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Determinants of Mortality in Patients Admitted to Intensive Care Unit Due to COVID-19 Pneumonia

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ABSTRACT

Objective: Coronavirus Disease-2019 (COVID-2019), which originated in Wuhan, China in December 2019 and became a global pandemic in March 2020, is a viral infectious condition. This study was planned due to the novel character of the virus, unexpected clinical course of the disease as well as due to the relative lack of data on determinants of severe disease.

Methods: This retrospective study was carried out with the inclusion of 80 patients admitted to the Intensive Care Unit (ICU), Medical Faculty of Erzincan Binali Yildirim University between 1st April 2020 and 1st October 2020 due to the diagnosis of COVID-19 pneumonia. Demographic, clinical, and laboratory data, as well as treatments complications, length of ICU stay and mortality rate were compared between patients who had survive or not.

Results: Of the 80 patients, 18 were died, and 62 were discharged. The mean age was 69.7 ± 14.7 years, with a female to male ratio of approximately 1:2. Systolic blood pressure and mean arterial pressure on admission were significantly lower in non-survivors (p=0.002, and p=0.026, respectively). Also, non-survivors had significantly higher levels of CRP, procalcitonin, D-dimer, urea, LDH, INR, lactate, and neutrophil count and significantly lower lymphocyte counts as compared to survivors. The predictors of mortality were determined as the need for mechanical ventilation, presence of complications, higher CRP and urea levels in a multivariate regression analysis .

Conclusion: Early estimation of patients with a high likelihood of severe illness, assessment of the intensive care unit admission, and convenient treatment strategies are important. This is a precious study that detects an early need for ICU admission and close follow-up of patients.

Keywords: COVID-19, Intensive Care Unit, prognosis, mortality

Introduction

Coronaviruses are generally pathogenic to animals, but in humans, six types of coronavirus can cause respiratory infections ranging from mild to severe illness (1). The clustering of pneumonia cases of unknown etiology originally observed in the Wuhan city of Hubei province in China in December 2019 were subsequently found to be caused by a novel type of β-coronavirus (2). The disease due to this novel type of coronavirus was then declared a pandemic by the World Health Organization in March 2020, and was referred to as Coronavirus Disease-2019 (COVID-19) (3). Since COVID-19 may lead to severe respiratory failure with significant morbidity and mortality, the disease has also been termed as Severe Acute Respiratory Syndrome – Coronavirus-2 (SARS-CoV-2) (4,5). Although most cases of COVID-19 infection have a mild disease course with a well-known set of symptoms, nearly 10% to 15% of the patients have moderate disease sometimes requiring hospital admission, and 3% to %5 may require admission to intensive care unit (ICU) as a result of acute respiratory failure (6). These severe cases may be further complicated with the development of Acute Respiratory Distress Syndrome (ARDS). Independent risk factors for mortality include advanced age, male gender, and certain comorbid conditions (7,8). In a recent study involving 5776 patients, the most common comorbidities identified in patients included hypertension, diabetes, and cardiovascular diseases. Again, in the same study, abnormal laboratory results associated with severe disease course were elevated lactate dehydrogenase (LDH), C-reactive protein (CRP), and ferritin. Also, 80% of the patients were found to have increased D-dimer (9).

