Peer Review File

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Reviewer A

In this research letter, the authors identified age as an important prognostic factor for non-survival. This conclusion is highly plausible, but the authors should address the following issues:

Comment 1: Age is virtually always an important prognostic factor in any critical condition, but it is not modifiable. What is the importance of this finding?

Reply 1: Thank you for your comments. Age is not a modifiable factor, but I think it will be important when we start thinking about whether to start ECMO or not. These results are expected to be helpful in determining which patient group should be applied when ECMO devices are limited.

Comment 2: The initial analysis was comparing survivors and non-survivors, but then in AUC finding it appears to be assessing age in prediction of non-survival in ECMO recipients. Please state clearly in each analysis that whether survivors are compared with non-survivors as a whole, or only in those receiving ECMO therapy.

Reply 2: Thank you for your comments. As commented by reviewer, we revised the manuscript as below.

Revised manuscript (Line 47-49)

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%).

Comment 3: The authors should focus on either survivors vs non-survivors for patients receiving MV, or for patients receiving ECMO. From the title, I guess the latter would be the authors' intention.

Reply 3: Thank you for your comments. The author revised the manuscript to focus on survivors versus non-survivors of patients receiving ECMO.

Revised manuscript (Line 47-49)

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%).

Reviewer B

Comment 1: Line 14-16: i would like to suggest adding the review by Combes on VV ECMO

Combes A, Peek GJ, Hajage D, Hardy P, Abrams D, Schmidt M, Dechartres A, Elbourne D. ECMO for severe ARDS: systematic review and individual patient data meta-analysis. Intensive Care Med. 2020 Nov;46(11):2048-2057. doi: 10.1007/s00134-020-06248-3. Epub 2020 Oct 6. PMID: 33021684; PMCID: PMC7537368.

Reply 1: Thank you for your comments. As commented by reviewer, we revised the manuscript as below.

Revised manuscript (Line 31-34)

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].

REFERENCES:

1. Munshi L, Walkey A, Goligher E, Pham T, Uleryk EM, Fan E. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. Lancet Respir Med 2019;7:163-72. eng.

2. Combes A, Peek GJ, Hajage D, Hardy P, Abrams D, Schmidt M, et al. ECMO for severe ARDS: systematic review and individual patient data meta-analysis. Intensive Care Med 2020;46:2048-57. eng.

3. Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, et al. Predicting

survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. Am J Respir Crit Care Med 2014;189:1374-82. eng.

4. Schmidt M, Zogheib E, Rozé H, Repesse X, Lebreton G, Luyt CE, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Intensive Care Med 2013;39:1704-13. eng.

Comment 2：In the introduction more emphasis should be placed on which is true for COVID-19 ARDS and 'non'COVID ARDS.

Reply : Thank you for your comments. As commented by reviewer, we revised the manuscript as below.

Revised manuscript (Line 38-43)

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.

REFERENCES:

3. Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, et al. Predicting

survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. Am J Respir Crit Care Med 2014;189:1374-82. eng.

4. Schmidt M, Zogheib E, Rozé H, Repesse X, Lebreton G, Luyt CE, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Intensive Care Med 2013;39:1704-13. eng.

5. Baek MS, Chung CR, Kim HJ, Cho WH, Cho YJ, Park S, et al. Age is major factor for predicting survival in patients with acute respiratory failure on extracorporeal membrane oxygenation: a Korean multicenter study. J Thorac Dis 2018;10:1406-17. eng.

6. Ramanathan K, Shekar K, Ling RR, Barbaro RP, Wong SN, Tan CS, et al. Extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis. Crit Care 2021;25:211. eng.

Comment 3: line 20: stating is age is an known important factor is too strong when only supporting this with 1 retrospective study. Please add additional evidence for this statment. Possibly ref 7-9?

Reply 3: Thank you for your comments. As commented by reviewer, we revised the manuscript as below.

Revised manuscript (Line 38)

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.

REFERENCES:

3. Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. Am J Respir Crit Care Med 2014;189:1374-82. eng.

4. Schmidt M, Zogheib E, Rozé H, Repesse X, Lebreton G, Luyt CE, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Intensive Care Med 2013;39:1704-13. eng.

5. Baek MS, Chung CR, Kim HJ, Cho WH, Cho YJ, Park S, et al. Age is major factor for predicting survival in patients with acute respiratory failure on extracorporeal membrane oxygenation: a Korean multicenter study. J Thorac Dis 2018;10:1406-17. eng.

