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Clinical Outcomes and Independent Risk Factors for 90-Day Mortality in Critically Ill Patients with Respiratory Failure Infected with SARS-CoV-2: A Multicenter Study in Turkish Intensive Care Units

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Background: There are limited data on the long-term outcomes of COVID-19 from different parts of the world.
Aims: To determine risk factors of 90-day mortality in critically ill patients in Turkish intensive care units (ICUs), with respiratory failure.
Study design: Retrospective, observational cohort.
Methods: Patients with laboratory-confirmed COVID-19 and who had been followed up in the ICUs with respiratory failure for more than 24 hours were included in the study. Their demographics, clinical characteristics, laboratory variables, treatment protocols, and survival data were recorded.
Results: A total of 421 patients were included. The median age was 67 (IQR: 57-76) years, and 251 patients (59.6%) were men. The 90-day mortality rate was 55.1%. The factors independently associated with 90-day mortality were invasive mechanical ventilation (IMV) (HR 4.09 [95% CI: [2.20-7.63], $P < .001$), lactate level >2 mmol/L (2.78 [1.93-4.01], $P < .001$), age ≥60 years (2.45 [1.48-4.06)], $P < .001$), cardiac arrhythmia during ICU stay (2.01 [1.27-3.20], $P = .003$), vasopressor treatment (1.94 [1.32-2.84], $P = .001$), positive fluid balance of ≥600 mL/day (1.68 [1.21-2.34], $P = .002$), PaO_2/FiO_2 ratio of ≤150 mmHg (1.66 [1.18-2.32], $P = .003$), and ECOG score ≥1 (1.42 [1.00-2.02], $P = .050$).
Conclusion: Long-term mortality was high in critically ill patients with COVID-19 hospitalized in intensive care units in Turkey. Invasive mechanical ventilation, lactate level, age, cardiac arrhythmia, vasopressor therapy, positive fluid balance, severe hypoxemia and ECOG score were the independent risk factors for 90-day mortality.

INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a global threat, causing critical illness in 5-26.4% of the affected patients.[1–5] At the beginning of the pandemic, acute respiratory failure caused by severe pneumonia and acute respiratory distress syndrome (ARDS) were the predominant complications of COVID-19, whereas subsequently, it was realized that the virus damages the vascular endothelium, causing multi-system inflammatory syndrome and several complications such as kidney, cardiac, liver and brain injury,[6, 7] vascular thrombosis,[8] and macrophage activation syndrome.[6] The short-term and long-term mortality rates of critically ill COVID-19 patients are quite high. While the intensive care unit (ICU), in-hospital, 28-day and 60-day mortality rates were reported to be up to 62%,[4, 6, 9–13] mortality was reported to be even higher in patients who were mechanically ventilated (35.7-100%).[11, 14–16] There are few studies reporting 90-day mortality in critically ill patients, varying between 26.9% and 31.0%.[17, 18] Patient results may differ according to the geographical characteristics and income levels of countries, as well as the surge capacity of ICUs. The aim of this study was to determine the risk factors of 90-day mortality in COVID-19 patients with respiratory failure who were admitted to the Turkish ICUs.

MATERIAL AND METHODS

This study was performed retrospectively in 26 ICUs of 23 hospitals in Turkey between March 11, 2020 and June 11, 2020. Approvals from the Ministry of Health (2020-05-04T09_48_29) and Erciyes University Ethics Committee were obtained for the study (Date: July 22, 2020, No: 2020/401). Informed consent was waived.

Data Collection

Data were collected from the hospital electronic record systems and patient charts. Data were collected on electronic case report forms (eCRFs) by the study investigators, and then entered into the database. The investigators were trained for the study protocol, and using the database. Patient recruitment and data plausibility controls were performed daily. For data collection and management, the OpenClinica open source software 3.3 (Copyright© OpenClinica LLC and collaborators, Waltham, MA, USA, www.OpenClinica.com) was used. Independent query management, data cleaning, and source data verification were provided by Omega CRO, Ankara, Turkey, to obtain high-quality data. Patients with laboratory-confirmed COVID-19 and who had been followed up in the ICUs with respiratory failure for more than 24 hours were included in the study.[19] Laboratory confirmation for SARS-CoV-2 was defined as a positive result of the real-time polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs or endotracheal aspirate, according to WHO guidelines,[20] or a positive result in antibody testing with typical thorax computed tomography (CT) findings according to the Radiological Society of North America Expert Consensus Statement,[21] excluding other diagnoses.

