

## A Research of the Factors Associated with Mortality of the Patients with COVID-19 in the Intensive Care Unit

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### ABSTRACT

**Aim:** The aim of this retrospective study is to investigate the clinical and laboratory factors associated with mortality of the patients with COVID-19 in the Intensive Care Unit.

**Methods:** The patients with COVID-19 who were under follow-up and treat in the Anesthesia Intensive Care Unit between March and May 2020 were retrospectively analyzed. The patients were divided into two groups as Survival Group and Mortal Group. Age, gender, body mass index (BMI), comorbidities, laboratory values such D-dimer, ALT, AST, CRP, ferritin, troponin, IL-6, bicarbonate and lactate, intubation and ventilation, all treatments, coagulopathies, duration of ventilation and stay in the ICU, nosocomial infections and complications were compared between the two groups.

**Results:** Body Mass Index (BMI), any comorbidity such hypertension and cardiovascular disease, APACHE II scores, oxygen saturation, and PaO<sub>2</sub>/FiO<sub>2</sub> rate were significant different between the Survival and Mortal groups. As laboratory markers; D-dimer, ALT, AST, CRP, ferritin, troponin, IL-6, bicarbonate and lactate values higher in Mortal group. Full dose of enoxaparin and vasopressor using were associated with mortality. As complications, ARDS, cardiac injury, cardiac arrest and sepsis were more in the Mortal group.

**Conclusion:** On admission higher BMI, APACHE II scores and some comorbidity such hypertension and cardiovascular disease, and lower PaO<sub>2</sub>/FiO<sub>2</sub> rate were associated with mortality. In addition, higher levels of D-dimer, ALT, AST, CRP, ferritin, troponin, IL-6, bicarbonate and lactate values, and full dose of enoxaparin and vasopressor using, and the development of ARDS, cardiac injury and sepsis is also associated with high mortality in the patients with COVID-19 in ICU follow-up.

### Keywords

COVID-19, mortality, Intensive Care Unit.

### Introduction

The World Health Organization officially declared that coronavirus infection (COVID-19) is a global pandemic on March 11, 2020. The clinical spectrum of COVID-19 varies from asymptomatic

from to requiring mechanical ventilation and advanced support in the Intensive Care Unit. The symptoms of COVID-19 can range from very mild to severe according to the disease severity. COVID-19 can cause pneumonia, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), cardiac problems, coagulopathies, acute kidney injury, cytokine storm syndrome and multiple organ failures [1].

In the results of some studies [2,3] were reported that old age, obesity (BMI  $\geq 30$ ), comorbidities such hypertension, COPD, cardiovascular disease, diabetes and some chronic disease were associated with higher mortality in the patients with COVID-19. Rosenberg and colleagues [3] reported that respiratory failure, cardiac arrest and sepsis were the causes of death in those patients.

The aim of this retrospective study is to investigate the clinical and laboratory factors associated with mortality of the patients with COVID-19 in the Intensive Care Unit.

## Materials and Methods

After the approval of the ethics committee of Clinical Research was obtained, the patients with COVID-19 who were under follow-up and treat in the Anesthesia Intensive Care Unit between March and May 2020 were retrospectively analyzed. In this study, a total of 69 patients who were under follow-up or treatment in Anesthesia Intensive Care Unit from March to end of the May 2020 were investigated. APACHE II scores (Acute Physiology and Chronic Health Evaluation II) of all patients were recorded. We planned to evaluate the demographic characteristics, the reason for admission, comorbidity, initial ICU laboratory values and ventilation statutes, duration of mechanical ventilation and intensive care unit, morbidity and mortality during the follow-up period of the patients. The patients were divided into two groups as Survival Group and Mortal Group. Age, gender, body mass index (BMI), comorbidities, laboratory values, intubation and ventilation, all treatments, coagulopathies, duration of ventilation and stay in the ICU, nosocomial infections and complications were compared between the two groups.

The exclusion criteria were as follows: being non COVID-19 patient and children who under 18 years.

