129 (72.5)                                                   | 0.004*  | -                            | -                            | -       |
|                                       | No                       | 66 (31.4)                    | 17 (53.1)                                                             | 49 (27.5)                                                    |         | -                            | -                            | -       |
| Respiratory<br>insufficiency          | Mild to moderate (%)     | 32 (15.2)                    | -                                                                     | -                                                            | -       | 17 (25.8)                    | 15 (10.4)                    | 0.004*  |
|                                       | Severe (%)               | 178 (84.8)                   | -                                                                     | -                                                            | -       | 49 (74.2)                    | 129 (89.6)                   |         |

Abbreviations: Diabetes mellitus (DM), Hypertension (HTN), Hyperkeratosis lenticularis perstans (HLP), End-Stage Renal Disease (ESRD), Acute Physiology and Chronic Health Evaluation (APACHE), Sequential Organ Failure Assessment (SOFA), Length of stay (LOS), Mechanical ventilation (MV), \*  $P < 0.05$  considered as significant.

terms of biochemical parameters in the patients with mild-moderate respiratory insufficiency than those with severe respiratory insufficiency ( $P > 0.05$ ), except LDH level was significantly higher in the patients with severe respiratory insufficiency than those with mild to moderate respiratory insufficiency (1027 U/L vs. 704 U/L,  $P = 0.002$ ). According to the results of comparing between survivors and non-survivors groups, BUN (32 vs. 22.5,  $P < 0.001$ ), blood sugar (168.5 mg/dL vs. 143.5 mg/dL,  $P = 0.036$ ), Cr (1.26 mg/dL vs. 1.01 mg/dL,  $P < 0.001$ ), LDH (1092 U/L vs. 788.5 U/L,  $P < 0.001$ ), CPK (256  $\mu$ g/L vs. 113.5  $\mu$ g/L,  $P < 0.001$ ) and ESR (53.91 mm/h vs. 42.69 mm/h,  $P = 0.033$ ) were significantly higher in the non-survivors than the survivors.

#### ABG parameters

Among the ABG indices, PCO<sub>2</sub> (39.75 mm Hg vs. 34.80 mm Hg,  $P = 0.002$ ) and FiO<sub>2</sub> (100% vs. 40%,  $P < 0.001$ ) were significantly higher in the patients with severe respiratory insufficiency than those with mild-moderate respiratory insufficiency. Meanwhile, PaO<sub>2</sub> (41 mm Hg

vs. 69.6 mm Hg,  $P < 0.001$ ) and PaO<sub>2</sub>/FiO<sub>2</sub> ratio (46 vs. 141.30,  $P < 0.001$ ) were significantly lower in the patients with severe respiratory insufficiency than those with mild-moderate respiratory insufficiency (Table 4). All ABG parameters were significantly differences between survivors and non-survivors; PCO<sub>2</sub> (40.4 mm Hg vs. 38.1 mm Hg,  $P = 0.019$ ) and FiO<sub>2</sub> (100% vs. 60%,  $P < 0.001$ ) were significantly higher in the non-survivors than the survivors. However, blood PH (7.3 vs. 7.4,  $P < 0.001$ ), HCO<sub>3</sub> (21.5 mEq/L vs. 23.7 mEq/L,  $P = 0.024$ ) and PaO<sub>2</sub>/FiO<sub>2</sub> ratio (46 vs. 68,  $P < 0.001$ ) were significantly lower in the non-survivors than the survivors (Table 4).

#### Unadjusted and adjusted binary logistic regression findings

In unadjusted binary logistic regression analysis, the odds ratio (OR) of mortality was significantly increased with higher levels of PMN/lymphocyte ratio (OR: 1.078, 95% CI: 1.035-3.123,  $P < 0.001$ ), D-dimer (OR: 1.701, 95% CI: 1.008-2.876,  $P = 0.022$ ), BUN (OR: 1.033, 95% CI: 1.013-3.054,  $P = 0.001$ ), Cr (OR: 2.033, 95% CI: 1.257-

