Clinical Outcomes and Independent Risk Factors for 90-day Mortality in Critically-ill Patients Infected With SARS CoV-2: a Multicenter Study in Turkish Intensive Care Units

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Abstract

Background: There are limited data on long-term outcome and mortality predictors of COVID-19 from different parts of the world. The aim of this study was to determine risk factors of 90-day mortality in critically-ill patients infected with SARS-CoV-2 in Turkish ICUs.

Methods: This multicenter, retrospective study was performed in 26 ICUs in Turkey. All patients with confirmed SARS-CoV2 infection, requiring more than 24 hours of ICU follow-up were included in the study. Demographics, clinical characteristics, laboratory variables, respiratory support, treatment types, and survival data were recorded.

Results: A total of 421 patients were included in the study. The median age was 67 (IQR: 57-76) years, and 251 patients (59.6%) were men. 90-day mortality rate was 55.1%. Factors independently associated with 90-day mortality were receiving invasive mechanical ventilation (HR 4.09 [95% CI: 2.20-7.63]), admission lactate level > 2 mmol/L (2.78 [1.93-4.01]), age $\geq$ 60 years (2.45 [1.48-4.06]), having cardiac arrhythmia during ICU stay (2.01 [1.27-3.20]), receiving vasopressor treatment (1.94 [1.32-2.84]), positive fluid balance of $\geq$ 600 ml/per day during ICU follow-up (1.68 [1.21-2.34]), admission PaO₂/FiO₂ ratio of $\leq$ 150 mmHg (1.66 [1.18-2.32]), and baseline ECOG score $\geq$ 1 (1.42 [1.00-2.02]).

Conclusion: This study has shown that long-term mortality was high in critically-ill COVID-19 patients in Turkish ICUs. Invasive mechanical ventilation, high lactate level, older age, presence of cardiac arrhythmia, need for vasopressor treatment, positive fluid balance, severe hypoxemia and not having fully-active performance were related with mortality.

Introduction

Coronavirus disease-2019 (COVID-19) pandemic caused by 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) was the predominant complication of COVID-19, whereas subsequently, it was realized that virus is damaging the vascular endothelium and causing multi-system inflammatory syndrome [6] and several complications such as kidney, cardiac, liver and brain injury [7, 8], vascular thrombosis [9, 10], and macrophage activation syndrome [4, 7, 11]. Short and long-term mortality of critically-ill COVID-19 patients are quite high. While intensive care unit (ICU), in-hospital, 28-day and 60-day mortality rates were reported to be up to 62% [4, 7, 12–15], mortality was reported to be even higher in patients who were mechanically ventilated (35.7–100%) [14, 16–18]. There is limited data about long term prognosis of COVID-19 patients. To the best of our knowledge, there is just one study reporting 90-day mortality which was 31.0% [19]. Patient results may differ according to the geographical characteristics, income levels of countries, as well as surge capacity of ICUs. The aim of this study was to determine risk factors of 90-day mortality in patients with COVID-19 who were admitted to the Turkish ICUs.

Method

This study was performed retrospectively in 26 intensive care units of 23 hospitals in Turkey between 11 March 2020-11 July 2020. Approvals from the Ministry of Health (2020-05-04T09_48_29) and Erciyes University Ethics Committee were obtained for the study (Date: 22.07.2020 no:2020/401). Informed consent was waived.

Data Collection

Data were collected from the hospital electronic record systems and patient charts. Patients with laboratory confirmed COVID-19 and who had been followed in the ICUs with respiratory failure for more than 24 hours were included in the study. Laboratory confirmation for SARS-CoV-2 was defined as a positive result of Real Time Polymerase Chain Reaction assay of nasal, pharyngeal swabs or endotracheal aspirate according to WHO guideline [20] or positive result in antibody testing with typical thorax computed tomography findings according to the Radiological Society of North America Expert Consensus Statement [21] excluding other diagnosis.

The following variables at admission, for the first 10 days of ICU follow-up 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, co-morbidities, admission place, symptoms, duration from symptom onset to hospital and ICU admission, partial arterial oxygen pressure (PaO_2) to fraction of inspired oxygen (FiO_2) ratio, lactate, neutrophil to lymphocyte ratio, D-dimer, respiratory support type (conventional O_2 , high flow nasal O_2 (HFNO), non-invasive ventilation (NIV) and invasive ventilation (IMV)), types of treatment, neuromuscular blocker use, vasopressor treatment, mean fluid balance per day (mean value of intake minus output per day for 10 days follow-up period), acute kidney injury (AKI) as assessed by 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, ICU, 28-day, hospital, 60 and 90-day mortality rates. For patients who were discharged from the hospital or transferred to another hospital prior to 90 days, national death notification system for mortality status was checked.