The following variables at admission, for the first 10 days of ICU follow-up, and till discharge from the hospital were collected on electronic case report forms, as follows: age, gender, Eastern Cooperative Oncology Group Performance Status (ECOG) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, comorbidities, department of admission at the hospital, symptoms, duration from symptom onset to hospital and ICU admission, the ratio of partial arterial oxygen pressure (PaO_2) to fraction of inspired oxygen (FiO_2), lactate, the neutrophil to lymphocyte ratio, D-dimer, respiratory support type (conventional O_2, high-flow nasal O_2 (HFNO), non-invasive ventilation (NIV), or invasive ventilation (IMV)), types of treatment, use of neuromuscular blocker, vasopressor treatment, mean fluid balance per day (mean value of intake minus output per day for a 10-day follow-up period), acute kidney injury (AKI) as assessed by the Kidney Disease: Improving Global Outcomes (KDIGO) score,[22] development of delirium, new-onset cardiac arrhythmia (including atrial fibrillation/flutter, sustained or non-sustained ventricular tachycardia), length of ICU

and hospital stay, and the rates of ICU, 28-day, in-hospital, 60-day, and 90-day mortality. For patients who were discharged from the hospital or transferred to another hospital prior to 90 days, the national death notification system for mortality status was checked.

Statistical Analysis

The data were analyzed using the PASW Statistics for Windows, Version 18.0 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistics were expressed as numbers and percentages (%) for categorical variables, and as median and interquartile range (IQR) for numerical variables. In the two-group and multiple group comparisons of categorical variables, the chi-square test or Fisher's exact test was used as appropriate. For numerical variables, in two-group comparisons, the *t*-test or Mann–Whitney *U*-test was used as appropriate. Multivariate Cox regression analysis was performed by the stepwise backward likelihood ratio method, using the variables to be related with the survival in the univariate analysis. Kaplan–Meier survival curves until day 90 were computed and were compared according to respiratory support using the log-rank test. The statistical significance level was accepted as $P < .05$.

RESULTS

Patients were included from 26 ICUs (16 university hospitals, 10 public hospitals) in 23 hospitals (Table S1 and Figure S1). A total of 421 patients were enrolled in the study between March 11, 2020 and June 11, 2020. Of the total number of patients, 376 were PCR (+) and 45 were antibody (+), with typical thorax CT findings for COVID-19. The patients' 90-day mortality rate was 55.1% (Figure 1).

The patient characteristics at admission and the 90-day survivor/non-survivor group comparisons are seen in Table 1. The median age was 67 (57-76) years, 297 (70.5%) patients being over 60 years old. The non-survivors were older than the survivors ($P < .001$). The median values of the APACHE II score and SOFA score were 17 (12-26) and 5 (3-8), respectively. The APACHE and SOFA scores of the non-survivor patients were higher than those of the survivors ($P < .001$ for both). Of the total patients, 87.6% had at least 1 comorbidity. Hypertension (51.3%) was the most common comorbidity, followed by diabetes (30.9%) and cardiac diseases (25.2%). The most common admission symptoms were shortness of breath (63.7%), cough (57.2%), and fever (55.1%). The median time from symptom onset to hospital admission was 3 (2-7) days and for ICU admission it was 7 (4-10) days. The median PaO_2/FiO_2 ratio was 140 (88.2-204.5) mmHg and was lower in the non-survivors ($P < .001$). Blood lactate ($P < .001$), neutrophil/lymphocyte ratio ($P < .001$), and D-dimer levels were higher in the non-survivor group than among the survivors ($P < .01$).

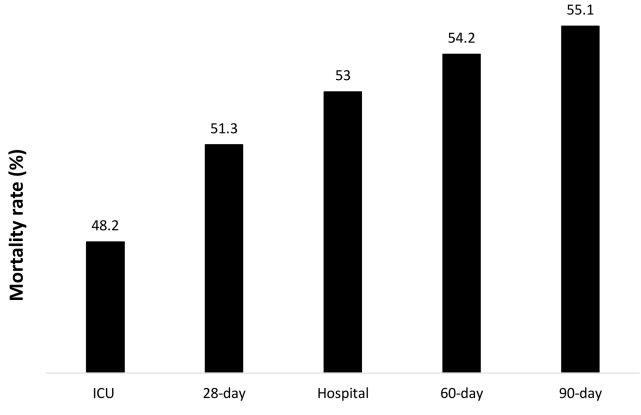

FIG. 1. ICU, 28-day, hospital, 60-day, and 90-day mortality rates.

The data on treatment approaches, complications, and length of stay from admission to discharge for the survivor and non-survivor groups are seen in Table 2. At admission and during 10-day follow-up, conventional oxygen support was provided to 31.6% of the patients. HFNO and NIV were provided to 8.3% and 6.2% of patients, respectively, and 53.9% of the patients were intubated and mechanically ventilated. Hydroxychloroquine (88.6%), favipiravir (82.7%), antibiotics (82.7%), azithromycin (56.8%), oseltamivir (47.7%), and corticosteroids (31.6%) were the medications most frequently administered to the patients. The mean fluid balance was 600 (275-1000) ml/per day and was higher in the non-survivor group ($P < .001$). The common complications observed in patients during the follow-up were delirium (9.7%) and cardiac arrhythmias (7.8%). The median values of length of stay in ICU and hospital were 7 (3-14) and 15 (9-23) days, respectively.