**Table 1:** Demographic characteristic of the patients.

	Survival Group (n=45)	Mortal Group (n=24)	P value
Age (years)	68.3 $\pm$ 13	73.1 $\pm$ 12	0,134
Gender (M/F)	22/23	14/10	0,589
BMI (kg/m <sup>2</sup> )	26 $\pm$ 6	34 $\pm$ 4	0,001*
Any comorbidity	18	22	0,001*
Hypertension	14	17	0,004*
Cardiovascular disease	5	9	0,024*
Diabetes	3	4	0,371
KOAH	4	5	0,299
APACHE II	19.4 $\pm$ 7.5	25.7 $\pm$ 9.6	0,003*
Mean blood pressure (mmHg)	95 $\pm$ 24	65 $\pm$ 26	0,001*
Heart rate (beats/minute)	101 $\pm$ 14	122 $\pm$ 12	0,001*
Respiration rate (per minute)	25 $\pm$ 6	36 $\pm$ 5	0,001*
Oxygen saturation (%)	85 $\pm$ 10	76 $\pm$ 15	0,004*
PaO <sub>2</sub> /FiO <sub>2</sub> rate	182 $\pm$ 28	102 $\pm$ 35	0,001*
NIMV(days)	0.9 $\pm$ 2.7	1.7 $\pm$ 2.2	0,217
MV(days)	3.3 $\pm$ 5.4	5.6 $\pm$ 4.3	0,076
Stay at ICU (days)	7.8 $\pm$ 6.9	6.5 $\pm$ 4.5	0,408

\*p<0.05 is statistically significant.

Statistics package program was used for statistical analyses of the data obtained in the study. Pearson's Chi-square test and Fisher's exact test were used to compare the categorical data. The t-test was used for the comparison of the groups. The results were evaluated in a 95% confidence interval and p<0.05 was accepted as statistically significant.

## Results

Body Mass Index (BMI), any comorbidity such hypertension and cardiovascular disease, APACHE II scores, oxygen saturation, and PaO<sub>2</sub>/FiO<sub>2</sub> rate were significant different between the Survival and Mortal groups. Age, gender (Male/ Female), duration of NIMV and MV days, and stay at ICU days were not significant between the two groups (Table 1).

When compared laboratory values between Survival and Mortal groups, D-dimer, ALT, AST, CRP, ferritin, troponin, IL-6, bicarbonate and lactate values higher in Mortal group (Table 2).

Treatments of the patients such enoxaparin and vasopressor using were significantly different between the two groups. All of the other treatments were the same between the groups.

As complications, ARDS, cardiac injury and arrhythmia, cardiac arrest and sepsis were more in the Mortal group (Table 3).

Data are presented as number (%). \*p<0.05 is statistically significant, NS is non-significant.

## Discussion

The symptoms of COVID-19 can range from very mild to severe according to the disease severity. COVID-19 can cause pneumonia, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), cardiac problems, coagulopathies, acute kidney injury, cytokine storm syndrome and multiple organ failures. The

**Table 2:** Laboratory values of the groups.

Parameters (normal values)	Survival Group (n= 45)	Mortal Group (n= 24)	P value
Leukocyte (4000-10000/mm <sup>3</sup> )	11387 ± 7511	9637 ± 5476	0.317
Neutrophil (per mm <sup>3</sup> )	8868 ± 5411	8445 ± 5370	0.757
Lymphocyte (per mm <sup>3</sup> )	1334 ± 1710	729 ± 347	0.092
Hemoglobin (12-17 g/L)	12.1 ± 2.2	12.3 ± 2.3	0.724
Platelet (100000-400000/mm <sup>3</sup> )	216800 ± 88001	195067 ± 108679	0.371
D-dimer (0-500 mg/L)	1191 ± 658	1949 ± 725	0.001*
ALT (0-35 U/L)	62 ± 14	76 ± 24	0.003*
AST (0-35 U/L)	71 ± 15	121 ± 33	0.001*
Creatinine (0.51-0.95 mmol/L)	1.6 ± 1.8	1.1 ± 0.4	0.185
BUN (8-20 mg/dL)	34 ± 31	29 ± 11	0.448
CRP (0-5 mg/dL)	104 ± 63	199 ± 128	0.001*
Fibrinogen (200-400 mg/dL)	444 ± 202	543 ± 199	0.055
Ferritin (11-306 ng/mL)	410 ± 401	691 ± 322	0.004*
Troponin (0-12 ng/mL)	652 ± 282	1221 ± 305	0.001*
Glucose (70-100 mg/dL)	144 ± 51	161 ± 80	0.285
INR (0.8-1.2 IU)	1.15 ± 0.41	1.38 ± 0.62	0.069
IL-6 (0-6 pg/mL)	14 ± 12	86 ± 34	0.001*
Bicarbonate (22-26 mmol/L)	22 ± 2	16 ± 3	0.019*
Lactate (0.5-1 mmol/L)	1.1 ± 0.8	2.3 ± 1,2	0.001*