**Table 2.** Comparison of hemodynamic, hematological and coagulation parameters in COVID-19 patients with different severity of respiratory insufficiency and in survivors and non-survivors groups

| Parameters                            | Normal range                                   | Patients with mild to moderate respiratory insufficiency (n=32) | Patients with severe respiratory insufficiency (n=178) | P value       | Survivors (n=66)   | Non-survivors (n=144) | P value       |
|---------------------------------------|------------------------------------------------|-----------------------------------------------------------------|--------------------------------------------------------|---------------|--------------------|-----------------------|---------------|
| Hemodynamic parameters                |                                                |                                                                 |                                                        |               |                    |                       |               |
| Pulse rate (PR)                       | 60-100 (BPM)                                   | 95.00±20.13                                                     | 96.22±22.23                                            | 0.772         | 94.32±18.45        | 96.82±23.30           | 0.443         |
| Respiratory rate (RR)                 | 12 to 20 (BPM)                                 | 28.5 (22.25-32.75)                                              | 30 (21-31.25)                                          | 0.911         | 29.08 (20-30)      | 29.94 (22.25-34.5)    | 0.272         |
| Systolic blood pressure (SBP)         | 120-130 (mm Hg)                                | 124.16±18.65                                                    | 123.47±28.15                                           | 0.895         | 123.03±18.68       | 123.83±29.96          | 0.843         |
| Diastolic blood pressure (DBP)        | <80 (mm Hg)                                    | 74.5 (70-80.75)                                                 | 75 (70-85)                                             | 0.801         | 76.06 (70-80.25)   | 77.11 (70-87)         | 0.819         |
| Oxygen saturation (SpO <sub>2</sub> ) | ≥95%                                           | 91 (84.5-94.75)                                                 | 85.5 (70-92)                                           | <b>0.005*</b> | 86.73 (83-95.25)   | 78.96 (66-91)         | <b>0.001*</b> |
| Temperature                           | 36.1°C to 37.2°C                               | 37 (37-37.1)                                                    | 37 (37-37.5)                                           | 0.330         | 36.8 (36.9-37.2)   | 37.2 (37-37.5)        | 0.176         |
| Hematological parameters              |                                                |                                                                 |                                                        |               |                    |                       |               |
| White blood cell (WBC)                | 4.5–11.0 x 10 <sup>9</sup> /L                  | 8.50 (7.25-11.75)                                               | 9.50 (6.25-13.75)                                      | 0.188         | 10.25 (5.60-12.75) | 11.25 (7.12-13.75)    | 0.092         |
| PMN                                   | 40% to 80%                                     | 86 (76-92)                                                      | 88 (81-92)                                             | 0.788         | 74.7 (75.1-90.1)   | 80.8 (81.9-92.6)      | <b>0.016*</b> |
| Lymphocyte                            | 1.0 - 4.8 x 10 <sup>9</sup> /L                 | 0.82 (0.53-1.19)                                                | 0.71 (0.5-1.31)                                        | 0.496         | 1.14 (0.57-1.41)   | 0.87 (0.42-1.24)      | <b>0.002*</b> |
| PMN/lymphocyte ratio                  | -                                              | 11.1 (6.7-18.1)                                                 | 12.4 (6.3-18.6)                                        | 0.523         | 10.1 (5.1-16.1)    | 16.5 (7.1-22.2)       | <b>0.001*</b> |
| Hemoglobin (Hb)                       | M: 13.2 to 16.6 (g/dL)<br>F: 11.6 to 15 (g/dL) | 12.462±2.351                                                    | 12.814±2.099                                           | 0.392         | 12.80±2.021        | 12.74±2.194           | 0.858         |
| Platelet (Plt)                        | 150-450 x 10 <sup>3</sup> per µL               | 218.50±73.36                                                    | 204.25±80.23                                           | 0.353         | 216.91±78.83       | 202.64±80.29          | 0.251         |
| Coagulation parameters                |                                                |                                                                 |                                                        |               |                    |                       |               |
| Partial thromboplastin time (PTT)     | 60-70 seconds                                  | 36 (30-43.75)                                                   | 34 (30-42.25)                                          | 0.464         | 40.23 (29.7-41.25) | 42.7 (30-43.75)       | 0.477         |
| International normalized ratio (INR)  | 0.8–1.2                                        | 1.2 (1.1-1.3)                                                   | 1.1 (1.1-1.3)                                          | 0.953         | 1.2 (1.0-1.2)      | 1.3 (1.1-1.3)         | <b>0.002*</b> |
| D-dimer                               | ≥500 (ng/mL)                                   | 1205 (1014.5-5410.5)                                            | 1398 (539.25-5375)                                     | 0.649         | 913 (300-2435.5)   | 1910 (848-7558.5)     | <b>0.005*</b> |

Polymorphonuclear leukocyte (PMN), \*  $P < 0.05$  considered as significant.

