Extracorporeal membrane oxygenation support for SARS-CoV-2: a multi-centered, prospective, observational study in critically ill 92 patients in Saudi Arabia

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Abstract

Background: Extracorporeal membrane oxygenation (ECMO) has been used as a rescue strategy in patients with severe with acute respiratory distress syndrome (ARDS) due to SARS-CoV-2 infection, but there has been little evidence of its efficacy.

Objectives: To describe the effect of ECMO rescue therapy on patient-important outcomes in patients with severe SARS-CoV-2.

Methods: A case series study was conducted for the laboratory-confirmed SARS-CoV-2 patients who were admitted to the ICUs of 22 Saudi hospitals, between March 1, 2020, and October 30, 2020, by reviewing patient’s medical records prospectively.

Results: ECMO use was associated with higher in-hospital mortality (40.2% vs. 48.9%; \( p = 0.000 \)); lower COVID-19 virological cure (41.3% vs 14.1%, \( p = 0.000 \)); and longer hospitalization (20.2 days vs 29.1 days; \( p = 0.000 \)), ICU stay (12.6 vs 26 days; \( p = 0.000 \)), and mechanical ventilation use (14.2 days vs 22.4 days; \( p = 0.000 \)) compared to non-ECMO group. Also, there was higher number of patients with septic shock (19.6%) and multiple organ failure (10.9%); and more complications occurred at any time during hospitalization [pneumothorax (5% vs 29.3%, \( p = 0.000 \)), bleeding requiring blood transfusion (7.1% vs 38%, \( p = 0.000 \)), pulmonary embolism (6.4% vs 15.2%, \( p = 0.016 \)), and gastrointestinal bleeding (3.3% vs 8.7%, \( p = 0.017 \))] in the ECMO group. However, PaO2 was significantly higher in the 72-h post-ECMO initiation group and PCO2 was significantly lower in the 72-h post-ECMO start group than those in the 12-h pre-ECMO group (62.9 vs. 70 mmHg, \( p = 0.002 \) and 61.8 vs. 51 mmHg, \( p = 0.042 \), respectively).

Conclusion: Following the use of ECMO, the mortality rate of patients and length of ICU and hospital stay were not improved. However, these findings need to be carefully interpreted, as most of our cohort patients were relatively old.
Background

Although the majority of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected individuals may have no or mild symptoms, SARS-CoV-2 infection is not simply a common cold [1, 2]. Studies shown up to 20% of the patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) develop high disease severity and need to be hospitalized [3, 4]. Intensive care unit (ICU) admission is a requirement for up to 26% among those who are hospitalized [5]. Evidence on the efficacy of current interventions like prone ventilation [6], pulmonary vasodilators [7] and neuromuscular blocking agents [8–10] for coronavirus disease 2019 (COVID-19) patients with acute respiratory distress syndrome (ARDS) is limited and based on anecdotal observations and data on outcomes are conflicting. Extracorporeal membrane oxygenation (ECMO) is a life support device that serves as a modified form of cardiopulmonary bypass and was regarded as a rescue therapy in previous H1N1 influenza and Middle East respiratory syndrome (MERS-CoV) outbreaks [11–13]. However, ECMO is complex and expensive to be delivered; and requires the recruitment of additional specialized healthcare providers with the potential for significant complications, in particular hemorrhage and hospital-acquired infections. Although ECMO has a role in critically ill patients, there is currently inadequate data to determine the efficacy, optimization of patients selection and management on ECMO. It is essential that we learn and understand throughout the current pandemic, in order to determine the risk–benefit ratio of ECMO in COVID-19. Therefore, observational studies are a reasonable alternative to randomized clinical trials; hence ECMO recruitment in critical COVID-19 patients is difficult and associated with ethical concerns.

Objectives

We aimed to describe the effect of ECMO rescue therapy on patient-important outcomes in patients with severe SARS-CoV-2.

Methods

Design

This prospective observational study was performed at the King Faisal Specialist Hospital & Research Centre (KFSH&RC), Riyadh, which is the national coordinating center for the Saudi ECMO Program implemented by the Saudi Ministry of Health in April 2014. All consecutive patients with laboratory-confirmed SARS-CoV-2 infection, admitted to one of the ICUs among selected 22 hospitals between 1st March and 30th October, 2020, were enrolled.

Definitions and ECMO Eligibility

Case definitions of confirmed human infection with SARS-CoV-2 were in accordance with the interim guidance from the WHO [14]. Only patients with a laboratory-confirmed infection were enrolled in this study. Extracorporeal Life Support Organization (ELSO) guidelines on COVID-19 [15] were used to help prepare and plan provision of ECMO for patients included in this study during the ongoing pandemic. The ECMO group included patients who were admitted to the ICU and on invasive mechanical ventilation, and received ECMO as they met the indications for ECMO initiation.

Indications for ECMO initiation were [15]:

- When PaO2/FiO2 < 60 mmHg for > 6 h and/or
- When PaO2/FiO2 < 50 mmHg for > 3 h and/or
- pH < 7.20 + PaCO2 > 80 mmHg for > 6 h.

ARDS was defined according to the Berlin definition [16]. Septic shock was defined as sepsis with circulatory and cellular or metabolic dysfunction associated with a higher risk of mortality. The septic shock definition followed the international guidelines for the management of septic shock: 2018 update [17].

We included all patients with SARS-CoV-2 who received ECMO during that period. The control group included patients who were admitted to the ICU and some received invasive mechanical ventilation, but never required ECMO.

Weaning from ECMO was primarily based on clinical improvement demonstrated by adequate oxygenation and gas exchange shown in vital signs, blood gases, and chest X-ray.

The decision for readiness of a patient to be weaned from ECMO was left to the judgment of treating clinician and the ECMO team. To maintain the highest quality of ECMO management, an ECMO team with 1 physician perfusionist, 1 ICU physician, and 1 pulmonologist, are...
available at all times to oversee ECMO management, participate in clinical evaluation and treatment, and communicate with the ECMO expert team in KFSH&RC in Riyadh, Saudi Arabia, for guidance.

The weaning process followed the ELSO criteria asfollow: tidal volume \( [VT] \leq 6–8 \text{ ml/kg} \), PEEP \( \leq 16 \text{ cm H}_2\text{O} \), PEEP \( \leq 30 \text{ cm H}_2\text{O} \), FiO\(_2\) \( \leq 0.5 \), pH > 7.3, and arterial oxygen saturation \([\text{SaO}_2]\) > 88% [15]. If gas exchange is adequate for a 2–4 h period, the patient can be decannulated.

No exclusion criteria were applied for all confirmed SARS-CoV-2 cases in this study.

### Main outcome measures

Research Electronic Data Capture (REDCap); a web-based software tool which allowed researchers to create secure online forms for data capture, management and analysis; developed by (Vanderbilt University, Nashville, TN, USA) [18], was used to collect required data on all targeted COVID-19 patients by each research coordinator at the participating hospitals under the supervision of the primary investigator intensivist.

Variables included patients' demographics, information on the name of the hospital and patient's data, co-morbid conditions, signs and symptoms of SARS-CoV-2 illness, chest radiological findings, laboratory abnormalities and microbiological testing, use of mechanical ventilation, ventilator modes and settings, interventions used to treat refractory hypoxemia (prone ventilation, pulmonary vasodilators and ECMO), indications for ECMO and outcomes at ECMO removal, results of blood gas analyses before and after ECMO, vasoactive support, medications offered to the patient and treatment outcomes (i.e., hospitalization, transferred, died, or discharged) on hospital admission, during patient's ICU stay and at hospital discharge.

Information sources were medical files, electronic health information records and laboratories reports of COVID-19 patients. If data were missing from the record, clarification is needed, data were gathered by direct communication with attending doctors and other health care providers.

Patients were stratified based on ECMO use status.

### Data management and analysis

Descriptive statistics were used to describe the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analyzed using the Chi-square \( (\chi^2) \) tests (or Fisher’s exact tests for expected cell count < 5 in more than 20% of the cells). For continuous variables, mean and standard deviation were used to summarize the data and analyses were performed using Student’s \( \bar{t} \)-tests (Mann–Whitney \( U \) test if data are not normally distributed). The difference in ventilatory settings, arterial blood gas analyses, and vital signs pre-ECMO, post-ECMO initiation and pre-ECMO removal were examined using the repeated measures analysis of variance (ANOVA). An a priori two-tailed level of significance was set at 0.05. Statistical analyses were performed using Microsoft Excel 2010 (Microsoft Corp., Redmond, USA) and IBM SPSS Statistics software, version 22.0 (IBM Corp., Armonk, NY, USA).

### Ethics considerations

This study obtained approval from the King Fahad Medical City (KACST) [Approval Number Federal Wide Assurance NIH, USA: FWA00018774]. Ethics approval from the Saudi Ministry of Health ethics review board and from individual centers’ ethics boards were also obtained. Study was performed in accordance with the Declaration of Helsinki. Unique patient codes were issued to each study participant to maintain anonymity and confidentiality was maintained throughout the study.

### Results

#### Patient demographics and baseline clinical characteristics

Patient baseline characteristics, categorized by ECMO and non-ECMO group and ECMO group are shown in Table 1. The overall mean age of the hospitalized SARS-CoV-2 cohort was 55.7 ± 15.2 years, ranging from 1 month to ≥ 90 years. A total of 73.7% (\( n=1,099 \)) of the patients were males and 49.8% (\( n=742 \)) were Saudi citizens. Diabetes, hypertension, obesity (BMI ≥ 30 kg/m\(^2\)) and ischemic heart disease were the most common comorbidities in all study patients (52%, 45%, 41% and 12%, respectively). The most prescribed pre-hospital medications were insulin therapy (16%; \( n=243 \)), aspirin (13.6%; \( n=203 \)), calcium channel blockers (11%; \( n=166 \)), beta blockers (9.8%; \( n=147 \)), ARBs (8%; \( n=122 \)) and ACEIs (7%; \( n=109 \)). MERS-CoV co-infection was confirmed in 8 (0.5%) and Legionella pneumophila co-infection was confirmed in 1 (0.1%) of 1,491 patients.

Baseline laboratory findings are shown in Table 1. Patients who were placed on ECMO were more likely to be presented with higher levels of the following: triglycerides (227 mg/dl vs 258 mg/dl; \( p=0.006 \)), white blood cell count (10.4 × 10\(^9\)/L vs 12.4 × 10\(^9\)/L; \( p=0.001 \)), absolute neutrophil count (11.2 × 10\(^9\)/L vs 21 × 10\(^9\)/L; \( p=0.003 \)), procalcitonin (6.2 ng/ml vs 55.5 ng/ml; \( p=0.000 \)), lactate dehydrogenase level (515 U/L vs 817 U/L; \( p=0.000 \)), Troponin I (4.2 ng/ml vs 515 ng/ml; \( p=0.001 \)), Troponin T (9.4 ng/ml vs 16.5 ng/ml; \( p=0.004 \)), creatinine kinase (459 U/l vs 867 U/l; \( p=0.005 \)), and D-dimer (14 mg/l vs 32 mg/l; \( p=0.000 \)). However, ECMO group had lower hemoglobin levels (12.6 g/dL vs 11.4 g/dL; \( p=0.000 \)), prothrombin time (15.5 s vs 13.6 s; \( p=0.046 \)), fibrinogen
| Variable               | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value |
|------------------------|----------------|--------------------------|---------------------|---------|
| Demographics           |                |                          |                     |         |
| Age, years             | 55.74 ± 15.25 (15–108) | 56.57 ± 15.18 (15–108) | 43.17 ± 9.35 (17–65) | 0.05    |
| Distribution           |                |                          |                     |         |
| 0–10 years             | 12 (0.8)       | 12 (0.9)                 | 0                   | 0.000*  |
| 11–20 years            | 11 (0.7)       | 9 (0.6)                  | 2 (2.2)             |         |
| 21–30 years            | 49 (3.3)       | 44 (3.2)                 | 4 (4.3)             |         |
| 31–40 years            | 182 (12.2)     | 153 (11)                 | 29 (3.1)            |         |
| 41–50 years            | 302 (20.3)     | 262 (18.9)               | 40 (4.3)            |         |
| 51–60 years            | 360 (24.1)     | 344 (24.8)               | 15 (1.7)            |         |
| 61–70 years            | 294 (19.7)     | 287 (20.7)               | 7 (7.6)             |         |
| 71–80 years            | 168 (11.3)     | 167 (12)                 | 0                   |         |
| 81–90 years            | 66 (4.4)       | 64 (4.6)                 | 0                   |         |
| ≥ 90 years             | 15 (1)         | 15 (1.1)                 | 0                   |         |
| Height, meters         | 1.65 ± 8.8 (1.29–1.98) | 1.65 ± 8.6 (1.29–1.95) | 1.69 ± 10 (1.45–1.98) | 0.001*  |
| Weight, kilograms      | 82.4 ± 17.9 (36–177) | 81.86 ± 17.73 (36–177) | 91.68 ± 19.43 (51.4–170) | 0.000*  |
| BMI, kg/m²              | 28.69 ± 7.03 (23.84–46.1) | 30.01 ± 6.94 (25.6–46.7) | 32.22 ± 7.11 (21.96–66.41) | 0.001*  |
| Distribution           |                |                          |                     |         |
| Underweight            | 6 (0.4)        | 9 (0.6)                  | 0                   | 0.012*  |
| Normal                 | 334 (22.4)     | 317 (22.8)               | 14 (15.2)           |         |
| Overweight             | 426 (28.6)     | 400 (28.9)               | 26 (28.3)           |         |
| Obese                  | 376 (25.2)     | 347 (25)                 | 29 (31.5)           |         |
| Extremely obese        | 246 (16.5)     | 218 (15.7)               | 27 (29.3)           |         |
| Gender                 |                |                          |                     |         |
| Male                   | 1,099 (73.7)   | 1,019 (73.4)             | 73 (79.3)           | 0.005*  |
| Female                 | 388 (26)       | 367 (26.4)               | 18 (19.6)           |         |
| Was patient a national?|                |                          |                     |         |
| Saudi                  | 92 (6.3)       | 695 (50)                 | 43 (46.7)           | 0.006*  |
| Non-Saudi              | 788 (53)      | 690 (49.7)               | 98 (10.7)           |         |
| Nationality            |                |                          |                     |         |
| Indian                 | 84 (6.3)       | 84 (6)                   | 7 (7.6)             | 0.001*  |
| Pakistani              | 88 (5.9)       | 82 (5.9)                 | 6 (6.5)             |         |
| Bengali                | 109 (7.3)      | 108 (7.8)                | 1 (1.1)             |         |
| Cooperation Council for the Arab States of the Gulf | 4 (0.3) | 4 (0.3) | 0 |         |
| Yemeni                 | 79 (5.3)       | 71 (5.1)                 | 7 (7.6)             |         |
| Sudanese               | 32 (2.1)       | 31 (2.2)                 | 0                   |         |
| Filipino               | 56 (3.8)       | 54 (3.9)                 | 2 (2.2)             |         |
| Palestinian            | 15 (1)         | 14 (1)                   | 1 (1.1)             |         |
| Jordan                 | 52 (3.5)       | 41 (3)                   | 11 (1.2)            |         |
| Jordanian              | 13 (0.9)       | 13 (0.9)                 | 0                   |         |
| Syrian                 | 27 (1.8)       | 24 (1.7)                 | 3 (3.3)             |         |
| Afghani                | 6 (0.4)        | 5 (0.4)                  | 1 (1.1)             |         |
| Lebanese               | 4 (0.3)        | 1 (0.1)                  | 2 (2.2)             |         |
| Myanmar                | 20 (1.3)       | 20 (1.4)                 | 0                   |         |
| Nepalese               | 4 (0.3)        | 2 (0.1)                  | 2 (2.2)             |         |
| Mauritian              | 2 (0.1)        | 2 (0.1)                  | 0                   |         |
| Chadian                | 7 (0.5)        | 6 (0.4)                  | 1 (1.1)             |         |
| Senegalese             | 7 (0.5)        | 7 (0.5)                  | 0                   |         |
| Eritrean               | 6 (0.4)        | 6 (0.4)                  | 0                   |         |
| Seychellean            | 2 (0.1)        | 2 (0.1)                  | 0                   |         |
| Indonesian             | 3 (0.2)        | 3 (0.2)                  | 0                   |         |
| Sri Lankan             | 1 (0.1)        | 1 (0.1)                  | 0                   |         |
| Ethiopian              | 4 (0.3)        | 4 (0.3)                  | 0                   |         |
### Table 1 (continued)

| Variable | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value |
|----------|----------------|---------------------------|---------------------|---------|
| Canadian/US | 6 (0.4) | 6 (0.4) | 0 | 0.000* |
| Turkish | 1 (0.1) | 1 (0.1) | 0 | 0.000* |
| Singaporean | 1 (0.1) | 1 (0.1) | 0 | 0.000* |
| Serbian | 3 (0.2) | 3 (0.2) | 0 | 0.000* |

