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ORIGINAL ARTICLE

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Association of obesity paradox with prognosis of veno-venous-extracorporeal membrane oxygenation in patients with coronavirus disease 2019

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Abstract

Aim: Although the obesity paradox is known for various diseases, including cancer and acute respiratory distress syndrome, little is known about veno-venous extracorporeal membrane oxygenation (VV-ECMO) in patients with coronavirus disease 2019 (COVID-19). In this study, we aimed to investigate the association between body mass index (BMI) and prognosis in critical patients with COVID-19 requiring VV-ECMO.

Methods: We conducted a retrospective observational single-center study at Yokohama City University Civic General Medical Center between March 2020 and October 2021. Participants were patients with COVID-19 who required VV-ECMO. They were classified into two groups: BMI ≤30 kg/m^2 and >30 kg/m^2.

Results: In total, 23 patients were included in the analysis, with a median BMI of 28.7 kg/m^2. Overall, 22 patients were successfully weaned from the ECMO. When comparing the two groups, there was a trend toward fewer days from onset to ECMO induction in the BMI >30 kg/m^2 group. Moreover, the two groups had a similar prognosis. There were no statistically significant differences in the number of days from onset to hospitalization or the duration of ECMO induction between the groups.

Conclusion: VV-ECMO induction for patients with COVID-19 may lead to earlier indications in patients with BMI >30 kg/m^2 than in those with BMI ≤30 kg/m^2.

KEYWORDS
acute respiratory distress syndrome, body mass index, coronavirus disease 2019, obesity paradox, veno-venous-extracorporeal membrane oxygenation

INTRODUCTION

According to the World Health Organization (WHO), overweight and obesity are defined as the accumulation of abnormal or excessive fat that poses health risks. Thus, the risk of obesity-related diseases, such as diabetes and chronic renal failure, increases with the progression of obesity.[1] Patients with hypertension, diabetes, and obesity have been reported to be susceptible to severe respiratory failure due to coronavirus disease 2019 (COVID-19).[2,3] By contrast, a paradoxical phenomenon called the obesity paradox has been reported in diseases such as acute respiratory distress syndrome (ARDS)[4] and cancer,[5] in which patients with obesity have a better prognosis than patients with a normal body mass index (BMI). In diseases with obesity paradox, a J-shaped correlation between BMI and prognosis is often observed, suggesting that moderate obesity itself may be protective compared with patients who are normal or severely obese; however, the mechanism remains not fully understood.[6] Reports showed that obesity has no effect on the mortality of

patients undergoing veno-venous extracorporeal membrane oxygenation (VV-ECMO) for severe respiratory failure,[7] and in Europe, patients with obesity with a BMI >30 kg/m^2 may have a better prognosis than patients with a BMI <30 kg/m^2 undergoing ECMO for COVID-19;[8] however, it is unclear whether a similar trend is observed in Japan. In this study, we aimed to investigate the relationship between BMI and prognosis in patients receiving VV-ECMO for COVID-19.

METHODS

Study setting

We retrospectively examined the association between ECMO withdrawal and BMI in patients who underwent VV-ECMO for COVID-19 at Yokohama City University Civic General Medical Center between March 2020 and October 2021.

We collected medical information, including age, sex, BMI, medical history, Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Respiratory ECMO Survival Prediction (RESP) score, Murray score, and whether or not patients received remdesivir (200 mg/day on day 1 only, 100 mg/day on days 2–10), dexamethasone (6.6 mg/day), unfractionated heparin (10,000 units/day on days 2–10), and supine therapy (at least 16 h). Data on the fraction of inspiratory oxygen (FiO_2), positive end-expiratory pressure (PEEP), maximum airway pressure, and arterial blood gas findings were also collected within 6 h before ECMO induction.

Primary and secondary outcomes

The primary outcome was death during the induction of ECMO. The secondary outcomes were the duration of ECMO and the number of days from onset to hospitalization, hospitalization to endotracheal intubation, onset to endotracheal intubation, endotracheal intubation to ECMO induction, and onset to ECMO induction.

The participants were divided into two groups based on the WHO definition of obesity[9]: BMI ≤30 kg/m^2 and BMI >30 kg/m^2 (Figure 1).