6. Ramanathan K, Shekar K, Ling RR, Barbaro RP, Wong SN, Tan CS, et al. Extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis. Crit Care 2021;25:211. eng.

Comment 4: Line 25-26 please specify type of hospital; are you in an ECMO referral center? since 33% of the patients qualified for ECMO.

Reply 4: Thank you for your comments. ECMO was performed in 3.9% of hospitalized patients and 33% of those who applied invasive mechanical ventilation. In addition, our hospital is an ECMO referral center, and this was additionally mentioned in the manuscript. As commented by reviewer, we revised the manuscript as below.

Revised manuscript (Line 45-46)

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%).

Comment 5: Line 26-28 please state the criteria which applied for the decision to put patients on ECMO. Where patients denied ECMO in the pandemic?

Reply 5: Thank you for your comments. As commented by reviewer, we revised the manuscript as below.

Revised manuscript (Line 53-57)

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 and severe ARDS (PaO_2/FiO_2 ratio $\leq$100 mmHg), then their caregivers agreed to ECMO. The initiation of ECMO was decided 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 Cox proportional hazards model.

Comment 6: Do the authors think that age was used as selection criterium in the pandemic in

their center?

Reply 6: Thank you for your comments. Our hospital has a total of 5 ECMO devices, and it was sufficient to apply the ECMO devices to patients who needed them. However, when there was a patient who needed ECMO but the hospital did not have the equipment, the ECMO equipment borrowed through another hospital or a thoracic surgery society. The age of the patient prior to initiation of ECMO application was one of the factors considering ECMO initiation.

Comment 7: Line 34: is the CFS validated in a population < 65 years?

Reply 7: Thank you for your comments. The Clinical frailty scale and other scales to assess frailty have been used in younger patients. Limited evidence suggests that frailty measures have predictive validity in younger populations in a recent analysis [1]. However, other studies in COVID-19 hospitalized patients (younger and older patients) have also used the clinical frailty scale, and frailty scale was associated with patient outcomes [2].

REFERENCES

1. Spiers GF, Kunonga TP, Hall A, Beyer F, Boulton E, Parker S, et al. Measuring frailty in younger populations: a rapid review of evidence. BMJ Open 2021;11:e047051. eng.

2. Hewitt J, Carter B, Vilches-Moraga A, Quinn TJ, Braude P, Verduri A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health 2020;5:e444-e51. eng.

Comment 8: Line 38: which percentage received steroids?

Reply 8: Thank you for your comments. As commented by reviewer, we revised the table as below.

Revised manuscript

Table. 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
Treatment (%)				
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

Comment 9: Line 40: can you explain the low use of tocilizumab in the severe ARDS population?

Reply 9: Due to Korea's medical insurance system, approval work was required for tocilizumab to be used in the hospital. In addition, in Korea, patient did not pay 100% of the cost of treatment for COVID-19 in this country, but in the case of tocilizumab, the patient had to pay 100% of the cost to administer it. Therefore, there were cases that tocilizumab could not be administered because patient consent could not be obtained. This seems to have contributed to the low use of tocilizumab.

Comment 10: How long was the duration of MV prior the initiation of ECMO?

Reply 10: Before the initiation of ECMO, the duration of MV was 2.0 (0.0 – 8.0) days, and for survivors and non-survivors, [0.0 (0.0 – 3.0) vs. 3.5 (1.0 – 9.5), p = 0.010].

Revised manuscript

Table. 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
Treatment applied before ECMO				
Invasive MV	39 (100.0)	13 (100.0)	26 (100.0)	> 0.999
Duration of MV before ECMO	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)	1.000
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

Comment 11: What was the ECMO duration?

Reply 11: Duration of ECMO was 12.0 (9.0 – 26.0) days in the all group.

in the survivor and non-survivor groups, the duration of ECMO was [11.0 (9.0 – 17.5) vs 14.5 (8.0 – 34.8), p = 0.145] days.

Revised manuscript

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

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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

Comment 12: Line 70-74; how can age be both an important factor and stating that little is known about age. Please explain this for me. Maybe I missed the nuance in this statement.

Reply 12: We are sorry for the confusion. We believe that research is needed to determine which of the age or scoring systems is better predictive of mortality. As commented by reviewer, we revised the manuscript as below.

Revised manuscript (Line 100-102)

Previously, age has been shown to be an important prognostic factor in ECMO studies conducted in South Korea [3] and COVID-19 [4-6]. However, whether the age and scoring system are better prognosis predictors for patients with COVID-19 who have received ECMO is unclear.