For non-Saudis, patient’s entry into Saudi was

| Source of transmission | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value |
|------------------------|----------------|---------------------------|---------------------|---------|
| Legal | 664 (44.5) | 619 (44.5) | 43 (47.5) | 0.000* |
| Illegal | 23 (1.5) | 21 (1.5) | 2 (2.2) | 0.000* |

Case travelled outside Saudi

| Case travelled outside Saudi | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value |
|-----------------------------|----------------|---------------------------|---------------------|---------|
| Case was in close contact with a person with fever and/or cough | 344 (23.1) | 321 (23.1) | 22 (23.9) | 0.000* |
| Case attended an event where a large number of people (i.e., wedding and umrah) | 41 (2.7) | 39 (2.8) | 2 (2.2) | 0.000* |
| Nosocomial infection (admitted with another diagnosis then transmitted COVID-19) | 65 (4.4) | 60 (4.3) | 3 (3.3) | 0.000* |

| Source of transmission | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value |
|------------------------|----------------|---------------------------|---------------------|---------|
| No clear data on COVID-19 source | 808 (54.2) | 749 (53.5) | 55 (59.8) | 0.036* |

Occupation

| Occupation | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value |
|------------|----------------|---------------------------|---------------------|---------|
| Healthcare worker | 74 (5) | 66 (4.7) | 9 (9.8) | 0.000* |
| Non-healthcare worker | 1,383 (92.8) | 1,297 (93.2) | 81 (88) | 0.000* |

Smoking status

| Smoking status | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value |
|----------------|----------------|---------------------------|---------------------|---------|
| Current smoker | 86 (5.8) | 80 (5.8) | 5 (5.4) | 0.000* |
| Not a smoker | 1,113 (74.6) | 1,063 (76.5) | 45 (48.9) | 0.000* |

Hospital or medical facility

| Hospital or medical facility | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value |
|-------------------------------|----------------|---------------------------|---------------------|---------|
| King Faisal Specialist Hospital and Research Centre-Riyadh | 113 (7.4) | 109 (7.9) | 2 (2.2) | 0.000* |
| King Faisal Specialist Hospital and Research Centre-Jeddah | 1 (0.1) | 0 | 1 (1.1) | 0.000* |
| National Guard Hospital-Riyadh | 1 (0.1) | 0 | 1 (1.1) | 0.000* |
| Armed Forces Hospital-Riyadh | 280 (18.8) | 279 (20.1) | 1 (1.1) | 0.000* |
| Habib Medical Group Qassim Hospital-Qassim | 1 (0.1) | 24 (1.7) | 0 | 0.000* |
| Habib Medical Group Rayan Hospital-Riyadh | 241 (16.2) | 239 (17.2) | 0 | 0.000* |
| Habib Medical Group Taleem Hospital-Riyadh | 18 (1.2) | 18 (1.3) | 0 | 0.000* |
| Habib Medical Group City Hospital-Riyadh | 80 (5.4) | 78 (5.6) | 0 | 0.000* |
| Habib Medical Group Awdah Hospital-Riyadh | 56 (3.8) | 56 (4) | 0 | 0.000* |
| King Fahd Hospital of the University-Dammam | 97 (6.5) | 97 (7) | 0 | 0.000* |
| King Saud Medical City-Riyadh | 229 (15.4) | 213 (15.3) | 16 (17.4) | 0.000* |
| Qatif Central Hospital-Qatif | 10 (0.7) | 10 (0.7) | 0 | 0.000* |
| Abha Central Hospital-Abha | 4 (0.3) | 0 | 4 (4.3) | 0.000* |
| King Faisal Hospital-Madinah | 37 (2.5) | 36 (2.6) | 1 (1.1) | 0.000* |
| Oak Hospital-Madinah | 20 (1.3) | 20 (1.4) | 0 | 0.000* |
| King Fahd Hospital-Makkah | 11 (0.7) | 11 (0.8) | 0 | 0.000* |
| King Abdullah Medical Complex-Jeddah | 77 (5.2) | 41 (3) | 36 (31.1) | 0.000* |
| King Fahd Medical City-Riyadh | 10 (0.7) | 0 | 10 (10.9) | 0.000* |
| King Abdullah Medical City Specialist Hospital-Makkah | 71 (4.8) | 56 (4) | 15 (16.1) | 0.000* |
| King Fahd General Hospital-Jeddah | 1 (0.1) | 1 (0.1) | 0 | 0.000* |
| King Abdulaziz University Hospital-Jeddah | 105 (7) | 101 (7.3) | 0 | 0.000* |
| King Khalid Hospital-Najran | 7 (0.5) | 0 | 7 (7.6) | 0.000* |

Hospital admission source

| Hospital admission source | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value |
|---------------------------|----------------|---------------------------|---------------------|---------|
| Home | 1,254 (84.1) | 1,214 (87.4) | 31 (33.7) | 0.000* |
| Nursing home | 3 (0.2) | 2 (0.1) | 1 (1.1) | 0.000* |
| Transfer from other facility | 226 (15.2) | 165 (11.9) | 60 (65.2) | 0.000* |
| Other | 3 (0.2) | 3 (0.2) | 0 | 0.000* |
Table 1 (continued)

| Variable | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value |
|----------|----------------|---------------------------|---------------------|---------|
| Comorbidities | | | | |
| Diabetes | 776 (52) | 735 (52.9) | 35 (38) | 0.015* |
| Hypertension | 678 (45.5) | 647 (46.6) | 25 (27.2) | 0.011* |
| Ischemic heart disease | 184 (12.3) | 179 (12.9) | 4 (4.3) | 0.001* |
| Heart failure | 74 (5) | 66 (4.8) | 5 (5.4) | 0.056 |
| Chronic lung disease | 39 (2.6) | 36 (2.6) | 3 (3.3) | 0.003* |
| Chronic obstructive pulmonary disease | 26 (1.7) | 25 (1.8) | 1 (1.1) | 0.001* |
| Bronchial asthma | 131 (8.8) | 124 (8.9) | 7 (7.6) | 0.000* |
| Chronic liver disease | 24 (1.6) | 22 (1.6) | 2 (2.2) | 0.002* |
| Hemoglobinopathy | 5 (0.3) | 5 (0.4) | 0 | 0.001* |
| Chronic kidney disease | 123 (8.2) | 115 (8.3) | 5 (5.4) | 0.147 |
| Renal replacement therapy (dialysis) | 54 (3.6) | 51 (3.7) | 2 (2.2) | 0.184 |
| Post solid organ/bone marrow transplant | 29 (1.9) | 26 (1.9) | 3 (3.3) | 0.038* |
| Immunocompromised status | 73 (4.9) | 68 (4.9) | 5 (5.4) | 0.033* |
| Chronic hematologic disease | 12 (0.8) | 12 (0.9) | 0 | 0.045* |
| HIV/AIDS | 1 (0.1) | 1 (0.1) | 0 | 0.057 |
| Cancer | 48 (3.2) | 45 (3.2) | 2 (2.2) | 0.192 |
| Recent surgery (within 30 days) | 30 (2) | 29 (2) | 1 (1) | 0.004* |
| Dyslipidemia | 59 (4) | 59 (4.2) | 0 | 0.000* |
| Stroke | 49 (3.3) | 49 (3.3) | 0 | 0.003* |
| Pregnant | 22 (1.47) | 22 (1.5) | 6 (6.5) | 0.157 |
| Symptoms on admission day to hospital | | | | |
| Asymptomatic | 36 (2.4) | 31 (2.2) | 5 (5.4) | 0.000* |
| Shortness of breath | 1,216 (81.6) | 1,140 (82.1) | 69 (7.6) | 0.000* |
| Runny nose | 101 (6.8) | 101 (7.3) | 0 | 0.000* |
| Diarrhea or vomiting | 143 (17.6) | 253 (18.2) | 7 (7.6) | 0.000* |
| Fever | 100 (73.3) | 1029 (74.1) | 63 (68.5) | 0.000* |
| Confusion | 17 (1.1) | 189 (13.6) | 7 (7.6) | 0.000* |
| Cough | 923 (65.2) | 906 (65.2) | 59 (64.1) | 0.000* |
| Abdominal pain | 261 (6.8) | 98 (7) | 2 (2.2) | 0.000* |
| Chest pain | 145 (9.7) | 140 (10.1) | 5 (5.4) | 0.000* |
| Seizures | 17 (1.1) | 17 (1.2) | 0 | 0.000* |
| Headache | 17 (1.1) | 17 (1.2) | 0 | 0.000* |
| Joint pain | 175 (11.7) | 172 (12.4) | 3 (3.3) | 0.000* |
| Muscle pain | 180 (12.1) | 174 (12.5) | 5 (5.4) | 0.000* |
| Fatigue | 279 (18.7) | 269 (19.4) | 10 (10.8) | 0.000* |
| Sore throat | 230 (15.4) | 225 (16.2) | 5 (5.4) | 0.000* |
| Angina | 40 (2.7) | 40 (2.9) | 0 | 0.000* |
| Loss of taste or smell | 30 (1.9) | 13 (0.9) | 0 | 0.000* |
| Dizziness | 8 (0.5) | 8 (0.5) | 0 | 0.465 |
| If yes to cough, what is the type | | | | |
| Dry | 498 (33.4) | 477 (34.3) | 20 (21.7) | 0.000* |
| Wet | 118 (7.9) | 115 (8.3) | 3 (3.3) | 0.000* |
| Bloody sputum | 6 (0.4) | 5 (0.3) | 1 (1.1) | 0.440 |
| Pre-hospital medications (home medications) | | | | |
| Angiotensin converting enzyme inhibitors (ACEIs) | 109 (7.3) | 108 (7.8) | 1 (1.1) | 0.000* |
| Angiotensin II receptor blockers (ARBs) | 122 (8.2) | 120 (8.6) | 2 (2.2) | 0.000* |
| Beta blockers | 147 (9.8) | 142 (10.2) | 4 (4.3) | 0.071 |
| Calcium channel blockers | 166 (11.1) | 163 (11.7) | 3 (3.3) | 0.010* |
| Diuretics | 58 (3.9) | 56 (4) | 2 (2.2) | 0.577 |
| Anticoagulation | 43 (2.9) | 41 (3) | 2 (2.2) | 0.001* |
| Type of anticoagulants | | | | |
| Warfarin | 13 (0.9) | 13 (0.9) | 0 | 0.440 |

**RETRACTED ARTICLE**
Table 1 (continued)

| Variable                                              | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value |
|-------------------------------------------------------|----------------|---------------------------|---------------------|---------|
| Novel oral anticoagulants (NOACs)                     | 11 (0.7)       | 11 (0.8)                  | 0                   |         |
| Low-molecular-weight heparin (LMWH)                   | 15 (1)         | 14 (1)                    | 1 (1.1)             |         |
| Antiplatelet                                          | 228 (15.3)     | 224 (16.1)                | 4 (4.3)             | 0.006*  |
| Type of antplatelets                                   |                |                           |                     |         |
| Aspirin                                               | 203 (13.6)     | 199 (14.3)                | 4 (4.3)             | 0.004*  |
| Clopidogrel                                           | 78 (5.2)       | 75 (5.4)                  | 3 (3.2)             | 0.477   |
| Ticagrel                                              | 5 (0.3)        | 5 (0.4)                   | 0                   | 0.725   |
| Non-steroidal anti-inflammatory drugs (NSAIDs)        | 57 (3.8)       | 56 (4)                    | 1 (1.1)             | 0.000*  |
| Insulin therapy                                       | 243 (16.3)     | 233 (16.8)                | 7 (7.0)             | 0.000*  |
| Corticosteroids                                       | 46 (3.1)       | 42 (3)                    | 4 (4.3)             | 0.000*  |
| Prednisolone                                          | 35 (2.3)       | 32 (2.3)                  | 3 (3.3)             | 0.407   |
| Hydrocortisone                                        | 3 (0.2)        | 2 (0.1)                   | 1 (1.1)             |         |
| Dexamethasone                                         | 6 (0.4)        | 6 (0.4)                   | 0                   |         |
| Prednisolone and fludrocortisone                     | 1 (0.07)       | 1 (0.1)                   | 0                   |         |
| Chemotherapy currently (in the last 3 months)        | 13 (0.9)       | 13 (0.9)                  | 0                   | 0.000*  |
| Immunotherapy (i.e., calcineurin inhibitors, monoclonal antibodies, thymoglobulin, and anti-proliferative) | 36 (2.4) | 34 (2.4) | 2 (2.2) | 0.000*  |
| Radiographic findings for patients on hospital admission |                |                           |                     |         |
| Chest X-ray was done                                  | 1186 (79.5)    | 1,145 (82.4)              | 33 (35.9)           | 0.382   |
| Was chest X-ray consolidation present or absent on hospital admission? | 1,044 (70) | 1011 (72.8) | 27 (29.3) | 0.162   |
| Present                                               | 129 (8.7)      | 121 (8.7)                 | 6 (6.5)             |         |
| Absent                                                |                |                           |                     |         |
| X-ray chest radiography shown                         |                |                           |                     |         |
| Unilateral abnormality                                | 72 (4.8)       | 70 (5)                    | 2 (2.2)             | 0.712   |
| Bilateral abnormality                                 | 367 (24.9)     | 936 (67.4)                | 25 (27.2)           |         |
| Laboratory data for patients on hospital admission    |                |                           |                     |         |
| Blood group                                           |                |                           |                     |         |
| A+                                                    | 249 (16.7)     | 226 (16.3)                | 22 (3.9)            | 0.158   |
| A−                                                    | 1 (0.07)       | 1 (0.1)                   | 0                   |         |
| B+                                                    | 157 (10.5)     | 142 (10.2)                | 15 (1.6)            |         |
| B−                                                    | 13 (0.9)       | 12 (0.9)                  | 1 (1.1)             |         |
| AB+                                                   | 44 (3)         | 35 (2.5)                  | 9 (9.8)             |         |
| AB−                                                   | 6 (0.4)        | 6 (0.4)                   | 0                   |         |
| O+                                                    | 307 (20.6)     | 284 (20.4)                | 20 (21.7)           |         |
| O−                                                    | 31 (2.1)       | 29 (2.1)                  | 2 (2.2)             |         |
| Lipase level, U/l                                     | 584.3 ± 3,441.9 (1–29,654) | 658.6 ± 3,691.4 (1–29,654) | 91.2 ± 99.5 (11–363) | 0.888   |
| Triglycerides, mg/dl                                  | 227 ± 295.5 (0.7–3,464) | 227 ± 301 (0.7–3,464)     | 258 ± 126 (129–531) | 0.006*  |
| Hemoglobin level, g/dl                                | 7.95 ± 2.3 (4.3–16.3) | 7.96 ± 2.3 (4.3–16.3)     | 7 ± (5.1–9.2)       | 0.292   |
| White blood cell count, x 10^9/L                       | 12.5 ± 2.6 (1.2–42.3) | 12.6 ± 2.6 (1.2–42.3)     | 11.4 ± 7.5–17.4)    | 0.000*  |
| Lymphocyte absolute count, x 10^9/L                   | 6.75 ± 123.4 (0.06–3,830) | 7 ± 126.4 (0.06–3,830)   | 1.9 ± (0.09–15.3)   | 0.881   |
| Absolute neutrophil count, x 10^9/L                   | 11.6 ± 69 (0.1–2,024) | 11.2 ± 70.4 (0.1–2,024)  | 21 ± (1.7–94.4)     | 0.000*  |
| Platelets, x 10^9/L                                   | 232.3 ± 103.9 (3.13–831) | 233 ± 103.6 (3.1–831)    | 206.4 ± 5–401)      | 0.090   |
| Prothrombin time, seconds                             | 39.6 ± 26.9 (10.5–489) | 39.5 ± 27.1 (10.5–489)   | 43.1 ± (16.3–160)   | 0.383   |
| Activated partial thromboplastin time, seconds         | 15.4 ± 12 (1.14–178) | 15.5 ± 12.3 (1.1–178)    | 13.6 ± (8.8–29)     | 0.046*  |
| Fibrinogen, mg/dl                                     | 60.7 ± 211.8 (0.92–1028) | 66.3 ± 221.5 (1–1,028)   | 5 ± (0.9–9.8)       | 0.014*  |
| Aspartate transaminase, U/l                           | 93.1 ± 250.3 (2.3–5156) | 87.9 ± 233 (2.3–5156)    | 171.1 ± (6.3–2,790) | 0.178   |
| Alanine transaminase, U/l                             | 68.9 ± 170.3 (3.4–3097) | 65.8 ± 153.8 (3.4–3097)  | 136 ± (5–2,501)     | 0.056   |
| Bilirubin, mg/dl                                      | 14.6 ± 25 (0.4–468) | 13.9 ± 20.9 (0.86–430)   | 27 ± (0.4–468)      | 0.003*  |
| Erythrocyte sedimentation rate, mm/hour               | 51.4 ± 69 (1–1221.6) | 50.9 ± 70.4 (1–1221.6)   | 59.6 ± (1–157)      | 0.234   |
| Creatinine, mg/dl                                     | 145.4 ± 280.3 (1.6–7606) | 144.3 ± 283.7 (1.6–7606) | 157.1 ± (29–1,038)  | 0.685   |
| Lactate, mmol/l                                       | 16.4 ± 99.9 (0.4–1964) | 17.2 ± 103 (0.4–1964)    | 2.3 ± (0.4–10.8)    | 0.065   |
higher heart rate ($p < 0.05$). All ECMO-group patients needed oxygen during the ICU stay (7.3% vs 100%; $p = 0.002$); and non-rebreather mask was the most common device used to deliver oxygen therapy (49.3%).