As seen in Figure 2, the multivariate Cox regression analysis revealed the following 8 variables relevant to 90-day mortality: invasive mechanical ventilation (IMV) (conventional oxygen as the reference), high lactate, age ≥60 years, presence of cardiac arrhythmia, vasopressor therapy, mean fluid balance ≥600 mL/day, PaO_2/FiO_2 ≤150 mmHg, ECOG score ≥1, adjusted for other variables SOFA ≥5 and APACHE II ≥17, presence of hypertension, diabetes mellitus, cardiac disease, cancer, cerebrovascular disease, end-stage renal disease, department of admission at the hospital, onset of symptoms to ICU admission <7 days; neutrophil/lymphocyte ratio ≥8; neuromuscular blocker use; and development of AKI.

As seen in Figure 3, the Kaplan–Meier survival analysis revealed significantly lower survival in patients who had received IMV, compared to those who had received conventional O_2, HFNO, and NIV (log-rank P value <.001).

DISCUSSION

This study, reporting the results of the first wave of the pandemic in Turkish ICUs, revealed a 90-day mortality of 55.1%. Invasive mechanical ventilation, high lactate level, age greater than 60 years, development of cardiac arrhythmia, need for vasopressor treatment, positive fluid balance, severe hypoxemia (PaO_2/FiO_2 ≤150), and an ECOG performance status that was not fully active were determined to be the independent risk factors for 90-day mortality.

There are few studies reporting 90-day mortality rate and the risk factors for mortality in critically ill patients with COVID-19.[17, 18] In a multicenter, prospective, cohort study conducted in patients with laboratory-confirmed COVID-19 who were admitted to ICUs

TABLE 1. Patients' Characteristics at ICU Admission

	All Patients, *n* = 421	90-Day Survivors, *n* = 189	90-Day Non-survivors, *n* = 232	*P*
Age, years, median (IQR)	67 (57-76)	58 (49-69)	72 (64-79)	<.001
Age ≥60 years, *n* (%)	297 (70.5)	89 (47.1)	208 (89.7)	<.001
Male, *n* (%)	251 (59.6)	111 (58.7)	140 (60.3)	.74
ECOG score,* *n* (%)				<.001
0	187 (45.6)	114 (62.3)	73 (32.2)	
1	76 (18.5)	30 (16.4)	46 (20.3)	
2	74 (18.0)	24 (13.1)	50 (22.0)	
3	53 (12.9)	13 (7.1)	40 (17.6)	
4	20 (4.9)	2 (1.1)	18 (7.9)	
APACHE II score, median (IQR)	17 (12-26)	13 (9-18)	23 (16-30)	<.001
APACHE II score ≥17, *n* (%)	205 (49.8)	47 (25.3)	158 (69.9)	<.001
SOFA score, median (IQR)	5 (3-8)	3 (2-5)	7 (4-10)	<.001
SOFA score ≥5, *n* (%)	199 (51.0)	51 (29.0)	148 (69.2)	<.001
Comorbid diseases, *n* (%)	369 (87.6)	151 (79.9)	218 (94)	<.001
Hypertension	216 (51.3)	80 (42.3)	136 (58.6)	.001
Diabetes mellitus	130 (30.9)	42 (22.2)	88 (37.9)	<.001
Cardiac disease	106 (25.2)	31 (16.4)	75 (32.3)	<.001
Respiratory disease	82 (19.5)	36 (19)	46 (19.8)	.84
Cancer	45 (10.7)	14 (7.4)	31 (13.4)	.049
Cerebrovascular disease	37 (8.8)	7 (3.7)	30 (12.9)	.001
Dementia	26 (6.2)	9 (4.8)	17 (7.3)	.27
End-stage renal disease	15 (3.6)	2 (1.1)	13 (5.6)	.01
Admission department of hospital, *n* (%)				
Ward	247 (58.6)	125 (66.1)	122 (52.7)	
Emergency department	119 (28.4)	43 (22.8)	76 (32.9)	.03
Other	55 (13.1)	23 (12.1)	31 (13.4)	
Admission symptoms, *n* (%)				
Shortness of breath	268 (63.7)	114 (60.3)	154 (66.4)	.20
Cough	241 (57.2)	120 (63.5)	121 (52.2)	.02
Fever	232 (55.1)	122 (64.6)	110 (47.4)	<.001
Weakness	126 (29.9)	57 (30.2)	69 (29.7)	.93
Myalgia	46 (10.9)	29 (15.3)	17 (7.3)	<.01
Diarrhea	20 (4.8)	10 (5.3)	10 (4.3)	.64
Chest pain	19 (4.5)	7 (3.7)	12 (5.2)	.47
Sore throat	6 (1.4)	3 (1.6)	3 (1.3)	1.00
Duration from symptom onset to hospital admission, days, median (IQR)	3 (2-7)	4 (2-7)	3 (2-5)	.02
Duration from symptom onset to ICU admission, days, median (IQR)	7 (4-10)	7 (5-10)	6 (3-10)	<.01
Symptom onset to ICU admission of <7 days, *n* (%)	192 (49.6)	79 (43.4)	113 (55.1)	.02
PaO_2/FiO_2, mmHg, median (IQR)	140 (88-205)	170 (110-222)	125 (75-188)	<.001
PaO_2/FiO_2 ≤150 mmHg, *n* (%)	210 (53.2)	73 (41.0)	137 (63.1)	<.001
Lactate, mmol/L, median (IQR)	1.4 (1-2)	1.2 (0.9-1.6)	1.6 (1.1-2.4)	<.001
Lactate >2 mmol/L, *n* (%)	98 (24.4)	18 (10.3)	80 (35.4)	<.001
Neutrophil/lymphocyte ratio, median (IQR)	8.0 (4.5-13.1)	6.4 (4.0-9.8)	9.8 (5.7-16.8)	<.001
Neutrophil/lymphocyte ratio ≥8, *n* (%)	192 (49.7)	61 (33.9)	131 (63.6)	<.001
D-dimer, ng/mL, median (IQR)	1016 (538-2186)	820 (460-1670)	1200 (600-2850)	<.01
D-dimer >1000 ng/mL, *n* (%)	123 (50.6)	49 (43.0)	74 (57.4)	.02