REFERENCES:

3. Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. Am J Respir Crit Care Med 2014;189:1374-82. eng.

4. Schmidt M, Zogheib E, Rozé H, Repesse X, Lebreton G, Luyt CE, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Intensive Care Med 2013;39:1704-13. eng.

5. Baek MS, Chung CR, Kim HJ, Cho WH, Cho YJ, Park S, et al. Age is major factor for

predicting survival in patients with acute respiratory failure on extracorporeal membrane oxygenation: a Korean multicenter study. J Thorac Dis 2018;10:1406-17. eng.

6. Ramanathan K, Shekar K, Ling RR, Barbaro RP, Wong SN, Tan CS, et al. Extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis. Crit Care 2021;25:211. eng.

Reviewer C

The authors retrospectively analyzed 115 patients with severe COVID-19 who were treated with mechanical ventilation. 39 out of the 115 patients (33.9%) were treated with ECMO.

After ECMO treatment, 13 patients survived and the 26 patients did not.

After their analysis, they found that RESP score is an optimal scoring system for predicting survival or death in ECMO-treated patients with severe COVID-19.

RESP score (DOI: 10.1164/rccm.201311-2023OC) was developed by Matthieu Schmidt et.al to predict survival for patients receiving ECMO for respiratory failure.

The authors' findings further proved that RESP score is a useful tool for predicting survival in respiratory failure.

Comment 1: However, I have one suggestion. It is better to add a baseline clinical characteristic table that includes age, malignancy, liver cirrhosis, ventilator setting, and other related factors and compare these factors between the survivals and nonsurvivors.

Reply 1: Thank you for your comments. As commented by reviewer, we revised the Table as below.

Revised manuscript

Table. 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	66.0 (55.0 – 72.0)	49.0 (42.5 – 63.0)	69.0 (65.3 – 73.5)	<0.001
Male (%)	23 (59.0)	6 (46.2)	17 (65.4)	0.250
Body mass index	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 (%)				
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 (%)				
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
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Tocilizumab	7 (17.9)	5 (38.5)	2 (7.7)	0.018

Reviewer D

This manuscript describes a retrospective, single-center observational study to investigate the factors to predict the prognosis of COVID-19 patients with ECMO.

The authors concluded that age and RESP score were the important prognostic factors. Some of the observations of this study are interesting, but there are several concerns in this study that the authors need to clarify. My detailed comments follow.

Comment 1: A more detailed description of the Methods is required. Your study design, a retrospective, single-center observational study, should be clearly stated. And what was the inclusion and exclusion criteria? Did the authors include all COVID-19 patients with ECMO during the study period? Also, it seems that the authors compared survivors and non-survivors of COVID-19 patients with ECMO to investigate the prognostic factor using univariate and multivariate analysis, though not clearly stated.

Reply 1: Thank you for your comments. As commented by reviewer, we revised the manuscript as below.

Revised manuscript (Line 52-59)

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 and severe ARDS (PaO_2/FiO_2 ratio ≤100 mmHg), then their caregivers agreed to ECMO. The initiation of ECMO was decided 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.

Comment 2: The authors included not only patients with VV-ECMO but also with VA-ECMO and VAV-ECMO. Though, the etiology among these patients was quite different. I believe authors should re-analyze only patients with VV-ECMO. Otherwise, using RESP score and PRESERVE score was inappropriate since these were prediction scores for patients with VV-ECMO.

Reply 2: Thank you for your comments. Although the ECMO mode was different, ECMO was implemented as ARDS due to COVID-19. In addition, it appears that ECMO application was required because P/F ratio of 75.0 (64.0 – 87.4) mmHg before ECMO application was low. In addition, in studies on other ECMOs [3,4,6], in addition to VV ECMO, an analysis was performed including patients who underwent VA and VAV ECMO, so even if there is a slight difference in etiology, it is not expected that the results will be significantly affected.

Comment 3: A more detailed description of the Results is required. Specifically, which factors in vital signs, laboratory data, and radiologic findings were analyzed? Also, the authors stated, "There was no difference in the application of positive end expiratory pressure, peak inspiratory pressure, neuromuscular blockade, and prone position with MV treatment before ECMO", but what were the specific values of these components? These data are important to know the severity of the patients and facility proficiency.

Reply 3: Thank you for your comments. We have added detailed information to the manuscript and table. As commented by reviewer, we revised the manuscript as below.

