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# Impact of BMI on outcomes in respiratory ECMO: an ELSO registry study

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## Abstract

**Purpose:** The impact of body mass index (BMI) on outcomes in respiratory failure necessitating extracorporeal membrane oxygenation (ECMO) has been poorly described. We aimed to assess: (i) whether adults with class II obesity or more ( $\text{BMI} \geq 35 \text{ kg/m}^2$ ) have worse outcomes than lean counterparts, (ii) the form of the relationship between BMI and outcomes, (iii) whether a cutoff marking futility can be identified.

**Methods:** A retrospective analysis of the Extracorporeal Life Support Organization (ELSO) Registry from 1/1/2010 to 31/12/2020 was conducted. Impact of  $\text{BMI} \geq 35 \text{ kg/m}^2$  was assessed with propensity-score (PS) matching, inverse propensity-score weighted (IPSW) and multivariable models (MV), adjusting for a priori identified confounders. Primary outcome was in-hospital mortality. The form of the relationship between BMI and outcomes was studied with generalized additive models. Outcomes across World Health Organisation (WHO)-defined BMI categories were compared.

**Results:** Among 18,529 patients,  $\text{BMI} \geq 35 \text{ kg/m}^2$  was consistently associated with reduced in-hospital mortality [PS-matched: OR: 0.878(95%CI 0.798–0.966),  $p = 0.008$ ; IPSW: OR: 0.899(95%CI 0.827–0.979),  $p = 0.014$ ; MV: OR: 0.900(95%CI 0.834–0.971),  $p = 0.007$ ] and shorter hospital length of stays. In patients with  $\text{BMI} \geq 35 \text{ kg/m}^2$ , cardiovascular (17.3% versus 15.3%), renal (37% versus 30%) and device-related complications (25.7% versus 20.6%) increased, whereas pulmonary complications decreased (7.6% versus 9.3%). These findings were independent of confounders throughout PS-matched, IPSW and MV models. The relationship between BMI and outcomes was non-linear and no cutoff for futility was identified.

**Conclusion:** Patients with obesity class II or more treated with ECMO for respiratory failure have lower mortality risk and shorter stays, despite increased cardiovascular, device-related, and renal complications. No upper limit of BMI indicating futility of ECMO treatment could be identified. BMI as single parameter should not be a contra-indication for respiratory ECMO.

**Keywords:** Extracorporeal membrane oxygenation, Obesity, Body mass index, Respiratory failure

## Introduction

Obesity is prevalent in up to 20% of critically ill patients [1]. Obesity compromises long-term health and survival due to increased cardiovascular disorders, metabolic diseases, cancer, and other health problems [2]. Management of critically ill obese patients poses specific challenges [3]. Also, obese patients have an increased risk of

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developing acute respiratory distress syndrome (ARDS) [4] and other respiratory problems [3].

Extracorporeal membrane oxygenation (ECMO) is an established treatment for patients with severe, potentially reversible respiratory failure, not responding to conventional treatment [5]. Hence, clinicians are increasingly confronted with potential ECMO indications in obese patients. ECMO is an invasive, high resource-demanding technology associated with complications [6]. Severely obese patients may challenge the risk–benefit balance because of anticipated difficulties with cannulation and reaching sufficient blood flows.

In overweight and moderately obese critically ill patients, lower mortality was reported compared to patients with normal weight, despite increased complications. This contra-intuitive finding is labeled the ‘obesity paradox’ [1]. Data on complications and outcomes of respiratory ECMO in extreme obesity are confined to small case series with limited numbers of patients in the upper body mass index (BMI) range and variable cutoffs in analyses. Most studies did not identify obesity as risk factor for poor outcomes, though data are inconsistent [7–20]. Given the paucity of data, hesitancy to consider ECMO in daily care of these patients persists [21]. This reluctance is translated into recent ELSO guidelines, considering BMI > 40 kg/m<sup>2</sup> as a relative contraindication for ECMO in patients affected by coronavirus disease 2019 (COVID-19) [22].

We aimed to assess whether adults with class II obesity or more (BMI ≥ 35 kg/m<sup>2</sup>) treated with ECMO for respiratory failure have worse outcomes and experience more complications than patients with BMI < 35 kg/m<sup>2</sup>. We evaluated the form of the relationship between BMI and outcomes to evaluate whether a cutoff for futility can be identified.

## Methods

### Data source

We queried the international ELSO registry [23], including data on primary diagnosis for ECMO and comorbidities based on the International Classification of diseases 9th and 10th (ICD9/10) revision. Patient and ECMO characteristics [24], treatments, complications, and outcomes are entered in dedicated fields. As data are de-identified, the Clinical Trial Center UZLeuven waived the need for local Ethical Committee approval.

### Patients

Adults (age ≥ 18 years) receiving ECMO for respiratory failure from 1/1/2010 to 31/12/2020 were eligible. Exclusion criteria involved other than first runs, pregnancy-related runs, and runs with missing data on height or weight. Patients were dichotomized at BMI ≥ 35 kg/m<sup>2</sup>,

## Take-home message

This large and multi-center registry study shows that patients with obesity class II or more (body mass index (BMI) ≥ 35 kg/m<sup>2</sup>) undergoing extracorporeal membrane oxygenation for respiratory failure have decreased mortality risk and decreased hospital length of stay, despite an increased risk of cardiovascular, device-related, and renal complications. The association between BMI and these outcomes is non-linear and no upper limit of BMI indicating futility was identified.

and further stratified according to groups as defined by the World Health Organisation (WHO): underweight (BMI < 18.5 kg/m<sup>2</sup>), normal weight (BMI 18.5–25 kg/m<sup>2</sup>), overweight (BMI 25–30 kg/m<sup>2</sup>), class I (BMI 30–35 kg/m<sup>2</sup>), class II (BMI 35–40 kg/m<sup>2</sup>) or class III obesity (> 40 kg/m<sup>2</sup>); the last group was further divided into three subgroups (BMI 40–50 kg/m<sup>2</sup>, 50–60 kg/m<sup>2</sup>, > 60 kg/m<sup>2</sup>). Extreme values (BMI < 12 kg/m<sup>2</sup> and > 70 kg/m<sup>2</sup>) were excluded [25].

### Outcomes

Primary outcome was in-hospital mortality. Secondary outcomes included ECMO duration, reason for discontinuation, complications (device-related, hemorrhagic, neurological, renal, cardiovascular, pulmonary, infectious, metabolic, limb), hospital length of stay and discharge destination (Supplemental Table 1).