Awake prone positioning was applied more in non-ECMO patients at least once (24.6% vs 16.3%; $p = 0.03$) and inhaled nitric oxide was used less before intubation during the ICU stay (0.8% vs 2.2%; $p = 0.043$). Use of dialysis was more in the ECMO group (14% vs 42%; $p = 0.000$). There were significant differences between the non-ECMO and ECMO groups for the use of paralysis infusion (38% vs 53%; $p = 0.035$), inhaled nitric oxide (4.2% vs 10.9%; $p = 0.023$), and high frequency oscillatory

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### Table 1 (continued)

| Variable                                      | All ($n = 1491$) | Non-ECMO group ($n = 1389$) | ECMO group ($n = 92$) | $p$-value |
|-----------------------------------------------|------------------|-----------------------------|-----------------------|-----------|
| Procalcitonin, ng/ml                           | 7.5 ± 46.3 (0.03–540) | 6.2 ± 40.7 (0.03–540)      | 55.5 ± 1 (0.1–387)    | 0.000*    |
| Lactate dehydrogenase, U/l                    | 530.1 ± 468.5 (12.7–5541) | 515.1 ± 439.1 (12.7–5541) | 817.6 ± 14.3 (5040)  | 0.020     |
| C-reactive protein, mg/L                      | 139.2 ± 218.2 (0.01–2761.3) | 140.6 ± 219.9 (0.2–2761)  | 89.5 ± 1 (0.01–675)  | 0.01      |
| Troponin I, ng/ml                              | 24.3 ± 421.4 (0.01–8727)  | 42.6 ± 264 (0.01–253.6)    | 515.3 ± 1 (0.01–387) | 0.001*    |
| Troponin T, ng/ml                              | 9.5 ± 38.1 (0.002–539)   | 9.4 ± 38.5 (0.002–539)     | 16.5 ± 0.0 (0.01–387) | 0.004*    |
| High-sensitivity cardiac troponin T test (hs-cTnT), ng/ml | 25.8 ± 37.3 (0.01–115) | 30.5 ± 39.5 (0.01–115)     | 2.4 ± 0.7 (17–41)    | 0.519     |
| Creatine kinase, U/l                           | 489.3 ± 950.6 (0.01–11,535) | 459.2 ± 880.2 (0.01–11,535) | 7.4 ± 1 (0.01–427)   | 0.005*    |
| D-dimer, mg/l                                  | 14.9 ± 114.3 (0.046–2520) | 14.1 ± 114.9 (0.05–2520)   | 3.2 ± 0.4 (0.6–639)  | 0.000*    |
| Ferritin, µg/L                                 | 1,413.5 ± 3504.3 (0.33–64165) | 1393.1 ± 3509.2 (0.33–64165) | 2058.1 ± 10 (10–14,094) | 0.648     |
| NT-proBNP, (ng/ml)                             | 25.8 ± 37.3 (0.01–115) | 30.5 ± 39.5 (0.01–115)     | 2.4 ± 0.7 (0.7–4.1)  | 0.519     |
| BNP, (pg/ml)                                   | 1191.7 ± 2082 (19–9675) | 1400 ± 2218.4 (38–9675)    | 2.2 ± 0 (19–393)     | 0.002*    |

**Microbiological testing for patients on hospital admission**

| Virus PCR was done | 377 (25.3) | 358 (25.8) | 18 (19.6) | 0.215 |
| PCR was negative   | 128 (8.6)  | 116 (8.4)  | 12 (13)   | 0.125 |
| Atypical pneumonia PCR was done | 28 (1.8) | 22 (1.6) | 3 (3.3) | 0.200 |
| PCR was negative   | 27 (1.7)   | 24 (1.7)   | 3 (3.3)   | 0.233 |
| Legionella Pneumophila, positive                | 1 (0.1)    | 1 (0.1)    | 0         | 0.062 |
| MERS-CoV PCR was done                            | 68 (4.6)   | 63 (4.5)   | 5 (5.4)   | 0.611 |
| PCR was negative                                      | 59 (4)     | 54 (4.9)   | 5 (5.4)   | 0.518 |
| PCR was positive                                      | 8 (0.5)    | 8 (0.6)    | 0         | –     |

**Days of symptoms before hospital admission**

| Less than 3 days | 268 (18) | 251 (18.1) | 14 (15.2) | 0.000* |
| 3–5 days         | 516 (34.6) | 499 (35.9) | 15 (16.3) | –     |
| 6–8 days         | 225 (15.1) | 215 (15.4) | 9 (9.7)   | –     |
| More than 8 days | 184 (12.3) | 171 (12.3) | 11 (11.9) | –     |
| Unknown          | 260 (17.4) | 219 (15.7) | 41 (44.5) | –     |

Data are presented as mean ± SD (minimum–maximum), or number (%), unless otherwise indicated.

AIDS, acquired immunodeficiency syndrome; BMI, body mass index; BNP, brain natriuretic peptide; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; HbA1c, glycated hemoglobin; HIV, human immunodeficiency virus; NT-proBNP, N-terminal pro b-type natriuretic peptide; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

Percentages do not total 100% owing to missing data.

*Represents significant differences.
ventilation (0.6% vs 4.3%; \( p = 0.01 \)) while patients were placed on mechanical ventilation.

Significant differences between the two groups were also found for most medications used as adjunctive pharmacotherapies in patients from hospital admission and during the ICU stay (\( p < 0.05 \)). Anticoagulation was indicated mainly as a part of the COVID-19 therapy protocol and LMWHs were the most prescribed anticoagulants (70%) at a higher frequency in the non-ECMO group (73% vs 37%; \( p = 0.000 \)). Favipiravir, tocilizumab, hydrocortisone and methylprednisolone were used significantly more often in the ECMO group compared to the non-ECMO group (20% vs 53%, \( p = 0.000 \); 28.5% vs 43.5%, \( p = 0.003 \); 15% vs 33%, \( p = 0.000 \) and 24% vs 50%, \( p = 0.000 \), respectively).

**Complications during hospitalization**

Overall, patients in the ECMO group experienced more complications at any time during hospitalization: pneumothorax (5% vs 29%; \( p = 0.000 \)), bleeding requiring blood transfusion (7% vs 38%; \( p = 0.000 \)), pulmonary embolism (6.4% vs 15.2%; \( p = 0.016 \)), gastrointestinal bleeding (3.3% vs 8.7%; \( p = 0.017 \)), low limb DVT (4.4% vs 5.4%; \( p = 0.016 \)), cardiac arrest (24% vs 45%; \( p = 0.000 \)), rhabdomyolysis (2.8% vs 14%; \( p = 0.000 \)), cardiac arrhythmias (4% vs 14%; \( p = 0.000 \)), bed sores (7.8% vs 16%; \( p = 0.01 \)), arterial lower limb ischemia (0.3% vs 1.4%; \( p = 0.000 \)), and intracerebral bleeding (1.4% vs 15%; \( p = 0.000 \)). Other investigations of the cohort are outlined in Table 2.

**Clinical course in patients treated with ECMO**

At day one of eligibility to ICU, all patients had a normal mean body temperature by day 21; however, patients’ level of consciousness estimated by Glasgow Coma Scale kept to decline and patients maintained a mean arterial pressure \( \geq 80 \) mmHg in both groups from day 1 to day 21 (Table 3). More patients in the ECMO group required hemodynamic support with epinephrine, dobutamine and dopamine. Throughout days 1–21, blood gas analysis showed lower PO2 levels and higher PCO2 levels, and lower respiratory rates in ECMO patients (Table 4). The \( \text{PaO}_2/\text{FiO}_2 \) ratio was improved from day 1 to day 21 in both groups: (non-ECMO group: 118 vs 144) and (ECMO group: 95.2 vs 119.4). For modes of ventilation, pressure and volume-controlled ventilations were used more in the ECMO group; however, pressure-regulated volume-controlled ventilation was applied more in the non-ECMO group. Peak pressure < 45 cmH2O and plateau pressure < 30 cmH2O were maintained during the 21 days in both groups to prevent barotrauma in patients. Tidal volume of 2–4 ml/kg per patient’s ideal body weight was also applied to prevent ventilator-induced lung injury. High mean PEEP was employed in the first few days to maintain oxygen saturation of 88–92% and as patients recovered, the value was gradually reduced (Table 4).

In the ECMO group, the venovenous mode was used in most patients (93.5%) via the percutaneous cannulation (92.4%) approach for vascular access (Table 5). The mean duration under ECMO was 15.1 (1–52) days. ECMO was indicated mainly for COVID-19 related ARDS (95.6%). About 42.4% of the ECMO patients underwent positioning within 24 h of ECMO initiation. Packed red blood cells (81.5%), fresh frozen plasma (43.5%) and platelets (35.8%) were most common blood transfusion products given while patients were on ECMO. ECMO mode conversion was made in few cases (4.3%). ECMO-related mechanical complications occurred in 45 (48.9%) patients; thirty patients (32.6%) had major bleeding from cannulation site, in eight patients (8.7%) there was oxygenator failure requiring circuit change, and in seven patients (7.6%) ECMO circuit clotting occurred. Of the 45 ECMO patients with a final disposition of death, discharged home alive or transferred to another facility, 45 (48.9%) died; 45 (48.9%) died. Forty-two (45.6%) patients were successfully decannulated, and 5 (5.4%) patients were discontinued from ECMO because of bad response. Main causes of death in ECMO patients were: septic shock (19.6%), multiple organ failure (10.9%), cardiac arrest (4.3%) and do-not-resuscitate order (4.3%).

Ventilatory settings, arterial blood gas analyses and vital signs in the ECMO patients obtained 12-h and 2-h before-ECMO initiation, 72 h after-ECMO initiation, and 12-h and 2-h before-ECMO treatment removal were compared (Table 6). Ventilatory setting of peak pressure pre-ECMO, post-ECMO and pre-ECMO removal was statistically different (\( p = 0.010 \)). \( \text{PaO}_2 \) was significantly higher 72 h after-ECMO start and 2 h before ECMO removal (62.9 mmHg vs 74 mmHg, and 62.9 mmHg vs 70 mmHg; \( p = 0.002 \), respectively) and \( \text{PCO}_2 \) was significantly lower 72 h after-ECMO and 2 h before ECMO removal (61.8 mmHg vs 49.3 mmHg, and 61.8 mmHg vs 51 mmHg; \( p = 0.042 \), respectively).

**Chest radiography, laboratory and microbiological culture findings**

Chest CT findings of patients on hospital admission for both groups were mainly ground glass opacity, multifocal infiltrate and pleural effusion in both groups (Table 7). In both non-ECMO and ECMO groups, a high percentage of all patients during the ICU stay shown consolidation with a bilateral infiltrate chest X-ray images consistent with pneumonia and/or ARDS.
### Table 2  Patients data on ICU admission and during ICU stay