Statistical analysis

Data were analyzed using the PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as numbers and percentages (%) for categorical variables and as median and interquartile range (IQR) for numerical variables. In two and multiple group comparisons of categorical variables, chi-square test or Fisher's exact test was used as appropriate. For numerical variables, in two group comparisons, t-test or Mann-Whitney U test was used as appropriate. Multivariate Cox regression analysis was performed by 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 log-rank test. Statistical significance level was accepted as $p < 0.05$.

Results

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

Patient characteristics at admission and 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. Non-survivor patients were older than survivors ($p < 0.001$). Median values of the APACHE II score and SOFA score were 17 (12–26) and 5 (3–8), respectively. APACHE and SOFA scores of the non-survivor patients were higher than the survivors ($p < 0.001$ for both). Of patients, 87.6% had at least one co-morbidity. Hypertension (51.3%) was the most common one, 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%). Median time from symptom onset to hospital admission was 3 (2–7) days and ICU admission was 7 (4–10) days. Median $\text{PaO}_2/\text{FiO}_2$ ratio was 140 (88.2-204.5) mmHg and was lower in non-survivors ($p < 0.001$). Blood lactate ($p < 0.001$), neutrophil / lymphocyte ratio ($p < 0.001$) and D-dimer levels were higher in the non-survivor group than the survivors ($p < 0.01$).

Table 1
Patients' characteristics at admission

	All patients n = 421	90-day Survivors n = 189	90-day Non- survivors n = 232	P value
Age, yrs, median (IQR)	67 (57–76)	58 (49–69)	72 (64–79)	< 0.001
Age ≥ 60 yrs, n (%)	297 (70.5)	89 (47.1)	208 (89.7)	< 0.001
Male gender, n(%)	251 (59.6)	111 (58.7)	140 (60.3)	0.74
ECOG score*, n (%)				< 0.001
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)	< 0.001
APACHE II score ≥ 17, n (%)	205 (49.8)	47 (25.3)	158 (69.9)	< 0.001
SOFA score, median (IQR)	5 (3–8)	3 (2–5)	7 (4–10)	< 0.001
SOFA score ≥ 5, n (%)	199 (51.0)	51 (29.0)	148 (69.2)	< 0.001
Co-morbid diseases, n (%)	369 (87.6)	151 (79.9)	218 (94)	< 0.001
Hypertension	216 (51.3)	80 (42.3)	136 (58.6)	0.001
Diabetes mellitus	130 (30.9)	42 (22.2)	88 (37.9)	< 0.001
Cardiac disease	106 (25.2)	31 (16.4)	75 (32.3)	< 0.001
Respiratory disease	82 (19.5)	36 (19)	46 (19.8)	0.84
Cancer	45 (10.7)	14 (7.4)	31 (13.4)	0.049
Cerebrovascular disease	37 (8.8)	7 (3.7)	30 (12.9)	0.001
Dementia	26 (6.2)	9 (4.8)	17 (7.3)	0.27
End-stage renal disease	15 (3.6)	2 (1.1)	13 (5.6)	0.01

*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.

	All patients n = 421	90-day Survivors n = 189	90-day Non- survivors n = 232	P value
Admission place, n (%)				0.03
Ward	247 (59.4)	125 (66.1)	122 (53.7)	
Emergency department	119 (28.6)	43 (22.8)	76 (33.5)	
Other	50 (12.0)	21 (11.1)	29 (12.8)	
Admission symptoms, n (%)				
Shortness of breath	268 (63.7)	114 (60.3)	154 (66.4)	0.20
Cough	241 (57.2)	120 (63.5)	121 (52.2)	0.02
Fever	232 (55.1)	122 (64.6)	110 (47.4)	< 0.001
Weakness	126 (29.9)	57 (30.2)	69 (29.7)	0.93
Myalgia	46 (10.9)	29 (15.3)	17 (7.3)	< 0.01
Diarrhea	20 (4.8)	10 (5.3)	10 (4.3)	0.64
Chest pain	19 (4.5)	7 (3.7)	12 (5.2)	0.47
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)	0.02
Duration from symptom onset to ICU admission, days, median (IQR)	7 (4–10)	7 (5–10)	6 (3–10)	< 0.01
Symptom onset to ICU admission of < 7 days, n (%)	192 (49.6)	79 (43.4)	113 (55.1)	0.02
PaO ₂ /FiO ₂ , mmHg, median (IQR)	140 (88–205)	170 (110–222)	125 (75–188)	< 0.001
PaO ₂ /FiO ₂ ≤ 150 mmHg, n (%)	210 (53.2)	73 (41.0)	137 (63.1)	< 0.001
Lactate, mmol/L, median (IQR)	1.4 (1–2)	1.2 (0.9–1.6)	1.6 (1.1–2.4)	< 0.001
Lactate > 2 mmol/L, n (%)	98 (24.4)	18 (10.3)	80 (35.4)	< 0.001