### Confounders

Analyses were corrected for literature search-based, a priori-selected variables [26], including demographics, comorbidities, admission characteristics, and pre-ECMO variables and treatments, associated with outcomes in respiratory ECMO and recorded in the ELSO registry (Supplemental Table 2). These included gender, age, primary diagnosis, pre-ECMO variables (respiratory rate, PO<sub>2</sub>/FiO<sub>2</sub>, peak inspiratory pressure, positive end-expiratory pressure (PEEP), pH, PCO<sub>2</sub>, HCO<sub>3</sub>, lactate, mean blood pressure), pre-ECMO treatments and characteristics (renal replacement therapy, nitric oxide, prone ventilation, neuromuscular blocking agents, vasopressors/inotropes, bicarbonate, corticosteroids, cardiac arrest, bridge-to-transplantation), ECMO characteristics (cannulation type, transport on ECMO), and year of ECMO. As the number of eligible patients before 2016 was small, these were grouped. Primary diagnoses were categorized into viral pneumonia, non-viral pneumonia, trauma/burn, chemical/aspiration, asthma, pulmonary embolism/pulmonary hypertension, lung transplant complications, unspecified ARDS/acute respiratory failure and other (Supplemental Table 3) [27, 28]. Comorbidities and co-existent conditions, including associated infection,

chronic respiratory and cardiac disease, and immunosuppressive condition, were identified as previously (Supplemental Table 4) [27, 28]. MP and GH independently reviewed ICD-9/10 codes and discrepancies were resolved by discussion.

### Statistics

Descriptives included mean and standard deviation for continuous variables, median and interquartile range for time variables, and numbers and percentages for categorical variables. Analyses were performed using R software (4.0.3) (see online supplement). *p* values were considered statistically significant if two-sided *p* values  $\leq 0.05$ .

### Association between class II obesity or more and outcomes

To assess impact of class II obesity or more (BMI  $\geq 35$  kg/m<sup>2</sup>) on outcomes, we adjusted for confounders through propensity-score matching, inverse propensity-score weighted (IPSW), and multivariable models. The propensity-based models constituted the primary analyses. For ECMO duration, inverse hyperbolic sign transformation was performed because of its skewed distribution.

Propensity scores were obtained by logistic regression including the literature search-based variables. Propensity methods included: (i) IPSW calculated with the propensity-score estimations using generalized boosted models [29–31], (ii) propensity-score matching using one-to-one nearest neighbor matching without replacement with BMI  $\geq 35$  kg/m<sup>2</sup> as the dependent variable within a caliper width of 0.2. Satisfactory matching was defined as an absolute value of the standardized mean difference (SMD)  $< 0.1$  for all variables [31, 32]. For binary outcomes, matched data were analyzed using logistic mixed effects regression models. For continuous data, linear mixed effects regression models were used.

Multivariable logistic regressions were used as an alternative approach to verify the impact of BMI  $\geq 35$  kg/m<sup>2</sup> on outcomes. Collinearity between confounders was checked and judged problematic in case of variation inflation factor  $> 5$ .

### Exploratory analyses

Differences in complications between BMI categories were further explored to define potential drivers by comparing the incidence of the subcategories of the complications of interest in the total and propensity-matched populations.

### Assessment of the shape of the relationship between BMI and outcomes and BMI subcategories

Anticipating a non-linear relationship, weighted generalized additive models (GAM) using the propensity scores were used to capture the effect of BMI as a

continuous variable on outcomes. The smooth effect of BMI was calculated using smoothed splines. We explored differences across BMI categories within BMI  $< 35$  kg/m<sup>2</sup> and BMI  $\geq 35$  kg/m<sup>2</sup> with Kruskal–Wallis rank-sum test, Chi-square, or Fisher's exact in the propensity-matched set.

### Missing data

Data were considered to be missing completely at random, except for proning. For propensity models, multivariable models and GAM analyses, multiple imputation for missing data was performed, generating five imputed datasets [33, 34]. Results were pooled by Rubin's rule.

### Sensitivity analyses

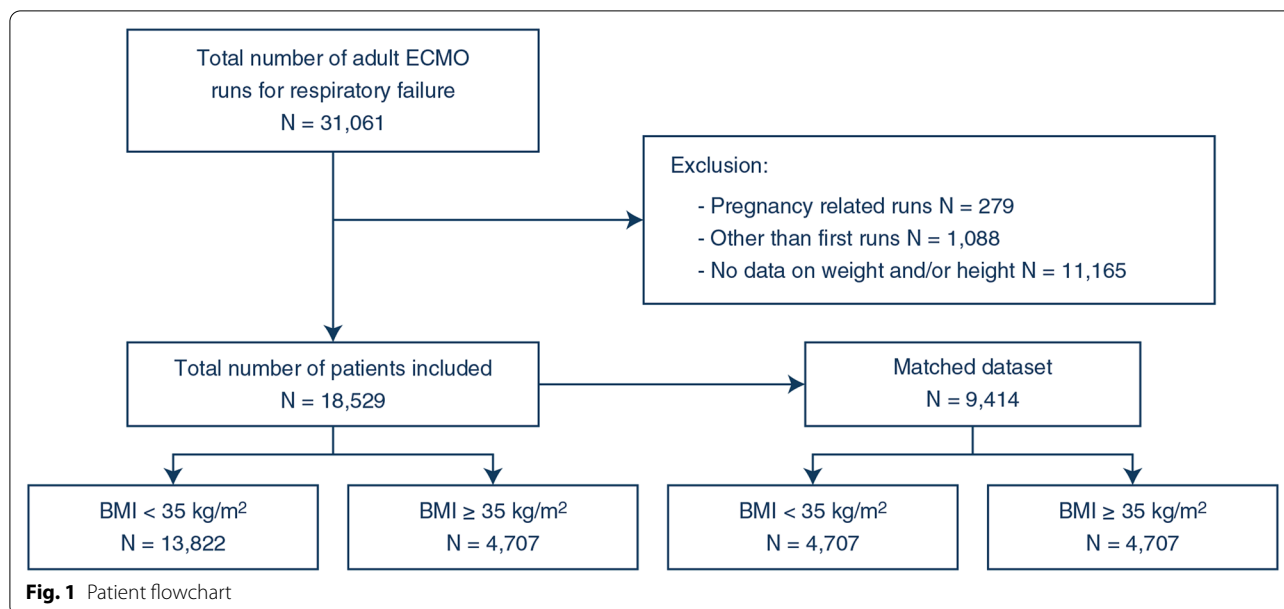
As prolonged prone ventilation was not recorded in the registry prior to December 2017, sensitivity analyses were performed limited to admissions from 2018 onward. As death is a competing risk for development of complications, sensitivity analyses for the secondary outcomes were performed on survivors only.

