Renal Replacement Therapy

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Effects of early and late continuous renal replacement therapy on intensive care unit mortality in patients with COVID-19 with acute respiratory distress syndrome and acute kidney injury: a comparative study

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Abstract

Introduction Acute kidney injury (AKI) is linked to disease severity and prognosis in patients with coronavirus disease 2019 (COVID-19), and mortality increases even with milder stages. This study primarily investigated the effects of continuous renal replacement therapy (CRRT) timing on intensive care unit (ICU) mortality in patients with COVID-19 with acute respiratory distress syndrome (ARDS) and AKI. Secondary goals were secondary goals for the ICU, days without life support treatment, and change in post-CRRT day biomarker levels, the length of ICU and overall hospital stay.

Methods In this retrospective study, patients with COVID-19 with ARDS and AKI were divided into CRRT initiated at AKI stages 1 and 2, early-CRRT (E-CRRT) and AKI stage 3, late-CRRT (L-CRRT) and followed until discharge or death.

Results E-CRRT had 20 patients and L-CRRT had 18 patients. No association between CRRT timing and ICU mortality was detected ($p=0.724$). Moreover, the timing was not associated with ICU, total hospital stay, or days without life support treatment. However, it was associated with D-dimer levels for both groups and ferritin and C-reactive protein (CRP) levels for E-CRRT. There were no associations for other markers, such as procalcitonin, troponin T, pro-brain natriuretic peptide (pro-BNP), interleukin-6, fibrinogen, or antithrombin III levels.

Conclusions CRRT timing was not associated with ICU mortality, total hospital stay, or days without life support treatment in this cohort. For E-CRRT, ferritin and CRP levels, and for both groups, D-dimer levels, were associated with CRRT timing. Randomized controlled trials are needed to examine the effects of CRRT timing in patients with COVID-19 with ARDS and AKI.

Keywords Acute respiratory distress syndrome, COVID-19, Continuous renal replacement therapy, Complications, Daily dialysis, Epidemiology, Hemodynamics

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Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), primarily manifests with pulmonary diseases such as pneumonia and acute respiratory distress

syndrome (ARDS), with the latter being seen in between 40% and 96% of patients with COVID-19 admitted to the intensive care unit (ICU) [1–5]. Although the proportion of these patients with ARDS requiring invasive mechanical ventilation (IMV) was reported differently in each study, it is crucial to note that it is always associated with high mortality [1, 3, 5–9]. ICU mortality of patients with COVID-19 with ARDS differs between 16% and as even high as 78% [2–5, 9–12]. In addition to extensive pulmonary damage, COVID-19 could cause extrapulmonary complications, such as thrombotic complications, myocardial injury, and acute kidney injury (AKI) [13, 14].

AKI is the most common ARDS-associated extrapulmonary complication and has been reported in up to 46% of hospitalized and 89% of critically ill patients with COVID-19 [15, 16]. This renal damage is acute tubular necrosis due to impaired renal perfusion caused by the decreased cardiac flow rate due to increased intrathoracic pressure attributable to mechanical ventilation. Additionally, extensive lung injury causes hypoxemia, hypercapnia, acidosis, and microthrombi on renal vascular resistance, which could contribute to renal hypoperfusion [17–19]. In addition, the development of AKI could impact gas exchange in the lungs via hypervolemia, inflammation, and decreased pulmonary capillary permeability, causing a destructive loop to both organs [20, 21].

Furthermore, AKI is an independent risk factor for mortality in patients with ARDS [15, 22, 23] and has been found to indicate multiple organ dysfunction syndrome and COVID-19 disease severity [24]. A multicentric study detected that AKI development significantly increases in-hospital mortality in patients with COVID-19 with ARDS [25]. Of these patients who develop AKI, continuous renal replacement therapy (CRRT) is required for up to 30% of them. Unfortunately, if CRRT is indicated in a critically ill patient with COVID-19-associated AKI, the risk of mortality becomes significantly higher (> 60%) [14, 26].

Renal replacement therapy (RRT) includes CRRT, intermittent RRT, and peritoneal dialysis techniques [27]. CRRT is the most common RRT modality used in the ICU to treat AKI, as it provides better volume management and electrolyte imbalance correction. Moreover, it increases metabolic control and decreases hypotension, especially in hemodynamically unstable patients [28]. It is reportedly required for up to 35% of critically ill patients with COVID-19 [29]. Among these patients, CRRT is helpful for those complicated with ARDS with fluid overload due to refractory hypernatremia and unresponsiveness to diuretics and conservative treatments [30].

