Letter to the Editor

Age is an important prognostic factor in COVID-19 patients treated with extracorporeal membrane oxygenation

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Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection affecting multiple organs and may progress to severe acute respiratory distress syndrome (ARDS). In South Korea, the shortage of intensive care unit (ICU) and application of extracorporeal membrane oxygenation (ECMO) are increasing due to the recent rapid increase in the number of critically ill patients with COVID-19. ECMO has been used in ARDS and reduces the 60-day mortality compared to that with conventional management (1). In the meta-analysis by Combes *et al.*, 90-day mortality was significantly lower in the ECMO group than in the conventional management group [36% *vs.* 48%; relative risk 0.75; 95% confidence interval (CI): 0.6–0.94; P=0.013] (2). Mortality-related factors in ECMO include the age, malignancy, liver cirrhosis, ventilator setting [positive end-expiratory pressure (PEEP)], peak inspiratory pressure (PIP)], respiratory ECMO survival prediction (RESP) score, and predicting death due to severe ARDS on VV-ECMO (PRESERVE) score (3,4).

Age is highly correlated with ECMO prognosis (3-5). The meta-analysis by Ramanathan *et al.*, patients with COVID-19 who underwent ECMO showed that the duration, age, and body mass index were associated with mortality (6). Various scores have been used to predict the prognosis after ECMO initiation. However, despite the increasing application of ECMO due to COVID-19, whether the scoring system and age are helpful in predicting the prognosis of patients with COVID-19 who underwent ECMO is unclear. Therefore, we investigated the patients with COVID-19.

This is a single-center retrospective study on patients admitted at the 1200-bed tertiary academic hospital and ECMO referral center in South Korea. All data were obtained from electronic medical records. A total of 991 patients with COVID-19 hospitalized from January 2020 to December 2021 were included, excluding 952 patients (96.1%) who did not undergo ECMO. So, 39 patients (3.9%) who underwent ECMO were included in this study. The types of ECMO were venovenous in 31 patients (79.5%), venoarterial in five patients (12.8%), and venoarterial-venous in three patients (7.7%).

Reverse transcription-polymerase chain reaction analysis confirmed SARS-CoV-2 infection. ECMO was considered for patients with COVID-19 who worsened rapidly despite invasive mechanical ventilation (MV) and severe ARDS (PaO_2/FiO_2 ratio ≤100 mmHg), then their caregivers agreed to ECMO. The initiation of ECMO was decided

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by consulting with the internal medicine department, which supervised the patients, and cardiovascular surgeon, perfusionist, and intensivist who specialize in ECMO. The ECMO insertion was performed by a cardiovascular surgeon and heparin was administered as an anticoagulant. The mortality risk factors were analyzed using the multivariate Cox proportional hazards model.

Among patients who underwent ECMO, 13 patients (33.3%) survived, and 26 patients (66.7%) did not. The non-survivors were older than the survivors [69.0 (65.3–73.5) *vs.* 49.0 (42.5–63.0) years, P<0.001] but there was no difference in the clinical frailty scale. Additionally, there was no difference for comorbidities; however, hypertension was more common in non-survivors (69.2% *vs.* 15.4%, P=0.002) (*Table 1*). There were no significant differences in the initial vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), laboratory data (white blood cell, hemoglobin, platelet, total bilirubin, albumin, blood urea nitrogen, creatinine, and C-reactive protein), and radiologic findings (unilateral, bilateral, and multifocal involvement of COVID-19).

There was no statistical difference in the use of remdesivir, antibiotics, and steroids for treatment; however, vasopressors (84.6% *vs.* 53.8%, P=0.048) and continuous renal replacement therapy (38.5% *vs.* 0%, P=0.010) were frequently used, and tocilizumab (7.7% *vs.* 38.5%, P=0.018) was less used in non-survivors. There was no difference in the application of PEEP, PIP, neuromuscular blockade, and prone position with MV treatment before ECMO (*Table 1*).

The patients' scores before ECMO for Acute Physiology and Chronic Health Evaluation (APACHE) II score [27.0 (21.0–30.0) *vs.* 18.0 (16.5–21.5), P=0.012], PRESERVE score [5.0 (4.0–6.0) *vs.* 4.0 (1.0–5.0), P=0.023], and score by Roch *et al.* (7) [4.0 (2.0–4.0) *vs.* 3.0 (2.0–3.0), P=0.040] were higher in the non-survivor group than in the survivor

Table 1 Baseline characteristics, treatment and clinical outcomes of COVID-19 patients who underwent ECMO