## Results

### Patient population and characteristics

The registry included 31,061 ECMO runs. We excluded 279 pregnancy-related runs, 1088 other than first runs and 11,165 runs with missing height or weight (Fig. 1). The characteristics of the 18,529 included patients are provided in Table 1. Missingness is reported in Supplemental Table 5. The mean age was  $48 \pm 15$  years. Most patients were male (64%). The mean BMI was  $31 \pm 9$  kg/m<sup>2</sup>, and 25% had BMI  $\geq 35$  kg/m<sup>2</sup>. This proportion significantly increased over time from 21% before 2016 up to 30% in 2020.

Patients with class II obesity or more differed from those with BMI  $< 35$  kg/m<sup>2</sup>, including being younger, more frequently female, and having different primary diagnoses. Less patients with BMI  $\geq 35$  kg/m<sup>2</sup> suffered from chronic respiratory disease or immunocompromised state, yet chronic heart disease was more frequent. Patients with BMI  $\geq 35$  kg/m<sup>2</sup> had lower PO<sub>2</sub>/FiO<sub>2</sub> despite receiving higher PEEP and more rescue treatments with neuromuscular blocking agent (NMBAs), prone ventilation, and nitric oxide (NO) prior to cannulation. Patients with BMI  $\geq 35$  kg/m<sup>2</sup> were more frequently transported on ECMO, had longer delays between intubation and ECMO, and more frequently received renal replacement therapy prior to cannulation. Bridge-to-transplantation was performed less frequently. A subset of 4707 patients with BMI  $\geq 35$  kg/m<sup>2</sup> were matched to 4707 patients with BMI  $< 35$  kg/m<sup>2</sup>, rendering satisfactory confounder balance (Table 1) (Supplemental Fig. 1). The characteristics



for the BMI subcategories are provided in Supplemental Table 6.

#### Association between class II obesity or more and hospital mortality

7394 (39.9%) patients died in hospital. Crude mortality was 37.9% in patients with BMI  $\geq 35$  kg/m<sup>2</sup> and 40.6% for those with BMI  $< 35$  kg/m<sup>2</sup> (Table 2). Propensity-matched (odds ratio (OR) 0.878, 95% confidence interval (CI) 0.798–0.996,  $p=0.008$ ) and IPSW analyses (OR 0.899, 95%CI 0.827–0.979,  $p=0.014$ ) showed that patients with BMI  $\geq 35$  kg/m<sup>2</sup> had a reduced mortality risk when adjusting for confounders. Multivariable logistic regression analysis (OR 0.900, 95%CI 0.834–0.971,  $p=0.007$ ) was consistent with these findings.

#### Association between class II obesity or more and secondary outcomes

Incidence of complications and duration of ECMO run and hospitalization according to BMI groups are shown in Table 2. Patients with BMI  $\geq 35$  kg/m<sup>2</sup> more frequently suffered from cardiovascular (17.3% versus 15.3%), renal (37% versus 30%), and device-related complications (25.7% versus 20.6%) compared to patients with BMI  $< 35$  kg/m<sup>2</sup>. For all complications, this increased risk was consistent across both propensity score-based and multivariable models. Exploratory analyses suggested that the increased risk for cardiovascular complications is possibly driven by an increased incidence of arrhythmia and need for cardio-pulmonary resuscitation (CPR) in patients with BMI  $\geq 35$  kg/m<sup>2</sup> (Supplemental Table 7). Increased incidence of

renal complications was observed across all subtypes (Supplemental Table 8). Excess device-related complications appear predominantly due to oxygenator failure (Supplemental Table 9). In contrast, 7.7% of patients with BMI  $\geq 35$  kg/m<sup>2</sup> compared to 9.3% of patients with BMI  $< 35$  kg/m<sup>2</sup> developed pulmonary complications. This observation remained present across all adjusted analyses (Table 2) and appears due to reduced incidence of pneumothorax (Supplemental Table 10). The risk of developing other complications was not different (Table 2).

In all confounder-adjusted analyses, ECMO duration was not affected, whereas duration of hospitalization (–3 days) was significantly shorter in patients with BMI  $\geq 35$  kg/m<sup>2</sup> compared to patients with BMI  $< 35$  kg/m<sup>2</sup>. Discharge destination significantly differed with more patients being transferred to long-term acute care, rehab, or hospice and less patients being discharged home in BMI  $\geq 35$  kg/m<sup>2</sup> (Table 2).

#### Sensitivity analyses

Sensitivity analyses in patients admitted from 2018 onward yielded similar results (Supplemental Table 11).

To assess whether the higher risk of cardiovascular, renal and device-related complications in patients with BMI  $\geq 35$  kg/m<sup>2</sup> could be explained by a higher survival rate and thus a longer time exposed to the potential development of these complications—the so-called ‘immortal time bias’—additional sensitivity analyses involved survivors only. This showed that the excess risk for developing these complications persisted in survivors only (Supplemental Table 11).