*ECOG score: 0, Fully active; 1, Restricted in physically strenuous activity; 2, Ambulatory and capable of all selfcare; up and about more than 50% of waking hours; 3, Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours; 4, Completely disabled; totally confined to bed or chair.

TABLE 2. Treatment, Complications and Length of Stay from ICU Admission Till Discharge

	All Patients, *n* = 421	90-Day Survivors, *n* = 189	90-Day Non-survivors, *n* = 232	*P*
Respiratory support, *n* (%)				
Conventional oxygen	133 (31.6)	104 (55.0)	29 (12.5)	
High-flow nasal oxygen	38 (8.3)	30 (15.9)	5 (2.2)	<.001
Non-invasive ventilation	26 (6.2)	15 (7.9)	11 (4.7)	
Invasive ventilation	227 (53.9)	40 (21.2)	187 (80.6)	
Treatment, *n* (%)				
Hydroxychloroquine	373 (88.6)	168 (88.9)	205 (88.4)	.86
Favipiravir	348 (82.7)	156 (82.5)	192 (82.8)	.95
Antibiotics	348 (82.7)	145 (76.7)	203 (87.5)	<.01
Azithromycin	239 (56.8)	112 (59.3)	127 (54.7)	.35
Oseltamivir	201 (47.7)	96 (50.8)	105 (45.3)	.25
Corticosteroids	133 (31.6)	55 (29.1)	78 (33.6)	.32
Vitamin C (more than RDA)	131 (31.1)	52 (27.5)	79 (34.1)	.14
Convalescent plasma	53 (12.6)	23 (12.2)	30 (12.9)	.81
Tocilizumab	44 (10.5)	17 (9.0)	27 (11.6)	.37
Zinc (more than RDA)	35 (8.3)	17 (9.0)	18 (7.8)	.64
Thiamine (more than RDA)	31 (7.4)	15 (7.9)	16 (6.9)	.68
Lopinavir/ritonavir	21 (5.0)	8 (4.2)	13 (5.6)	.52
Intravenous immunoglobulin	10 (2.4)	4 (2.1)	6 (2.6)	1.00
Cytokine removal	9 (2.1)	3 (1.6)	6 (2.6)	.73
Plasmapheresis	5 (1.2)	2 (1.1)	3 (1.3)	1.00
Neuromuscular blocker use, *n* (%)	98 (23.5)	17 (9)	81 (35.4)	<.001
Vasopressor therapy, *n* (%)	173 (41.1)	21 (11.1)	152 (65.5)	<.001
Mean fluid balance per day, median (IQR)	600 (275-1000)	393 (167-663)	872 (400-1431)	<.001
Mean fluid balance of ≥600 per day, *n* (%)	202 (50.4)	60 (33.7)	142 (63.7)	<.001
Acute kidney injury, *n* (%)	155 (38.9)	26 (14.4)	129 (59.4)	<.001
Delirium, *n* (%)	41 (9.7)	22 (11.6)	19 (8.2)	.24
Cardiac arrhythmia, *n* (%)	33 (7.8)	3 (1.6)	30 (12.9)	<.001
Length of ICU stay, days, median (IQR)	7 (3-14)	6 (3-13)	8 (4-16)	.04
Length of hospital stay, days, median (IQR)	15 (9-23)	17 (12.5-25.5)	13 (7-22)	<.001

RDA, recommended daily allowance.

of 138 hospitals in France, Belgium, and Switzerland, the 90-day mortality rate was found to be 31%, and older age, immunosuppression, severe obesity, diabetes mellitus, higher renal and cardiovascular SOFA scores, lower PaO_2/FiO_2 ratios, and shorter time between onset to first symptoms and ICU admission were found to be independent risk factors for 90-day mortality.