3.295,  $P = 0.004$ ), LDH (OR: 3.001, 95% CI: 1.001-5.002,  $P = 0.004$ ), CPK (OR: 1.323, 95% CI: 1.001-3.523,  $P = 0.007$ ), ESR (OR: 1.095, 95% CI: 1.021-3.29,  $P = 0.035$ ), PCO<sub>2</sub> (OR: 1.337, 95% CI: 1.011-3.064,  $P = 0.006$ ) and FiO<sub>2</sub> (OR: 1.438, 95% CI: 1.025-3.051,  $P < 0.001$ ). However, the OR of mortality was significantly decreased with higher SpO<sub>2</sub> (OR: 0.961, 95% CI: 0.438-0.985,  $P = 0.001$ ), lymphocyte (OR: 0.947, 95% CI: 0.008-0.988,  $P = 0.012$ ) and PaO<sub>2</sub>/FiO<sub>2</sub> ratio (OR: 0.991, 95% CI: 0.605-0.997,  $P = 0.003$ ). According to the adjusted analysis, minimal evidence of reduce OR for mortality was obtained from higher levels of SpO<sub>2</sub> (OR: 0.763, 95% CI: 0.037-0.990,  $P = 0.008$ ) and PaO<sub>2</sub>/FiO<sub>2</sub> ratio (OR: 0.894, 95% CI: 0.387-1,  $P = 0.047$ ). Meanwhile, the risk of mortality was increased with age (OR: 1.838, 95% CI: 1.204-2.062,  $P = 0.002$ ), comorbidities (OR: 2.493, 95% CI: 1.309-4.604,  $P = 0.027$ ), higher score of APACHE IV (OR: 1.69, 95% CI: 1.217-2.167,  $P = 0.015$ ), SOFA score (OR: 1.313, 95% CI: 1.127-2.529,  $P < 0.001$ ), and higher level of PMN/lymphocyte ratio (OR: 1.999, 95% CI: 1.224-3.008,  $P = 0.008$ ), LDH (OR: 1.711, 95% CI: 1.222-2.051,  $P = 0.045$ ), CPK (OR: 1.712, 95% CI: 1.323-2.004,  $P = 0.038$ ) and FiO<sub>2</sub> (OR: 1.736, 95% CI: 1.419-2.052,  $P < 0.001$ ) (Figure 1).

In adjusted binary logistic regression, the OR of severe respiratory insufficiency was reduced with higher level of SpO<sub>2</sub> (OR: 0.853, 95% CI: 0.517-0.991,  $P = 0.015$ ), PaO<sub>2</sub>

(OR: 0.831, 95% CI: 0.608-0.955,  $P < 0.001$ ) and PaO<sub>2</sub>/FiO<sub>2</sub> ratio (OR: 0.733, 95% CI: 0.411-0.956,  $P < 0.001$ ). However, the OR of severe respiratory insufficiency was reduced with higher level of LDH (OR: 1.689, 95% CI: 1.344-3.002,  $P = 0.009$ ) and FiO<sub>2</sub> (OR: 1.567, 95% CI: 1.344-3.091,  $P < 0.001$ ) (Figure 2).

## Discussion

In this single-center, prospective, observational study, several risk factors for respiratory insufficiency and mortality were identified in ICU patients with severe COVID-19. Consistent with other research, we also found that older age, having comorbidities, and higher severity illness based on APACHE IV and SOFA scores were independently associated with mortality. While none of these factors were not related to respiratory insufficiency in severe COVID-19 patients. Patients with poor blood oxygen saturation (SpO<sub>2</sub> ≤ 80), higher inflammation and lower immunity with elevated PMN/lymphocyte ratio (PMN/lymphocyte ratio > 16.5), lung infections with elevated LDH (LDH > 1000 U/L), muscle damage with elevated CPK (≥ 250 µg/L), high level of FiO<sub>2</sub> (100% after intubation) and severity of hypoxemia with low level of PaO<sub>2</sub>/FiO<sub>2</sub> ratio had increased risk of ICU mortality. In addition, lower blood oxygen saturation (SpO<sub>2</sub> ≤ 80), decreased oxygen levels in the inhaled air with low PaO<sub>2</sub>