| Variable                                                                 | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value   |
|--------------------------------------------------------------------------|----------------|--------------------------|---------------------|-----------|
| **Reason of ICU admission**                                              |                |                          |                     |           |
| Shock                                                                    | 91 (6.1)       | 80 (5.8)                 | 10 (10.9)           | 0.066     |
| Acute respiratory distress syndrome                                       | 1,289 (86.5)   | 1,197 (86.2)             | 87 (94.6)           | 0.007*    |
| Decreased level of consciousness                                         | 145 (9.7)      | 142 (10.2)               | 1 (1.1)             | 0.001*    |
| Diabetic ketoacidosis                                                    | 11 (0.7)       | 9 (0.6)                  | 1 (1.1)             |           |
| Post-operative monitoring                                                | 10 (0.7)       | 10 (0.7)                 | 0                   |           |
| Increased severity of COVID-19                                           | 40 (2.7)       | 40 (2.9)                 | 0                   |           |
| Acute coronary syndrome                                                  | 5 (0.3)        | 5 (0.4)                  | 0                   |           |
| Likelihood to deteriorate                                                | 49 (3.3)       | 49 (3.5)                 | 0                   |           |
| Other                                                                    | 135 (9.1)      | 134 (9.6)                | 0                   | 0.000*    |
| Patient arrived from another hospital and was already intubated          | 162 (10.9)     | 111 (8)                  | 50 (54.3)           | 0.000*    |
| Patient was intubated and on mechanical ventilation during the ICU stay | 817 (54.8)     | 725 (52.2)               | 92 (100)            | 0.005*    |
| APACHE II score                                                         | 38 ± 2.7 (29–40) | 34 ± 1.9 (29)          | 42 ± 3.4 (33–47)    | 0.000*    |
| **Vital signs in the first 24 h of ICU admission**                       |                |                          |                     |           |
| Systolic blood pressure, mmHg                                            | 124.9 ± 22.2 (48–206) | 125.5 ± 4.1 (29–39) | 112.4 ± 23.2 (71–190) | 0.000*    |
| Diastolic blood pressure, mmHg                                           | 70.6 ± 13.2 (33–129) | 70.8 ± 13.1 (33–120) | 66.6 ± 16.1 (43–129) | 0.013*    |
| Mean arterial pressure, mmHg                                             | 85.9 ± 16.6 (35–195) | 85.9 ± 16.6 (35–195) | 85.4 ± 17 (58–138)   | 0.478     |
| Heart rate, beats/minute                                                 | 91.9 ± 20.8 (36–168) | 91.4 ± 20.5 (36–168) | 100.2 ± 23 (50–160)  | 0.000*    |
| Respiratory rate, breaths/minute                                         | 26.7 ± 6.3 (4–41) | 27 ± 6.4 (7–41)      | 21.7 ± 8.4 (4–40)   | 0.000*    |
| O2 saturation, %                                                         | 83.4 ± 2.2 (60–100) | 84.6 ± 4.2 (60–100) | 83.1 ± 9.1 (60–100)  | 0.541     |
| Temperature (highest within the first 24 h), °C                          | 37.2 ± 1.5 (15–40.2) | 37.2 ± 1.4 (15–40) | 36.9 ± 2.5 (16–39.9) | 0.385     |
| Glasgow Coma Score                                                       | 12.5 ± 4.5 (2–15) | 12.8 ± 4.2 (2–15) | 7.5 ± 5.6 (3–15)    | 0.000*    |
| **Radiographic findings in the first 24 h of ICU admission**            |                |                          |                     |           |
| Chest X-ray was done                                                     | 1319 (88.5)    | 1,231 (88.6)             | 82 (89.1)           | 0.708     |
| Was chest X-ray consolidation present or absent?                         |                |                          |                     |           |
| Present                                                                  | 1,226 (82.2)   | 1,148 (82.6)             | 73 (79.3)           | 0.344     |
| Absent                                                                   | 83 (5.6)       | 76 (5.5)                 | 7 (7.6)             |           |
| X-ray chest radiography                                                  |                |                          |                     |           |
| Unilateral abnormality                                                   | 58 (3.9)       | 56 (4)                   | 2 (2.2)             | 0.770     |
| Bilateral abnormality                                                    | 1158 (77.7)    | 1085 (78.1)              | 68 (73.9)           |           |
| **Respiratory status in the first 6 h of ICU admission**                 |                |                          |                     |           |
| Arterial blood gas (ABG) analysis                                        |                |                          |                     |           |
| pH                                                                       | 7.35 ± 0.13 (6.8–7.6) | 7.35 ± 0.13 (6.8–7.6) | 7.30 ± 0.11 (7–7.5) | 0.476     |
| PaCO2, mmHg                                                              | 39.89 ± 11.01 (19–95.9) | 39.68 ± 10.91 (19–95.9) | 42.64 ± 12.39 (19.7–70) | 0.023*    |
| PaO2, mmHg                                                               | 69.8 ± 33.4 (38.4–375) | 70.7 ± 34.5 (38.4–375) | 60.4 ± 13.2 (40.3–101) | 0.202     |
| % O2 saturation                                                          | 81.9 ± 8.9 (60–100) | 82.1 ± 8.9 (60–100) | 77.6 ± 7.9 (63–88)  | 0.128     |
| Mode of O2 delivery at the time of gas sampling                          |                |                          |                     |           |
| Nil                                                                      | 97 (6.5)       | 94 (6.8)                 | 2 (2.2)             | 0.000*    |
| NC                                                                       | 88 (5.9)       | 86 (6.2)                 | 1 (1.1)             |           |
| FM                                                                       | 164 (11)       | 160 (11.5)               | 2 (2.2)             |           |
| NRM                                                                      | 330 (22.1)     | 320 (23)                 | 7 (7.6)             |           |
| HFNO                                                                     | 238 (16)       | 235 (16.9)               | 3 (3.3)             |           |
| NIPPV/BiPAP                                                              | 65 (4.4)       | 62 (4.5)                 | 3 (3)               |           |
| **Oxygen flow rate and FiO2 given by**                                   |                |                          |                     |           |
| NC and FM: flow rate, L/minute                                          | 7 ± 8.6 (1–95) | 6.98 ± 8.7 (1–95) | 9.67 ± 5.5 (4–15)   | 0.228     |
| HFNO: flow rate, L/minute                                                | 45.1 ± 13.9 (0.8–100) | 75 ± 13.9 (0.8–100)   | 79.6 ± 24.2 (30–60) | 0.487     |
| HFNO: FiO2, %                                                            | 77.9 ± 23.1 (21–100) | 77.7 ± 23.1 (21–100) | 79.6 ± 24.2 (30–100) | 0.488     |
| MV: FiO2, %                                                              | 79.6 ± 23.2 (21–100) | 79.7 ± 23 (21–100) | 91.7 ± 10.4 (80–100) | 0.897     |
Table 2 (continued)

| Variable                                           | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value |
|----------------------------------------------------|----------------|---------------------------|---------------------|---------|
| During the ICU stay, patients required             |                |                           |                     |         |
| No oxygen supply was needed                        | 102 (6.8)      | 102 (7.3)                 | 0                   | 0.002*  |
| NC                                                 | 327 (21.9)     | 324 (23.3)                | 1 (1.1)             | 0.000*  |
| FM                                                 | 317 (21.3)     | 308 (22.2)                | 6 (6.5)             | 0.000*  |
| NRM                                                | 735 (49.3)     | 706 (50.8)                | 27 (30.3)           | 0.000*  |
| Patient was started on HFNC                        | 452 (30.3)     | 438 (31.5)                | 14 (14.1)           | 0.720   |
| HFNC use, days                                     | 4.82 ± 4.86 (1–38) | 4.87 ± 4.9 (1–38)     | 2.9 ± 2.6 (1–14)   | 0.106   |
| HFNO: flow rate, L/minute                          | 45.2 ± 14.6 (3–100) | 45.2 ± 14.5 (5–100)   | 35.8 ± 14.8 (10–60) | 0.229   |
| HFNO: FiO₂, %                                      | 85 ± 20.9 (25–100) | 84.8 ± 21.1 (25–100)  | 92.2 ± 12.7 (55–100) | 0.067   |
| Patient was started on BiPAP                       | 210 (14.1)     | 199 (14.3)                | 10 (10.9)           | 0.052   |
| BiPAP use, days                                    | 3.9 ± 7.7 (1–100) | 3.9 ± 7.9 (1–100)       | 3.6 ± 3.5 (1–12)    | 0.874   |
| BiPAP: FiO₂, %                                     | 84 ± 20.9 (10–100) | 83.7 ± 21.2 (10–14)    | 92.2 ± 12.2 (70–100) | 0.276   |
| Awake prone positioning was performed              | 358 (24)       | 341 (24.6)                | 15 (16.3)           | 0.03*   |
| Awake prone positioning, days                      | 4.4 ± 4 (1–28)  | 4.4 ± 4 (1–28)            | 4.4 ± 3.9 (1–15)    | 0.972   |
| Duration of prone positioning                      |                |                           |                     |         |
| ≤ 4 days                                           | 147 (9.9)      | 140 (10.1)                | 7 (7.6)             | 0.793   |
| > 4 days                                           | 199 (13.3)     | 191 (13.6)                | 8 (8.7)             |         |
| Inhaled nitric oxide was used before intubation    | 13 (0.9)       | 12 (0.8)                  | 2 (2.2)             | 0.043*  |
| Use of renal replacement therapy (dialysis)        | 238 (16)       | 199 (14.3)                | 39 (24.2)           | 0.000*  |
| Therapies patient underwent while on mechanical ventilation |            |                           |                     |         |
| Paralysis infusion                                  | 539 (36.8)     | 529 (38.1)                | 49 (53.3)           | 0.035*  |
| Recruitment maneuvers                               | 6 (0.4)        | 6 (0.4)                   | 10 (10.9)           | 0.277   |
| Inhaled nitric oxide                                | 691 (45.3)     | 59 (42)                   | 10 (10.9)           | 0.023*  |
| Prone positioning                                   | 356 (24.5)     | 338 (24.3)                | 26 (28.3)           | 0.514   |
| Airway pressure release ventilation (APRV)         | 22 (1.5)       | 19 (1.4)                  | 3 (3.3)             | 0.205   |
| High Frequency oscillatory ventilation (HFV)       | 13 (0.9)       | 9 (0.6)                   | 4 (4.3)             | 0.010*  |
| Medications used (from hospital admission to during ICU stay) |        |                           |                     |         |
| Hydroxychloroquine                                  | 420 (28.2)     | 408 (29.4)                | 12 (13)             | 0.001*  |
| Chloroquine                                         | 18 (1.2)       | 15 (1.1)                  | 2 (2.2)             | 0.277   |
| Azithromycin                                        | 1,077 (72.2)   | 1,042 (75)                | 29 (31.5)           | 0.000*  |
| Lopinavir/ritonavir                                 | 349 (23.4)     | 340 (24.5)                | 8 (8.7)             | 0.000*  |
| Favipiravir                                         | 330 (22.1)     | 279 (20.1)                | 49 (53.3)           | 0.000*  |
| Remdesivir                                         | 14 (0.9)       | 12 (0.9)                  | 2 (2.2)             | 0.212   |
| Ribavir                                             | 242 (16.2)     | 233 (16.8)                | 8 (8.7)             | 0.054   |
| IVGs                                                | 52 (3.5)       | 51 (3.7)                  | 1 (1.1)             | 0.369   |
| Interferon                                          | 152 (10.2)     | 146 (10.5)                | 6 (6.5)             | 0.285   |
| Oxacillin                                           | 321 (21.5)     | 308 (22.2)                | 10 (10.9)           | 0.011*  |
| B-lactamase inhibitors (piperacillin/tazobactam, amoxicillin/clavulanate, ampicillin/sulbactam) | 592 (39.7)     | 559 (40.2)                | 30 (32.6)           | 0.215   |
| Cephalosporins (ceftazidime, ceftriaxone, cefazolin, cefuroxime, cefepime) | 732 (49.1)     | 697 (50.2)                | 30 (32.6)           | 0.001*  |
| Carbapenems (meropenem, imipenem, ertapenem)        | 600 (40.2)     | 525 (37.8)                | 72 (78.3)           | 0.000*  |
| Aminoglycosides (gentamycin, amikacin, tobramycin)  | 45 (3)         | 35 (2.5)                  | 9 (9.8)             | 0.001*  |
| Colistin                                            | 232 (15.6)     | 178 (12.8)                | 53 (57.6)           | 0.000*  |
| Ceftazidime/avibactam                               | 47 (3.2)       | 32 (2.3)                  | 15 (16.3)           | 0.000*  |
| Ceftazidime/tazobactam                              | 91 (6.1)       | 80 (5.8)                  | 10 (10.9)           | 0.062   |
| Vancomycin                                          | 538 (36.1)     | 461 (33.2)                | 75 (81.5)           | 0.000*  |
| Linezolid                                           | 208 (14)       | 172 (12.4)                | 36 (39.1)           | 0.000*  |
| Antifungals                                         | 199 (13.3)     | 166 (12)                  | 33 (35.9)           | 0.000*  |
| Tocilizumab                                         | 438 (29.4)     | 396 (28.5)                | 40 (43.5)           | 0.003*  |
Table 2 (continued)

| Variable                                                   | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value |
|-------------------------------------------------------------|----------------|---------------------------|---------------------|---------|
| Convalescent plasma                                        | 54 (3.6)       | 45 (3.2)                  | 9 (9.8)             | 0.004*  |
| Plasmapheresis                                              | 26 (1.7)       | 23 (1.7)                  | 3 (3.3)             | 0.31    |
| Anakinra                                                    | 4 (0.3)        | 4 (0.3)                   | 0                   | 0.79    |
| Sildenafil                                                  | 1 (0.1)        | 0                         | 1 (1.1)             | 0.0061  |
| Iloprost inhalation                                         | 4 (0.3)        | 0                         | 4 (4.4)             | 0.000*  |
| **Anticoagulation administration during hospitalization**   |                |                           |                     |         |
| **Indication for anticoagulation**                         |                |                           |                     |         |
| DVT prophylaxis only                                       | 786 (52.7)     | 754 (54.3)                | 32 (34.7)           | 0.000*  |
| ECMO protocol                                               | 78 (5.2)       | 0                         | 78 (84.8)           | 0.000*  |
| PE (history of PE prior to hospital admission)             | 1 (0.1)        | 1 (0.1)                   | 0                   | 0.938   |
| PE (diagnosed during current admission)                    | 19 (1.3)       | 17 (1.2)                  | 2 (2.2)             | 0.333   |
| DVT (history of DVT prior to current admission)            | 7 (0.5)        | 6 (0.4)                   | 1 (1.1)             | 0.362   |
| DVT (new diagnosis during current hospital admission)      | 10 (0.7)       | 10 (0.7)                  | 0                   | 0.526   |
| Atrial fibrillation                                        | 16 (1.1)       | 16 (1.1)                  | 0                   | 0.618   |
| Mechanical valve                                           | 6 (0.4)        | 6 (0.4)                   | 0                   | 0.680   |
| Past history of thromboembolic disease                     | 8 (0.5)        | 7 (0.7)                   | 1 (1.1)             | 0.638   |
| Part of COVID-19 therapy protocol                          | 876 (58.8)     | 850 (61.2)                | 25 (27.2)           | 0.000*  |
| Current malignancy                                         | 1 (0.1)        | 1 (0.1)                   | 0                   | 0.938   |
| Other                                                       | 47 (3.2)       | 46 (3.3)                  | 1 (1.1)             | 0.360   |
| **Choice of anticoagulation therapy**                      |                |                           |                     |         |
| LMWHs (enoxaparin, tinzaparin, or dalteparin)              | 1050 (70.4)    | 1013 (72.9)               | 34 (37)             | 0.000*  |
| Duration of use, days                                      | 10.5 ± 15.1    | 10.6 ± 15.2               | 10.1 ± 10.4         | 0.629   |
| Heparin SC                                                  | 314 (21.1)     | 303 (21.8)                | 9 (9.8)             | 0.005*  |
| Duration of use, days                                      | 11 ± 14.8      | 10.8 ± 14.5               | 20.4 ± 22.2         | 0.056   |
| Heparin infusion                                           | 297 (26.6)     | 309 (22.2)                | 82 (89.1)           | 0.000*  |
| Duration of use, days                                      | 10.8 ± 14.2    | 9.7 ± 13.2                | 15.3 ± 17.7         | 0.000*  |
| Warfarin                                                   | 7 (0.5)        | 6 (0.4)                   | 0                   | 0.680   |
| Duration of use, days                                      | 28.2 ± 45.5    | 8 ± 6.5                   | 0                   | -       |
| NOACs (apixaban, dabigatran, rivaroxaban, or edoxaban)     | 6 (0.4)        | 6 (0.4)                   | 0                   | 0.680   |
| Duration of use, days                                      | 4.4 ± 4.1      | 4.4 ± 4.1                 | 0                   | -       |
| Fondaparinux                                               | 13 (0.9)       | 12 (0.9)                  | 0                   | 0.462   |
| Duration of use, days                                      | 17.6 ± 17.2    | 18.1 ± 18.2               | 0                   | -       |
| Use of corticosteroids during ICU stay                     | 1069 (71.7)    | 986 (71)                  | 81 (88)             | 0.000*  |
| Hydrocortisone                                             | 247 (16.6)     | 216 (15.6)                | 31 (33.7)           | 0.000*  |
| Duration of use, days                                      | 8.7 ± 15.6     | 8.2 ± 16.1                | 11.5 ± 11.6         | 0.017*  |
| Methylprednisolone                                         | 390 (26.2)     | 344 (24.8)                | 46 (50)             | 0.000*  |
| Duration of use, days                                      | 10.1 ± 18      | 9.7 ± 16.6                | 13.9 ± 25.6         | 0.192   |
| Dexamethasone                                              | 617 (41.4)     | 579 (41.7)                | 36 (39.1)           | 0.663   |
| Duration of use, days                                      | 9.9 ± 7.3      | 10 ± 7.3                  | 9.4 ± 6.5           | 0.499   |
| Prednisone                                                 | 36 (2.4)       | 34 (2.4)                  | 2 (2.2)             | 0.610   |
| Duration of use, days                                      | 9.5 ± 8.3      | 8.5 ± 7.5                 | 22.5 ± 10.6         | 0.045*  |
| **Complications patients experienced at any time during hospitalization** | | | | |
| Pneumothorax                                               | 97 (6.5)       | 69 (5)                    | 27 (29.3)           | 0.000*  |
| Pulmonary embolism                                         | 103 (6.9)      | 89 (6.4)                  | 14 (15.2)           | 0.016*  |
| Gastrointestinal bleeding                                  | 54 (3.6)       | 46 (3.3)                  | 8 (8.7)             | 0.017*  |
| Stroke                                                     | 33 (2.2)       | 31 (2.2)                  | 2 (2.2)             | 0.664   |
| Cardiac ischemia or infarction                             | 63 (4.2)       | 57 (4.1)                  | 6 (6.5)             | 0.279   |
| Bowel ischemia                                             | 4 (0.3)        | 3 (0.2)                   | 1 (1.1)             | 0.225   |
Laboratory data for non-ECMO and ECMO patients during the ICU stay are shown in Table 8. In both groups, only hemoglobin, absolute lymphocyte count, platelet count, and activated partial thromboplastin time were in normal ranges. However, most laboratory parameters were either very high and increased, including white blood cell count, absolute neutrophil count, bilirubin, troponin T, d-dimer, ferritin, ProBNP and BNP. Other parameters were very high and decreased, including aspartate transaminase and alanine transaminase, erythrocyte sedimentation rate, lactate dehydrogenase, high-sensitivity cardiac troponin T test and creatine kinase. Few parameters were high and either increased or decreased, including lactate, C-reactive protein and Troponin I.