Zettersten et al. performed a nationwide cohort study about the long-term outcome for COVID-19 patients in Swedish ICUs. The rate for 90-day mortality was found to be 26.9%. In Cox regression analysis, male sex, older age, comorbid diseases, and month of admission were found to be associated with mortality.[18]

Mortality rates in critically ill COVID-19 patients differ worldwide, with the ICU mortality rates reported from 29% to 51.8%,[16, 23] hospital mortality from 42% to 60.4%,[24, 25] 28-day mortality at 35.4%,[24] and 60-day mortality at 61.5%.[13]

These differences might be due to differences in disease severity, surge capacity, available resources, and other related factors. Turkey has a sufficient number of intensive care beds, reported to be more than 30 adult ICU beds per 100 000 population, with around 30% of them located in private hospitals which had limited roles in the pandemic. However, there is a severe shortage of intensive care workers, especially nurses, in Turkey. In the OECD countries, the number of physicians per 100 000 population is 348 and the number of nurses per 100 000 population is 938. In Turkey, these numbers are 348 and 301, respectively. During the COVID-19 pandemic, surge-capacities were enhanced in many countries.[26–29] In a study conducted in Australia, the number of intensive care beds in the first wave of the pandemic was increased by 191%, the number of ventilators by 120%, the number of senior doctors by 240%, and the number of intensive care nurses by 249%.[28] However, in Turkey, even prior to COVID-19,

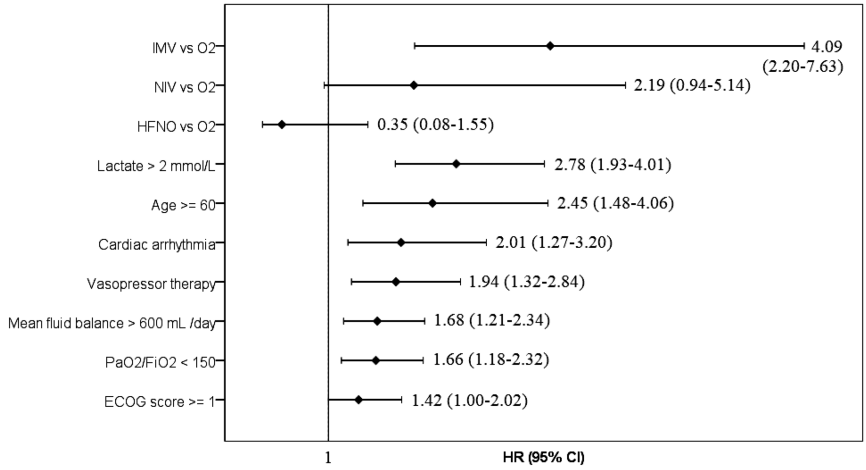

FIG. 2. Multivariate Cox Proportional Hazard Regression Analysis of factors associated with 90-day mortality, as a forest plot graph. IMV, invasive mechanical ventilation; O_2, oxygen; NIV, non-invasive mechanical ventilation; HFNO, high-flow nasal oxygen; PaO_2, partial arterial oxygen pressure; FiO_2, fraction of inspired oxygen; ECOG, astern Cooperative Oncology Group Performance Status; HR, hazard ratio.

the number of patients per nurse could be as high as 4-5 in the third-level comprehensive units. The number of physiotherapists are still more negligible.

Acute respiratory failure is the most common cause of intensive care admission in COVID-19 patients.[17, 30, 31] Most of these patients require IMV. In some studies, the frequency of IMV has