Clinical workflow and disease staging

Ventilator management was limited to a maximum PEEP of 15 cmH_2O, and airway pressure did not exceed 30 cmH_2O. The lung protection strategy aimed at a tidal volume of 6–8 mL/kg, and deep sedation and muscle relaxants were used if the patient presented with large excess breaths. If computed tomography showed a strong image of pneumonia on the dorsal side and PaO_2/FiO_2 (P/F) was below 200, the patient was placed in the prone position. VV-ECMO was introduced when oxygenation could not be maintained despite

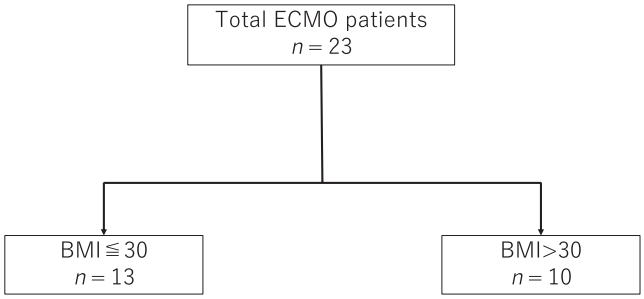

FIGURE 1 Patient flow diagram. BMI, body mass index.

the aforementioned respiratory management. The indications for VV-ECMO were as follows: patients with hypoxemia with FiO_2 ≥0.8 and P/F <100, respiratory acidosis with pH ≤7.2 and plateau pressure >32 cmH_2O, Murray score >3, or in the prone position despite treatment intervention for the original disease, lung protection strategy + high PEEP strategy and prone therapy, and poor response to therapy (Figure 2).

Statistical analysis

The distribution of each variable in the two groups, classified according to BMI, was compared. The Mann–Whitney *U* test was used for continuous variables, and Fisher exact test was used for categorical variables. All statistical analyses were performed using JMP version 16 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $p < 0.05$.

RESULTS

In total, 23 patients were included in the analysis (Appendix S1). The included patients were 57 [51–61] (median [interquartile range]) years old, 17 (74%) were male, BMI was 28.7 [26.5–36.2] kg/m^2, SOFA score was 10 [8–12], APACHE score was 22 [19–26], Murray score was 3.3 [3.0–3.5], and RESP score was 2 [1–4]. Remdesivir, dexamethasone, unfractionated heparin, and supine therapy were administered to 14 (61%), 18 (78%), 23 (10%), and 10 (41.6%) patients, respectively.

Onset to hospitalization was 5 [4–9] days, hospitalization to endotracheal intubation was 1 [0–3] days, onset to endotracheal intubation was 7 [6–10] days, endotracheal intubation to ECMO induction was 3 [0–5] days, onset to ECMO induction was 12.5 [7.3–15.0] days, and ECMO duration was 10.0; 2 (8.3%) patients died during ECMO induction (Table 1).

Comparison of two groups classified according to BMI

The included patients were divided into two groups: BMI ≦30 kg/m^2 ($n = 13$) and BMI >30 kg/m^2 ($n = 10$). As

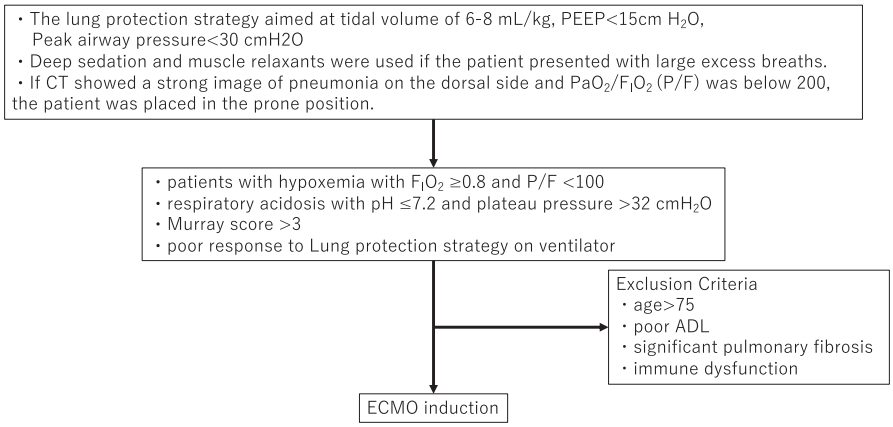

FIGURE 2 ECMO induction criteria. ADL, activities of daily living; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; P/F ratio, PaO_2/FiO_2 ratio; PEEP, positive end-expiratory pressure.