Cultures taken from patients on hospital admission till extubation and/or ICU discharge in non-ECMO and ECMO groups were mainly blood, respiratory or from tracheal aspirate and sputum (Table 9). Overall, microbial growth of Gram-positive [Gram-positive bacteria (no specific resistance pattern), VRE, MSSA, and MRSA] and Gram-negative [sensitive Enterobacteriaceae, Pseudomonas, and Acinetobacter; in addition to the species of Enterobacteriaceae, Pseudomonas, and Acinetobacter with the following resistance trends: ESBL, CRE, MDR, and XDR] bacteria, Aspergillus, Candida and other pathogens were detected more in the ECMO patients.

### Treatment outcomes

Compared to the non-ECMO group, the ECMO group had significantly lower SARS-CoV-2 virological cure (2 consecutive negative PCR samples) rate (41.3% vs 14.1%; \( p = 0.000 \)); higher proportion of patients remained ventilated in the ICU (3.5% vs 33.7%; \( p = 0.000 \)); lower proportion of patients were discharged from ICU (90.1% vs 55.4%; \( p = 0.000 \)); higher in-hospital mortality (40.2% vs. 48.9%; \( p = 0.000 \)); longer hospitalization (20.2 days vs 29.1 days; \( p = 0.000 \)), ICU stay (12.6 vs 26 days; \( p = 0.000 \)) and use of mechanical ventilation (14.2 days vs 22.4 days; \( p = 0.000 \)) (Table 10).
Table 3  Hemodynamic data and circulatory support during the ICU stay

|                      | Day 1          | Day 2          | Day 3          | Day 4          | Day 5          | Day 7          |
|----------------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                      | Non-ECMO (n = 343) | ECMO (n = 35) | Non-ECMO (n = 325) | ECMO (n = 39) | Non-ECMO (n = 221) | ECMO (n = 24) | Non-ECMO (n = 184) | ECMO (n = 19) | Non-ECMO (n = 203) | ECMO (n = 16) | Non-ECMO (n = 187) | ECMO (n = 19) |
| Highest temperature (°C) | 37.3 (0.8) | 37.1 (1) | 37.2 (0.8) | 36.9 (0.9) | 37.1 (0.8) | 36.9 (0.8) | 37.1 (0.8) | 36.8 (0.8) | 37.1 (0.8) | 36.8 (0.9) |
| Glasgow coma score (GCS) | 12.5 (4.5) | 7.5 (5.7) | 10 (5.3) | 8.6 (4.9) | 11.6 (5.1) | 6.75 (5.4) | 10.2 (6.1) | 6.5 (4.8) | 10.8 (4.4) | 6.7 (4.3) | 10.8 (5.4) | 6.6 (4.9) |
| Mean arterial pressure (MAP) (mmHg) | 83.7 (14.9) | 849 (148) | 84.4 (13.9) | 83.6 (15.3) | 83.9 (14.4) | 84.4 (14.4) | 84.1 (14.7) | 86.6 (15.5) | 846 (13.4) | 87.9 (14.5) | 83.7 (13.9) | 83.8 (16.5) |
| Use of epinephrine | 11 (3.2%) | 3 (8.6%) | 9 (28%) | 3 (7.7%) | 8 (3.6%) | 2 (83%) | 5 (15.8%) | 3 (15.8%) | 10 (4.9%) | 4 (25%) | 12 (6.4%) | 3 (15.8%) |
| Maximum dose (mcg/kg/min) | 0.3 (0.3) | 0.1 (0.05) | 0.2 (0.1) | 0.2 (0.1) | 0.7 (0.1) | 0.3 (0.4) | 0.5 (0.4) | 0.4 (0.4) | 39 (94) | 0.3 (0.2) | 1.7 (2.8) | 0.3 (0.3) |
| Use of norepinephrine | 178 (51.9%) | 29 (82.8%) | 183 (56.3%) | 34 (87.2%) | 194 (95.8%) | 16 (55%) | 14 (73.7%) | 168 (82.7%) | 13 (81.2%) | 155 (82.9%) | 17 (89.5%) |
| Maximum dose (mcg/kg/min) | 2.4 (3.5) | 0.9 (19) | 0.6 (1.3) | 0.9 (1.7) | 0.84 (1.4) | 1.6 (19) | 0.7 (13) | 0.9 (18) | 1.1 (1) | 0.9 (1.8) | 1.3 (1.9) |
| Use of dopamine | 24 (7%) | 1 (28%) | 20 (6.1%) | 1 (2.6%) | 19 (8.6%) | 2 (8.3%) | 16 (8.7%) | 0 | 18 (89%) | 1 (6.2%) | 14 (7.5%) | 0 |
| Maximum dose (mcg/kg/min) | 9.2 (6.3) | 5 (00) | 7.5 (6.7) | 5 (00) | 8.3 (6.7) | 5 (00) | 6.3 (5.1) | 0 | 4.4 (44) | 6.0 (00) | 6.5 (5.5) | 0 |
| Use of dobutamine | 14 (4.1%) | 3 (8.6%) | 11 (3.4%) | 3 (7.7%) | 6 (2.7%) | 1 (4.2%) | 4 (2.2%) | 1 (5.3%) | 3 (15.5%) | 1 (6.2%) | 3 (1.6%) | 0 |
| Maximum dose (mcg/kg/min) | 5 (00) | 3 (1.7) | 6.7 (2.9) | 2 (00) | 5.4 (2.7) | 2 (00) | 7 (2.4) | 2 (00) | 6.2 (12) | 2 (0) | 6.2 (1.2) | 0 |
| Use of phenylephrine | 29 (8.4%) | 3 (8.6%) | 21 (6.5%) | 2 (5.1%) | 9 (4.1%) | 0 | 8 (4.3%) | 1 (5.3%) | 10 (4.9%) | 1 (6.2%) | 8 (4.3%) | 1 (5.3%) |
| Maximum dose (mcg/kg/min) | 3 (3.3) | 4.3 (4.2) | 1.3 (0.7) | 1.6 (1.9) | 1.2 (1.9) | 0 | 5.8 (4.3) | 3 (00) | 2.7 (2.9) | 3 (00) | 2 (2) | 3 (0.0) |
Table 3 (continued)

| Day | Non-ECMO (n = 143) | ECMO (n = 23) | Non-ECMO (n = 133) | ECMO (n = 18) | Non-ECMO (n = 95) | ECMO (n = 20) | Non-ECMO (n = 83) | ECMO (n = 20) | Non-ECMO (n = 63) | ECMO (n = 20) | Non-ECMO (n = 57) | ECMO (n = 20) |
|-----|------------------|--------------|-------------------|--------------|------------------|--------------|------------------|--------------|------------------|--------------|------------------|--------------|
|     | Highest temperature (°C) | 37.1 (0.8) 36.8 (0.7) 37.1 (0.8) | 36.9 (0.8) 37.1 (0.7) 37.1 (0.7) 37.1 (0.7) 37.1 (0.7) 37.1 (0.7) 36.9 (1) 37.1 (0.8) 36.8 (0.8) 37.1 (0.7) 36.9 (0.8) 37.1 (0.7) 36.8 (0.7) 37.1 (0.7) 36.9 (0.8) |     | Glasgow coma score (GCS) | 9.8 (4.4) 6.1 (4.7) 9.1 (5.1) | 5.6 (3.7) | 86.4 (4.7) 4.1 (4.1) | 8.9 (5.1) 5.3 (4.8) | 7.6 (4.9) 5.1 (4.4) | 7.1 (4.4) 4.8 (3.9) | 6.7 (5.1) 4.3 (3.1) |     | Mean arterial pressure (MAP) (mmHg) | 83.2 (14) 86.8 (16.1) 81.8 (14.7) | 82 (12.9) | 81.8 (15) 843 (13.3) | 81.3 (14.1) 843 (12.8) | 80.9 (13.8) 821 (13.9) | 81.8 (14.5) 798 (14) | 80.1 (14) 799 (17) |     | Use of epi-nephrine | 0.9 (0.7) 0.8 (0.2) 1.8 (1.3) | 0.4 (0.4) | 8.6 (6.2%) 3.1 (16.7%) | 4 (4.2%) 4.2 (20%) | 3 (3.6%) 3 (15%) | 1 (1.6%) 3 (15%) | 3 (5.3%) 3 (15%) |     | Maximum dose (mcg/kg/min) | 0.9 (0.7) 0.8 (0.2) 1.8 (1.3) | 0.4 (0.4) | 0.3 (0.3) 0.1 (0.05) | 0.9 (0.2) 0.2 (0.2) | 0.5 (0.6) 5.5 (9.1) | 1 (0.0) 0.5 (0.4) | 0.6 (0.4) 0.3 (0.2) |     | Use of norepinephrine | 130 (90.9%) 19 (82.6%) 124 (93.2%) | 17 (77.3%) | 113 (88.3%) 15 (83.3%) | 83 (87.4%) 15 (83.3%) | 74 (89.1%) 16 (80%) | 55 (87.3%) 17 (85%) | 51 (89.5%) 16 (80%) |     | Maximum dose (mcg/kg/min) | 0.3 (0.5) 0.3 (0.3) 0.7 (1.3) | 1 (1.9) | 0.7 (1.7) 0.33 (0.1) | 0.2 (0.3) 1 (1.9) | 0.4 (0) 0.3 (0.3) | 0.4 (0.6) 0.3 (0.4) | 0.3 (0.5) 0.5 (0.5) |     | Use of dopamine | 6 (4.2%) 0 3 (2.2%) | 1 (4.5%) | 6 (4.7%) 0 6 (6.3%) 0 6 (7.2%) 0 4 (6.3%) 0 2 (3.5%) 0 |     | Maximum dose (mcg/kg/min) | 5.9 (6.9) 0 8.7 (9.8) 2 (0.0) | 6.9 (7.3) 0 3.9 (0.6) 0 4.9 (3) 0 4.1 (0.9) 0 3.5 (1.5) 0 |     | Use of dopamine | 1 (0.7%) 1 (4.3%) 2 (1.5%) | 0 0 0 | 0 0 | 0 0 | 0 1 (1.6%) 0 0 0 |     | Maximum dose (mcg/kg/min) | 7.5 (0.0) 1 (0.0) 2.7 (0.3) | 0 0 0 | 0 0 | 0 0 | 0 0 | 0 0 |     | Use of dobutamine | 4 (2.8%) 1 (4.3%) 6.4 (5.5%) | 2 (9.1%) 4 (3.1%) 1 (5.5%) | 4 (4.2%) 0 3 (3.6%) 1 (5%) | 3 (4.8%) 3 (5%) | 3 (6.3%) 1 (5%) | 3 (4.8%) 3 (5%) |     | Maximum dose (mcg/kg/min) | 3.2 (0.3) 2 (0.0) 0 | 2 (1.4) 3.5 (3.5) 0.8 (0.0) | 1 (0.0) 0 1.1 (0.1) 1.5 (0.0) | 1 (0.0) 3 (0.0) | 0.7 (0.4) 3 (0.0) | 3 (0.0) 3 (0.0) |

Data are presented as number (%) or mean (SD)
### Table 4 Ventilatory support variables following the intubation and mechanical ventilation during the ICU stay

| Day 1 | Day 2 | Day 3 | Day 4 | Day 5 |
|-------|-------|-------|-------|-------|
|       | Non-ECMO | ECMO | Non-ECMO | ECMO | Non-ECMO | ECMO | Non-ECMO | ECMO | Non-ECMO | ECMO |
|       | (n=986) | (n=891) | (n=67) | (n=798) | (n=63) | (n=668) | (n=58) |
| PC    | 91 (9.2%)  | 32 (45.1%)  | 91 (10.2%)  | 34 (50.7%)  | 36 (50.7%)  | 81 (10.1%)  | 44 (69.8%)  | 74 (11.1%)  | 41 (70.7%)  |
| VC    | 258 (26.2%)  | 29 (40.8%)  | 238 (26.7%)  | 33 (43.4%)  | 233 (26.6%)  | 24 (33.8%)  | 212 (26.6%)  | 18 (28.6%)  | 189 (28.3%)  | 21 (36.2%)  |
| PRVC  | 366 (37.1%)  | 17 (23.9%)  | 342 (38.6%)  | 17 (25.4%)  | 321 (36.6%)  | 16 (22.5%)  | 289 (36.2%)  | 15 (23.8%)  | 260 (38.9%)  | 13 (22.4%)  |
| PS    | 1 (0.1%)  | 0 (0.0%)  | 5 (0.6%)  | 0 (0.0%)  | 13 (1.5%)  | 0 (0.0%)  | 16 (2.0%)  | 0 (0.0%)  | 22 (3.3%)  | 0 (0.0%)  |
| Other | 4 (0.4%)  | 0 (0.0%)  | 8 (0.9%)  | 2 (0.3%)  | 11 (1.2%)  | 2 (0.3%)  | 10 (1.2%)  | 2 (0.3%)  | 9 (1.3%)  | 2 (0.3%)  |
| PO2 value on ABG (mmHg) | 96.9 (52.7) | 76.2 (36.7) | 90 (35.8) | 79.2 (43.5) | 85.2 (40.7) | 71.9 (29.7) | 82.5 (33.7) | 63.9 (17) | 79.9 (29) | 69.6 (26.2) |
| PCO2 value on ABG (mmHg) | 46 (13) | 47.2 (12.1) | 46 (11.7) | 46.8 (10) | 46.4 (11.9) | 47.1 (11.1) | 48.8 (25) | 49.1 (14.2) | 48.7 (18.6) | 49 (16.3) |
| FiO2 (%) | 82.1 (22) | 80 (23.5) | 62.9 (21.9) | 61.4 (22.8) | 57.2 (20) | 58.1 (22) | 56.3 (24.8) | 59.5 (21.7) | 55.5 (24.8) | 56.9 (18.9) |
| PaO2/FiO2 ratio | 118 | 95.2 | 143.1 | 129 | 123.7 | 146.5 | 107.4 | 146.5 | 107.4 |
| Peak pressure (cmH2O) | 31.2 (6.8) | 30 (6.6) | 30.5 (6.4) | 30.4 (84) | 29.9 (7.8) | 30 (15.9) | 29.5 (7.8) | 28.3 (7.7) | 28.5 (8.2) | 29.5 (5.8) |
| Plateau pressure (cmH2O) | 26.9 (5.8) | 27.2 (6) | 26.9 (6.4) | 25.3 (5) | 26.6 (6) | 25.4 (5.2) | 26.4 (6) | 27.2 (5.1) | 26.1 (5.2) | 27.2 (5.4) |
| PEEP (cmH2O) | 11.3 (3.7) | 10.6 (2.8) | 11.3 (3.1) | 10.2 (2.6) | 11.3 (3.7) | 11.3 (3.7) | 11.3 (3.7) | 10.2 (2.6) | 10.8 (3.5) | 10.3 (2.2) |
| Tidal volume (ml) | 409.9 (72) | 327.1 (101.7) | 414.9 (66.4) | 307 (108.8) | 412.1 (72) | 325.1 (104.6) | 407.4 (75.3) | 288.8 (127.8) | 409.6 (63.1) | 294.3 (126.6) |
| Respiratory rate (bpm) | 24.3 (5.6) | 19.6 (6.9) | 25.7 (6) | 18.2 (7.2) | 25.6 (6) | 18 (6.7) | 25.9 (6.4) | 18 (6.5) | 26 (6.3) | 19 (13.4) |