**Table 1 Demographic, clinical, pre-ECMO, and cannulation characteristics**

	Total population				Propensity matched			SMD
	Total N = 18,529	BMI < 35 kg/m <sup>2</sup> N = 13,822	BMI ≥ 35 kg/m <sup>2</sup> N = 4707	p value <sup>a</sup>	Total N = 9414	BMI < 35 kg/m <sup>2</sup> N = 4707	BMI ≥ 35 kg/m <sup>2</sup> N = 4707	
<b>Demographics</b>								
Age	48 (15)	49 (15)	47 (13)	<0.001	47 (14)	47 (15)	47 (13)	0.016
Sex, male	11,828 (64%)	9104 (66%)	2724 (58%)	<0.001	5453 (58%)	2722 (58%)	2731 (58%)	0.020
BMI (kg/m <sup>2</sup> )	30.7 (8.6)	26.7 (4.6)	42.4 (6.9)	<0.001	35 (10)	27 (5)	42 (7)	NA
<b>Primary diagnosis</b>				<0.001				0.026
Viral pneumonia	3958 (22%)	2637 (20%)	1321 (29%)		2686 (29%)	1329 (28%)	1357 (29%)	
Non-viral pneumonia	1149 (6.4%)	947 (7.1%)	202 (4.4%)		407 (4.3%)	195 (4.1%)	212 (4.5%)	
Chemical/aspiration	265 (1.5%)	200 (1.5%)	65 (1.4%)		129 (1.4%)	63 (1.3%)	66 (1.4%)	
Trauma/burn	595 (3.3%)	453 (3.4%)	142 (3.1%)		295 (3.1%)	151 (3.2%)	144 (3.1%)	
Asthma	329 (1.8%)	278 (2.1%)	51 (1.1%)		112 (1.2%)	57 (1.2%)	55 (1.2%)	
Pulmonary embolism/pulmonary hypertension	327 (1.8%)	224 (1.7%)	103 (2.2%)		213 (2.3%)	108 (2.3%)	105 (2.2%)	
Lung transplant complications	476 (2.7%)	466 (3.5%)	10 (0.2%)		25 (0.3%)	15 (0.3%)	10 (0.2%)	
Unspecified ARDS/ARF	7223 (40%)	5165 (39%)	2058 (45%)		4248 (45%)	2134 (45%)	2114 (45%)	
Other	3627 (20%)	2996 (22%)	631 (14%)		1299 (14%)	655 (14%)	644 (14%)	
<b>Comorbidities and associated conditions</b>								
Chronic respiratory disease	2864 (15%)	2426 (18%)	438 (9.3%)	<0.001	856 (9.1%)	418 (8.9%)	438 (9.3%)	0.004
Chronic heart disease	1452 (7.8%)	1034 (7.5%)	418 (8.9%)	0.002	850 (9%)	432 (9.2%)	418 (8.9%)	0.002
Immunocompromised	2053 (11%)	1837 (13%)	216 (4.6%)	<0.001	439 (4.7%)	223 (4.7%)	216 (4.6%)	0.018
Associated infection	788 (4.3%)	592 (4.3%)	196 (4.2%)	0.73	394 (4.2%)	198 (4.2%)	196 (4.2%)	0.014
<b>Pre-ECMO variables and treatments</b>								
RR (/min)	24 (7)	24 (7)	24 (7)	<0.001	24 (7)	24 (7)	24 (7)	0.008
pO <sub>2</sub> /FiO <sub>2</sub>	0.71 (0.56, 0.99)	0.73 (0.57, 1.03)	0.67 (0.54, 0.88)	<0.001	0.68 (0.55, 0.91)	0.69 (0.55, 0.93)	0.67 (0.54, 0.89)	0.012
PIP (cmH <sub>2</sub> O)	34 (8)	33 (8)	35 (8)	<0.001	35 (8)	35 (9)	35 (8)	0.003
PEEP (cmH <sub>2</sub> O)	13 (5)	12 (5)	14 (5)	<0.001	14 (5)	14 (5)	14 (5)	0.012
pH	7.25 (0.14)	7.25 (0.14)	7.25 (0.13)	0.38	7.25 (0.14)	7.25 (0.14)	7.25 (0.14)	<0.001
pCO <sub>2</sub> (cmH <sub>2</sub> O)	63 (22)	63 (23)	62 (20)	0.74	62 (21)	62 (21)	62 (20)	0.007
HCO <sub>3</sub> (mmol/l)	26 (7)	26 (7)	26 (7)	0.024	26 (7)	26 (7)	26 (7)	0.008
Lactate	3.4 (3.9)	3.5 (4)	3.2 (3.6)	<0.001	3.1 (3.5)	3.2 (3.5)	3.1 (3.5)	0.004
Mean BP (mmHg)	76 (17)	76 (17)	77 (17)	<0.001	77 (17)	77 (17)	77 (17)	<0.001
pre-ECMO arrest	1659 (9%)	1214 (9%)	445 (9.6%)	0.21	912 (9.7%)	462 (9.8%)	450 (9.6%)	0.002
Bridge to transplant	1178 (6.7%)	1126 (8.6%)	52 (1.2%)	<0.001	128 (1.4%)	72 (1.5%)	56 (1.2%)	<0.001
Intubation-to-time to ECMO (hours)	33 (8–110)	29 (8–107)	45 (12–116)	<0.001	42 (11–119)	40 (10–120)	45 (12–117)	0.014
pre-ECMO RRT	1663 (9%)	1205 (8.7%)	458 (9.7%)	0.036	935 (9.9%)	477 (10%)	458 (9.7%)	0.004
pre-ECMO NO	2170 (12%)	1600 (12%)	570 (12%)	0.33	1137 (12%)	567 (12%)	570 (12%)	0.025
pre-ECMO prone	3888 (21%)	2696 (20%)	1192 (25%)	<0.001	2351 (25%)	1159 (25%)	1192 (25%)	0.015
pre-ECMO NMBA	9914 (54%)	7018 (51%)	2896 (62%)	<0.001	5757 (61%)	2861 (61%)	2896 (62%)	<0.001
pre-ECMO vasopressors/inotropes	11,132 (60%)	8401 (61%)	2731 (58%)	<0.001	5498 (58%)	2767 (59%)	2731 (58%)	<0.001
pre-ECMO bicarbonate	2131 (12%)	1591 (12%)	540 (11%)	0.94	1080 (11%)	540 (11%)	540 (11%)	0.004

**Table 1 (continued)**

	Total population				Propensity matched			SMD
	Total N = 18,529	BMI < 35 kg/m <sup>2</sup> N = 13,822	BMI ≥ 35 kg/m <sup>2</sup> N = 4707	p value <sup>a</sup>	Total N = 9414	BMI < 35 kg/m <sup>2</sup> N = 4707	BMI ≥ 35 kg/m <sup>2</sup> N = 4707	
pre-ECMO corticosteroids	212 (1.1%)	181 (1.3%)	31 (0.7%)	< 0.001	55 (0.6%)	24 (0.5%)	31 (0.7%)	0.008
<b>ECMO</b>								
Cannulation				< 0.001				0.020
VV	16,575 (89%)	12,242 (89%)	4333 (92%)		8667 (92%)	4334 (92%)	4333 (92%)	
Non-VV								
VA	915 (4.9)	773 (5.6)	142 (3)		281 (3)	139 (3)	142 (3)	
VVA	146 (0.8)	118 (0.9)	28 (0.6)		55 (0.6)	27 (0.6)	28 (0.6)	
Other	892 (4.8)	688 (5)	204 (4.3)		406 (4.4)	202 (4.3)	204 (4.3)	
<b>Year</b>				< 0.001				0.025
2010–2016	1649 (9%)	1305 (9%)	344 (7%)		716 (8%)	372 (8%)	344 (7%)	
2017	2843 (15%)	2254 (16%)	589 (13%)		1190 (13%)	601 (13%)	589 (13%)	
2018	3524 (19%)	2724 (20%)	800 (17%)		1597 (17%)	797 (17%)	800 (17%)	
2019	4071 (22%)	3052 (22%)	1019 (22%)		2038 (22%)	1019 (22%)	1019 (22%)	
2020	6442 (35%)	4487 (32%)	1955 (42%)		3873 (41%)	1918 (41%)	1955 (42%)	
Transported on ECMO	4150 (28%)	2890 (26%)	1260 (32%)	< 0.001	3016 (32%)	1509 (32%)	1507 (32%)	0.010

Continuous variables are presented as mean (SD); time variables and PO<sub>2</sub>/FIO<sub>2</sub> are presented as median (interquartile range); categorical variables are presented as numbers (proportions)

BMI body mass index; ECMO extracorporeal membrane oxygenation; ARDS acute respiratory distress syndrome; ARF acute respiratory failure; PIP peak inspiratory pressure; PEEP positive end-expiratory pressure; BP blood pressure; RRT renal replacement therapy; NO nitric oxide; NMBA neuromuscular blocking agent; RR respiratory rate; VV veno-venous; SMD absolute standardized mean difference

<sup>a</sup> p values are calculated with Wilcoxon signed-rank test, Chi-square, or Fisher exact as appropriate

The effect on the duration of hospitalization further increased, implying that this is a true effect and cannot be explained by deaths occurring earlier during the disease course of patients with BMI ≥ 35 kg/m<sup>2</sup>.