*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.

	All patients n = 421	90-day Survivors n = 189	90-day Non- survivors n = 232	P value
Neutrophil / lymphocyte ratio, median (IQR)	8.0 (4.5–13.1)	6.4 (4.0-9.8)	9.8 (5.7–16.8)	< 0.001
Neutrophil / lymphocyte ratio $\geq$ 8, n (%)	192 (49.7)	61 (33.9)	131 (63.6)	< 0.001
D-dimer, ng/mL, median (IQR)	1016 (538–2186)	820 (460–1670)	1200 (600–2850)	< 0.01
D-dimer > 1000 ng/mL, n (%)	123 (50.6)	49 (43.0)	74 (57.4)	0.02
*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.				

Treatment, complications and length of stay from admission till discharge in the survivor and non-survivor groups are seen in Table 2. At admission and during 10-day follow-up, conventional oxygen support was applied to 28.5% of the patients. HFNO and NIV were applied in 7.7% and 6.2% of patients, respectively, and 57.6% 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 most frequently given medications to the patients. Mean fluid balance was 600 (275–1000) ml/per day and was higher in the non-survivor group ($p < 0.001$). 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.

Table 2
Treatment, complications and length of stay from admission till discharge

	All patients n = 421	90-day Survivors n = 189	90-day Non- survivors n = 232	P value
Respiratory support, n (%)				< 0.001
Conventional oxygen	119 (28.5)	101 (54.3)	18 (7.8)	
High-flow nasal oxygen	32 (7.7)	28 (15.1)	4 (1.7)	
Non-invasive ventilation	26 (6.2)	16 (8.6)	10 (4.3)	
Invasive ventilation	240 (57.6)	41 (22.0)	199 (86.1)	
Treatment, n (%)				
Hydroxychloroquine	373 (88.6)	168 (88.9)	205 (88.4)	0.86
Favipiravir	348 (82.7)	156 (82.5)	192 (82.8)	0.95
Antibiotics	348 (82.7)	145 (76.7)	203 (87.5)	< 0.01
Azithromycin	239 (56.8)	112 (59.3)	127 (54.7)	0.35
Oseltamivir	201 (47.7)	96 (50.8)	105 (45.3)	0.25
Corticosteroids	133 (31.6)	55 (29.1)	78 (33.6)	0.32
Vitamin C (more than RDA)	131 (31.1)	52 (27.5)	79 (34.1)	0.14
Convalescent plasma	53 (12.6)	23 (12.2)	30 (12.9)	0.81
Tocilizumab	44 (10.5)	17 (9.0)	27 (11.6)	0.37
Zinc (more than RDA)	35 (8.3)	17 (9.0)	18 (7.8)	0.64
Thiamine (more than RDA)	31 (7.4)	15 (7.9)	16 (6.9)	0.68
Lopinavir/ritonavir	21 (5.0)	8 (4.2)	13 (5.6)	0.52
Intravenous immunoglobulin	10 (2.4)	4 (2.1)	6 (2.6)	1.00
Cytokine removal	9 (2.1)	3 (1.6)	6 (2.6)	0.73
Plasmapheresis	5 (1.2)	2 (1.1)	3 (1.3)	1.00
Neuromuscular blocker use, n (%)	98 (23.5)	17 (9)	81 (35.4)	< 0.001
Vasopressor therapy, n (%)	173 (41.1)	21 (11.1)	152 (65.5)	< 0.001