| Day 7 | Day 9 | Day 11 | Day 13 | Day 17 |
|-------|-------|-------|-------|-------|
|       | Non-ECMO | ECMO | Non-ECMO | ECMO | Non-ECMO | ECMO | Non-ECMO | ECMO | Non-ECMO | ECMO |
|       | (n=690) | (n=630) | (n=608) | (n=64) | (n=589) | (n=69) | (n=73) | (n=668) | (n=58) |
| PC    | 73 (10.6%)  | 45 (88.2%)  | 58 (9.2%)  | 47 (79.7%)  | 51 (8.4%)  | 44 (68.7%)  | 41 (7%)  | 33 (47.8%)  | 5 (11.1%)  | 27 (5.3%)  | 12 (20%)  |
| VC    | 146 (21.1%)  | 15 (29.4%)  | 122 (19.3%)  | 14 (22.7%)  | 92 (15.1%)  | 15 (23.4%)  | 61 (10.3%)  | 16 (23.2%)  | 42 (76%)  | 12 (16.4%)  | 23 (4.5%)  | 12 (20%)  |
| PRVC  | 206 (29.3%)  | 14 (27.4%)  | 170 (26.9%)  | 7 (11.9%)  | 142 (23.3%)  | 4 (6.2%)  | 111 (18.8%)  | 6 (8.7%)  | 68 (123.3%)  | 5 (6.8%)  | 43 (8.4%)  | 7 (11.7%)  |
| PS    | 33 (4.8%)  | 1 (1.9%)  | 24 (3.8%)  | 1 (1.7%)  | 25 (4.1%)  | 2 (3.1%)  | 14 (2.4%)  | 2 (2.9%)  | 12 (2.2%)  | 1 (1.7%)  | 4 (0.8%)  | 1 (1.7%)  |
| Other | 14 (2%)  | 0 (0.0%)  | 11 (1.7%)  | 0 (0.0%)  | 5 (0.8%)  | 1 (1.6%)  | 8 (1.3%)  | 0 (0.0%)  | 11 (2%)  | 0 (0.0%)  | 3 (0.6%)  | 3 (5%)  |
| PO2 value on ABG (mmHg) | 99.1 (381.2) | 68.5 (15.4) | 81.2 (30) | 69.2 (17.1) | 80.5 (28.1) | 68.4 (16.8) | 81.3 (29.2) | 70.3 (25.1) | 80.4 (25.7) | 68.2 (15.1) | 79.3 (25.1) |
| PCO2 value on ABG (mmHg) | 50.6 (31) | 45.8 (10.5) | 48.5 (16.7) | 47.9 (14.3) | 49 (17.4) | 46.2 (13.6) | 50.5 (16.2) | 47.6 (11.2) | 49 (15.8) | 48.5 (13.2) | 51 (4.9) | 19 (15) |
**Table 4** (continued)

|          | Day 7       |   | Day 9     |   | Day 11    |   | Day 13    |   | Day 15    |   | Day 21    |   |
|----------|-------------|---|-----------|---|-----------|---|------------|---|------------|---|-----------|---|
|          | Non-ECMO    |   | ECMO      |   | Non-ECMO  |   | ECMO       |   | Non-ECMO  |   | ECMO      |   |
|          | (n = 690)   |   | (n = 51)  |   | (n = 630) |   | (n = 59)  |   | (n = 568) |   | (n = 64)  |   |
| FiO₂ (%) | 55.8 (26.8) |   | 61.7 (22.2) |   | 57.5 (22.8) |   | 60 (23.4)  |   | 59.4 (22.7) |   | 57.9 (23.5) |   |
| PaO₂/FiO₂ ratio | 177.6 |   | 111 |   | 141.2 |   | 115.3 |   | 135.2 |   | 119 |   |
| Peak pressure (cmH₂O) | 27.9 (8.8) |   | 30.6 (23.4) |   | 28.3 (6.6) |   | 28.4 (66) |   | 28.7 (9.1) |   | 28.3 (7.2) |   |
| Plateau pressure (cmH₂O) | 26.6 (66) |   | 27.2 (4.7) |   | 26.1 (6.7) |   | 25.8 (4.7) |   | 26.4 (8) |   | 26.3 (5) |   |
| PEEP (cmH₂O) | 10.6 (3.4) |   | 10 (2.5) |   | 10.6 (5.3) |   | 10 (2.4) |   | 10.1 (3.2) |   | 9.2 (2.5) |   |
| Tidal volume (ml) | 408.3 (70.3) |   | 326.9 (484.2) |   | 414.6 (688.8) |   | 266.6 (132.5) |   | 415.3 (80.8) |   | 287.8 (132.6) |   |
| Respiratory rate (bpm) | 25.7 (63) |   | 18.2 (6.6) |   | 25.7 (6.5) |   | 19.5 (9.5) |   | 25.8 (6.7) |   | 18.7 (5.7) |   |

Data are presented as number (%) or mean (SD).

A  B  G  arterial blood gas, bpm breaths per minute, FiO₂ inspired oxygen fraction, PC pressure control, PEEP positive end-expiratory pressure, PRVC pressure-regulated volume control, PS pressure support, SD standard deviation, VC volume control.
| Variable                                                                 | ECMO group (n = 92) |
|-------------------------------------------------------------------------|---------------------|
| Duration of ECMO use, days                                              | 15.4 ± 10.1 (1–52)  |
| Indication for ECMO insertion                                           |                     |
| COVID-19-related ARDS                                                   | 88 (95.6%)          |
| Other                                                                   | 4 (4.3%)            |
| Cannulation procedure                                                   |                     |
| Percutaneous                                                            | 85 (92.4%)          |
| Cutdown                                                                 | 2 (2.2%)            |
| ECMO insertion location                                                 |                     |
| Same center the patient is in now                                      | 45 (48.9%)          |
| Another hospital then transported to this center                        | 45 (48.9%)          |
| Type of transportation                                                  |                     |
| Ground transport                                                        | 38 (41.3%)          |
| Air medical transport                                                  | 7 (7.6%)            |
| Distance from the referring facility to the receiving hospital, kilometers | 155.9 ± 279.2 (2–1,045) |
| Duration of transportation, minutes                                    | 4.7 ± 6.5 (0.6–34.8) |
| Initial ECMO mode                                                       |                     |
| VV ECMO                                                                 | 86 (93.5%)          |
| VA ECMO                                                                 | 3 (3.3%)            |
| VAV ECMO                                                                | 1 (1.1%)            |
| Prone positioning within 24 h of ECMO initiation                        | 39 (42.4%)          |
| Mode of ventilation 2 h pre-ECMO                                        |                     |
| PC                                                                      | 14 (0.9%)           |
| VC                                                                      | 23 (1.5%)           |
| PRVC                                                                    | 17 (1.1%)           |
| SIMV                                                                    | 1 (0.1%)            |
| HFOV                                                                    | 1 (0.1%)            |
| Other                                                                   | 3 (0.2%)            |
| Mode of ventilation 72 h post-ECMO                                      |                     |
| PC                                                                      | 51 (55.4%)          |
| VC                                                                      | 25 (27.2%)          |
| PRVC                                                                    | 8 (8.7%)            |
| HFOV                                                                    | 1 (1.1%)            |
| CMV                                                                    | 1 (1.1%)            |
| Prone positioning after 72 h of ECMO initiation                         | 3 (3.3%)            |
| ECMO maximum (highest) blood flow, L/minute                             | 4.5 ± 0.8 (2–8)     |
| ECMO maximum (highest) sweep gas flow, L/minute                        | 6 ± 1.8 (3–10)      |
| Blood transfusion products used while patient was on ECMO              |                     |
| Packed red blood cells                                                  | 75 (81.5%)          |
| Fresh frozen plasma                                                     | 40 (43.5%)          |
| Platelets                                                               | 33 (35.8%)          |
| Cryoprecipitate                                                         | 14 (15.2%)          |
| Factor VII                                                              | 2 (2.2%)            |
| Tranexamic acid                                                         | 4 (4.3%)            |
| ECMO mode conversion data                                              |                     |
| Patient underwent conversion (change) of ECMO mode                      | 4 (4.3%)            |
| Mode of ECMO was changed (from-to)                                      |                     |
| VV to VAV                                                               | 1 (1.1%)            |
| VV to VA                                                                | 2 (2.2%)            |
| VAV to VV                                                               | 1 (1.1%)            |
In this prospective cohort study, we found that ECMO use as rescue therapy in patients with severe SARS-CoV-2 was associated with higher in-hospital mortality; lower COVID-19 virological cure; and longer hospitalization, ICU stay and mechanical ventilation use compared to non-ECMO group control offered the usual care. In addition, there was a high number of patients with septic shock and multiple organ failure; and more complications occurred at any time during hospitalization [pneumothorax, bleeding requiring blood transfusion, pulmonary embolism and gastrointestinal bleeding] in the ECMO group. However, PaO₂ was significantly higher in the 72-h post-ECMO initiation group and PCO₂ was significantly lower in the 72-h post-ECMO start group than those in the 12-h pre-ECMO group.

Extracorporeal membrane oxygenation has been used in Saudi Arabia for nearly 8 years [12]. Since the role of ECMO in the management of COVID-19 is unclear during the pandemic surge, the national coordinating center for the Saudi ECMO Program (KFSH&RC, Riyadh) registered with the ELSO; adapted to facilitate the systematic collection of new data in order to address lack of evidence on the benefit of ECMO intervention in COVID-19 treatment. However, there are many centers that are still not ELSO-registered, which makes it challenging to assess the actual global ECMO capacity and capability. Real-time data collection and sharing, establishing global biobanks, and nurturing an international collaborative research culture is crucial to rapidly identify populations at risk, the patients that stand to benefit from therapies such as ECMO.

ECMO use in respiratory failure for COVID-19 patients has been reported with variable survival rates [15, 19–23]. Reports from retrospective studies have suggested variable use, ranging from 1 to 52%, an observation that may reflect varying availability of ECMO equipment and experienced personnel [15, 19–23]. Patients included in the present study were among the first ones who have been treated with ECMO therapy for COVID-19-related ARDS in Saudi Arabia. At that time, use of ECMO as a rescue therapy in patients with COVID-19 was not supported [23]. Therefore, each health facility has adapted its own treatment policy based on a strict patient selection and the availability of this expensive therapy. The analysis of our data showed that ECMO was used in rather young...
Table 6  Comparison of ventilatory settings, arterial blood gas analyses and vital signs in the ECMO group (pre-ECMO and post-ECMO)

| Variable                  | 12-h before-ECMO initiation (n = 83) | 2-h before-ECMO initiation (n = 78) | 72-h after-ECMO initiation (n = 71) | 12-h before-ECMO removal (n = 67) | 2-h before-ECMO removal (n = 62) | p-value     |
|---------------------------|---------------------------------------|-------------------------------------|-------------------------------------|-----------------------------------|----------------------------------|-------------|
| Ventilatory settings      |                                       |                                     |                                     |                                   |                                  |             |
| Peak pressure, cmH₂O      | 34.2 ± 7.2 (15–45)                    | 35.4 ± 5.8 (19–45)                 | 30 ± 6 (10–50)                     | 29.7 ± 7.4 (5–51)                 | 32.1 ± 5.8 (15–50)              | 0.010*      |
| Plateau pressure, cmH₂O  | 30 ± 5.1 (17–38)                      | 30.4 ± 5.8 (17–41)                 | 26.6 ± 4.7 (10–38)                 | 26.5 ± 5.8 (15–41)                | 27.7 ± 6.8 (15–50)              | 0.214       |
| PEEP, cmH₂O              | 125 ± 2.9 (5–18)                      | 131 ± 2.6 (5–19)                   | 111 ± 3 (5–17)                     | 9.2 ± 2.8 (2–16)                  | 9.6 ± 3 (5–22)                  | 0.588       |
| FiO₂, %                  | 9.53 ± 10.8 (55–100)                  | 952 ± 12.2 (50–100)                | 54.8 ± 11.8 (30–110)               | 62.6 ± 25.5 (30–100)              | 669 ± 28.2 (30–100)             | 0.817       |
| Tidal volume, ml         | 4009 ± 50.6 (280–500)                 | 377 ± 74.3 (45–491)                | 266.2 ± 111.3 (10–531)             | 275 ± 142.7 (20–595)              | 290.8 ± 161.1 (2.8–625)         | 0.708       |
| ABG analyses             |                                       |                                     |                                     |                                   |                                  |             |
| pH in ABG                | 7.2 ± 0.13 (7–7.45)                   | 73 ± 0.12 (6.95–7.48)              | 73 ± 0.12 (7–7.6)                  | 73 ± 0.12 (7.1–7.5)               | 73 ± 0.15 (6.8–7.53)            | 0.514       |
| PaO₂ in ABG, mmHg        | 629 ± 15.7 (38.2–107)                 | 611 ± 17.7 (39–124)                | 74 ± 28 (34.2–79)                  | 71 ± 27.1 (36–177)                | 70 ± 26.3 (29–169)              | 0.002*      |
| PCO₂ in ABG, mmHg        | 618 ± 20.3 (33.7–126)                 | 668 ± 29.3 (29.3–150)              | 49.3 ± 13.7 (32–98)                | 50.3 ± 14.3 (22.4–106)            | 51 ± 15 (20.5–96)               | 0.042*      |
| HCO₃ in ABG, mEq/L       | 244 ± 5.9 (12.4–39)                   | 248 ± 5.9 (14.9–40)                | 24.5 ± 5.6 (6.3–34.8)              | 23.8 ± 6.4 (5.4–34.8)             | 23 ± 26.6 (5.2–35.1)            | 0.598       |
| Lactate in ABG, mmol/l   | 29.2 ± 5.9 (0.9–10.7)                 | 39 ± 6.7 (0.8–37.1)                | 3.7 ± 5 (0.7–21)                   | 3.8 ± 4.9 (0.6–18)                | 5.4 ± 6.6 (0.5–30)             | 0.398       |
| Vital signs              |                                       |                                     |                                     |                                   |                                  |             |
| Mean arterial pressure,  | 81.4 ± 13.7 (60–116)                  | 787 ± 14.4 (54–124)                | 76.1 ± 15.9 (43–133)               | 73 ± 12.1 (45–181)                | 715 ± 21.2 (33–145)            | 0.322       |
| mmHg                     |                                       |                                     |                                     |                                   |                                  |             |
| Heart rate, beats per    | 104.5 ± 20.7 (54–148)                 | 104 ± 22.6 (50–165)                | 103.1 ± 22.4 (53–158)              | 97.8 ± 23.2 (56–159)              | 91.1 ± 25.8 (34–133)           | 0.251       |
| minute                   |                                       |                                     |                                     |                                   |                                  |             |
| Central venous pressure, | 134 ± 4.5 (7–22)                      | 221 ± 31.5 (7–111)                 | 20.8 ± 13.4 (8.3–88)               | 13.1 ± 28.9 (2–280)              | 174 ± 21.5 (6–97)              | 0.293       |
| mmHg                     |                                       |                                     |                                     |                                   |                                  |             |

Data are presented as mean± SD (minimum–maximum), or number (%), unless otherwise indicated.

ABG arterial blood gas, ECMO extracorporeal membrane oxygenation, FiO₂ fraction of inspired oxygen, PaCO₂ partial pressure of carbon dioxide, PaO₂ partial pressure of oxygen, PEEP positive end-expiratory pressure, SD standard deviation.

*Represents significant differences
patients [about 24\% (n = 360) were aged 51–60 years, 19\% (n = 294) were aged 61–70 years and 16.7\% (n = 249) were aged 71 years and older] and without severe comorbidities [diabetes, hypertension, obesity (BMI $\geq$ 30 kg/m$^2$) and ischemic heart disease were the most common comorbidities in all study patients (52\%, 45\%, 41\% and 12\%, respectively)]. Therefore, these results should be viewed in light of a strict patient selection policy and may not be replicated in patients with advanced age or multiple comorbidities [24].