#### Assessment of the shape of the relationship between BMI and outcomes and study of BMI subcategories

GAM analysis confirmed a non-linear relationship between BMI and mortality (Fig. 2). The shape of the relationship between BMI and mortality suggests that mortality is the highest for patients with BMI 30–35 kg/m<sup>2</sup>. Subsequently, mortality decreases until BMI values around 60 kg/m<sup>2</sup>, after which mortality appears to increase up to BMI 70 kg/m<sup>2</sup>. The confidence interval between 60 and 70 kg/m<sup>2</sup>, however, is wide because of the small number of patients. At BMI < 25 kg/m<sup>2</sup>, mortality decreases, although the margin of error is high for BMI < 20 kg/m<sup>2</sup> due to the small sample size. Cardiovascular, renal, and device-related complications appear to increase up to a BMI of 40–50 kg/m<sup>2</sup>, after which a plateau is reached. The risk of pulmonary complications appears to gradually decrease between BMI of 25 and 45 kg/m<sup>2</sup>. For duration of ECMO, an inverse U-shape relationship was observed between the BMI and duration

of ECMO and with a peak around BMI 30 kg/m<sup>2</sup>. Hospital length of stay decreased across the entire range of BMI values. Outcomes for the BMI subcategories are reported in Supplemental Table 6. Consistent with GAM analyses, data do not suggest an upper limit of BMI, above which treatment appears futile although the margin of error in BMI > 60 kg/m<sup>2</sup> is large.

#### Discussion

In this large multicenter ELSO registry, we documented significantly lower mortality for adults with class II obesity or more requiring ECMO for respiratory failure, compared to those with BMI < 35 kg/m<sup>2</sup>, despite increased cardiovascular, device-related, and renal complications in the former. Hospital stay was also decreased in patients with BMI ≥ 35 kg/m<sup>2</sup>, not explained by a disproportionate number of early deaths. The findings were consistent throughout multiple confounder-adjusted statistical approaches. No BMI limit could be identified that would mark futility, albeit that the margin of error for BMI > 60 kg/m<sup>2</sup> is large.

Obesity was considered a relative contraindication for ECMO [21] and during the COVID-19 pandemic, it was formally listed as such [22]. Previous studies on the

**Table 2 Primary and secondary outcomes for patients with class II obesity or more**

	BMI < 35 kg/m <sup>2</sup>	BMI ≥ 35 kg/m <sup>2</sup>	Analysis	Effect size	p value
<b>Primary outcome</b>					
<i>In-hospital mortality</i>					
Total population	5608 (40.6%)	1786 (37.9%)	Univariable analysis	0.8916 (0.8333–0.9540) <sup>d</sup>	0.001
PS-matched set	1904 (40.4%)	1786 (37.9%)	Multivariable analysis <sup>a</sup>	0.8999 (0.8337–0.9714) <sup>d</sup>	0.007
			PS-matched analysis <sup>b</sup>	0.8782 (0.7982–0.9662) <sup>d</sup>	0.008
			Inverse PS weighted analysis <sup>c</sup>	0.8994 (0.8266–0.9787) <sup>d</sup>	0.014
<b>Secondary outcomes</b>					
<i>Cardiovascular complications</i>					
Total population	2117 (15.3%)	813 (17.3%)	Univariable analysis	1.1493 (1.0523–1.2552) <sup>d</sup>	0.002
PS-matched set	681 (14.5%)	813 (17.3%)	Multivariable analysis <sup>a</sup>	1.2363 (1.1232–1.3609) <sup>d</sup>	< 0.001
			PS-matched analysis <sup>b</sup>	1.2381 (1.0901–1.4061) <sup>d</sup>	0.001
			Inverse PS weighted analysis <sup>c</sup>	1.2101 (1.0830–1.3521) <sup>d</sup>	0.001
<i>Hemorrhagic complications</i>					
Total population	2279 (16.5%)	749 (15.9%)	Univariable analysis	0.9584 (0.8758–1.0488) <sup>d</sup>	0.356
PS-matched set	760 (16.1%)	749 (15.9%)	Multivariable analysis <sup>a</sup>	0.9908 (0.9000–1.0908) <sup>d</sup>	0.851
			PS-matched analysis <sup>b</sup>	0.9696 (0.8632–1.0893) <sup>d</sup>	0.603
			Inverse PS weighted analysis <sup>c</sup>	0.9463 (0.8458–1.0586) <sup>d</sup>	0.335
<i>Limb complications</i>					
Total population	234 (1.7%)	70 (1.5%)	Univariable analysis	0.8765 (0.6697–1.1473) <sup>d</sup>	0.337
PS-matched set	82 (1.7%)	70 (1.5%)	Multivariable analysis <sup>a</sup>	0.8618 (0.6482–1.1458) <sup>d</sup>	0.306
			PS-matched analysis <sup>b</sup>	0.7360 (0.3959–1.3683) <sup>d</sup>	0.318
			Inverse PS weighted analysis <sup>c</sup>	0.8599 (0.6222–1.1885) <sup>d</sup>	0.361
<i>Infectious complications</i>					
Total population	541 (3.9%)	176 (3.7%)	Univariable analysis	0.9535 (0.8017–1.1341) <sup>d</sup>	0.591
PS-matched set	192 (4.8%)	176 (3.7%)	Multivariable analysis <sup>a</sup>	1.1059 (0.9145–1.3374) <sup>d</sup>	0.299
			PS-matched analysis <sup>b</sup>	1.1472 (0.8243–1.5965) <sup>d</sup>	0.403
			Inverse PS weighted analysis <sup>c</sup>	1.0611 (0.8540–1.3186) <sup>d</sup>	0.592
<i>Device-related complications</i>					
Total population	2850 (20.6%)	1210 (25.7%)	Univariable analysis	1.3320 (1.2330–1.4391) <sup>d</sup>	< 0.001
PS-matched set	1044 (22.2%)	1210 (25.7%)	Multivariable analysis <sup>a</sup>	1.2240 (1.1252–1.3314) <sup>d</sup>	< 0.001
			PS-matched analysis <sup>b</sup>	1.2177 (1.0846–1.3673) <sup>d</sup>	0.001
			Inverse PS weighted analysis <sup>c</sup>	1.1882 (1.0763–1.3116) <sup>d</sup>	0.001
<i>Renal complications</i>					
Total population	4142 (30%)	1743 (37%)	Univariable analysis	1.3615 (1.2706–1.4588) <sup>d</sup>	< 0.001
PS-matched set	1487 (31.6%)	1743 (37)	Multivariable analysis <sup>a</sup>	1.3241 (1.2282–1.4274) <sup>d</sup>	< 0.001
			PS-matched analysis <sup>b</sup>	1.2895 (1.1755–1.4146) <sup>d</sup>	< 0.001
			Inverse PS weighted analysis <sup>c</sup>	1.2857 (1.1802–1.4008) <sup>d</sup>	< 0.001
<i>Pulmonary complications</i>					
Total population	1283 (9.3%)	358 (7.6%)	Univariable analysis	0.9619 (0.8207–1.1275) <sup>d</sup>	0.001
PS-matched set	513 (10.9%)	358 (7.6%)	Multivariable analysis <sup>a</sup>	0.8333 (0.7039–0.9865) <sup>d</sup>	< 0.001
			PS-matched analysis <sup>b</sup>	0.8231 (0.6465–0.9654) <sup>d</sup>	< 0.001
			Inverse PS weighted analysis <sup>c</sup>	0.8530 (0.7046–0.9678) <sup>d</sup>	< 0.001
<i>Metabolic complications</i>					
Total population	1203 (8.7%)	477 (10.1%)	Univariable analysis	1.1883 (1.0636–1.3277) <sup>d</sup>	0.002
PS-matched set	422 (9%)	477 (10.1%)	Multivariable analysis <sup>a</sup>	1.1594 (1.0296–1.3055) <sup>d</sup>	0.015
			PS-matched analysis <sup>b</sup>	1.1361 (0.9548–1.3516) <sup>d</sup>	0.145
			Inverse PS weighted analysis <sup>c</sup>	1.1353 (0.9903–1.3016) <sup>d</sup>	0.069
<i>Neurological complications</i>					
Total population	917 (6.6%)	340 (7.2%)	Univariable analysis	1.0956 (0.9629–1.2466) <sup>d</sup>	0.165