RRT should be started without delay if life-threatening AKI complications such as hyperkalemia, metabolic acidosis, and pulmonary edema are present [28]. Early initiation of CRRT might be considered to achieve negative fluid balance and fluid restriction in patients with complicated COVID-19. Therefore, exploring the effects of initiation timing (early or late) of CRRT on mortality in patients with COVID-19 with ARDS and AKI is required to determine the optimal time to initiate CRRT.

The primary aim of this study was to compare the effects of early and late CRRT on ICU mortality in patients with COVID-19 with ARDS and AKI. The secondary aims compared the length of ICU stay, total hospital stay, days without life support treatment in ICU, and change in pre- and post-CRRT day biomarker levels in the same groups.

Methods

This retrospective study was approved by the Istanbul University Hospital Institutional Review Board with decision number 2020/523 on 8 May 2020. Written informed consent was waived due to the retrospective design of the study. Furthermore, all methods were performed following the relevant guidelines and regulations. Finally, the manuscript is written per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [31].

Selection and description of participants

The study was conducted on patients admitted to the ICU of Istanbul University Hospital between 19 March and 12 June 2020.

Inclusion criteria

- Being older than 18 years
- Being admitted to the ICU
- Having a COVID-19 diagnosis with ARDS and AKI:
    - Infection with COVID-19 was determined by a positive result on a reverse transcriptase-polymerase chain reaction assay of a nasopharyngeal swab collected by the local hospital health authority
    - ARDS diagnosis and staging were made according to the Berlin definition [32]
    - AKI diagnosis and staging were made according to creatinine levels (only) in the Kidney Disease Improving Global Outcome (KDIGO) Clinical Practice Guideline for Acute Kidney Injury [28]
- Requiring CRRT

Exclusion criteria

- Being younger than 18 years
- Already undergoing regular dialysis treatment
    - Chronic dialysis
    - Patients who underwent kidney transplantation

Technical information

Research Question: In a population of patients with COVID-19 with ARDS and AKI, is early CRRT more associated with lower ICU mortality than late CRRT?

Study design

In this retrospective cohort study, patients were divided into two groups according to AKI stages [28, 33] for a more focused evaluation of factors, stratified as AKI stage 1–2 and AKI stage 3, as stated in Levey et al. [34]:

1. CRRT initiated at AKI stages 1 and 2 (early-CRRT group: E-CRRT): Patients with hypervolemia unresponsive to medical treatment (unresponsive to diuretics for more than 12 h and < 0.5 mL/kg/h urine output)
2. CRRT initiated at AKI stage 3 (Late-CRRT group: L-CRRT): Patients with urgent need of RRT [acidosis, hyperkalaemia, and anuria (12 h of no urine output or output of < 0.3 mL/kg/h urine output in the last 24 h)]

Aims

- **Primary:** to compare the effects of early- and late-CRRT on ICU mortality in patients with COVID-19 with ARDS and AKI
- **Secondary:** to compare the effects of early- and late-CRRT on:
    - ICU stay
    - Total hospital stay (ICU and ward days combined)
    - Days without life support treatment in the ICU (not requiring any of the below)
        - CRRT
        - IMV
        - Vasopressor (VP)
    - Change in pre- and post-CRRT day biomarker levels
        - C-reactive protein (CRP)
        - Procalcitonin (PCT)
        - Ferritin
        - Troponin-T (TnT)
        - Pro-brain natriuretic peptide (pro-BNP)
        - Interleukin 6 (IL-6)
        - D-dimer
        - Fibrinogen
        - Antithrombin III (AT III)

in patients with COVID-19 with ARDS and AKI. The patients were followed from admission to discharge from the ICU or death.