Revised manuscript

Additionally, there was no difference for comorbidities; however, hypertension was more common in non-survivors (69.2% vs. 15.4%, p=0.002)(Table). 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).

Table. 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
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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	36 (92.3)	12 (92.3)	24 (92.3)	1.000

blockade				
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

Reviewer E

The authors investigated the prognostic impact of age in patients with COVID-19 receiving ECMO in the draft entitled "age is an important prognostic factor in COVID-19 patients treated with extracorporeal membrane oxygenation". They performed ROC analyses and multivariable analyses to demonstrate the association between age and mortality following ECMO use in patients with COVID-19.

Comment 1: It is well known that age is associated with mortality in patients using ECMO and in patients with COVID-19, respectively. It might not be so surprising that age was associated with mortality in patients with COVID-19 and ECMO. Consistently, ECMO use is not encouraged in the elderly patients with COVID-19 in many institutes. The novelty of this study is unclear.

Reply 1: Thank you for your valuable comments. Age is a well-known mortality-associated risk factor in patients with COVID-19 and ECMO. In the absence of ECMO, it is recommended not to apply ECMO to elderly COVID -19 patients, but it is not well-known that there are few studies comparing age and scoring system after applying ECMO to the elderly COVID-19 patients. Therefore, this manuscript which compared the results of applying ECMO in the

elderly COVID-19 patients, may be helpful in deciding whether to start ECMO in elderly COVID-19 patients.

Comment 2: There are three major modes of ECMO: VV, VA, and VA-V, which might have affected their findings.

Reply 2: Thank you for your comments. Although the ECMO mode was different, ECMO was implemented as ARDS due to COVID-19. In addition, it appears that ECMO application was required because P/F ratio of 75.0 (64.0 – 87.4) mmHg before ECMO application was low. In addition, in studies on other ECMOs [3,4,6], in addition to VV ECMO, an analysis was performed including patients who underwent VA and VAV ECMO, so even if there is a slight difference in etiology, it is not expected that the results will be significantly affected.

REFERENCES

3. Baek MS, Chung CR, Kim HJ, Cho WH, Cho YJ, Park S, et al. Age is major factor for predicting survival in patients with acute respiratory failure on extracorporeal membrane oxygenation: a Korean multicenter study. J Thorac Dis 2018;10:1406-17. eng.

4. Ramanathan K, Shekar K, Ling RR, Barbaro RP, Wong SN, Tan CS, et al. Extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis. Crit Care 2021;25:211. eng.

5. Nesseler N, Fadel G, Mansour A, Para M, Falcoz PE, Mongardon N, et al. Extracorporeal Membrane Oxygenation for Respiratory Failure Related to COVID-19: A Nationwide Cohort Study. Anesthesiology 2022 2022/03/30 [Epub]. http://doi.org/10.1097/aln.0000000000004168. eng.

6. Barbaro RP, MacLaren G, Boonstra PS, Iwashyna TJ, Slutsky AS, Fan E, et al.

Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. Lancet 2020;396:1071-8. eng.

Reviewer F

Comment 1: First of all, I would like to express my gratitude for the opportunity to review this valuable paper. This study evaluated the performance of various scores to predict prognosis in COIVD-19 patients undergoing ECMO in South Korea.The study has some concerns regarding the presentation of background information and the methods of statistical analysis, which the authors need to correct.

Reply 1: Thank you for your comment. I will do my best to write a paper in the current situation of COVID-19.

Comment 2: First, the background of the cases is not adequately described. The study should clearly dictate the source of information. I could not understand this study was based on what information such as single-center or multi-center, registry study, etc.

Reply 2: Thank you for your comments. As commented by reviewer, we revised the manuscript as below.

Revised manuscript (Line 45-47)

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.

Comment 3: The time period in which case information was collected includes the early stages of the COVID-19 pandemic, and information regarding the diagnosis of COVID-19 should be presented. Information on the tools used for diagnoses, such as PCR and rapid antigen testing, should be provided, if available.

Reply 3: Thank you for your comments. As commented by reviewer, we revised the manuscript as below.

Revised manuscript (Line 52)

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 and severe ARDS (PaO_2/FiO_2 ratio ≤100 mmHg), then their caregivers agreed to ECMO.

Comment 4: For some indicators in the text, it was unclear what they are. For example, the clinical frailty scale. Also, it should be clearly stated what exactly authors compared with "comorbidity for other diseases," "initial vital signs," "laboratory data," "radiologic findings," and so on.