**Table 2 (continued)**

	BMI < 35 kg/m <sup>2</sup>	BMI ≥ 35 kg/m <sup>2</sup>	Analysis	Effect size	p value
PS-matched set	359 (7.6%)	340 (7.2%)	Multivariable analysis <sup>a</sup>	0.9834 (0.8577–1.1277) <sup>d</sup>	0.812
			PS-matched analysis <sup>b</sup>	0.9981 (0.7595–1.3116) <sup>d</sup>	0.989
			Inverse PS weighted analysis <sup>c</sup>	0.9651 (0.8264–1.1270) <sup>d</sup>	0.654
<i>Repair</i>					
Total population	5091 (36.8%)	1719 (36.5%)	Univariable analysis	0.9837 (0.9187–1.0532) <sup>d</sup>	0.638
PS-matched set	1690 (35.9)	1719 (36.5)	Multivariable analysis <sup>a</sup>	1.0235 (0.9515–1.1010) <sup>d</sup>	0.531
			PS-matched analysis <sup>b</sup>	1.0183 (0.9353–1.1088) <sup>d</sup>	0.675
			Inverse PS weighted analysis <sup>c</sup>	1.0196 (0.9355–1.1112) <sup>d</sup>	0.658
<i>Time on ECMO (hours)</i>					
Total population	206 (95–432)	237 (126–433)	Univariable analysis	0.1451 (0.0215) <sup>e,g</sup>	< 0.001
PS-matched set	230 (112–472)	237 (126–433)	Multivariable analysis <sup>a</sup>	– 0.0161 (0.0200) <sup>e,g</sup>	0.419
			PS-matched analysis <sup>b</sup>	– 0.0058 (0.0273) <sup>e,g</sup>	0.832
			Inverse PS weighted analysis <sup>c</sup>	– 0.0026 (0.0176) <sup>e,g</sup>	0.883
<i>Reason for discontinuation</i>					
Total population			NA	NA	< 0.001
Died or poor prognosis	4591 (34%)	1503(32%)			
Expected recovery	8368 (62%)	3067 (66%)			
Transplantation	440 (3.2%)	14 (0.3%)			
Other	179 (1.3%)	60 (1.3%)			
Matched population			NA	NA	< 0.001 <sup>f</sup>
Died or poor prognosis	1589 (34%)	1514 (32%)			
Expected recovery	3010 (64%)	3115 (66%)			
Transplantation	48 (1%)	17 (0.4%)			
Other	60 (1.3%)	61 (1.3%)			
<i>Hospital length of stay</i>					
Total population	27 (14–47)	25 (14–41)	Univariable analysis	– 4.9460 (0.6266) <sup>e</sup>	< 0.001
PS-matched set	27 (14–44)	25 (15–41)	Multivariable analysis <sup>a</sup>	– 2.9107 (0.6318) <sup>e</sup>	< 0.001
			PS-matched analysis <sup>b</sup>	– 2.7546 (0.6856) <sup>e</sup>	< 0.001
			Inverse PS weighted analysis <sup>c</sup>	– 2.8285 (0.4882) <sup>e</sup>	< 0.001
<i>Discharge destination<sup>d</sup></i>					
Total population			NA	NA	< 0.001
Home	3329 (37%)	874 (28%)			
Other hospital	1741 (19%)	608 (20%)			
Transfer to LTAC/rehab/hospice	2238 (25%)	1137 (37%)			
Other	1692 (19%)	487 (16%)	NA	NA	< 0.001 <sup>f</sup>
<i>Matched population</i>					
Home	1201 (26%)	985 (21%)			
Other hospital	681 (14%)	644 (14%)			
Transfer to LTAC/rehab/hospice	667 (19%)	1202 (26%)			
Other	1938 (41%)	1,876 (40%)			

BMI body mass index; LTAC long-term acute care; PS propensity score; ECMO extracorporeal membrane oxygenation

<sup>a</sup> Multivariable model for imputed datasets (pooled by Rubin's rule)

<sup>b</sup> Logistic mixed effects model with imputed matched datasets (pooled by Rubin's rule)