**Table 3.** Comparison of biochemical parameters in COVID-19 patients with different severity of respiratory insufficiency and in survivors and non-survivors groups

| Parameters                           | Normal range                                   | Patients with mild to moderate respiratory insufficiency (n=32) | Patients with severe respiratory insufficiency (n=178) | P-value | Survivors (n=66)       | Non-survivors (n=144) | P-value |
|--------------------------------------|------------------------------------------------|-----------------------------------------------------------------|--------------------------------------------------------|---------|------------------------|-----------------------|---------|
| Blood urea nitrogen (BUN)            | 6 to 24 (mg/dL)                                | 25 (18-35)                                                      | 30 (20.75-45)                                          | 0.091   | 22.5 (15-30.25)        | 32 (23-47)            | <0.001* |
| Blood sugar                          | <140 (mg/dL)                                   | 148 (111.5-274.5)                                               | 160 (121.5-245)                                        | 0.733   | 143.5 (106.5-247.25)   | 168.5 (125-244.5)     | 0.036*  |
| Creatinine (Cr)                      | M: 0.7 to 1.3 (mg/dL)<br>F: 0.6 to 1.1 (mg/dL) | 1.04 (0.85-1.50)                                                | 1.19 (0.92-1.71)                                       | 0.129   | 1.01 (0.85-1.22)       | 1.26 (1-1.94)         | <0.001* |
| Lactic Acid Dehydrogenase (LDH)      | 140 to 280 units per liter (U/L)               | 747 (560-1046)                                                  | 1027 (728-1401.5)                                      | 0.002*  | 788.5 (556.75-1098.25) | 1092 (816-1472)       | <0.001* |
| C-Reactive Protein (CRP)             | <10 (mg/L)                                     | 51 (18-169)                                                     | 62.5 (24-119)                                          | 0.902   | 54 (18.12-97.65)       | 63 (23.25-128)        | 0.531   |
| Ferritin                             | M: 24 to 336 (µg/L)<br>F: 11 to 307 (µg/L)     | 618.96±340.33                                                   | 764.13±542.58                                          | 0.392   | 612±523.60             | 821.9±509.5           | 0.074   |
| Creatinine phosphokinase (CPK)       | 10 to 120 (µg/L)                               | 231 (64-360)                                                    | 165.5 (76-375.75)                                      | 0.986   | 113.5 (57-280.5)       | 256 (93-523)          | <0.001* |
| Erythrocyte sedimentation rate (ESR) | M: 0 to 22 (mm/hr)<br>F: 0 to 29 (mm/hr)       | 46.57±27.42                                                     | 50.84±30.63                                            | 0.534   | 42.69±24.10            | 53.91±32.16           | 0.033*  |
| Aspartate aminotransferase (AST)     | 8 to 33 units per liter (U/L)                  | 41 (30-59)                                                      | 54 (33-83)                                             | 0.055   | 47 (29-71)             | 53 (35.25-83)         | 0.111   |
| Alanine aminotransferase (ALT)       | 4 to 36 units per liter (U/L)                  | 28.5 (19.5-52.75)                                               | 38.5 (22-59)                                           | 0.102   | 42 (22.75-62.75)       | 33 (22-54)            | 0.235   |
| Alkaline Phosphatase (ALP)           | 44 to 147 (IU/L)                               | 193.5 (143-275.25)                                              | 200.5 (154.25-275.5)                                   | 0.496   | 191 (149.25-254.25)    | 203 (154.75-280.75)   | 0.528   |

All data presented in median (IQR), except ferritin and ESR are presented in mean±SD. \*  $P<0.05$  considered as significant.