Variables	All patients (n=39)	Survivor (n=13)	Non-survivor (n=26)	P value
Age (years)	66.0 (55.0–72.0)	49.0 (42.5–63.0)	69.0 (65.3–73.5)	<0.001
Male, n (%)	23 (59.0)	6 (46.2)	17 (65.4)	0.250
Body mass index (kg/m^2)	27.1 (24.4–29.8)	25.2 (23.4–28.6)	27.7 (25.0–30.9)	0.267
Clinical frailty scale	3.0 (2.0–3.0)	2.0 (1.5–3.0)	3.0 (2.0–3.0)	0.190
Comorbidity, n (%)				
Hypertension	20 (51.3)	2 (15.4)	18 (69.2)	0.002
DM	16 (41.0)	3 (23.1)	13 (50.0)	0.107
COPD	1 (2.6)	1 (7.7)	0 (0)	0.152
Heart failure	4 (10.3)	0 (0)	4 (15.4)	0.135
Liver cirrhosis	1 (2.6)	0 (0)	1 (3.8)	0.474
Chronic kidney disease	1 (2.6)	0 (0)	1 (3.8)	0.474
Malignancy	4 (10.3)	1 (7.7)	3 (11.5)	0.709
Treatment, n (%)				
Remdesivir	24 (61.5)	9 (69.2)	15 (57.7)	0.485
Antibiotics	31 (79.5)	9 (69.2)	22 (84.6)	0.262
Vasopressor	29 (74.4)	7 (53.8)	22 (84.6)	0.048
CRRT	10 (25.6)	0 (0)	10 (38.5)	0.010
Steroid	38 (97.4)	12 (92.3)	26 (100.0)	0.152
Tocilizumab	7 (17.9)	5 (38.5)	2 (7.7)	0.018

Table 1 (*continued*)

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Variables	All patients (n=39)	Survivor (n=13)	Non-survivor (n=26)	P value
Treatment applied before ECMO				
Invasive MV	39 (100.0)	13 (100.0)	26 (100.0)	>0.999
Duration of MV before ECMO (days)	2.0 (0.0–8.0)	0.0 (0.0–3.0)	3.5 (1.0–9.5)	0.010
PIP of MV	28.0 (25.0–31.0)	28.0 (23.0–31.5)	28.5 (26.0–31.3)	0.642
PEEP of MV	10.0 (10.0–12.0)	10.0 (10.0–11.5)	10.0 (10.0–12.0)	0.177
P/F ratio	75.0 (64.0–87.4)	77.0 (61.0–104.0)	71.0 (63.0–82.3)	0.201
Neuromuscular blockade	36 (92.3)	12 (92.3)	24 (92.3)	>0.999
Prone position	2 (5.1)	2 (15.4)	0 (0)	0.105
Duration of ECMO	12.0 (9.0–26.0)	11.0 (9.0–17.5)	14.5 (8.0–34.8)	0.145
Length of hospital stay (days)	33.0 (23.0–49.0)	33.0 (24.0–66.0)	33.0 (22.3–48.3)	0.282

Data are presented as median (interquartile range) or number (%) unless otherwise indicated. COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; MV, mechanical ventilation; PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; P/F ratio; PaO_2/FiO_2 ratio; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen.

group. The RESP score [1.5 (0.0–3.3) *vs.* 4.0 (3.0–7.0), P<0.001] was lower in the non-survivor group than in the survivor group. The sequential organ failure assessment (SOFA) score [12.0 (8.0–15.0) *vs.* 10.0 (8.5–11.0), P=0.118] showed no statistical difference between the two groups.

A comparison of the area under the curve for age and scoring system to predict the overall prognosis of patients with ECMO were as follows: age, 0.902 (95% CI: 0.805–0.999), APACHE II score, 0.741 (95% CI: 0.571–0.912), SOFA score, 0.651 (95% CI: 0.474–0.828), RESP score, 0.132 (95% CI: 0.020–0.244), PRESERVE score, 0.709 (95% CI: 0.541–0.877), and score by Roch *et al.*, 0.691 (95% CI: 0.519–0.862). The optimal cutoff point for age was 65 years (sensitivity, 76.9%; specificity, 100%).

The in-hospital mortality predictors using multivariate Cox regression analysis were the old age (≥65 years) [odds ratio (OR), 7.614; 95% CI: 1.066–54.393; P=0.043] and RESP score (OR, 0.487; 95% CI: 0.263–0.900; P=0.022). However, the APACHE II, SOFA, PRESERVE, and Roch *et al.* scores did not show statistical significance.

In this study, old age (≥65 years) was significantly associated with the prognosis of patients with COVID-19 who underwent ECMO and RESP score was associated with in-hospital mortality. Moreover, patients who underwent ECMO for COVID-19 have similar characteristics to those who underwent ECMO at ARDS. ECMO is usually performed in patients with severe ARDS, and prognosis is related to the experience of the ECMO center (8,9). Additionally, several scoring systems attempt to predict the patient's prognosis and appropriately apply ECMO according to the patient's financial burden and center's workload. Previously, age has been shown to be an important prognostic factor in ECMO studies conducted in South Korea (5) and COVID-19 (6,10). However, whether the age and scoring system are better prognosis predictors for patients with COVID-19 who have received ECMO is unclear. Although this study was conducted in a limited number of patients and single center, it revealed that age is an important factor related to the prognosis of ECMO. We recommend determining ECMO treatment by considering age with the RESP score in situations of ICU shortage and lack of critical care resources.

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Footnote

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