<sup>c</sup> Inverse probability weighted regression model with propensity-score estimates for imputed datasets (pooled by Rubin's rule)

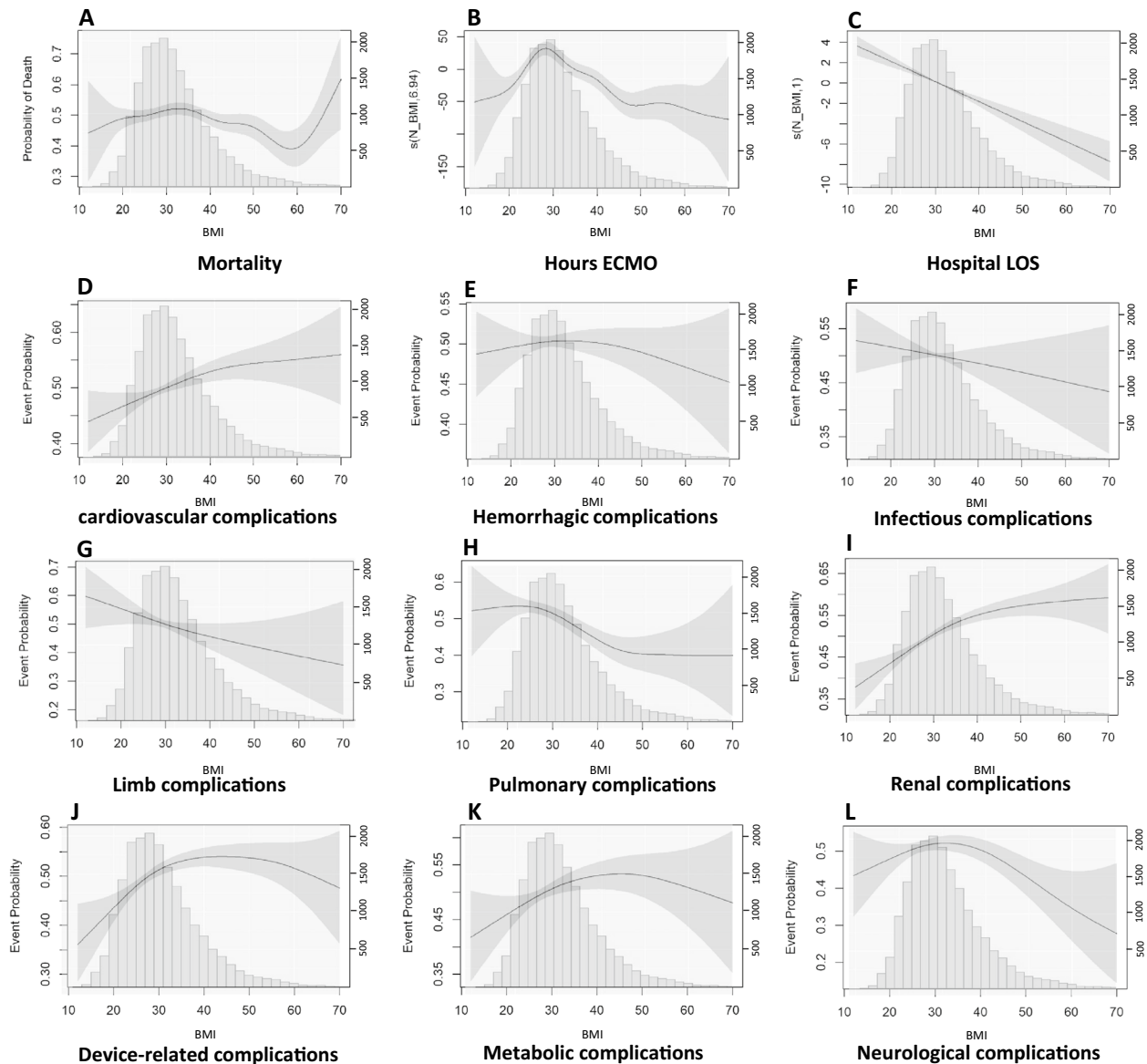
<sup>d</sup> Effect size: odds ratio (95% confidence interval)

<sup>e</sup> Coefficient (standard deviation)

<sup>f</sup> McNemar test for paired data

<sup>g</sup> Time on ECMO was transformed with inverse hyperbolic sign transformation because of skewness





**Fig. 2** Relationship between BMI and outcomes. **A** Adjusted relationship between BMI and mortality risk (EDF: 6.848,  $p = 0.002$ ); **B** adjusted relationship between BMI and duration of ECMO (EDF: 6.943,  $p < 0.001$ ); **C** adjusted relationship between BMI and hospital length of stay (EDF: 1,  $p < 0.001$ ); **D** adjusted relationship between BMI and cardiovascular complications (EDF: 1.76,  $p = 0.004$ ); **E** adjusted relationship between BMI and hemorrhagic complications (EDF: 1.004,  $p = 0.988$ ); **F** adjusted relationship between BMI and infectious complications (EDF: 1.059,  $p = 0.311$ ); **G** adjusted relationship between BMI and limb complications (EDF: 1.264,  $p = 0.086$ ); **H** adjusted relationship between BMI and pulmonary complications (EDF: 3.114,  $p < 0.001$ ); **I** adjusted relationship between BMI and renal complications (EDF: 2.331,  $p < 0.001$ ); **J** adjusted relationship between BMI and device-related complications (EDF: 2.992,  $p < 0.001$ ); **K** adjusted relationship between BMI and metabolic complications (EDF: 2.105,  $p = 0.047$ ); **L** adjusted relationship between BMI and neurological complications (EDF: 2.449,  $p = 0.006$ ). Y-axis (left) represents the probability for the binary variables, and for continuous variables the scaled centered effect. Y-axis (right) represents the numbers of patients in the histogram.  $p$  values are calculated by generalized additive models,  $p$  values  $< 0.05$  indicate non-linear relationship. The degree of freedom (EDF) represents the degree of the smooth relationship between the outcome and BMI. A value of 1 is considered a linear relationship, and larger values are considered as a more complex effect of BMI on the outcome

impact of obesity on mortality in respiratory ECMO yielded inconsistent results. Al-Soufi reported no mortality difference according to weight quartiles in 1,334 adults in an earlier ELSO registry analysis, though a trend toward decreased mortality was noted among the highest quartile [18]. Small case series found no survival difference with BMI dichotomized at 30 kg/m<sup>2</sup> [19], 35 kg/m<sup>2</sup> [20], or 40 kg/m<sup>2</sup> [11], as a continuous variable [8, 9, 35] or stratified by subcategories [9, 10, 12], although a trend toward improved survival was suggested for the highest BMI values [11, 12]. A systematic review and meta-analysis of mixed cardiac and respiratory ECMO patients found no association of BMI  $\geq$  30 kg/m<sup>2</sup> with mortality [36]. Others observed lower mortality for patients with BMI  $\geq$  25 kg/m<sup>2</sup> [13] or BMI  $\geq$  40 kg/m<sup>2</sup> [14]. In a large United States nationwide readmission database including 23,876 ECMO patients, 25% of which were respiratory indications, BMI  $\geq$  30 kg/m<sup>2</sup> was not associated with mortality [37]. Confounder adjustment in this study was limited to demographics and comorbidities. Paucity of data in COVID-related ECMO are contradictory [15–17, 38]. We consistently showed decreased mortality among patients with BMI  $\geq$  35 kg/m<sup>2</sup> across multiple analyses extensively adjusted for confounders, associated with reduced hospital length of stay. This was not attributable to early deaths. No cutoff in the upper BMI range was identified, at which outcomes were clearly compromised.