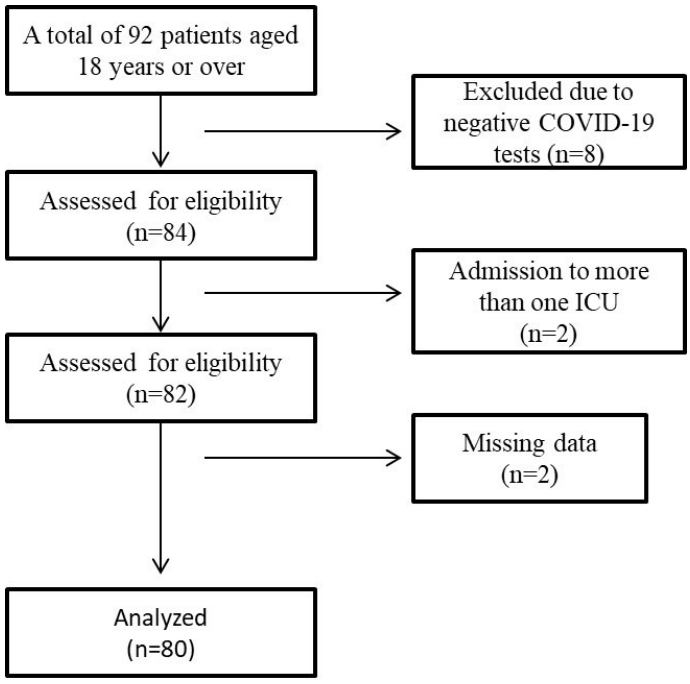

Figure 1. Flow chart of patients included in the study

There are no established treatments with confirmed efficacy for COVID-19, despite its continuing role in the global pandemic. Most of these treatments are currently being tested in clinical trials. Main therapeutic approaches include the use of anti-viral drugs, anti-inflammatory drugs, corticosteroids, macrolide antibiotics (e.g. azithromycin, clarithromycin), hydroxychloroquine, interleukin-1 (IL-1) and interleukin-6 (IL-6) inhibitors and conservative treatments (1). The morbidity and mortality in COVID-19 infection is closely related with hyperinflammation. The early detection and appropriate management of hyperinflammation are among important determinants of the disease course. Therefore, comparison of laboratory parameters between surviving patients and those who are admitted to ICU or die is also important. The objective of the present study was to examine the predictors of mortality in COVID-19 patients admitted to ICU due to respiratory failure.

Materials and Methods

A total of 92 patients aged 18 years or over who were admitted to the Chest Diseases ICU of the Medical Faculty of Erzincan Binali Yildirim University (EBYU) due to respiratory failure caused by COVID-19 pneumonia between 1st April 2020 and 1st October 2020 were retrospectively screened. Of these, 8 were excluded due to negative COVID-19 tests, 2 due to admission to more than one ICU during to their disease course, and 2 due to missing data, leaving out a total of 80 patients for study inclusion (Figure 1). Demographic data, vital parameters on admission, treatments administered, duration of invasive mechanical ventilation (IMV) if present, complications, and duration of ICU stay were compared between patients who died or who survived. Furthermore, results of all relevant laboratory parameters were retrieved from the automated Hospital Information Management System (HIMS). The differences between study groups were examined in an effort to determine the predictors of mortality. The study protocol was approved by the Medical Faculty of EBYU Ethics Committee for Clinical Research (date: 27th April 2021, meeting no: 06, decision no: 06/02).

Statistical Analyses

Statistical analyses were performed using IBM SPSS V.19 software (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as numbers and percentages, while continuous variables were presented as mean ± standard deviation and minimum-maximum. For comparison of the categorical variables between study groups, chi-square or Fisher's exact tests were utilized. The normal distribution of continuous variables was ascertained with Kolmogorov-Smirnov test. The independent continuous variables between the two groups were compared with Student's t test or Mann-Whitney U test. For regression analysis, variables which were found to be significant as a result of univariate analysis were added to multiple logistic regression model and forward LR method was used to create the final model. After regression analysis, odds-ratios (OR) and confidence intervals (95% CI) were reported. For all tests, a p value of < 0.05 was considered significant.

Results

Of the 80 patients included in the study between 1st April 2020 and 1st October 2020, 18 (22.5%) died, while 62 (77.5%) were discharged with cure. There were 26 female (32.5%) and 54 (67.5%) male participants, with an overall mean age of 69.7 ± 14.7 years. Sixty-nine patients (86%) had at least one chronic comorbid condition, including, in the decreasing order of frequency, hypertension (HT), diabetes mellitus (DM), and coronary artery disease (CAD). There were 51 (64%) active smokers or ex-smokers. The most common manifestations at presentation were shortness of breath (94%), fever (70%), and cough (58%), with only 4 patients (5%) having productive cough. Patients who survived or died were not significantly different in terms of age, gender, smoking status or symptoms at presentation ($p > 0.05$).

There was no significant difference between the CCI values of the two groups (p=0.055; Table 1). However, when the median value of CCI was calculated and the two groups were compared, CCI was found to be statistically significantly higher in 83.3% (n=15) of the patients who died and 54.8% (n=28) of the patients who survived. (p=0.029; Table 2)

An examination of the vital signs on admission to intensive care showed no differences in pulse rate, diastolic blood pressure, and O2 saturation (SaO2) between the two groups, while systolic blood pressure (SBP) and mean arterial pressure (MAP) were significantly lower in those who died (Table 2). In the study, 25 (35%) of 80 patients needed IMV. The mortality rate was significantly higher in patients who needed IMV ($p < 0.001$). Complications developed in 8 patients during intensive care follow-up, and 5 of these patients died (p=0.004). Complications that developed in these 8 patients were acute myocardial infarction (n=4), acute renal failure (n=2), pulmonary embolism (n=1) and cerebrovascular hemorrhage (n=1).