CRRT application CRRT was applied as continuous venovenous hemodiafiltration using Ultraflux® AV1000S (Fresenius Medical Care, Bad Hamburg, Germany). The settings were 100 mL/min for blood flow rate, 2000 mL/h for replacement fluid, 1000 mL/h for dialysate fluid, and 20–25 mL/h for the ultrafiltration rate. The parameters were adjusted individually according to the cardiac situation, volume load, and urine output. Anticoagulation was achieved with regional citrate. Hemofilter and extracorporeal circuits were changed every 72 h unless obstructed, or any other mechanical complications arose, and then they were changed earlier. The patients received CRRT in a continuous manner, meaning 24/7 following its initiation in the ICU. They were followed up daily clinically (fluid input/output) and with routine renal function tests. Once the kidney function was evaluated to be ready for weaning off, first, the ultrafiltration feature of the machine was turned off, and then the patient was observed. If there was satisfactory urine output, the hemofiltration feature was also turned off, concluding the entire CRRT process.

Data collection Data were collected from the hospital's electronic health records system. Gender, age, ARDS severity, comorbidities, Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiology Score (SAPS) scores were obtained on ICU admission. The scores mentioned were used to evaluate the comorbidities systematically. Patients presenting with active cancer of any kind were classified as having a malignant condition. In addition, complications such as cardiac complications, liver failure, secondary infections, and coagulopathy were collected.

Additionally, the need for life support treatment (CRRT, IMV, and VP within the first 28 days after ICU admission) was obtained. The length of hospital and ICU stay and mortality were recorded. Finally, the following

laboratory data on the day of AKI development (pre-CRRT) and the first day after CRRT (post-CRRT) were recorded: CRP, PCT, ferritin, TnT, pro-BNP, IL-6, D-dimer, fibrinogen, AT III. Post-CRRT values were the results after the end of each patient's continuous treatment.

Statistics

Descriptive statistics were presented using mean and standard deviation, median (and minimum–maximum).

The normality test was done with the Shapiro–Wilk test. Non-parametric statistical methods were used for values with skewed (non-normally distributed. Shapiro–Wilk $p > 0.05$) distribution. Furthermore, non-parametric statistical methods were used for values with skewed distribution.

Finally, the Mann–Whitney *U* test compared two non-normally distributed independent groups. The χ^2 test (Fisher's exact test) was used for categorical variables and expressed as observation counts (and percentages). In addition, logistic regression was used to investigate the effect of parameters on the CCRT.

Statistical significance was accepted when the two-sided *p*-value was lower than 0.05. Statistical analysis was performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba. Ostend. Belgium; http://www.medcalc.org; 2013).

Results

In total, 38 patients ($N = 38$) were included. E-CRRT had 20 patients and L-CRRT had 18 patients. The baseline characteristics of the study population are presented in Table 1.

The only statistically significant difference was between E-CRRT and L-CRRT regarding malignity during admittance ($p < 0.05$). The proportion of malignity was found to be higher in L-CRRT.

Outcomes

The primary aim of this study was to investigate and compare the effects of early- and late-CRRT on ICU mortality. The secondary outcomes were length of ICU stay, total hospital stay, and days without life support treatment in the ICU (CRRT, IMV, and VP). The analyses for both aims, except the biomarkers (presented separately below), are presented in Table 2.

There was no statistically significant difference between pre- and post-CRRT ICU mortality, ICU stay, total hospital stay ($p = 0.724$, $p = 0.426$, $p = 0.654$, respectively), or days without life support treatment (days without CRRT $p = 0.111$, days without IMV $p = 0.199$, days without VP $p = 0.553$).

Effect of CCRT timing on biomarkers

The early or late initiation of CRRT was not associated with significant differences in post-CRRT levels in PCT, TnT, pro-BNP, IL-6, fibrinogen, or AT III. Furthermore, CRP, ferritin, and D-dimer had significant results, and their analyses are presented in Table 3.

In E-CRRT, there were statistically significant differences between pre- and post-CRRT CRP, ferritin, and D-dimer levels ($p = 0.013$, $p = 0.03$, $p = 0.015$, respectively). The mean of CRP and D-dimer was lower on post-CRRT first day than pre-CRRT levels. On the contrary, the mean of ferritin was higher on post-CRRT first day than pre-CRRT levels. Moreover, for D-dimer, there was a statistically significant difference between pre- and post-CRRT levels in terms of L-CRRT ($p = 0.015$ and $p = 0.011$, E- and L-CRRT, respectively).