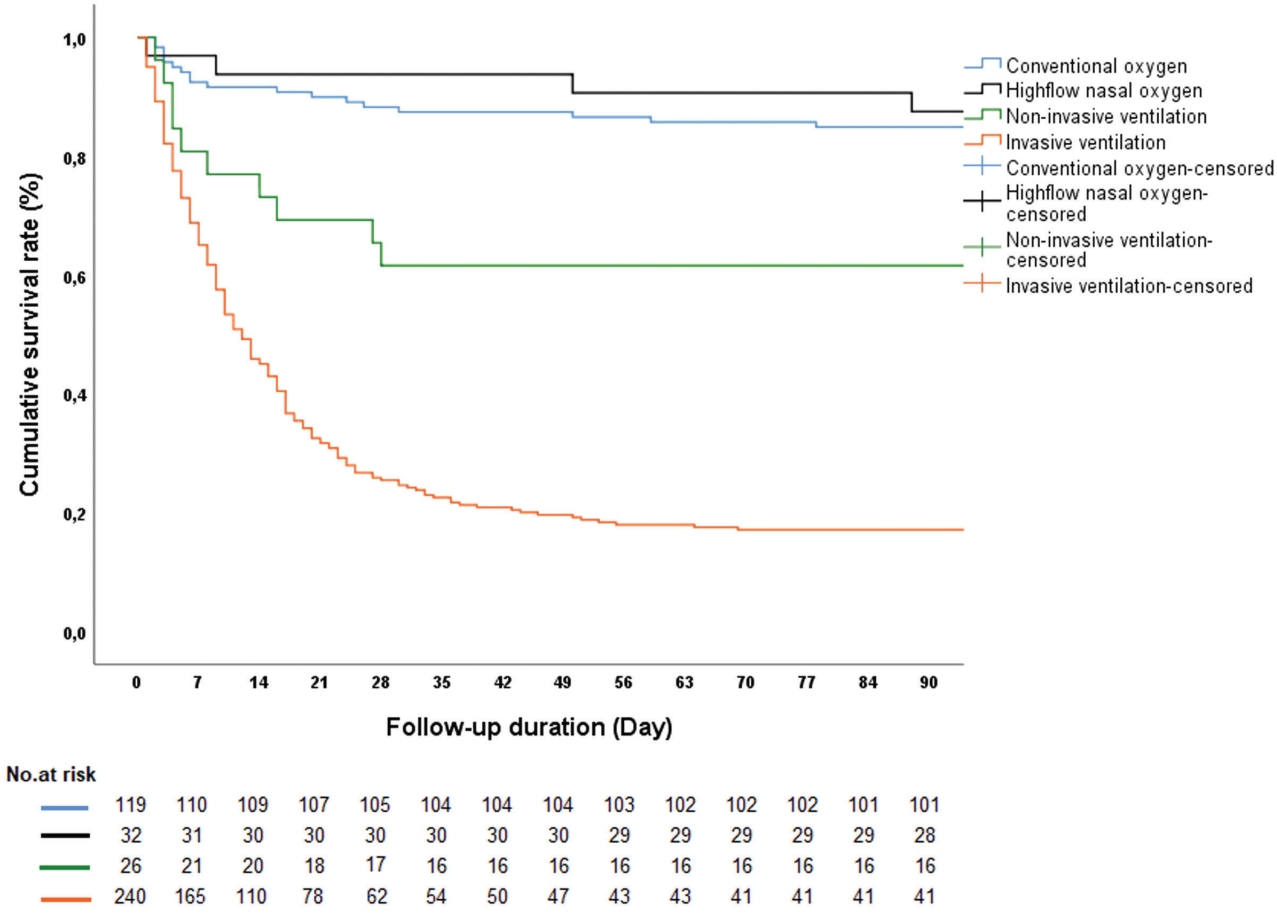

FIG. 3. Kaplan–Meier survival curves for 90-day mortality according to respiratory support. Log-rank test $P < .001$.

been shown to vary between 12.2% and 88%.[1, 13, 24, 32] In our study, 52.4% of the patients had PaO_2/ FiO_2 ratio below 150%, and 53.9% of the patients needed IMV at admission or during the follow-up. In this study, both the IMV and PaO_2/FiO_2 ≤150 were found to be risk factors determining 90-day mortality. In studies conducted in different parts of the world, the mortality rates have been shown to vary between 35.7% and 100% in invasively ventilated patients.[11, 14, 16] This variety among studies might be due to differences in the standards of care, surge capacity, resources, and due to different treatment approaches in the first wave.[26]

Blood lactate levels are used mostly to follow-up on tissue perfusion in critically ill patients.[33] Even minor increases in lactate levels are associated with higher mortality rates.[34] In this study, the non-survivors had higher lactate levels compared to the survivors, and a lactate level >2 mmol/L was an independent predictor of mortality. In COVID-19 patients, the lactate levels were reported to be high in the non-survivors.[17, 24, 31] However, it was not determined to be a risk factor for any of these patients, in the multivariate analysis.

In this study, vasopressor treatment, which was administered to 41.1% of the patients, was also an independent predictor of mortality. Although we have not recorded the underlying reasons for vasopressor use, this is a predictor of disease severity, and to our knowledge, there is no other study reporting vasopressor treatment as an independent risk factor for mortality, except the REVA network study revealing the cardiovascular SOFA score as being an independent risk factor for mortality.[17]

In this study, positive fluid balance was found to be an independent risk factor for 90-day mortality in ICU patients. It was well known that positive fluid balance increases morbidity and mortality in critically ill patients with sepsis, septic shock, and ARDS.[35, 36] It had also been shown that negative fluid balance reduces respiratory failure and the need for renal replacement therapy in critically ill patients.[37, 38] To our knowledge, this is the first study reporting positive fluid balance as an independent predictor of mortality. This finding necessitates meticulous control of fluid balance in critically ill COVID-19 patients.

The ECOG scoring system is used to evaluate the physical performance of patients in chronic diseases such as cancer.[39] In this study, we preferred to use the ECOG score as it is easy to use and is widely known. Patients who were not fully active had poor prognosis. To our knowledge, this factor was not evaluated in other studies. However, in the REVA network-COVID-ICU study, the clinical frailty scale (CFS) was found to be higher in patients who died within 90 days,[17] as in the VIP1 study, where CFS was found to be related with 30-day mortality in critically ill very elderly patients.[40]

In some studies, cardiac damage/arrhythmia was reported to be common in COVID-19 patients, and related with increased mortality.[41, 42] We observed cardiac arrhythmia in 33 (7.8%) patients, and this was a risk factor that increased the 90-day mortality, similar to other studies. This may be due to medications and/or due to the disease itself. In the early days of the COVID-19 pandemic, hydroxychloroquine, alone or combined with azithromycin, was used frequently in some parts of the world [24, 41, 43] and in our country[2] as well. In this study, hydroxychloroquine had been given to 86% and azithromycin to 56.8% of the patients.