for the patients' background, age was 57 versus 56.5 years ($p = 0.83$) in the BMI ≦30 kg/m^2 and BMI >30 kg/m^2 groups, BMI was 26.5 kg/m^2 versus 36.5 kg/m^2 ($p < 0.001$), and sex (male) was 69% versus 80% ($p = 0.66$). As for the prognostic score, SOFA score was 8 versus 10 ($p = 0.43$), APACHE II score was 20 versus 23 ($p = 0.13$), Murray score was 3.3 versus 3.2 ($p = 0.68$), RESP score was 2 versus 2.5 ($p = 0.90$), with no statistical difference between the two groups. The time from onset to admission, 5 versus 5.5 days ($p = 0.87$); from admission to intubation, 3 versus 0.5 days ($p = 0.23$); from onset to intubation, 8 versus 6.5 days ($p = 0.30$); from intubation to ECMO, 4 versus 2 days ($p = 0.17$); from onset to ECMO, 14 versus 8 days ($p = 0.07$); and ECMO duration, 12 versus 8 days ($p = 0.14$). As a treatment, 53.9% versus 70% ($p = 0.67$) received remdesivir, 100% versus 100% received unfractionated heparin, 76.9% versus 80% ($p = 1.00$) received dexamethasone, and 53.9% versus 40% ($p = 0.68$) were received prone position therapy. For ventilator or respiratory status within 6 h before ECMO, FiO_2 was 0.8 versus 1.0 ($p = 0.06$), PEEP was 15 versus 15 cmH_2O ($p = 0.95$), maximum airway pressure 26 versus 30 cmH_2O ($p = 0.22$), P/F ratio 70.8 versus 60 ($p = 0.39$), pH 7.40 versus 7.32 ($p = 0.19$), and partial pressure of carbon dioxide (pCO_2) 55.1 versus 67.9 mmHg ($p = 0.14$). There was no statistical difference in patients' history of preexisting medical conditions: 54% versus 70% had hypertension ($p = 0.66$), 38% versus 70% had diabetes ($p = 0.21$), 31% versus 40% had dyslipidemia ($p = 0.69$), 15% versus 0% had coronary artery disease ($p = 0.48$), 0% versus 10% had chronic lung disease ($p = 0.43$), 8% versus 10% had chronic kidney disease ($p = 1.00$), and 0% versus 10% had immunosuppression ($p = 0.43$). Two patients died in the group with BMI <30 kg/m^2 because of pulmonary fibrosis (ECMO duration was 56 days); another reason was sepsis (ECMO duration was 16 days; Table 2).

There were no statistically significant differences between the two groups in terms of age, sex, SOFA, APACHE, Murray, and RESP scores, whether patients received remdesivir, dexamethasone, unfractionated heparin, or the percentage of patients receiving supine therapy. Moreover, there were no statistically significant differences in PEEP, maximum airway pressure, P/F ratio, pH, or pCO_2 within 6 h before ECMO induction. There was no statistically significant difference in ECMO survival and withdrawal rates between the two groups. However, 100% survival and withdrawal rates were achieved in the group with BMI >30 kg/m^2.

The number of days from disease onset to ECMO induction tended to be shorter in the BMI >30 kg/m^2 group. There were no statistically significant differences between the two groups in terms of the number of days from onset to hospitalization, hospitalization to endotracheal intubation, onset to endotracheal intubation, intubation to ECMO induction, and ECMO duration (Table 2).

DISCUSSION

In this study, patients with severe respiratory failure due to COVID-19 and in the BMI >30 kg/m^2 group required earlier ECMO induction compared with those in the BMI ≤30 kg/m^2 group. In addition, inhaled oxygen concentrations before ECMO tended to be higher in the BMI >30 kg/m^2 group than in the BMI ≤30 kg/m^2 group.

A prospective observational cohort study by Daviet et al.[8] consisting of 76 patients with COVID-19 requiring ECMO showed that a higher BMI was a positive independent factor for 90-day survival, with better outcomes in the BMI >30 kg/m^2 than in the BMI ≤30 kg/m^2 group. Moreover, the study reported that the time from intensive care unit admission to endotracheal intubation and the time from intensive care unit admission to ECMO were significantly shorter in the BMI >30 kg/m^2 group than in the BMI ≤30 kg/m^2 group.[8] Mongero et al.[9] reported a shorter time from diagnosis to ECMO in the good prognosis group than in the poor prognosis group. This study cites the involvement of specific respiratory mechanics in patients with obesity, such as decreased chest wall compliance, increased intra-abdominal pressure, and decreased lung volume, as reasons for the earlier induction of ECMO. In our study, the number of days from onset to ECMO

TABLE 1 Patients' characteristics.