Discussion

The current study primarily investigated and compared the effects of early- and late-CRRT on ICU mortality in patients with COVID-19 with ARDS and AKI. The secondary aims were length of ICU stay, total hospital stay, days without life support treatment in ICU, and change in pre- and post-CRRT day biomarker levels. The results demonstrated that the timing of CRRT was not associated with ICU mortality. Moreover, it had no association with ICU and combined hospital stay or days without life support treatment such as IMV, VP, or CRRT. Contrarily, the timing was associated with a significant change in pre- and post-CRRT day biomarkers: D-dimer levels for both groups and ferritin and CRP levels for E-CRRT (Table 3).

The COVID-19 strain in Turkey during the period of study is thought to be analogous to 19A, 20A, and 20B variants of the virus [35]. The most common extrapulmonary manifestation of them is kidney involvement [36]. In COVID-19, AKI may develop due to direct viral damage, hypoxemia, coagulopathy, hypovolemia, use of nephrotoxic agents, and cytokine storm [37]. AKI is associated with the severity and prognosis of the disease in patients with COVID-19, and mortality increases even with the milder AKI stages [38–40]. Therefore, AKI should be approached quickly and effectively. The best management of AKI involves reducing risks to a minimum and utilizing best-supporting treatments [41].

Previously identified risk factors for AKI development in patients with COVID-19 are advanced age, comorbidities associated with cardiovascular complications, and severe disease requiring ICU follow-up, IMV, and VP [37]. In our study, E-CRRT and L-CRRT patients had similar comorbidities and were not statistically significant except for malignity. However, their APACHE II, SOFA,

Table 1 Characteristics of the early and late continuous renal replacement therapy (CRRT) groups

Parameters	Early (*N* = 20)		Late (*N* = 18)		*p*
	N	%	*N*	%	
Gender					0.144
Male	17	85.0	11	61.1	
Female	3	15.0	7	38.9	
Age (years)					1.000
< 60	4	20.0	4	22.2	
> 60	16	80.0	14	77.8	
AKI stage					–
Stages 1 and 2	20	100.0	0	0.0	
Stage 3	0	0.0	18	100.0	
Comorbidity					0.093
Yes	14	70.0	17	94.4	
No	6	30.0	1	5.6	
Cardiovascular					0.746
Yes	9	45.0	10	55.6	
No	11	55.0	8	44.4	
Hypertension					0.532
Yes	10	50.0	11	61.1	
No	10	50.0	7	38.9	
Diabetes					0.735
Yes	6	30.0	7	38.9	
No	14	70.0	11	61.1	
Pulmonary					1.000
Yes	5	25.0	5	27.8	
No	15	75.0	13	72.2	
Cerebrovascular					0.218
Yes	0	0.0	2	11.1	
No	20	100.0	16	88.9	
Transplant					0.474
Yes (Liver)	0	0.0	1	5.6	
No	20	100.0	17	94.4	
Malignity					0.041*
Yes	0	0.0	4	22.2	
No	20	100.0	14	77.8	
Renal					0.395
Yes	2	10.0	4	22.2	
No	18	90.0	14	77.8	
Hepatic					0.474
Yes	0	0.0	1	5.6	
No	20	100.0	17	94.4	
ARDS stage first day					0.272
Mild	4	20.0	3	16.7	
Moderate	5	25.0	9	50.0	
Severe	11	55.0	6	33.3	
	Med (min–max)		**Med (min–max)**		
Start of COVID-19-related symptoms to ICU admission (days)	8 (2–31)		8 (3–17)		0.675[a]
APACHE II score	21 (12–33)		26 (12–44)		0.072[a]
SOFA score	5 (3–14)		7 (3–16)		0.149[a]
SAPS II score	45 (32–81)		57 (34–82)		0.087[a]

Table 1 (continued)

N, number; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; SD, standard deviation; Med, median; Min, minimum; Max, maximum; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; SAPS, Simplified Acute Physiology Score. Fisher's exact test, Mann–Whitney *U* test[a], Significance*