**Table 4.** Comparison of arterial blood gas (ABG) parameters in COVID-19 patients with different severity of respiratory insufficiency and in survivors and non-survivors groups

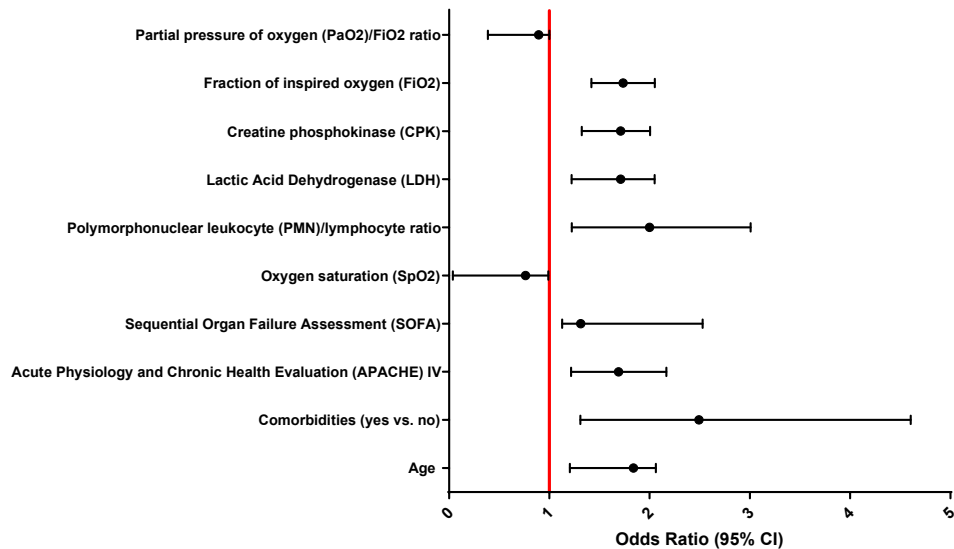
| Parameters                                             | Normal range      | Patients with mild to moderate respiratory insufficiency (n=32) | Patients with severe respiratory insufficiency (n=178) | P value | Survivors (n=66)  | Non-survivors (n=144) | P value |
|--------------------------------------------------------|-------------------|-----------------------------------------------------------------|--------------------------------------------------------|---------|-------------------|-----------------------|---------|
| Blood PH                                               | 7.35 to 7.45      | 7.38 (7.30-7.44)                                                | 7.36 (7.26-7.41)                                       | 0.104   | 7.4 (7.36-7.45)   | 7.32 (7.24-7.4)       | <0.001* |
| Partial pressure of carbon dioxide (PCO <sub>2</sub> ) | 35 to 45 (mm Hg)  | 34.80 (28.65-40.85)                                             | 39.75 (34.77-48.70)                                    | 0.002*  | 38.1 (32.8-42.7)  | 40.4 (34.7-51.15)     | 0.019*  |
| Bicarbonate (HCO <sub>3</sub> )                        | 22 to 28 (mEq/L)  | 21.25 (17.65-24.52)                                             | 22.15 (18.77-25.50)                                    | 0.343   | 23.7 (19.8-25.7)  | 21.5 (18-24.97)       | 0.024*  |
| Partial pressure of oxygen (PaO <sub>2</sub> )         | 75 to 100 (mm Hg) | 69.60 (50.42-93.50)                                             | 41 (30.57-57.12)                                       | <0.001* | 44.05 (30.1-60.2) | 43.7 (33.9-60)        | 0.862   |
| Fraction of inspired oxygen (FiO <sub>2</sub> )        | 21%               | 40 (40-60)                                                      | 100 (80-100)                                           | <0.001* | 60 (40-100)       | 100 (100-100)         | <0.001* |
| PaO <sub>2</sub> /FiO <sub>2</sub> ratio               | -                 | 141.30 (118.56-179.62)                                          | 46 (35-63)                                             | <0.001* | 68 (46-103)       | 46 (35-69)            | <0.001* |

All data presented in median (IQR). \*  $P<0.05$  considered as significant.