\*p<0.05 is statistically significant.

**Table 3:** The treatments and complications of the groups in the ICU.

Treatments	Survival group (n=45)	Mortal group (n=24)	P value
Hydroxychloroquine	45 (100)	24 (100)	NS
Azithromycin	5 (11)	3(12)	NS
Favipiravir	45 (100)	24 (100)	NS
Tocilizumab	24 (53)	12 (50)	NS
Enoxaparin (full dose)	40 (88)	14 (58)	0.01*
Streoid use	25 (55)	12 (50)	NS
Vitamin C	45 (100)	24 (100)	NS
Vitamin D	45 (100)	24 (100)	NS
Paracetamol	45 (100)	24 (100)	NS
Vasopressor using	18 (40)	20 (83)	0.001*
Dialysis (CHDF)	2 (4)	2 (8)	NS
Immune plasma	3 (6)	2 (8)	NS
Stem cell	1 (2)	1 (4)	NS
ECMO	0 (0)	3 (12)	NS
<b>Complications</b>			
ARDS	2 (4)	7 (29)	0.01*
Cardiac injury, Arrhythmia	4 (8)	10 (41)	0.01*
Renal injury	2 (4)	2 (8)	NS
Hepatic injury	0 (0)	1 (4)	NS
Cardiac arrest	0 (0)	8 (33)	0.001*
Sepsis	2 (4)	6 (25)	0.02*
Shock	1 (2)	4 (16)	NS
Secondary infection	2 (4)	3 (12)	NS

Angiotensin I Converting Enzyme 2 (ACE2) may play a role of pathogenesis of coronavirus. The S protein on coronavirus surface specially recognizes the spike protein in the ACE2 of exposed cell and after binding, the virus enters the cell thereby infecting it. Absolutely, the ACE2 receptor is widely disturbed on human cell surface, especially the lungs, heart, liver, kidneys and digestive organs. This can explain why beyond lung failure, the patients with COVID-19 may also exposure to acute myocardial injury,

arrhythmia, myocarditis, acute kidney injury, coagulopathy, shock, and death from multiple organ failures [1]. In our study, we observed that multi-organ dysfunctions such as lung, heart, liver and sepsis increase the mortality rate in the patients with COVID-19.

In this clinical study, we observed that higher BMI, APACHE II scores, respiratory rates, heart rates, and comorbidities like

hypertension, diabetes mellitus and cardiovascular disease on admission in ICU increased, in addition lower oxygen saturation, PaO<sub>2</sub>/FiO<sub>2</sub> rate and mean arterial blood pressures also increased the mortality. Obesity or higher of BMI is not a good situation for health. Some studies reported that obesity was a strong independent risk factor for hospitalization in COVID-19 and obese patients were vulnerable to an adverse clinical course of COVID-19. Consequently, obesity or higher BMI was associated with increased morbidity and mortality in the patients with COVID-19 [4,5]. However, Sousa GJB and colleagues [6] reported that mortality was enhanced by the variables: older age, neurological diseases, pneumopathies and cardiovascular diseases but not male sex, diabetes, hematologic disease, obesity and renal disease in COVID-19. As in the results of our study, Chand S and colleagues [7] reported that obesity or BMI was associated higher mortality in the patients with COVID-19. As a result, obesity is associated higher mortality in the patients with COVID-19 because of decreased lung compliance, expanded adipose tissue and other comorbidities.