Table 2 Outcome analyses

Outcomes	Early (*N* = 18)		Late (*N* = 20)		*p*
	N	%	*N*	%	
ICU mortality					
Alive	5	25.0%	6	33.3%	0.724[a]
Dead	15	75.0%	12	66.7%	
	Mean ± SD med (min–max)		Mean ± SD med (min–max)		
ICU stay (days)	15 ± 14		11 ± 9		0.426
	12 (2–55)		10 (3–39)		
Total hospital stay (ICU and ward days combined)	22 ± 15		21 ± 17		0.654
	20 (2–65)		17 (3–68)		
Days without life support treatment					
Without CRRT	8 ± 8		5 ± 8		0.111
	6 (0–33)		1 (0–32)		
Without invasive mechanic ventilation	2 ± 4		4 ± 5		0.199
	0 (0–14)		1 (0–16)		
Without vasopressor	3 ± 4		4 ± 5		0.553
	2 (0–16)		2 (0–14)		

N, number; ICU, intensive care unit; SD, standard deviation; Med, median; Min, minimum; Max, maximum; CRRT, continuous renal replacement therapy. Mann–Whitney *U* test, Fisher's exact test[a]

Table 3 Biomarkers in the first day of AKI development compared with the post-continuous renal replacement therapy (CRRT) first day according to CRRT timing

Blood marker	Early	Late
	Mean ± SD med (min–max)	Mean ± SD med (min–max)
C-reactive protein (mg/L)		
Day of AKI development	173.26 ± 174.07	242.59 ± 137.42
	140.5 (0.93–597)	241.5 (16–557)
First day after CRRT	67.07 ± 87.96	220.04 ± 112.2
	27.74 (0–311)	207 (13.9–364.3)
p	0.013*	0.088
Ferritin (ng/mL)		
Day of AKI development	7003.26 ± 23,259.7	6194.92 ± 11,547.75
	1172 (91.71–100,000)	1504 (223.5–43,545)
First day after CRRT	7554.2 ± 25,585.6	3170.3 ± 4578.2
	707 (0–100,000)	1363 (0–15,704)
p	0.030*	0.496
D-dimer (ng/mL)		
Day of AKI development	9193 ± 8676	8228 ± 6560
	4035 (560–20,000)	5740 (660–20,000)
First day after CRRT	5247 ± 6292	3745 ± 4340
	3245 (0–18,700)	3070 (0–16,760)
p	0.015*	0.011*

SD, standard deviation; Med, median; Min, minimum; Max, maximum; AKI, acute kidney injury; CRRT, continuous renal replacement therapy. Wilcoxon test

* statistical significance

and SAPS scores, calculators for severity and mortality, were not statistically significant. Therefore, malignity did not have an overall impact because the established scoring systems had already incorporated it into their calculation [42].

Patients with COVID-19 in ICU requiring CRRT have been reported to be between 5% and 23% [1, 2, 9, 12]. For managing AKI with ARDS, CRRT is vital in treating associated complications such as hemodynamic instability. CRRT increases oxygenation, decreases extravascular fluid in the lungs, and restores acid–base balance in patients with ARDS [43]. Therefore, the early initiation of CRRT might facilitate the management of volume status in COVID-19 [44].

A literature gap exists regarding CRRT timing on COVID-19 mortality [43]. Only a single study at the time of manuscript revision was found regarding CRRT in a patient population with all of the sample size having AKI and ARDS simultaneously. However, the timing was not studied there, too [45]. Hence, the current study was conducted to shed light on this unexplored side: CRRT timing in severely ill patients with COVID-19.

Furthermore, a vast amount of research is evaluating the effect of CRRT timing and conservative approaches on mortality in patients with AKI who do not have COVID-19. Among them, the advantages of early CRRT initiation have been demonstrated in observational studies, but different results were indicated in a meta-analysis of randomized studies in patients without COVID-19 [33, 46, 47]. Therefore, a consensus is yet to be achieved about the effects of early CRRT intervention. In the current study, decreasing the inflammatory markers and hypervolemia with early initiation of CRRT was not associated with ICU mortality, total hospital or ICU stay duration, or the number of days without IMV, VP, or CRRT. These results concur with the literature on patients with AKI who do not have COVID-19 [46].