Characteristics	All patients ($N=23$), median (interquartile range)/frequency (%)
Patient background	
Age (years)	57.0 (51.0–61.0)
Male	17 (74)
BMI (kg/m^2)	28.7 (26.5–36.2)
Comorbidities	
Hypertension	14 (60.8)
Diabetes	12 (52.2)
Dyslipidemia	8 (34.8)
Coronary artery disease	2 (8.7)
Chronic lung disease	1 (4.3)
Chronic kidney disease	2 (8.7)
Chronic liver disease	0 (0)
Immunosuppression	1 (4.3)
Metastatic solid tumor	0 (0)
Scores	
SOFA score	10 (8–12)
APACHE score	22 (19–26)
Murray score	3.3 (3.0–3.5)
RESP score	2 (1–4)
Within 6 h before ECMO	
FiO_2	1.0 (0.8–1.0)
PEEP	15 (13–15)
Maximum airway pressure	30 (26–30)
P/F ratio	69.5 (48.9–75.4)
pH	7.38 (7.27–7.42)
pCO_2	58.4 (48.9–72.8)
Treatment	
Remdesivir	14 (61)
Dexamethasone	18 (78)
Unfractionated heparin	23 (100)
Prone position	11 (42)
Disposition	
Onset to admission (days)	5 (4–9)
Admission to intubation (days)	1 (0–3)
Onset to intubation (days)	7 (6–10)
Intubation to ECMO (days)	3 (0–5)
Onset to ECMO (days)	12 (7–15)
ECMO duration (days)	10 (8–18)
Death	2 (8)

Abbreviations: APACHE score, Acute Physiology and Chronic Health Evaluation Score; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspiratory oxygen; P/F ratio, PaO_2/FiO_2 ratio; pCO_2, partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; RESP score, Respiratory ECMO Survival Prediction score; SOFA score, Sequential Organ Failure Assessment score.

induction tended to be fewer in the BMI >30 kg/m^2 than in BMI ≤30 kg/m^2 group, corroborating the results of previous studies.

In the present study, there was no statistically significant difference in ECMO duration or mortality between the BMI >30 kg/m^2 and BMI ≤30 kg/m^2 groups. Obesity has been reported to be a risk factor for severe COVID-19,[3] while patients with obesity have been reported to have a similar or better prognosis in ARDS cases with COVID-19 using ECMO compared with patients with normal weight,[8,10] which is similar to the results of the present study.

The mechanism of the obesity paradox in ARDS remains unclear; however, several possibilities have been reported. One possibility is due to decreased inflammatory cytokines in patients with obesity. A study of peripheral blood from 1409 patients with acute lung injury reported an inverse relationship between high BMI and levels of inflammatory cytokines, such as interleukin-6 and interleukin-8, and surfactant protein D.[11]

Another possibility is the hypothesis that ventilatory management difficulties in patients with obesity lead to early introduction of ECMO and early implementation of a thorough lung protection strategy. Patients with ARDS with BMI >25 kg/m^2 have been shown to have lower pulmonary compliance due to decreased thoracic compliance compared with patients with BMI ≤25 kg/m^2.[12] Patients with obesity may have difficulty with ventilatory management as a result of thoracic restrictive mechanics even with less severe lung parenchyma, resulting in an earlier introduction of ECMO. Lowering drive pressure during ventilatory management of patients with ARDS has been reported to reduce mortality,[13] and the use of higher drive pressure during ECMO induction for ARDS has been associated with increased mortality.[14] In a report comparing patients on ventilatory management for COVID-19 ARDS in three groups (BMI <25 kg/m^2, 25 ≤ BMI ≤ 30 kg/m^2, and BMI >30 kg/m^2), the higher BMI group required higher drive pressures and showed decreased pulmonary compliance.[15] These findings suggest that early introduction of ECMO results in lower driving pressure and less ventilator-related lung injury, which may explain the favorable prognosis of patients with obesity with early introduction of ECMO. This hypothesis has been discussed in several studies.[16–18] Thus, we believe that the introduction of ECMO for respiratory failure in patients with obesity should not be withheld because of obesity itself.

By contrast, the use of ECMO in patients with respiratory failure requires significant medical resources[19] and prognosis may vary greatly depending on the balance between medical supply and demand,[20] and depression and decreased sexual activity have been reported[21] as 1-year outcomes for patients with COVID-19 on ECMO, so its use should be carefully considered.