In our study, the mortality rate was higher in the patients with higher APACHE II scores, respiratory and heart rates and comorbidities such hypertension, diabetes and cardiovascular disease. These results have been reported in many studies in COVID-19 patients. Sanyaolu A and colleagues [8] reported that leading comorbidities among COVID-19 patients were hypertension, diabetes, hyperlipidemia, coroner artery disease and renal disease. On the other hand, Xu J and colleagues [9] reported that higher APACHE II scores were associated with mortality but not the most common preexisting comorbidities such hypertension, chronic cardiac disease, chronic pulmonary disease and diabetes for COVID-19 patients. However, Ferrando C and colleagues [10] reported that COVID-19 patients with higher APACHE II scores on admission, those who developed Acute Kidney Injury grades ii or iii and/or septic shock during ICU stay had an increased risk of death. On the other hand, lower oxygen saturation and PaO<sub>2</sub>/FiO<sub>2</sub> rate were associated with mortality for the patients with COVID-19 in our study. Similar to our study, Grasselli [2], Chand [7] and Xu [9] reported the same observation in their studies.

In the inflammatory phase of coronavirus-19 disease, many laboratory parameters increase. In our study, we observed that D-dimer, ALT, AST, CRP, ferritin, troponin, IL-6, bicarbonate and lactate values higher in Mortal group when compared with Survival group's values. Similar to the results of our study, Chand and colleagues [7] found significant increases in D-dimer, AST, CRP, troponin, LDH and lactate values in the non-survivors. However, they reported that did not differ between survivors and non-survivors for the levels of ALT and ferritin. However, Li and colleagues [11] reported the mortality was significantly higher in patients with elevated LDH and IL-6 levels in a meta-analysis and systematic review. They strongly recommended the close monitoring of cardiac injury-related markers in the patients with COVID-19. Higher level of inflammatory markers including CRP, D-dimer, ferritin and IL-6, and troponin that reflects myocardial injury were associated with higher mortality in the patients with COVID-19.

In our study demonstrated, that full dose of enoxaparin and vasopressor using were significantly different between the Survival and Mortal groups. The dysfunction of endothelial cells induced by infection results in excess thrombin generation and fibrinolysis shutdown, which indicated a hypercoagulable state in patient with infection [12], such as COVID-19. It has been described in a recent study [13], severe COVID-19 is commonly complicated with coagulopathy, venous thromboembolism, and disseminated intravascular coagulation may exist in the majority of death. Tang and colleagues [14] have recently reported that anticoagulant treatment is associated with decreased mortality in severe COVID-19 patients with coagulopathy. And they reported that anticoagulant therapy mainly with low molecular weight heparin to be associated with better prognosis. In addition, Rico-Mesa and colleagues [15] reported that COVID-19-induced hypercoagulability has been demonstrated to play a significant role in overall COVID-19 outcomes. They recommended the use of anticoagulation in COVID-19 patients who meet criteria by way of risk stratification using the sepsis-induced coagulopathy (SIC) scoring system and/or D-dimer levels.

In our study, we observed that ARDS, cardiac injury and arrhythmia, cardiac arrest and sepsis were more in the Mortal group as a cause of death. Chand and colleagues [7] reported that ARDS, and Acute Kidney Injury (AKI) were independent predictors for mortality in the first 300 critically ill COVID-19 patients admitted to ICU. In addition, Huang and colleagues [1] reported that ARDS, acute cardiac injury, acute kidney injury, secondary infection and shock were complications associated with mortality in the patients infected with 2019 novel coronavirus in Wuhan, China. However, Rosenberg and colleagues [3] reported respiratory failure, cardiac arrest, pneumonia and sepsis were the causes of death in the patients with COVID-19 in New York State.

## Conclusion

On admission higher BMI, APACHE II scores and some comorbidity such hypertension and cardiovascular disease, and lower oxygen saturation and PaO<sub>2</sub>/FiO<sub>2</sub> rate were associated with mortality for COVID-19 patients. In addition, higher levels of D-dimer, ALT, AST, CRP, ferritin, troponin, IL-6, bicarbonate and lactate values, and full dose of enoxaparin and vasopressor using, and the development of ARDS, cardiac injury and sepsis is also associated with higher mortality in the patients with COVID-19 in ICU follow-up.

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