RDA: Recommended daily allowance

	All patients n = 421	90-day Survivors n = 189	90-day Non- survivors n = 232	P value
Mean fluid balance per day, median (IQR)	600 (275–1000)	393 (167–663)	872 (400–1431)	< 0.001
Mean fluid balance of ≥ 600 per day, n(%)	202 (50.4)	60 (33.7)	142 (63.7)	< 0.001
Acute kidney injury, n (%)	155 (38.9)	26 (14.4)	129 (59.4)	< 0.001
Delirium, n (%)	41 (9.7)	22 (11.6)	19 (8.2)	0.24
Cardiac arrhythmia, n (%)	33 (7.8)	3 (1.6)	30 (12.9)	< 0.001
Length of ICU stay, days, median (IQR)	7 (3–14)	6 (3–13)	8 (4–16)	0.04
Length of hospital stay, days, median (IQR)	15 (9–23)	17 (12.5–25.5)	13 (7–22)	< 0.001
RDA: Recommended daily allowance				

As seen in Fig. 2 multivariate cox regression analysis revealed 8 variables relevant to 90-day mortality as invasive mechanical ventilation (conventional oxygen as the reference), high lactate, age ≥ 60 years, presence of cardiac arrhythmia, vasopressor therapy, mean fluid balance ≥ 600 ml/day, $\text{PaO}_2/\text{FiO}_2 \leq 150$ mmHg, ECOG score ≥ 1 , adjusted for other variables (SOFA ≥ 5 ; APACHE II ≥ 17 ; presence of hypertension, diabetes mellitus, cardiac disease, cancer, cerebrovascular disease, end-stage renal disease; admission place; onset of symptoms to ICU admission < 7 days; neutrophil/lymphocyte ratio ≥ 8 ; neuromuscular blocker use; development of acute kidney injury.

As seen in Fig. 3, Kaplan Meier survival analysis revealed significantly lower survival in patients who had received invasive mechanical ventilation compared to conventional O_2 , HFNO and NIV (Log-rank p value < 0.001).

Discussion

This study reporting the first pandemic wave results in Turkish intensive care units revealed 90-day mortality of 55.1%. Invasive mechanical ventilation, high lactate level, age more than 60 years, development of cardiac arrhythmia, need for vasopressor treatment, positive fluid balance, severe hypoxemia ($\text{PaO}_2/\text{FiO}_2 \leq 150$) and not being fully active in performance status were determined to be the independent risk factors for 90-day mortality.

There is only one study published so far that demonstrated the 90-day mortality rate and the risk factors for mortality in critically-ill patients with COVID-19 [19]. It was a multicenter, prospective, cohort study conducted in patients with laboratory-confirmed COVID-19 who were admitted to ICUs of 138 hospitals in France, Belgium, and Switzerland. In this study 90-day mortality was found to be 31% and older age, immunosuppression, severe obesity, diabetes mellitus, higher renal and cardiovascular SOFA score, lower $\text{PaO}_2/\text{FiO}_2$ ratio and shorter time between onset to first symptoms and ICU admission were found to be independent risk factors for 90-day mortality.

Mortality rates in critically-ill COVID-19 patients vary. In studies conducted in New York City, ICU and hospital mortality rates were found to be 39% and 60.4% respectively. [12, 23] In a multicenter, cohort study performed in 65 USA hospitals, the 28-day mortality was 35.4% [24]. In another multicenter study conducted in Mexico, ICU mortality was determined as 51.8% [18]. In the Italy-Lombardy region, ICU mortality was reported to be 48.7% and hospital mortality was 53.4% [13]. In another study conducted in England, Wales and Northern Ireland region, hospital mortality was found to be 42% [26]. ICU mortality was found to be 29% [27] in a study from Germany. In a retrospective study from China, 60-day mortality was reported as 61.5% [6]. These differences might be due to differences in disease severity, in surge-capacity, in resources, etc. Turkey has sufficient number of intensive care beds, reported to be more than 30 adult ICU beds per 100,000 population, around 30% of them located in private hospitals which had limited roles in the pandemic. However, there is severe shortage of intensive care workers, especially nurses in Turkey. In the OECD countries, number of physicians per 100,000 population is 348 and number of nurses per 100,000 population is 938. In Turkey, these numbers are 348 and 301, respectively. During the COVID-19 pandemic, surge-capacity were enhanced in many countries 28–30%[24]. In a study conducted in Australia, the number of intensive care beds in the first wave of 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% [29]. However, in Turkey, even prior to COVID-19, number of patients per nurse could be as high as 4–5 in third level comprehensive units. Number of physiotherapists are even negligible.

As observed in our study, advanced age [13, 25] and accompanying comorbidities (hypertension, diabetes mellitus cardiovascular disease, etc.) [17] determine the short and long-term prognosis in patients with COVID-19.