In patients with respiratory failure from SARS-CoV-2 infection who required the use of ECMO, the mortality rate varied considerably between studies ranging from 31 to $>$ 80\% [25–29]. We report a higher mortality rate (48.9\%) in severe SARS-CoV-2 patients treated with ECMO due to ARDS; compared to the rates reported by three studies in Paris, France (31\%) [25], Michigan, USA (< 40\%) [26], and an international study conducted in the Middle East and India (41.7\%) [29]. Nevertheless, we report a very similar and slightly lower survival rate (51.1\%) compared to the previous study done in the USA (53.8\%) [30], which was compatible to the data from the European branch of the Extracorporeal Life Support Organization international survey [31]. Very high mortality rates (>80\%) were reported in the earliest studies which investigated ECMO benefit for ARDS due to COVID-19 in China [28] and Europe [27]; however, most subsequent studies shown more promising results [20, 23, 25, 26, 29, 30, 32–38]. In our study, regional variation in hospital mortality is likely multifactorial and might be related to the initial burden of the pandemic in Saudi Arabia, which was greatest in Riyadh and Jeddah. The lack of association between potential COVID-19 therapeutics and survival, in particular steroids, which have been shown to reduce mortality in hospitalized patients [39] could be related to the extreme severity of illness in patients who underwent ECMO support; however, the efficacy of such regimens cannot be determined using our registry-based study design and with concurrent administration of multiple therapies. There was a large variation in mortality rates, which could be explained by differences in patients’ baseline characteristics and severity of illness. Another important factor is the center experience and volume of cases; this could have contributed to the variability in mortality rates with ECMO use. ECMO is a resource-intensive therapy requiring a multidisciplinary

### Table 7 Radiological data

|                     | 1st CT | 1st CT | 2nd CT | 2nd CT | 3rd CT | 3rd CT |
|---------------------|--------|--------|--------|--------|--------|--------|
|                     | Non-ECMO | ECMO | Non-ECMO | ECMO | Non-ECMO | ECMO |
| Chest CT findings of patient during the hospital admission | | | | | | |
| Ground glass opacity | 192 (13.8\%) | 20 (21.7\%) | 23 (1.7\%) | 1 (1.1\%) | 5 (0.4\%) | 0 |
| Crazy paving | 22 (1.6\%) | 2 (2.2\%) | 1 (0.1\%) | 1 (1.1\%) | 1 (0.1\%) | 0 |
| Multifocal infiltrate | 60 (4.3\%) | 14 (15.2\%) | 7 (0.5\%) | 1 (1.1\%) | 0 | 0 |
| Unilateral infiltrate | 6 (0.4\%) | 2 (2.2\%) | 1 (0.1\%) | 0 | 1 (1.1\%) | 0 |
| Pleural effusion | 34 (2.4\%) | 10 (10.9\%) | 4 (0.3\%) | 0 | 1 (1.1\%) | 0 |
| Pulmonary embolism | 16 (1.2\%) | 0 | 2 (0.1\%) | 1 (1.1\%) | 0 | 0 |
| Plum trunk | 1 (0.1\%) | 0 | 0 | 0 | 0 | 0 |
| Main plum artery | 1 (0.1\%) | 0 | 1 (0.1\%) | 0 | 0 | 0 |
| Segmental | 9 (0.6\%) | 0 | 0 | 0 | 0 | 0 |
| Subsegmental | 2 (0.1\%) | 0 | 1 (0.1\%) | 0 | 0 | 0 |
| Other | 68 (4.9\%) | 4 (4.3\%) | 9 (0.6\%) | 3 (0.2\%) | 0 | 0 |

|                     | 1st CT | 1st CT | 2nd CT | 2nd CT | 3rd CT | 3rd CT |
|---------------------|--------|--------|--------|--------|--------|--------|
|                     | Non-ECMO | ECMO | Non-ECMO | ECMO | Non-ECMO | ECMO |
| Chest X-ray findings of patient during ICU stay (from ICU admission until ICU discharge) | | | | | | |
| Consolidation present | 1183 (85.2\%) | 83 (90.2\%) | 804 (57.9\%) | 81 (88\%) | 337 (24.3\%) | 70 (76.1\%) | 177 (10.6\%) | 48 (52.2\%) |
| Consolidation absent | 86 (6.2\%) | 6 (6.5\%) | 78 (5.6\%) | 7 (7.3\%) | 66 (4.8\%) | 3 (3.3\%) | 64 (6.4\%) | 5 (5.4\%) |
| Not done within 24 h | 52 (3.7\%) | 3 (3.3\%) | 173 (11.5\%) | 5 (5.4\%) | 325 (23.4\%) | 6 (6.5\%) | 268 (26.5\%) | 12 (13\%) |
| Location of infiltrate | | | | | | |
| Unilateral | 45 (3.2\%) | 2 (2.2\%) | 26 (1.9\%) | 4 (4.3\%) | 13 (0.9\%) | 5 (5.4\%) | 5 (0.4\%) | 3 (3.3\%) |
| Bilateral | 1130 (81.4\%) | 72 (78.3\%) | 785 (55.3\%) | 67 (72.8\%) | 317 (22.8\%) | 57 (62\%) | 136 (9.8\%) | 37 (40.2\%) |

Data are presented as number (%) or mean (SD)

Percentages do not total 100\% owing to missing data
Table 8 Laboratory data

| Laboratory data of patients during ICU stay | Day 1 | Day 2 | Day 4 | Day 7 | Day 11 | Day 15 | Day 21 | Day 28 |
|--------------------------------------------|------|------|------|------|-------|-------|-------|-------|
| Hemoglobin level, g/dl                     | 12.3 (6.2) | 12.2 (14.9) | 12.8 (4.4) | 13.6 (3.9) | 14.1 (19.2) | 18.9 (27.5) | 12.6 (18.1) | 20 (29.4) |
| White blood cell count, x 10⁹/L            | 11.9 (34.3) | 14 (9.3) | 11 (8.2) | 13.6 (3.3) | 17.4 (8.9) | 14.6 (9.4) | 17 (8.9) | 13.3 (8.6) |
| Absolute lymphocyte count, x 10⁹/L         | 24 (163) | 2 (4.6) | 24 (324.5) | 16 (2.7) | 18 (6.6) | 2.3 (4.7) | 3.1 (28.3) | 1.9 (3.1) |
| Absolute neutrophil count, x 10⁹/L         | 13.3 (55.8) | 18.9 (22.1) | 12.2 (36.4) | 13.1 (11) | 11.1 (12) | 1.7 (4.3) | 1.3 (20.7) | 1.66 (13.6) |
| Platelets, x 10⁹/L                         | 253.5 (115) | 205.7 (100.7) | 288.6 (131.6) | 194 (106.6) | 309.4 (176.6) | 189 (101) | 280.4 (146.7) | 1528 (294) |
| Activated partial thromboplastin time, seconds | 41 (25.9) | 54.9 (42.9) | 44.1 (51.5) | 523 (258) | 43.1 (24.7) | 57.6 (33.5) | 498 (50.3) | 607 (72.2) |
| Prothrombin time, seconds                  | 16.6 (383) | 13.8 (2.7) | 16.2 (15.2) | 13.5 (2.7) | 15.2 (7.1) | 16.9 (18.2) | 15.2 (8.2) | 16 (7.1) |
| Fibrinogen, mg/dl                          | 161.2 (324.7) | 4.9 (4.3) | 171.6 (456.5) | 128 (484) | 137 (303.1) | 8.8 (30.2) | 177.5 (300.2) | 17 (474) |
| Aspartate transaminase, U/l                | 176.2 (1462.9) | 157.6 (510.1) | 114.5 (228.6) | 233.2 (998.7) | 94.5 (348.6) | 249.1 (1095.8) | 94.6 (259.3) | 1908 (704) |
| Alanine transaminase, U/l                  | 105.1 (438.4) | 86.4 (148.1) | 108.7 (198.4) | 1674 (221.2) | 92.7 (228.4) | 148.4 (361.2) | 78 (90.6) | 112 (171.9) |
| Bilirubin, mg/dl                           | 175 (69) | 25.1 (51.9) | 19.4 (30) | 489 (270) | 17.4 (39.9) | 59.4 (300) | 18.1 (31) | 25.7 (26) |
| Erythrocyte sedimentation rate, mm/hour    | 793 (414.7) | 63.5 (68.2) | 63.6 (39.5) | 65.5 (46) | 91.5 (204.9) | 44.8 (403.3) | 70.7 (41.4) | 41.6 (41) |
| Creatinine, mg/dl                          | 1463 (374.8) | 147.6 (176.8) | 155.4 (276) | 157.6 (179.1) | 151.8 (167) | 136.9 (121.7) | 162.7 (172.8) | 136.9 (142.4) |
| Lactate, mmol/l                            | 11 (548) | 51.4 (188.7) | 7.1 (44.8) | 2.1 (3.1) | 14.1 (87.9) | 43.4 (179.7) | 10.5 (70.5) | 24.7 (111.1) |
| Procalcitonin, ng/ml                       | 20.4 (171.4) | 24.4 (80.5) | 15.3 (98.4) | 19.8 (39) | 6.8 (48.1) | 53 (135) | 21.3 (197.4) | 6.7 (12.4) |

**Note:** All values are presented as mean (standard deviation).
|                           | Day 1              | Day 4              | Day 7              | Day 11             | Day 15             | Day 21             | Day 28             |
|---------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
|                           | Non-ECMO           | ECMO               | Non-ECMO           | ECMO               | Non-ECMO           | ECMO               | Non-ECMO           | ECMO               |
| Lactate dehydrogenase, U/l| 637.3 (827)        | 752.3 (675.6)      | 749.2 (3797.2)     | 1,094.2 (2570.4)   | 611 (564.2)        | 109.5 (2714.7)     | 578.2 (4163)       | 597.2 (359.8)      |
|                           | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               |
| C-reactive protein, mg/L  | 160.8 (327.6)      | 60.6 (77)          | 92.2 (1078)        | 357 (48)           | 73.5 (109.6)       | 47.1 (70)          | 74.1 (231.4)       | 126.6 (301)        |
|                           | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               |
| Troponin I, ng/ml         | 85 (53)            | 219.7 (1285.7)     | 31.7 (370.9)       | 12 (44)            | 31.9 (296.4)       | 3.9 (99)           | 5.4 (70.7)         | 87 (25.2)          |
|                           | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               |
| Troponin T, ng/ml         | 8.9 (35)           | 13.5 (20.6)        | 21.7 (75.2)        | 11.4 (224)         | 25 (87.4)          | 24.5 (32.3)        | 24.4 (55.3)        | 38.2 (335)         |
|                           | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               |
| hs-cTnT, ng/l             | 34 (46.1)          | 117.9 (219.5)      | 0.01 (0)           | 117.5 (219.7)      | 12 (16.9)          | 166.4 (284.6)      | 0.1 (0)            | 13 (101)           |
|                           | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               |
| Creatine kinase, U/l      | 643.5 (3404.3)     | 687.1 (1597.4)     | 640.4 (2285)       | 581 (1160)         | 506.8 (2107.5)     | 1,361.7 (57973)    | 447.6 (926)        | 408.4 (609)        |
|                           | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               |
| D-dimer, mg/l             | 30.3 (2308)        | 7 (9.8)            | 6.2 (35)           | 6.3 (7.4)          | 21.3 (44.7)        | 269.7 (1192)       | 32.2 (472)         | 166.1 (533.7)      |
|                           | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               |
| Ferritin, µg/L            | 1704 (4579.4)      | 1581.5 (2629)      | 2706.1 (22776)     | 1313.8 (2021.7)    | 2535.4 (23851)     | 2676.1 (11540.2)   | 1972.5 (9918)      | 991.8 (1279.7)     |
|                           | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               |
| NT-proBNP, (pg/ml)        | 2943.8 (9193.3)    | 2312.3 (2648)      | 1923.5 (7945)      | 6250 (13990)       | 2377 (6050)        | 4526 (6318.7)      | 1662.2 (2752)      | 3078 (5932)        |
|                           | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               |
| BNP, (pg/ml)              | 3407.6 (12,607.7)  | 446.7 (705.3)      | 387.9 (535.1)      | 1485 (3,361.7)     | 230.7 (147.2)      | 1398.1 (2804.2)    | 1406.9 (1899.4)    | 20 (29.4)          |
|                           | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               | (SD)               |

Data are presented as mean (SD)

BNP: brain natriuretic peptide, hs-cTnT: high-sensitivity cardiac troponin T test, NT-proBNP: terminal pro-B-type natriuretic peptide

RETRACTED ARTICLE
Table 9  Microbiological testing

| Cultures taken from patients on hospital admission till extubation and/or ICU discharge | 1st collection | 2nd collection | 3rd collection | 4th collection | 5th collection | 6th collection |
|---|---|---|---|---|---|---|
|  | Non-ECMO | ECMO | Non-ECMO | ECMO | Non-ECMO | ECMO | Non-ECMO | ECMO | Non-ECMO | ECMO | Non-ECMO | ECMO |
| Biospecimen type |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood | 735 (52.9) | 52 (56.5) | 3 (27.9) | 42 (45.7) | 233 (16.8) | 17 (18.5) | 166 (12) | 15 (16.3) | 95 (6.8) | 9 (9.8) | 60 (4.3) | 6 (6.5) |
| Respiratory culture or tracheal aspirate | 87 (63) | 2 (2.2) | 115 (8.3) | 10 (10.9) | 137 (9.9) | 12 (13) | 83 (6) | 10 (10.9) | 53 (3.8) | 8 (8.7) | 32 (2.3) | 3 (3.3) |
| Sputum | 118 (8.5) | 6 (6.5) | 82 (6.3) | 15 (16.3) | 76 (5.5) | 20 (21.7) | 28 (2) | 10 (10.9) | 13 (0.9) | 8 (8.7) | 6 (0.4) | 5 (5.4) |
| Urine | 222 (16) | 7 (7.6) | 6 (0.4) | 17 (18.5) | 210 (15.1) | 11 (12) | 83 (6) | 13 (14.1) | 34 (2.4) | 10 (10.9) | 34 (2.4) | 9 (9.8) |
| Bronchoalveolar lavage | 4 (0.3) | 1 (1.1) | 3 (0.2) | 4 (0.3) | 2 (2.2) | 3 (0.2) | 1 (1.1) | 0 | 0 | 0 | 0 | 0 |
| Result |  |  |  |  |  |  |  |  |  |  |  |  |
| Negative | 958 (69) | 39 (42.4) | 781 (56.2) | 34 (37) | 223 (16.1) | 18 (19.6) | 122 (8.8) | 11 (12) | 72 (5.2) | 13 (14.1) |  |  |
| Positive | 202 (14.5) | 53 (57.6) | 185 (13.3) | 39 (42.4) | 140 (10.1) | 31 (33.7) | 74 (5.3) | 24 (26.1) | 60 (4.3) | 10 (10.9) |  |  |
| Pathogen detected (if positive) |  |  |  |  |  |  |  |  |  |  |  |  |
| Gram-positive bacteria (no specific resistance pattern) | 41 (3) | 4 (4.3) | 22 (1.6) | 15 (1.1) | 18 (1.3) | 2 (2.2) | 5 (0.4) | 0 | 1 (0.1) | 0 |  |  |
| Vancomycin resistant enterococcus (VRE) | 3 (0.2) | 1 (1.1) | 3 (0.2) | 0 | 3 (0.2) | 0 | 1 (0.1) | 0 | 1 (0.1) | 0 |  |  |
| Methicillin-sensitive Staphylococcus aureus (MSSA) | 7 (0.5) | 2 (2.2) | 4 (0.3) | 1 (1.1) | 4 (0.3) | 1 (1.1) | 2 (0.1) | 0 | 1 (0.1) | 0 |  |  |
| Methicillin-resistant Staphylococcus aureus (MRSA) | 7 (0.5) | 3 (3.3) | 9 (0.6) | 0 | 2 (0.1) | 0 | 3 (0.2) | 0 | 1 (0.1) | 0 |  |  |
| Enterobacteriaceae (sensitive) | 5 (0.4) | 2 (2.2) | 5 (0.4) | 1 (1.1) | 6 (0.4) | 0 | 2 (0.1) | 2 (0.1) | 0 | 1 (1.1) |  |  |
| Enterobacteriaceae (ESBL) | 7 (0.5) | 2 (2.2) | 11 (0.8) | 3 (3.3) | 6 (0.4) | 2 (2.2) | 4 (0.3) | 1 (1.1) | 4 (0.3) | 1 (1.1) | 2 (0.1) | 0 |
| Enterobacteriaceae (CRE) | 6 (0.4) | 6 (6.5) | 3 (0.2) | 4 (4.3) | 7 (0.5) | 6 (0.4) | 2 (2) | 7 (0.5) | 5 (5.4) | 5 (5.4) | 0 |  |
| Enterobacteriaceae (MDR) | 2 (0.1) | 1 (1.1) | 8 (0.6) | 2 (2.2) | 3 (0.2) | 0 | 2 (0.1) | 1 (1.1) | 4 (0.3) | 1 (1.1) | 4 (0.3) | 0 |
| Enterobacteriaceae (XDR) | 0 | 0 | 1 (0.1) | 0 | 0 | 1 (0.1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Pseudomonas (Sensitive) | 9 (0.6) | 3 (3.3) | 7 (0.5) | 2 (2.2) | 14 (1) | 0 | 5 (0.4) | 4 (0.3) | 1 (1.1) | 1 (1.1) | 0 | 0 |
| Pseudomonas (MDR) | 3 (0.2) | 1 (1.1) | 3 (0.2) | 6 (0.6) | 8 (0.6) | 5 (5.4) | 3 (0.2) | 7 (0.6) | 3 (0.3) | 3 (3.3) | 1 (1) | 1 (1.1) |
| Pseudomonas XDR | 0 | 1 (1.1) | 0 | 1 (1.1) | 0 | 1 (0.1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Acinetobacter (sensitive) | 4 (0.3) | 1 (1.1) | 4 (0.3) | 1 (1.1) | 3 (0.2) | 0 | 3 (0.2) | 0 | 1 (0.1) | 0 | 0 | 0 |
| Acinetobacter (MDR) | 24 (1.7) | 6 (6.5) | 33 (2.4) | 9 (9.8) | 31 (2.2) | 8 (8.7) | 32 (2.3) | 3 (3.3) | 10 (0.7) | 1 (1.1) | 8 (0.6) | 5 (5.4) |
| Aspergillus | 3 (0.2) | 0 | 0 | 2 (0.1) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Candida | 43 (3.1) | 5 (5.4) | 48 (3.5) | 8 (8.7) | 62 (4.5) | 6 (6.5) | 29 (2.1) | 3 (3.3) | 18 (1.3) | 4 (4.3) | 17 (1.2) | 2 (2.2) |
| Other | 56 (4) | 26 (28.3) | 45 (3.2) | 18 (19.6) | 51 (3.7) | 15 (16.3) | 38 (2.7) | 12 (13) | 24 (1.7) | 9 (9.8) | 23 (1.7) | 3 (3.3) |