The major strength of this study is that it has been conducted as a multicenter study in Turkish ICUs. As the pandemic is a major threat globally, data from various countries and geographic regions with different income levels and resources are needed. In addition, there are few studies reporting long-term mortality rates in COVID-19 patients, to our knowledge, with this one being the second reporting 90-day mortality. We need studies on outcomes for even longer terms. Lastly, some novel independent predictors of mortality such as positive fluid balance, baseline performance status, high admission lactate and vasopressor use have been determined, which need to be validated in future studies.

However, this study has several limitations. The number of ICUs and patients are limited due to the short study duration, and although ICUs entering the study are from different regions of Turkey, the results might not be representative of the whole country. The study was conducted during the first wave, and might not reflect the current situation. In addition, there might be other factors influencing mortality, which could not have been included in the study due to its design.

In this multicenter cohort study of critically ill adult patients with COVID-19 in Turkey, more than half of the patients died within 90 days after ICU admission. Receiving invasive mechanical ventilation, a lactate level >2 mmol/L, age ≥60 years, cardiac arrhythmia during ICU stay, receiving vasopressor treatment during ICU stay, a positive fluid balance of ≥600 mL per day during ICU follow-up, an admission PaO_2/FiO_2 ratio of ≤150 mmHg, and a baseline ECOG score ≥1 have been found to be independent risk factors for 90-day mortality. Some factors, such as positive fluid balance, are modifiable risk factors which need to be paid attention to during follow-up of these patients. In addition, patients should be protected from complications such as cardiac arrhythmias by close monitoring, avoiding electrolyte imbalances, and administering related medications.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Erciyes University (Date: July 22, 2020 no: 2020/401).

Patient Consent for Publication: Written informed consent was waived.

Data-sharing Statement: After publication, data are available upon reasonable request. A proposal with a detailed description of study objectives and a statistical analysis plan will be needed for evaluation of the reasonability of requests. Additional materials might also be required during the process of evaluation.

Preprint History: Previously posted to Research Square as a preprint on January 21, 2021 (DOI:10.21203/rs.3.rs-150961/v1).

Author Contributions: Concept, design of the work, data acquisition, and analysis - KG, IHA, PH, BH, ST, and AT; Interpretation of data, the creation of new software used in the work, drafting, and revising the manuscript - KG, IHA, PH, BH, ST, ZG, KI, YB, FTB, FY, MS, RCY, EE, NDA, LT, GE, GG, IK, EA, SY, TM, SS, TA, BAC, AAA,DAO, TKS, AUE, AF, FA, MCG, AZ, AG, MT, MA, RU, JBC, CB, CK, EK, EO, EOE, SO, IAS, IHT, BC, BE, KTS, JE, UGY, NT, MS, and AT.

Conflict of Interest: The authors have no conflicts of interest to declare.