These findings appear in line with the obesity paradox, referring to improved survival in obese critically ill patients. The obesity paradox was observed in general intensive care unit (ICU) populations [39], in pneumonia [40] and ARDS [41]. Obese COVID-19 patients have a higher risk for severe disease, but once admitted to the ICU, mortality is not higher than in non-obese patients [40]. Possible explanations include more adequate nutritional reserves, adipose tissue-released factors exerting favorable immune-modulatory effects, lower weight-based treatment dosing, and selection bias [1, 3]. Obese patients have altered pulmonary mechanics due to increased abdominal compression, promoting atelectasis and complete airway closure [42]. Increased metabolic demands and work of breathing may further predispose to the development of respiratory failure earlier in the disease course, when there is less severe parenchymal lung disease compared with non-obese patients [43]. Obese patients require higher PEEP and physicians may be hesitant to prone these patients. Optimal ventilation may necessitate transpulmonary pressure guidance, accepting airway pressures exceeding traditional safety guidelines. Hence, conventional ventilation may not be fully exploited prior to ECMO [3]. The lower incidence of pneumothorax in patients with BMI  $\geq$  35 kg/m<sup>2</sup> in our

cohort supports these findings and reduced length of stay might reflect lower illness severity.

Improved survival came with increased cardiovascular, device-related and renal complications. Previous small cohorts did not identify increased complications in obese patients undergoing respiratory ECMO. Studied complications include vasopressor use [14], renal replacement therapy [12, 19], bleeding or thrombotic events [11], including cannulation site bleeding [10] and cannulation-associated deep vein thrombosis [12], cerebrovascular accidents [11], and oxygenator clotting [8]. Percutaneous cannulation appeared feasible and safe [20]. The excess of cardiovascular complications in our study was explained by a higher incidence of arrhythmia and the need for CPR. Obesity is associated with increased cardiovascular morbidity, including hypertension, ventricular hypertrophy, ischemic heart disease, pulmonary hypertension, and atrial fibrillation, further promoted by co-existent diabetes, metabolic syndrome, and immune effects [1, 44]. Although the registry misses granularity on the nature of the cardiovascular events, it is conceivable that these comorbidities predispose to acute events in the critical setting. Increased renal complications in ECMO patients with BMI  $\geq$  35 kg/m<sup>2</sup> is consistent with increased risk of acute kidney injury (AKI) associated with obesity in general ICU patients [45]. Vulnerability for AKI is likely multifactorial, including increased renal blood flow and hyperfiltration, possibly increasing vulnerability to acute damage, increased oxidative stress, altered immunometabolic state, challenging intravascular volume assessment, and increased abdominal pressure [46]. Finally, device-related complications were more likely to occur. Only oxygenator failure was consistently more frequent in patients with BMI  $\geq$  35 kg/m<sup>2</sup>. This could be linked with a procoagulant state and challenging anticoagulation management. No other clot-related problems occurred more frequently. Cannulation, theoretically, may be more challenging because of poor anatomical reference, poor visualization, and sharper entrance angle of the guidewire [10]. Strikingly, cannula problems requiring intervention for misplacement, dislodgement, clots/fibrin, mechanical failure, or inappropriate position were not more frequent in the matched population. In contrast to veno-arterial ECMO in obesity [10], we observed no excess cannula-related bleeding or limb complications. Markedly, the increased complications in obese patients, consistent with other reports [1, 39, 47, 48], did not counterbalance the mortality benefit.

Our study has several strengths. This is the largest study on the relationship between BMI and outcomes in adult respiratory ECMO. Multiple statistical approaches to correct for confounding showed consistent results. Data from over 500 centers worldwide, represent real-life

daily care practice. This study also has limitations. First, the ELSO registry gathers voluntarily entered information. Participating centers may be more experienced, possibly leading to selection bias. Second, the registry format is characterized by variable missingness of data (e.g., absence of delay between intubation and ECMO in 15%). We attempted to mitigate this with multiple imputation, reducing bias compared to complete case analyses. Whether low rates of proning (21%) and use of NMBA (54%) represent underreporting and/or suboptimal treatment remains unclear. Third, the registry likely suffers from underreporting of comorbidities, treatments and complications, imprecision in diagnosis (e.g., unspecified ARDS/acute respiratory failure in 40%), and lack of ventilation data during ECMO. Fourth, we cannot exclude residual confounding by unmeasured variables, or variables not released by ELSO (e.g., center information). Fifth, the decision to start ECMO in obese patients may have been scrutinized more compared to non-obese counterparts, resulting in additional selection bias. Sixth, the registry is limited to the hospital stay; longer-term patient-centered outcomes such as quality of life are not available. Seventh, the cutoff to dichotomize BMI may be considered somewhat arbitrary. However, dichotomization allowed matching and multiple other statistical approaches were performed to study the relation between BMI and outcomes. Finally, as this is a retrospective analysis, causality cannot be inferred, although we attempted to approximate a random design by different propensity-score methods.

## Conclusion

Patients with obesity class II or more treated with respiratory ECMO have decreased mortality and shorter hospital length of stays, despite increased cardiovascular, device-related, and renal complications. The relationship between BMI and outcomes is non-linear. No upper limit of BMI indicating futility was identified. BMI as a single parameter should not be a contraindication for ECMO in respiratory failure.

## Supplementary Information

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## Author contributions

GH conceived the study; GH and IGF conceived the analysis plan; GH, MP, IGF, AV, and AC designed the study; IGF led the data analyses, supported by GH; GH, MP, and IGF drafted the initial manuscript. All authors revised and approved the manuscript for submission. GH and IGF have directly accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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## Data availability

The ELSO registry data are available from ELSO for investigators upon research requests.

## Declarations

## Conflicts of interest

The authors have no conflict of interest.

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