Table 1. Demographic and laboratory parameters of the study groups on admission to intensive care unit

	Survivors (n=62)	Non-survivors (n=18)	p
Age (Years)	70 (18-96)	75 (59-94)	0.284
Female/Male	22/40	4/14	0.290
CCI	4(0-8)	4.5 (3-6)	0.055
CRP (mg/L)	114.5 (8.1-363.0)	170.5 (14.0-489.0)	0.002
PCT (ng/mL)	0.3 (0.1-100.0)	1.8 (0.1-100.0)	0.011
Ferritin (ng/mL)	345.5 (10.0-1650.0)	705.5 (66.0-1760.0)	0.062
Fibrinogen (mg/dL)	347.5 (72.0-518.0)	353.5 (150.0-460.0)	0.699
D-Dimer (µg/L)	1453.0 (236.0-90400.0)	2960.0 (737.0-100000.0)	0.027
Lactate (mmol/L)	1.7 (0.9-11.5)	2.8 (1.2-7.1)	0.011
Troponin (ng/L)	10.0 (7.0-4100.0)	11.5 (8.0-200.0)	0.474
Glucose (mg/dL)	137.5 (79.0-350.0)	137.0 (54.0-369.0)	0.913
Urea (mg/dL)	45.5 (13.0-182.0)	88.0 (28.0-278.0)	<0.001
Creatine (mg/dL)	1.0 (0.4-3.1)	1.4 (0.5-5.2)	<0.001
Na (mmol/L)	138.0 (123.0-160.0)	140.5 (117.0-162.0)	0.150
K (mmol/L)	4.2±0.7	4.4±0.6	0.467*
ALT (u/L)	30.5 (6.0-249.0)	27.5 (8.0-81.0)	0.637
AST (u/L)	39.5 (10.0-345.0)	42.0 (20.0-273.0)	0.410
CK (u/L)	66.0 (14.0-8410.0)	153.0 (26.0-7006.0)	0.070
LDH (u/L)	364.5 (164.0-1339.0)	503.0 (265.0-1075.0)	0.017
Cholesterol (mg/dL)	149.5±39.8	146.1±56.5	0.771*
HDL (mg/dL)	31.8±9.6	28.3±6.9	0.147*
LDL (mg/dL)	94.9±30.9	86.2±36.2	0.317*
TG (mg/dL)	126.0 (36.0-460.0)	182.0 (42.0-356.0)	0.086
WBC (µL)	8400.0 (1700.0-35000.0)	10500.0 (2300.0-26200.0)	0.056
HGB (gr/dL)	12.0±2.2	11.0±2.2	0.090*
PLT (µL)	216822.6±84511.8	187388.9±89314.5	0.203*
Lymphocyte (µL)	800.0 (200.0-4500.0)	700.0 (190.0-2060.0)	0.213
Lymphocyte %	9.8 (1.2-27.5)	5.2 (2.5-36.0)	0.004
Neutrophils (µL)	7235.0 (1000.0-34000.0)	9260.0 (1200.0-23100.0)	0.017
Neutrophils %	83.5 (45.0-95.0)	90.5 (52.0-93.0)	0.002
INR	1.1 (0.9-3.3)	1.3 (1.0-2.3)	0.044
PT (Sn)	13.7 (11.0-36.6)	14.8 (12.0-23.0)	0.057

The results are presented as mean ± standard deviation or median (minimum-maximum). *For independent samples, t-test was used. Mann-Whitney U test was used for other variables.
(CCI: Charlson Comorbidity Index; CRP: C-Reactive Protein; PCT: Procalcitonin; Na: Sodium; K: Potassium; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CK: Creatine kinase; LDH: Lactate dehydrogenase; HDL: High density lipoprotein; LDL: Low density lipoprotein; TG: Triglycerides; WBC: White blood cells; HGB: Hemoglobin; PLT: Platelets; INR: International normalized ratio; PT: Prothrombin time.)