Reply 4: Thank you for your comments. We added these to the manuscript and table. As commented by reviewer, we revised the manuscript as below.

Revised manuscript (Line 64-68)

Additionally, there was no difference for comorbidities; however, hypertension was more common in non-survivors (69.2% vs. 15.4%, p=0.002)(Table). 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).

Table. 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	66.0 (55.0 – 72.0)	49.0 (42.5 – 63.0)	69.0 (65.3 – 73.5)	<0.001
Male (%)	23 (59.0)	6 (46.2)	17 (65.4)	0.250
Body mass index	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 (%)				
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

Comment 5: The authors applied multivariate analysis to predict prognosis in COVID-19

patients undergoing ECMO according to various scoring systems. Six variables seemed to be introduced for 39 patients on ECMO. However, the number of patients was not sufficient for this multivariate analysis, and the results may include underestimation or overestimation. I do not think that multivariate analysis should be applied to this study. In addition, age was introduced into the analysis besides various scoring systems, but the reason for selecting this variable was unclear. Furthermore, it isn't easy to interpret whether each score was introduced as continuous variables or pre-calculated cut-off values.

Reply 5: Thank you for your comments. In the ROC curve, age was most valuable factor for prognosis of COVID-19 patient with ECMO. The optimal cut-off points for the age were 65 (sensitivity 76.9%, specificity 100%). So, we use the age over 65years in the cox regression analysis. Although age and most of the scoring systems were useful, multivariate analysis was performed to find the most meaningful among them. Multivariate analysis values are shown in the table below. We consulted with the Department of Statistics for statistical evaluation.

Table 4. Univariate and multivariate risk factors associated with in hospital mortality

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age ≥ 65years	18.333	3.150 – 106.703	0.001	7.614	1.066 – 54.393	0.043
APACHE II score	1.158	1.023 – 1.312	0.021	1.083	0.909 – 1.291	0.371
SOFA score	1.201	0.951 – 1.516	0.123			
RESP score	0.436	0.256 – 0.742	0.002	0.487	0.263 – 0.900	0.022
PRESERVE score	1.534	1.032 – 2.279	0.034	0.707	0.368 – 1.360	0.299

Score by Roch et al.	2.190	1.011 – 4.747	0.047	0.814	0.162 – 4.079	0.802

As commented by reviewer, we revised the manuscipt as below.

Revised manuscript

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.

Comment 6: Finally, some English expressions in the text may not be natural, and the authors should consider having them professionally proofread.

Reply 6: Thank you for your comments. We performed English proofreading with the help of a web site that specializes in English editing.

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Editing Certificate

This document certifies that the manuscript listed below has been edited to ensure language and grammar accuracy and is error free in these aspects. The edit was performed by professional editors at Editage, a division of Cactus Communications. The sections titled tables and references were not edited by Editage upon the author's request.

The author's core research ideas were not altered during the editing process. Editage guarantees the quality of editing with the assumption that our suggested changes have been accepted and the edited text has not been altered without the knowledge of our editors.

MANUSCRIPT TITLE

Age Is an Important Prognostic Factor in COVID-19 Patients Treated with Extracorporeal Membrane Oxygenation

AUTHORS

Song-I Lee, Da Hyun Kang, Hong Joon Ahn, Mi Joo Kim, Man-Shik Shim, Jeong Eun Lee

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May 25, 2022

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THE EDITAGE Promise QUALITY GUARANTEE

Vikas Narang

Vikas Narang
Chief Operating Officer - Editage

Reviewer G

In this paper, the authors review their covid ecmo outcomes for a small cohort of 39 outcomes. In this series, the present a survival of only 33%. to their credit, they attempted to support many older patients with ecmo and found that these patients had a higher mortality. anecdotally, this has been our experience in the united states as well and we do not offer ecmo to covid patients over the age of 60 as the survival is extremely low.

Comment 1: I do think this letter would benefit by more clearly delineating the ages of the cohort - maybe a box plot showing min, max, median, interquartile range, and mean age. i would also tone down the complex statistics - there is a no way a cohort of this size can support it

Reply 1: Thank you for your comments. However, only one figure or table can be attached in Letter to the editor. So, we decided to insert a table that can show the overall contents. We are sorry that we couldn't show additional details summarized with figure. In addition, we consulted with the Department of Statistics for statistical evaluation.

Reviewer H

Comment 1: Needs careful statistical editing and language editing.

Reply 1: Thank you for your comments. We performed English proofreading with the help of a web site that specializes in English editing.

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