Data are presented as number (%)

CRE carbapenem-resistant Enterobacteriaceae, ECMO extracorporeal membrane oxygenation, ESBL extended-spectrum b-lactamase, ICU intensive care unit, MDR multidrug-resistant, XDR extensively drug-resistant
team of experienced medical professionals with training and expertise in initiation, maintenance, and discontinuation of ECMO in severely ill patients [40–43]. Adequate planning, thoughtful resource allocation, and training of personnel to provide complex therapeutic interventions while adhering to strict infection control measures are all essential components of an ECMO action plan.

ECMO cannot be blamed for the increased mortality; it is merely a tool and clinicians still need to understand when to use it for the greatest benefit [44]. Some studies have advocated the early initiation of ECMO therapy in intubated patients due to ARDS with severe SARS-CoV-2 for more efficacy [30, 32, 36, 37, 45]. Indeed, late ECMO initiation in patients with ARDS induced by SARS-CoV-2 who had been on ventilator for longer than 7 days demonstrated a 100% mortality in a small case-series study [30], therefore, prolonged pre-ECMO ventilation (≥ 7 days) was considered a contraindication for ECMO therapy in some institutions [46]. Initiation of ECMO beyond 7 days of mechanical ventilation seems to be acceptable in exceptional cases or when lung transplant is a possibility if lung recovery does not occur [47]. Earlier ECMO initiation is assumed to improve patient outcome in appropriately selected COVID-19 cases with ARDS and should be further investigated. Addressing this will require comparisons between early initiation and late initiation groups.

We noted a very high incidence of pneumothorax (29.3%) in the ECMO- group. Pneumothorax is frequent and fatal complication in severely ill SARS-CoV-2 patients with ARDS and; most likely associated with reduction of neuromuscular blocking agents use, recruitment maneuver, severe cough, changes of lung structure and function; despite the use of protective ventilation strategies [48]. Consistent with other studies [49, 50], a high rate of pulmonary embolism (15.2%) in SARS-CoV-2 patients receiving venovenous ECMO treatment was observed in the ECMO-patients despite an early increase of our anticoagulation targets for all the patients. High occurrence of thromboembolic events in SARS-CoV-2 patients receiving venovenous ECMO support suggests that other strategies, beyond systemic anticoagulation, are warranted to care for SARSCoV-2 induced lung endothelial injuries. In our study, septic shock was the primary cause of death in 18 (19.6%) of 92 patients but only three of them were converted to venoarterial or venoarterial–venous ECMO for cardiovascular support. Although relatively rare, conversion of VV ECMO to VA ECMO may be appropriate in selected COVID-19 patients [15, 21]. Use of these types of ECMO is proposed in patients with septic shock with severe myocardial dysfunction and decreased cardiac index [51, 52]. Adequacy of anticoagulation is even more critical during VA ECMO compared with VV ECMO therapy since arterial or intracardiac thromboembolic events have serious
table 10 Treatment outcomes in non-ECMO group vs ECMO group

| Variable                                | All (n = 1491) | Non-ECMO group (n = 1389) | ECMO group (n = 92) | p-value |
|-----------------------------------------|----------------|---------------------------|---------------------|---------|
| Discharge data                          |                |                           |                     |         |
| Microbiological cure (defined as 2 consecutive negative PCR samples for SARS-CoV-2) | 587 (39.4)     | 574 (41.3)                | 13 (14.1)           | 0.000*  |
| ICU discharge data                      |                |                           |                     |         |
| At 28 days of ICU stay, the patient was |                |                           |                     |         |
| Still in ICU, ventilated                | 81 (5.4)       | 49 (3.5)                  | 31 (33.7)           | 0.000*  |
| Still in ICU, not ventilated            | 27 (1.8)       | 24 (1.7)                  | 3 (3.3)             |         |
| Discharged from ICU                     | 1310 (87.9)    | 1251 (90.1)               | 59 (6.4)            |         |
| Hospital discharge data                 |                |                           |                     |         |
| Transferred to another facility         | 99 (6.6)       | 89 (6.4)                  | 10 (10.9)           | 0.000*  |
| Discharged home alive                   | 779 (52.3)     | 742 (53.4)                | 14 (15.3)           |         |
| Death                                   | 603 (40.4)     | 558 (40.2)                | 45 (48.9)           |         |
| Days of hospitalization                 | 20.8 ± 18.7 (1–152) | 20.2 ± 18.3 (1–152)    | 29.1 ± 20.9 (3–108) | 0.000*  |
| Days of patient’s stay in ICU           | 13.4 ± 13.8 (0–139) | 12.6 ± 13.2 (0–139)     | 26 ± 17.1 (3–95)    | 0.000*  |
| Days of mechanical ventilation          | 15 ± 16.5 (1–154) | 14.2 ± 16.5 (1–154)     | 22.4 ± 14.4 (2–92)  | 0.000*  |
| Days taken to be SARS-CoV-2 PCR-negative| 22.3 ± 12.9 (2–85) | 22.2 ± 13.1 (2–85)     | 22.2 ± 11.2 (6–46)  | 0.998   |

Data are presented as mean ± SD (minimum–maximum), or number (%), unless otherwise indicated.
COVID-19: coronavirus disease 2019, ECMO: extracorporeal membrane oxygenation, ICU: intensive care unit, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, SD: standard deviation.
* Represents significant differences.
Percentages do not total 100% owing to missing data.
consequences [52, 53]. ECMO is also frequently complicated by hemorrhage, necessitating daily transfusion of 2–5 units of packed red blood cells and 3–9 units of platelet concentrate to maintain normal hemoglobin levels, although massive blood transfusion (defined as > 10 units of packed red blood cells per day) was suggested [54].

It should be noted that many of our patients received favipiravir, tocilizumab, hydrocortisone, methylprednisolone remdesivir, lopinavir/ritonavir and antibiotics. Extensive use of antibiotics, especially in the ECMO group, can be reflected by the longer use of mechanical ventilation, risk of nosocomial infections and bacteremia or SARS-CoV-2 induced immuno-paralysis. Lack of well-defined management plan for COVID-19 disease results in the use of various treatment and adjuvant therapies in patients during hospital stay. Nonetheless, considering the high number and severity of bacterial co-infections previously reported in patients with SARS-CoV-2, initiation of antibiotic therapy for all hospitalized patients with COVID-19 is recommended [55, 56]. The approach of administering empiric antibiotic therapy solely to patients who were admitted for SARS-CoV-2 and who presented with a chest X-ray suggestive of bacterial infection, have a need for direct ICU admission, or are severely immunocompromised should be reconsidered [55, 56].

Limitation of the study
This study has few limitations. First, it is possible that there was selection bias in this study, even though ECMO placement was determined by a multidisciplinary team of physicians. Second, the follow-up was limited through November 30th, 2020, hindering the possibility of including all outcomes as some patients still remained hospitalized. Consequently, there may have been some partiality regarding the prognosis of the patients. Finally, some follow-up data were unavailable.

Conclusion
ECMO support might be an integral part of the critical care provided for COVID-19 patients in centers with advanced ECMO expertise, however, ECMO needs to be evaluated for benefits/risks on a case-by-case basis. We report a high mortality rate and unfavorable treatment outcomes in SARS-CoV-2 patients with ARDS who underwent ECMO, however, these findings need to be carefully interpreted, as most of our cohort patients were relatively old and had multiple severe comorbidities. Future randomized trials, although challenging to conduct, are highly needed to confirm or dispute reported observations.

Abbreviations
ABG: Arterial blood gas; ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; ECMO: Extracorporeal membrane oxygenation; FiO2: Fraction of inspired oxygen; ICU: Intensive care unit; MAP: Mean arterial blood pressure; PaCO2: Partial pressure of carbon dioxide; PaO2: Partial pressure of oxygen; PEEP: Positive end-expiratory pressure; RT-PCR: Reverse transcription-polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; VA: Venoarterial; VV: Venovenous.

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Authors’ contribution
SA, AA, AAR, XX and JA contributed equally to this article. SA, AA, AAR, and JA—Conceptualization, Methodological, Ethical approval, recruitment, data analysis, and manuscript preparation. Data collection was done by HA, AJA, HAA, SAA, JSA, AAM, MA, ZMA, AK, AAA and TS. All authors read and approved the final manuscript.

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Availability of data and materials
Data are available upon request, please contact author for data requests.

Declarations
Ethics approval and consent to participate
This study obtained approval from the King Fahad Medical City (KACST) [Approval Number Federal Wide Assurance NIH, USA: FWA00018774]. Ethics approval from the Saudi Ministry of Health ethics review board and from individual centers’ ethics boards were also obtained.

Consent for publication
All authors agreed to this publication.

Competing interests
The authors have no conflicts of interest to declare.

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33. Mustafa AK, Alexander PJ, Joshi DJ, Tabachnick DR, Cross CA, Pappas PS, Tatooles AJ. Extracorporeal membrane oxygenation for patients with COVID-19 in severe respiratory failure. JAMA Surg. 2020;155(10):990–2.

34. Osho AA, Momsamy P, Hibbert KA, Shelton KT, Trahanas JM, Attia RQ, Bloom JP, Omwohbufor MT, D’Alessandro DA, Villavicencio MA. Venovenous extracorporeal membrane oxygenation for respiratory failure in COVID-19 patients: early experience from a major academic medical center in North America. Ann Surg. 2020;272(2):e75.

35. Diaz RA, Graf J, Zambrano JM, Ruiz C, Espinoza JA, Bravo SI, Salazar PA, Bahamondes JC, Castillo LB, Gajardo AI. Extracorporeal membrane oxygenation for COVID-19-associated severe acute respiratory distress syndrome in Chile: a nationwide incidence and cohort study. Am J Respir Crit Care Med. 2021;204(1):34.

36. Giraud R, Legous D, Assouline B, De Charriere A, Decosterd D, Brunner ME, Moret-Bochatay M, Fumeaux T, Bendjelid K. Timing of VV-ECMO therapy implementation influences prognosis of COVID-19 patients. Physiol Rep. 2021;9(9):e14715.

37. Lebretton G, Schmidt M, Ponnaiah M, Folliguet T, Para M, Guilhaire J, Lansac E, Sage E, Cholley B, Mégarbane B. Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study. Lancet Respir Med. 2021;9(8):851–62.

38. Lorusso R, Combes A, Coco VL, De Piero ME, Belohlavek J. ECMO for COVID-19 patients in Europe and Israel. Intensive Care Med. 2021;47(3):544–8.

39. Infectious Diseases Society of America. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. 2021. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 25 Nov 2021.

40. Quintel M, Bartlett RH, Grocott MP, Combes A, Ranieri MV, Bacigalupo A, Nava S, Brodie D, Camporota L, Vasques F. Extracorporeal membrane oxygenation for respiratory failure. Anesthesiology. 2020;133(1):257.

41. Zochios V, Brodie D, Charlesworth M, Parhar K. Delivering extracorporeal membrane oxygenation for patients with COVID-19: what, when and how? Anaesthesia. 2020. https://doi.org/10.1111/anae.15094.

42. Ramanathan K, Antognini D, Combes A, Paden M, Zakhray B, Ogino M, MacLaren G, Brodie D, Shaker K. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic: experiences of the outbreak of emerging infectious diseases. Lancet Respir Med. 2020;8(5):S1–26.

43. MacLaren G, Fisher D, Brodie D. Preparing for the worst: critically ill patients with COVID-19: the potential role of extracorporeal membrane oxygenation. JAMA. 2020;323(11):1249–50.

44. Vuyyuru K. ECMO in COVID-19 does not blame the tool. Lancet. 2021;398(10307):1197.

45. Greco G, De Paolis R, Atturi P. Establishment and management of mechanical circulatory support during the COVID-19 pandemic. Circulation. 2020;142(21):2082–93.

46. Chanda A, Querey M, Markov NS, Kim S, Kunhara C, Garza-Castillon R, Manrique-Castellafard A, Tomic R, Politanska Y. Lung transplantation for patients with severe COVID-19. Sci Transl Med. 2020. https://doi.org/10.1126/scitranslmed.abl4282.

47. Wang K-h, Duan J, Han X, Liu X, Zhou J, Wang X, Zhu L, Mou H, Guo S. High incidence and mortality of pneumonia in critically ill patients with COVID-19: Heart Lung. 2020;50(1):37–43.

48. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, Merdji H, Clere-Jehl R, Schenck M, Gandet FF. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089–98.

49. Zuo Y, Zuo M, Yalavarthi S, Gockman K, Madison JA, Shi H, Woodard W, Lezak SP, Lugogo NL, Knight JS. Neutrophil extracellular traps and thrombosis in COVID-19. J Thromb Thrombolysis. 2020. https://doi.org/10.1007/s12359-020-02324-z.

50. Augustides JG. Cardiovascular consequences and considerations of coronavirus infection—perspectives for the cardiothoracic anesthesiologist and intensivist during the coronavirus crisis. J Cardiothorac Vasc Anesth. 2020;34(7):1713.

51. Hoyler MM, Flynn B, Jannaccone EM, Jones M-M, Ivascu NS. Clinical management of venoarterial extracorporeal membrane oxygenation. J Cardiothorac Vasc Anesth. 2020. https://doi.org/10.1053/j.jvca.2019.12.047.

52. Williams B, Bernstein W. Review of venoarterial extracorporeal membrane oxygenation and development of intracardiac thrombosis in adult cardiothoracic patients. J Extra Corpor Technol. 2017;48(4):169–71.

53. Koeckerling D, Pan D, Mudalige NL, Oyefeso O, Becker J. Blood transfusion strategies and ECMO during the COVID-19 pandemic. Lancet Respir Med. 2020;8(5):e40.

54. Alhumaid S, Al Mutair A, Al Alawi Z, Alshawi AM, Alomar A, Almuhanna MS, Almuslim AA, Bu SHAFA AH, Alotabi A, Ahmed GY. Coinfections with bacteria, fungi, and respiratory virus in patients with SARS-CoV-2: a systematic review and meta-analysis. Pathogens. 2021;10(7):809.

55. Garcia-Vidal C, Sanjuan G, Moreno-Garrido F, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, Fernandez-Pittol M, Priat C, Inciarte A, Bodro M. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a prospective cohort study. Clin Microbiol Infect. 2021;27(1):83–8.