Table 2. CCI scores and vital parameters on admission to intensive care unit

		Survivors (n=62)		Non-survivors (n=18)		
		n	%	n	%	p
CCI	≥4	34	69.4	15	30.6	0.029
	<4	28	90.3	3	9.7	
MAP (mmHg)	≤55	0	0.0	4	22.2	0.002
	>55	62	100.0	14	77.8	
Systolic BP (mmHg)	≤90	7	11.3	6	33.3	0.026
	>90	55	88.7	12	66.7	
Diastolic BP (mmHg)	≤60	23	37.1	10	55.6	0.161
	>60	39	62.9	8	44.4	
Pulse (bpm)	<100	27	43.5	8	44.4	0.946
	≥100	35	56.5	10	55.6	
SaO_2 (%)	<90	29	46.8	10	55.6	0.512
	≥90	33	53.2	8	44.4	

CCI: Charlson Comorbidity Index; MAP: Mean arterial pressure; BP: Blood pressure;
SaO2: Arterial oxygen saturation

Table 3. Comparison of the treatments that patients receive in intensive care unit

	Survivors (n=62)		Non-survivors (n=18)		
	n	%	n	%	p
Favipiravir	35	56.5	11	61.1	0.725
Oseltamivir	8	12.9	6	33.3	0.052
Hydroxychloroquine	60	96.8	18	100.0	0.440
Steroid	47	75.8	17	94.4	0.082
Azithromycin	11	17.7	5	27.8	0.349
IVIG	1	1.6	1	5.6	0.346
Tocilizumab	13	21.0	6	33.3	0.278

IVIG: Intravenous immune globulin

Table 4. Multiple regression analyses to determine risk factors for mortality

			95% CI for OR	
	p	OR	Lower	Upper
IMV	0.011	10.1	1.7	60.1
Complication	0.016	27.5	1.9	409.5
CRP	0.015	1.01	1.003	1.025
Urea	0.005	1.03	1.008	1.047

IMV: Invasive mechanical ventilation, CRP: C - reactive protein; OR: Odds-Ratio, CI: Confidence Interval.

Antiviral, anti-inflammatory, steroid, hydroxychloroquine, empirical antibiotic and anti-cytokine treatments were applied to the patients in accordance with the recommendations of the COVID-19 treatment guidelines of the Ministry of Health of the Republic of Turkey. Antibiotic treatment was given to all patients. There was no significant difference between survivors and non-survivors with respect to other treatments. The treatments that all patients received were given in Table 3 as a comparison between the two groups.

In the study, urea, lactate, CRP, procalcitonin (PCT) and LDH levels were found to be significantly higher in non-survivors compared to survivors. In addition, while D-dimer, INR, neutrophil count and percentage were higher in patients who died, the percentage of lymphocytes was significantly lower (Table 1). However, duration of intensive care stay, number of intubated days, and length of hospital stay did not differ significantly. A multiple regression analysis showed that predictors of mortality were the need for IMV, development of complications and urea (Table 4). Accordingly, the need for IMV was associated with an approximately 10-fold increased risk of death (OR: 10.1; 95% CI: 1.7-60.1), while development of complications was associated with a 27-fold increased risk of death (OR: 27.5; 95% CI: 1.9-409.5). Furthermore, elevated urea and CRP resulted in an increased likelihood of mortality (OR: 1.01, 95% CI: 1.003-1.025; and OR: 1.03, 95% CI: 1.008-1.047, respectively).

Discussion

Most cases of COVID-19 infection have a mild disease course with a well-known set of symptoms. However, nearly 10% to 15% of the patients have moderate disease sometimes requiring hospital admission, and 3% to 5% may require admission to intensive care unit (ICU) as a result of acute respiratory failure and may be complicated with ARDS (6). Indeed, the main cause of COVID-19 morbidity and mortality consists of ARDS caused by acute viral pneumonia and subsequent multi-organ failure (10). The estimated mortality rates for the previous Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) outbreaks were 9.5% and 34.4%, respectively, while the corresponding figure for COVID-19 is approximately 3%, according to recent data (11–13). Independent predictors of mortality include advanced age, male gender, and comorbid conditions (7,8). In our study, although male patients were more than twice as many as females (67.5%-32.5%), in another study, the F:M ratio was reported to be 1:1 (14). In a recent study, the most common comorbidities identified in patients included HT, DM, and cardiovascular diseases, with others reporting higher mortality rates in those with DM and CAD (9,15). In the current study, although the most common morbidities included HT, DM, and CAD, we failed to detect significant mortality differences according to the absence or presence of these comorbidities, which may be due to the small number of patients who died. In another report, CCI, which is a risk prediction tool combining age and comorbidities, was suggested to be useful in determining patients with a higher risk of mortality (16). In our study, although CCI was higher in non-survivors, the difference was insignificant.