Organ cross-talk significantly affects the course of COVID-19, which is a cytokine-mediated process. Among these, IL-6 is one of the most critical proinflammatory cytokines linked to mortality [48]. Its upregulation resulting from renal tubular epithelial damage causes ARDS through extensive lung epithelial and endothelial injury. This insult causes hypoxia and further damages the oxygen supply-sensitive renal medulla [48]. Furthermore, the correlation between IL-6 and fibrinogen levels in COVID-19 with ARDS indicates that thrombotic complications are associated with an inflammatory response (immunothrombosis) [49]. As a result, organ failures, including AKI, occur through similar hemodynamic and cellular mechanisms in COVID-19. To treat these, Raina et al. reported that CRRT could filter inflammatory mediators and stabilize immunity non-selectively to restore balance to the immune system [50]. Current results suggested no association between CRRT timing and post-CRRT IL-6 or fibrinogen levels.

Among other biomarkers, TnT levels were reported to be correlated with CRP, PCT, D-dimer, and pro-BNP levels, and patients with high TnT levels have been reported to develop ARDS, malignant arrhythmias, coagulopathy, and AKI at a higher rate [51]. In the reported study, CRRT timing was not associated with TnT, PCT, pro-BNP, or AT III levels. However, it was associated with D-dimer levels for both groups and ferritin and CRP levels for E-CRRT. It is essential to note the significant change in D-dimer levels for both groups, which is shown to correlate with COVID-19 disease severity in a systematic review and meta-analysis [52]. For ferritin and CRP levels associated with E-CRRT, it could be because the earlier CRRT starts, the less likely it is to be a significant change as the already-mild levels regularly decrease.

These results suggest that E-CRRT could decrease inflammation by clearing various inflammatory markers and mediators concurrent with the literature [53]. However, CRRT alone is inadequate in controlling cytokine levels [43]. Different methods, such as direct hemoperfusion with a neutro-macroporous sorbent, plasma adsorption on a resin after separation of plasma from whole blood, CRRT with hollow fiber filters with adsorptive properties, and high-dose CRRT with medium or high cutoff membranes are available to control the cytokines and prevent a cytokine storm [48, 54].

In summary, this study demonstrated that the timing of CRRT initiation was not associated with ICU mortality. Moreover, it was not associated with ICU, combined hospital stay, or days without life support treatment such as IMV, VP, or CRRT. Additionally, there were no significant changes in IL-6 or fibrinogen levels. Therefore, initiation of CRRT should only be reserved in patients with COVID-19 with ARDS and AKI, where AKI and its complications cannot be managed or must be prevented.

Limitations

The current study has a few major limitations. Firstly, this was a single-center study, which impacts sample size and generalizability. Secondly, the data were retrospectively obtained from the electronic medical records, which led to some chunks of data being unavailable, which could have hindered looking into potential associations. These include, but might not be limited to, the continuous data for diuretic use and urine output for evaluating renal function during the totality of ICU stay (including the post-CRRT ICU stay) and the time between the onset of COVID-19-related symptoms and the start of CRRT for

correlating kidney function with pre-CRRT disease progression. To address these limitations, multicentric studies with larger sample sizes, preferably randomized trials, should be conducted to understand the importance of CRRT timing further.

Conclusions

In this cohort, the timing of CRRT was not associated with ICU mortality. However, it was associated with D-dimer levels for both groups and ferritin and CRP levels for E-CRRT, though it had no association with ICU stay, combined hospital stay, or days without life support treatment such as IMV, VP, or CRRT. Moreover, there was no association between CRRT timing and PCT, TnT, pro-BNP, IL-6, fibrinogen, or AT III levels. Randomized clinical trials with larger sample sizes are required to understand the impact of CRRT timing in patients with COVID-19 with ARDS and AKI deeply.

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Author contributions
V.T.: conceptualization, formal analysis, methodology, writing—original draft, writing—review and editing. E.S.: data curation, project administration. G.O.: data curation, validation. O.P.: data curation, project administration. I.A.: data curation, project administration. G.A.: data curation, validation. E.C.: data curation, writing—review and editing. M.K.: data curation, writing—review and editing. M.M.: data curation, validation. E.F.: supervision, methodology. P.E.G.: supervision, writing—review and editing.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This retrospective study was approved by the Istanbul University Hospital Institutional Review Board with decision number 2020/523 on 8 May 2020. The study was conducted on the patients admitted to the Istanbul University Hospital, Intensive Care Unit (ICU), Istanbul (Turkey), between 19 March and 12 June 2020. Written informed consent was waived due to the study's retrospective design.

Consent for publication
Waived due to the retrospective design of the study.

Competing interests
The authors declare no conflict of interest to disclose.

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