Acute respiratory failure is the most common cause of intensive care admission in COVID-19 patients. [19, 26, 27]. Most of these patients require invasive mechanical ventilation. In studies, frequency of IMV varies between 12.2–88% [1, 6, 23, 28]. In our study, 52.4 % of the patients had $\text{PaO}_2/\text{FiO}_2$ ratio below 150 and 57.6% of the patients needed IMV at admission or during the follow-up. In this study, both IMV and $\text{PaO}_2/\text{FiO}_2 \leq 150$ were found to be risk factors determining 90-day mortality. In studies conducted in different parts of the world, mortality rates vary between 35.7–100% in invasively ventilated patients [14, 16, 18]. This variety among studies might be due to differences in standards of care, in surge-capacity, in resources and due to different treatment approaches in the first-wave[29].

In our study, the 90-day survival rate was found to be higher in patients who received HFNO, although patient numbers are few and HFNO or NIV failure rates have not been recorded in this study. With the COVID-19 pandemic, HFNO therapy has become widespread around the world [34]. One of the advantages of this treatment is that it can be used in wards as well as in the ICU. It has been shown that HFNO therapy reduced the need for IMV in COVID-19 patients with respiratory failure [35].

Blood lactate levels are used mostly to follow tissue perfusion in critically-ill patients [30]. Even minor increases in lactate levels are associated with higher mortality rates [31, 32]. In this study, non-survivors had higher lactate levels compared to survivors and lactate level > 2 mmol/L was an independent predictor of mortality. In COVID-19 patients, lactate levels were reported to be high in non-survivors [19, 23, 27], however, in none of them it was determined to be a risk factor in multivariate analysis.

In this study, vasopressor treatment, which was given 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 REVA network study revealing cardiovascular SOFA score being an independent risk factor for mortality [19].

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 [33, 34]. It had also been shown that negative fluid balance reduces the need for renal replacement therapy and respiratory failure in critically-ill patients [35, 36]. 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 [34]. In this study, we preferred to use 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 REVA network-COVID-ICU study, clinical frailty scale (CFS) was found to be higher in patients who died within 90 days [19], as was the VIP1 study where CFS was found to be related with 30-day mortality in critically-ill very elderly patients [37].

In studies, cardiac damage / arrhythmia was common in COVID-19 patients and it was related with increased mortality [25, 26, 38–40]. We observed cardiac arrhythmia in 33 (7.8%) patients, and this was a risk factor that increased 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 together with azithromycin was used frequently in some parts of the world [23, 25, 41] and in our country [2], as well. In this study, hydroxychloroquine had been given to 86% and azithromycin to 56.8% 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, this one being the second one reporting 90-day mortality. We even need longer term outcome. And, finally some new 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. 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 reflect 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.

Conclusion

In this multicenter cohort study of critically-ill adult patients with COVID-19 in Turkey, more than half of patients died within 90 days after ICU admission. Receiving invasive mechanical ventilation, lactate level > 2 mmol/L, age ≥ 60 years, having cardiac arrhythmia during ICU stay, receiving vasopressor treatment during ICU stay, positive fluid balance of ≥ 600 ml per day during ICU follow-up, admission $\text{PaO}_2/\text{FiO}_2$ ratio of ≤ 150 mmHg, and baseline ECOG score ≥ 1 have been found to be independent risk factors for 90-day mortality.

Declarations

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Authors contributions

KG, IHA, PH, BH, ST and AT: Conception, design of the work and the acquisition, analysis. 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, AT: Interpretation of data, the creation of new software used in the work, have drafted the work or substantively revised. All authors read and approved the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

The case series was approved by Ethics Committee of Erciyes University (Date: 22.07.2020 no:2020/401). Written informed consent was waived.

Consent for publication

Written informed consent for publication was obtained from all authors.

Competing interests

All the authors state that there are no conflict of interest related to this study.

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Figures

Figure 1

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

Figure 2

Multivariate Cox Proportional Hazard Regression Analysis of factors associated with 90-day mortality as a forest plot graph. IMV: Invasive mechanical ventilation, O2: Oxygen, NIV: Non-invasive mechanical ventilation, HFNO: High-flow nasal oxygen, PaO2: Partial arterial oxygen pressure FiO2: Fraction of inspired oxygen, ECOG: Eastern Cooperative Oncology Group Performance Status, HR: Hazard ratio, CI: Confidence interval.

Figure 3

Kaplan-Meier survival curves for 90-day mortality according to respiratory support. Log-rank test $p < 0.001$.

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