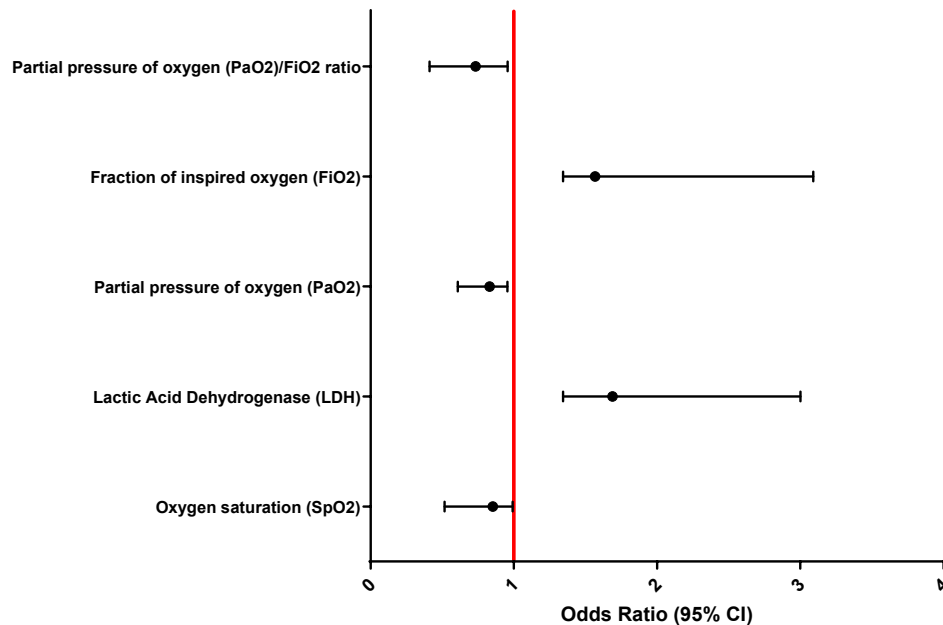
(PaO<sub>2</sub><70 mm Hg), severity of hypoxemia with low level of PaO<sub>2</sub>/FiO<sub>2</sub> ratio, high level of FiO<sub>2</sub> and high lung infection with elevated LDH had increased risk of severe respiratory insufficiency in patients with severe COVID-19.

Consistent with previous literature, in adjusted analysis, we observed that elevated LDH and CPK to be associated with mortality in COVID-19 patients. LDH is an intracellular enzyme found in cells in almost all organ systems with highest levels in heart, liver, lungs, muscles, kidneys and blood cells. LDH enzyme involved in energy production that converts lactate into pyruvate due to severe tissue destruction caused by sepsis, malign

diseases, and severe infections in many tissues. LDH is a general indicator of an acute or chronic tissue damage and is considered an inflammatory marker.<sup>29</sup> LDH has been described to be increased during acute and severe lung damage, and elevated LDH values has been found in other interstitial lung infections.<sup>30,31</sup> In CoVID-19 patients, LDH and CRP might represent an expression of lung damage and might reflect the respiratory distress consequent to the abnormal inflammation status. A pooled analysis study by Henry et al.<sup>32</sup> on 9 published studies showed that the elevated LDH levels were associated with approximately 6-fold increase in odds of developing severe disease and a 16-fold increase in odds



**Figure 1.** Forest plot of adjusted binary logistic regression analysis to show the association of parameters with the risk of mortality in patients with COVID-19



**Figure 2.** Forest plot of adjusted binary logistic regression analysis to show the association of parameters with the risk of respiratory insufficiency in patients with COVID-19

of mortality in patients with COVID-19. In a study by Wu et al,<sup>33</sup> on 87 cases confirmed by COVID-19 infection, significant differences in LDH levels were found between non-severe and severe group. The authors stated that LDH level was an indicator for pneumonia caused by COVID-19, which increases with severe pneumonia and decreases when pneumonia was resolved.<sup>33</sup> CPK is a marker of muscle damage; when a muscle is damaged, CPK leaks into the bloodstream. It has also been found to increase in patients who have died and those with severe illnesses.<sup>34,35</sup> A systematic review and meta-analysis study by Akbar et al,<sup>36</sup> on 14 studies showed that the elevated CPK levels were associated with increased mortality and

severity in patients with COVID-19. SARS-CoV-2 uses the angiotensin converting enzyme 2 (ACE2) receptor to invade human airway cells and cause infection. Due to its presence in various tissues, the virus can directly invade skeletal muscle and the nervous system via the same pathway. Immune pathways may also help cause muscle damage in patients with COVID-19. In addition, dehydration and hypovolemia in patients with COVID-19 may contribute to renal dysfunction and subsequent elevated CPK levels.<sup>35,37</sup>