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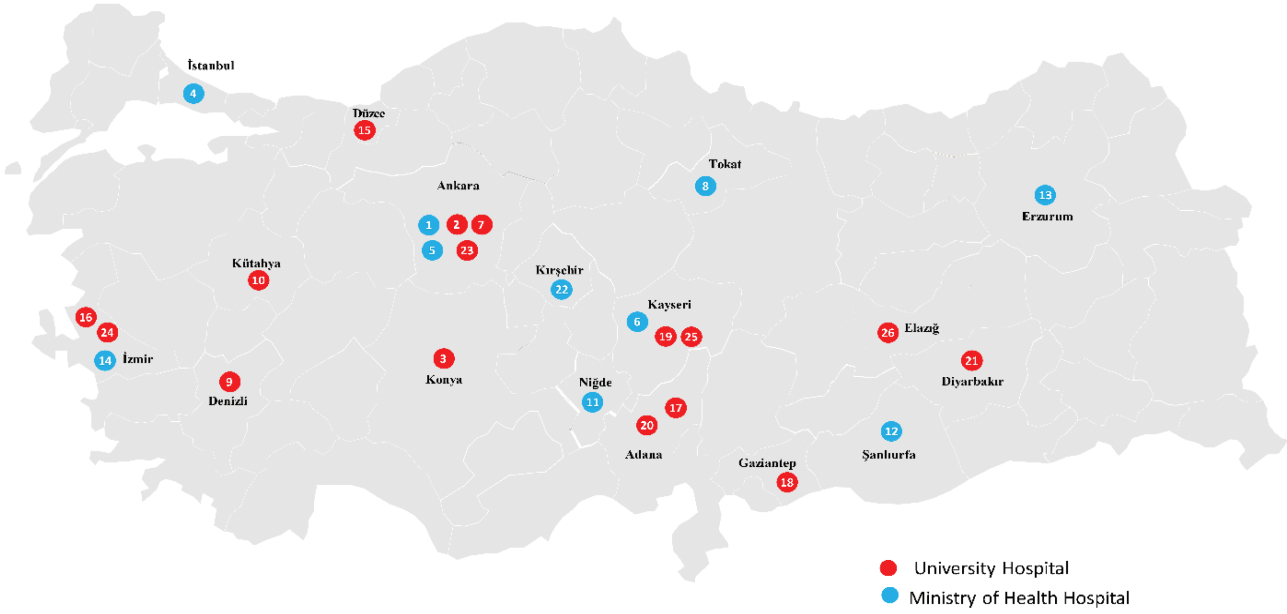
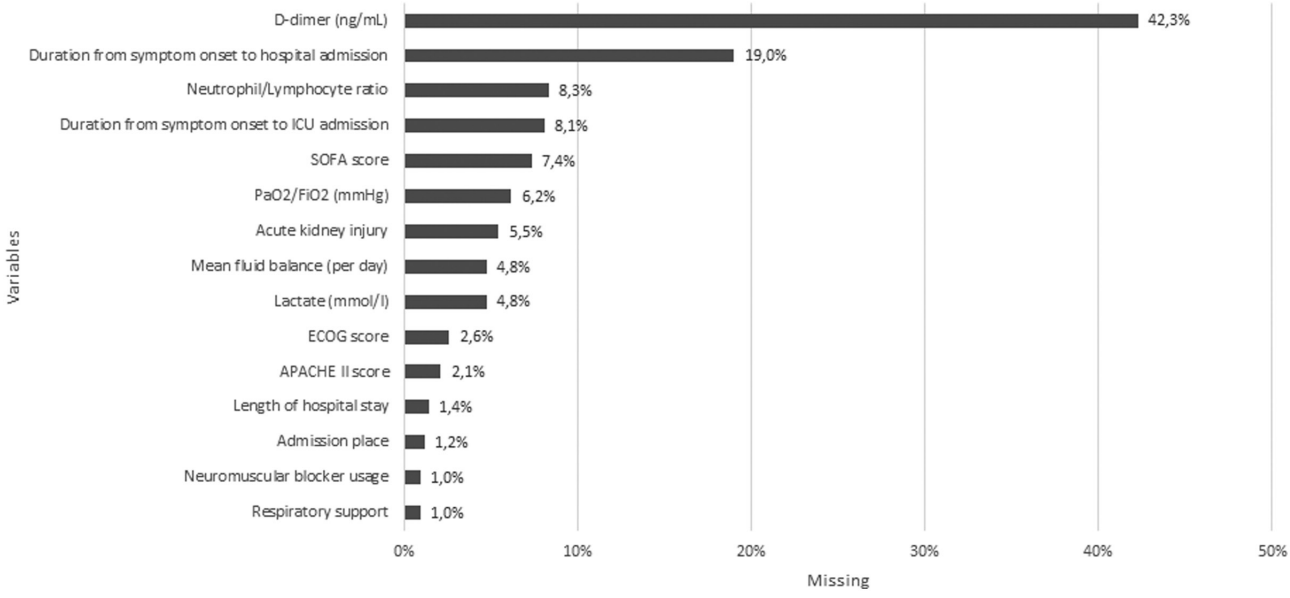


Supplementary FIG. 1. List of participant sites - —Map of Turkey.



Supplementary FIG. 2. List of missing data.

SUPPLEMENTARY TABLE 1. List of participparticipating ating hospitals and number of patients

		n
1.	Ministry of Health, Ankara Diskapi Educational and Training Hospital Intensive Care Unit	40
2.	Hacettepe University, Medical Intensive Care Unit	31
3.	Selcuk University Anesthesiology Intensive Care Unit	31
4.	Ministry of Health, Istanbul Lutfi Kirdar Educational and Training Hospital Intensive Unit	28
5.	Ministry of Health, Ankara Yenimahalle Educational and Training Hospital Intensive Care Unit	28
6.	Ministry of Health, Kayseri City Hospital, Intensive Care Unit	24
7.	Ankara University, Medical Intensive Care Unit	22
8.	Ministry of Health, Tokat State Hospital, Intensive Care Unit	21
9.	Pamukkale University, Medical Intensive Care Unit	18
10.	Kutahya University, Anesthesiology Intensive Care Unit	17
11.	Nigde Omer Halisdemir University, Intensive Care Unit	15
12.	Ministry of Health, Mehmet Akif Inan Educational and Training Hospital, Intensive Care Unit	14
13.	Ministry of Health, Erzurum State Hospital, Intensive Care Unit	13
14.	Ministry of Health, Izmir Suat Seren Educational and Training Hospital	13
15.	Duzce University, Medical Intensive Care Unit	13
16.	Dokuz Eylul University, Medical Intensive Care Unit	12
17.	Cukurova University, Medical Intensive Care Unit	11
18.	Gaziantep University, Medical Intensive Care Unit	11
19.	Erciyes University, Medical Intensive Care Unit	10
20.	Cukurova University, Pulmonary Intensive Care Unit	10
21.	Dicle University, Medical Intensive Care Unit	10
22.	Ahi Evran University, Intensive Care Unit	9
23.	Gazi University, Intensive Care Unit	8
24.	Dokuz Eylul University, Pulmonary Intensive Care Unit	5
25.	Erciyes University, Pulmonary Intensive Care Unit	4
26.	Fırat University, Medical Intensive Care Unit	3
Total		**421 patients**