In COVID-19, predicting the disease course from the onset of symptoms is a challenging task, requiring prognostic tools and biomarkers (17). In a study from Wuhan, China, 138 of the admitted patients required transfer to an ICU, nearly half of whom required IMV (18). In a recent study with 5776 COVID-19 patients, elevated LDH, CRP, and ferritin levels were found among those with all patients, while 80% of the patients had increased D-dimer (9). In our study, CRP, D-dimer, and LDH levels were found to be significantly higher in non-survivors than in survivors. Although the ferritin level was higher in non-survivors, there was no statistically significant difference between the two groups. In another retrospective study, parameters that were found to be associated with an increased risk of mortality included lymphopenia, leukocytosis, and elevations in ALT, LDH, high-sensitivity cardiac troponin I, creatine kinase, D-dimer, ferritin, IL-6, prothrombin time, PCT, and creatinine (15). In a study conducted by Zhang et al. with 140 patients, it was determined that D-dimer, CRP, and PCT levels were significantly higher in patients with a severe course than in non-severe patients (14). In a recent meta-analysis involving 1994 patients, showed that severe patients' laboratory parameters were lymphopenia (64.5%) and leukopenia (29.4%), increased CRP and LDH (44.3%, 28.3%, respectively) (19). In a study evaluating the effect of acute-phase reactants on the prognosis in COVID-19, it was found that D-dimer, ferritin and, CRP levels were significantly correlated with the severity of the disease (20). Similarly, in our study non-survivors had elevated CRP, LDH, D-dimer, lactate, urea, creatinine, INR, and neutrophils levels, and these parameters were found as statistically significant in analyses. Also, these patients had significantly lower lymphocyte count.

In COVID-19 patients, the development of complications is associated with a significantly increased risk of mortality. Severe COVID-19 may lead to acute cardiac, kidney, and liver injury, in addition to cardiac arrhythmias, rhabdomyolysis, coagulopathy, and shock (5,21). In many studies, the most common complications after ARDS included shock (30%), myocardial dysfunction (20%-30%), and acute kidney injury (10%-30%) in severe COVID-19 patients who were followed in ICU. (7,18,22,23). In one of these studies, among 21 COVID-19 patients, 14 patients (67%) were reported to require vasopressor treatment despite absence of the findings of shock (22). Our patients with lower systolic blood pressure and MAP on admission had a higher risk of mortality (Table 2), which might be due to cardiac effects as a complication or due to the effects of the cytokine storm. Although the number of patients developing complications is small in our study (n=8), the observed complication rate was similar to previous reports, which indicate that the most common complication is AMI. Multiple regression analysis showed a 27-fold increased risk of mortality in patients with complications.

Thrombosis may occur via several mechanisms during the course of COVID-19. Furthermore, elevation of D-dimer as a sign of coagulopathy has been found to be associated with mortality (24). Although both groups had elevated D-dimer, non-survivors had significantly higher D-dimer levels in our study. Therefore, elevation in D-dimer levels may represent a predictor of mortality.

Limitations of the current study include small sample size, retrospective design, and the small number of patients who died.

Conclusions

COVID-19 pandemic has resulted in devastating effects on healthcare systems in many countries. In fact, many of the pathogenetic mechanisms of this new disease remain unclear. Early diagnosis of patients with a higher probability of severe illness, assessment of potential need for intensive care unit admission, and appropriate management strategies are important. We think that the results of our study may be useful in this regard. Further well-designed, randomized, and controlled trials are needed to support our results.

AUTHOR CONTRIBUTIONS:

Concept: MT; **Design:** MT; **Supervision:** HO; ; **Materials:** MT; **Data Collection and/or Processing:** MT, HO; **Analysis and/or Interpretation**: MT; **Literature Search:** MT, HO; **Writing Manuscript**: MT; **Critical Review:** HO.

Ethics Committee Approval: The study protocol was approved by Medical Faculty of EBYU Ethics Committee for Clinical Research (meeting date: 27th April 2021; meeting no: 06; decision no: 06/02).

Informed Consent: Informed consent was not taken because it is a retrospective observational study

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