The PMN/lymphocyte ratio in peripheral blood reflects the balance between systemic inflammation (as indicated by the PMN count include neutrophils, eosinophils,

basophils, and mast cells) and adaptive immunity (lymphocyte count) and is emerging as a prognostic biomarker in many diseases.<sup>38-41</sup> In the current study, we observed the significantly lower level of lymphocytes (lymphopenia) and higher level of PMN in non-survivor patients than the survivors. An increase in PMN/lymphocyte ratio is determined by an increase of PMN and/or reduction in lymphocytes. High levels of PMN/lymphocyte ratio in the blood are most often caused by infections that showed high inflammation and low immunity. In addition, higher PMN/lymphocyte ratio was associated with increased ICU mortality. A cohort study by Liu et al,<sup>42</sup> on 245 COVID-19 patients showed that the 8% higher risk of in-hospital mortality for each unit increases in higher neutrophil to lymphocyte ratio (NLR). According to evidence, cytokine storm induced by virus invasion is a phenomenon of an excessive inflammatory reaction that rapidly produces many cytokines, especially IL-6, in response to microbial infection.<sup>43</sup> This phenomenon is considered an important contributor to COVID-19. Persistent stimulation by the virus may lead to a reduction in lymphocytes and increase in PMN.<sup>44-46</sup> Similarly, many previous studies showed lymphopenia in patients with COVID-19.<sup>47,48</sup>

Early identification and adequate treatment of COVID-19 patients at high risk for acute respiratory failure and mortality is very important. Today, chest CT scan plays a key role in diagnosing and assessing the severity of lung involvement in COVID-19 pneumonia,<sup>49</sup> but unfortunately CT scans are not always available in addition to the high cost. Several limitations need to be acknowledged. Firstly, the sample size is relatively small, though we collected all confirmed patients with COVID-19 admitted to the general ICU in single-center according to convenience sampling. Secondly, some laboratory tests (for example ferritin, ESR and D-dimer) were not performed on all patients; missing data might lead to bias in clinical characteristics between groups. Thirdly, our study participants only included severe cases of COVID-19, leading to limited generalizability to cases with mild symptoms. Fourthly, several potential confounders including health-related behaviors and the detailed treatment history for COVID-19 before admission, which has a significant impact on adverse clinical events, were not available to collect. Our study has limitations i.e. not multicenter study and small sample size.

## Conclusion

A better understanding of the clinical characteristics of patients with severe COVID19 in the early stages of hospitalization is timely for patients at risk of poor outcome, as laboratory data from the onset of the disease to admission are often not clinically available. The predictive value of dynamic changes in LDH, CPK, PMN/lymphocyte ratios, FiO<sub>2</sub>, SpO<sub>2</sub>, and PaO<sub>2</sub>/ FiO<sub>2</sub> ratios

## Study Highlights

### What is current knowledge?

- Hematological, coagulation, and biochemical parameter alterations are well-documented in COVID-19 and correlate with disease severity.
- Elevated inflammatory markers (CRP, D-dimer, LDH) and lymphopenia are established prognostic indicators.
- ABG parameters, particularly PaO<sub>2</sub>/FiO<sub>2</sub> ratio, are crucial for assessing respiratory failure in critical COVID-19 cases.
- Age, comorbidities, and illness severity scores remain consistent mortality predictors in ICU settings.

### What is new here?

- This prospective study provides comprehensive multi-parameter analysis in Middle-Eastern severe COVID-19 patients, addressing regional literature gaps.
- We identify PMN/lymphocyte ratio, CPK, and LDH as independent mortality predictors in confounder-adjusted models.
- LDH demonstrates significant association with respiratory insufficiency severity, offering valuable stratification utility.
- The study establishes a novel combination of accessible parameters for early detection of high-risk patients, enabling timely intervention in ICU settings.

contribute to early detection of COVID patients at high risk of death in the ICU and provide early supportive. These findings may assist physicians in early triage of patients with severe COVID-19 with a high risk of mortality.

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**Writing – original draft:** Mansour Rezaei, Amir Vahedian-Azimi.

**Writing – review & editing:** All authors.

### Competing Interests

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

### Ethical Approval

The protocol study was reviewed and approved by the Research Council of Tabriz University of Medical Sciences under ethics code (IR.TBZMED.REC.1399.772), in accordance with the Declaration of Helsinki of the World Medical Association. In addition, this study was conducted based on recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. 25 Written informed consent was obtained from all patients or their legal representatives if they were unable to provide consent.

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