This study has certain limitations. This was a single-center, retrospective study; therefore, selection bias may have been present, and caution should be exercised when generalizing these findings. Moreover, the sample size was limited and the statistical power may have been inadequate. Future studies should be conducted in a multicenter setting, with a large number of participants.

TABLE 2 Comparison of patients' information classified according to BMI.

Patient information	BMI ≦30 kg/m^2 (n = 13)	BMI >30 kg/m^2 (n = 10)	p value
Patient background			
Age	57 (51.5–60)	56.5 (49–62.25)	0.83
Male	9 (69)	8 (80)	0.66
BMI (kg/m^2)	26.5 (24.3–28.7)	36.5 (33.2–40.5)	<0.001
Comorbidities			
Hypertension	7 (54)	7 (70)	0.66
Diabetes	5 (38)	7 (70)	0.21
Dyslipidemia	4 (31)	4 (40)	0.69
Coronary artery disease	2 (15)	0 (0)	0.48
Chronic lung disease	0 (0)	1 (10)	0.43
Chronic kidney disease	1 (8)	1 (10)	>0.99
Chronic liver disease	0 (0)	0 (0)	—
Immunosuppression	0 (0)	1 (10)	0.43
Metastatic solid tumor	0 (0)	0 (0)	—
Scores			
SOFA score	8 (8–12)	10 (7.75–13)	0.43
APACHE score	20 (18–23)	23 (19.75–28.75)	0.13
Murray score	3.3 (2.8–3.6)	3.2 (3.0–3.6)	0.68
RESP score	2 (1.5–3.5)	2.5 (1–4.5)	0.90
Within 6 h before ECMO			
FiO_2	0.8 (0.75–1.0)	1.0 (0.975–1.0)	0.06
PEEP	15 (12.5–15.5)	15 (14.25–15)	0.95
Maximum airway pressure	26 (25–30)	30 (26.5–32.5)	0.22
P/F ratio	70.8 (48.9–94.3)	60 (51.5–73.3)	0.39
pH	7.40 (7.33–7.49)	7.32 (7.25–7.41)	0.19
pCO_2	55.1 (49.2–82.1)	67.9 (56.7–98.9)	0.14
Treatment			
Remdesivir	7 (53.9)	7 (70)	0.67
Dexamethasone	10 (76.9)	8 (80)	1.00
Unfractionated heparin	13 (100)	10 (100)	—
Prone position	7 (53.9)	4 (40)	0.68
Disposition			
Onset to admission (days)	5 (4–9.5)	5.5 (3–8.5)	0.87
Admission to intubation (days)	3 (0–4)	0.5 (0–2.25)	0.23
Onset to intubation (days)	8 (6–12)	6.5 (5.75–10)	0.30
Intubation to ECMO (days)	4 (2–5)	2 (0–4.5)	0.17
Onset to ECMO (days)	14 (9.5–16.5)	8 (6.5–13)	0.07
ECMO duration (days)	12 (8–25)	8 (7.5–12)	0.14
Death	2 (15.4)	0 (0)	0.48

Note: Data presented as median (interquartile range) or frequency (%).

Abbreviations: APACHE score, Acute Physiology and Chronic Health Evaluation Score; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspiratory oxygen; P/F ratio, PaO_2/FiO_2 ratio; pCO_2, partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; RESP score, Respiratory ECMO Survival Prediction score; SOFA score, Sequential Organ Failure Assessment score.

CONCLUSION

In the case of VV-ECMO induction for COVID-19, patients with BMI >30 kg/m^2 may have received earlier induction than those with BMI ≤30 kg/m^2. Failure of early ventilatory management leads to the early introduction of ECMO, reduction of ventilator-related lung injury, and early implementation of a thorough lung protection strategy.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest for this article.

DATA AVAILABILITY STATEMENT

Data requests should be made to the corresponding author.

ETHICS STATEMENT

Approval of the research protocol: The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution, and it conforms to the provisions of the Declaration of Helsinki (Committee of the Yokohama City University Medical Center, Approval Number B200200049).
Informed consent: All informed consent was obtained from the subject(s) and/or guardian(s).
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

CONSENT FOR PUBLICATION

Written informed consent was obtained from patients for the publication of this case report and the relevant images. A copy of the written consent is available for review by the Editor-in-Chief of Acute Medicine and Surgery.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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