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Suhel Al-Soufi
Hergen Buscher
Nguyen Dinh Nguyen
Peter Rycus
Priya Nair

Lack of association between body weight and mortality in patients on veno-venous extracorporeal membrane oxygenation

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S. Al-Soufi (✉) · H. Buscher · P. Nair
Intensive Care Unit, St Vincent's Hospital, Victoria Street Darlinghurst, Sydney, NSW 2010, Australia
e-mail: suhelsoufi@gmx.de
Tel.: +61-83822581
Fax: +61-83833947

N. D. Nguyen
Garvan Institute of Medical Research, Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia

P. Rycus
Extracorporeal Life Support Organization, 2800 Plymouth Rd, Ann Arbor, MI, USA

Abstract *Purpose:* To analyse the association of body weight with hospital mortality of adult patients supported with veno-venous extracorporeal membrane oxygenation (VV ECMO). *Methods:* Retrospective analysis of the international Extracorporeal Life Support Organization (ELSO) registry. Univariate and multivariable logistic regression analyses were used to estimate the odds ratio (OR) of hospital death for each body weight quartile. Adjustment was made for demographic, physiologic and ECMO-related characteristics. We undertook a similar analysis for the subgroup of patients with confirmed H1N1 infection on VV ECMO. *Results:* The study group consisted of 1,334 adult patients supported with VV ECMO between 2005 and 2011 with a median (Q1, Q3) body weight of 80 kg (69, 101 kg). Univariate analysis identified increased body weight to be associated with a reduced risk of death. In multivariable analysis, only age greater than 53 years, primary diagnosis other than pneumonia and intubation time longer than 3 days prior to initiation of ECMO were independent risk factors for mortality, whereas the association between high body weight and adjusted risk of death (OR 0.73, 95 % CI 0.52–1.04, $P = 0.08$) was no longer statistically significant. The body weight of the 196 patients with confirmed H1N1 infection was significantly higher than that of the remaining study group. Body weight was not significantly associated with risk of death for these patients either (univariate OR for Q4 vs. Q1: 0.75, 95 % CI 0.33–1.72, $P = 0.49$). *Conclusions:* Increased body weight was not a risk factor for hospital mortality in adult patients who required support with VV ECMO. High body weight should therefore not be regarded as a contraindication to initiation of VV ECMO in adult patients. Data collection and reporting that include patient height in addition to body weight would facilitate future research into the association of obesity with outcome of ECMO patients.

Keywords Extracorporeal membrane oxygenation · ECMO · Body weight · Influenza A H1N1 · Mortality · Obesity

Introduction

The prevalence of overweight and obesity has risen over recent decades and is high in most regions of the world [1]. This trend is expected to continue with the majority of adults in the USA, UK and Australia projected to be overweight by 2020 [2]. Obesity has been identified as a risk factor for the development of acute respiratory

distress syndrome [3], primary graft dysfunction after lung transplantation [4] and more severe disease in patients with H1N1 pandemic influenza in 2009 [5–9]. As such, obesity is common in critically ill patients with severe respiratory failure requiring support with extracorporeal membrane oxygenation (ECMO) [10–13].

Theoretically, the cardiac output increase associated with high body weight may surpass the oxygenation capacity of the ECMO membrane [14]. As a result, veno-venous ECMO (VV ECMO) may be of limited utility for the management of hypoxia in overweight patients [15]. This theoretical concern has led some organisations to view high body weight as an absolute contraindication for all forms of ECMO [16, 17], thus excluding a large subpopulation from potentially life-saving treatment.

We hypothesized that increased body weight independently increases the risk of death among adult patients on VV ECMO. To test this hypothesis, we interrogated a large international database of patients on extracorporeal life support to investigate the association of body weight with hospital mortality.

Patients and methods

Study population

Since 1986, the ECMO Registry of the Extracorporeal Life Support Organization (ELSO, Ann Arbor, Michigan, USA) has maintained a registry with data of over 2,500 adults with respiratory and cardiac failure on extracorporeal life support contributed by over 170 international centres. Each institution approves data reported to the registry through their local institutional review board. The decision to commence ECMO is made at each centre without standardization and reporting is voluntarily. We queried the ELSO registry for adult patients (age $\geq$ 18 years) on ECMO from 1 January 2005 to 31 December 2011. We considered that data from prior years was not representative of current practice. Only patients who had venous cannulation i.e. veno-venous (VV), veno-venous double lumen (VVDL) or VVDL with additional venous drainage (VVDL + V) ECMO were included. Cases were excluded if the ECMO configuration involved arterial cannulation such as for veno-arterial, veno-venoarterial, venovenous–venoarterial, venoarterial–venovenous or venoarterial–venous ECMO or if the configuration mode could not be identified. For patients with multiple episodes of ECMO, we limited the analysis to the last ECMO run. Patients were excluded if the body weight was not reported or implausible (i.e. <10 kg). The primary outcome assessed was survival to hospital discharge. This analysis was approved by the ECMO Registry Committee of ELSO.

Study design

We described the association of body weight and death adjusted for the following variables: gender, race, age, primary diagnosis (pneumonia or other), time on mechanical ventilation before institution of ECMO, arterial blood gas data (pH, bicarbonate, pCO_2 and pO_2) and relevant ventilation parameters (positive end expiratory pressure, peak inspiratory pressure, respiratory rate and FiO_2) prior to institution of ECMO, year of ECMO run (before or after H1N1 pandemic), mode of ECMO (VV, VVDL or VVDL + V), pump flow 4 and 24 h after institution of ECMO, time spent on ECMO and number of ECMO runs. Furthermore, we analysed the association of body weight and survival for the subgroup of patients with confirmed H1N1 infection on VV ECMO.

Statistical analysis

Continuous variables were expressed as median (Q1, Q3). Accordingly, the Mann–Whitney *U* test was used to test two independent variables and the Kruskal–Wallis *H* test was used to test for more than two independent variables. Discrete data were displayed as number and percentage, and analysed by using the chi-squared test. The main outcome was hospital mortality defined whether patients were dead or alive at hospital discharge. Univariate and multivariable logistic regression analyses were used to estimate odds ratio (OR) and 95 % confidence interval (95 % CI) for each quartile with the lowest quartile used as reference for categorized risk factors. All factors associated with mortality in the univariate analysis were introduced in the multivariable logistic regression. Diagnostic regression analysis was performed to test model assumptions. Collinearity was also investigated. Non-parametric variables then were categorized in quartile groups in final models. The goodness of fit of models was also examined. All statistical analyses were performed by using the R statistical language (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 2,017 ECMO runs were reported for the years of 2005–2011 as of mid August 2012. There were 1,502 VV ECMO (VV, VVDL, VVDL + V modes) runs identified in 1,433 patients. The datasets of 1,334 patients with a reported body weight of at least 10 kg were used for further analysis (Fig. 1).

The median (Q1, Q3) body weight of the study group was 80.4 kg (69.3, 101.0 kg, Supplemental Table). The median body weight of survivors and non-survivors was

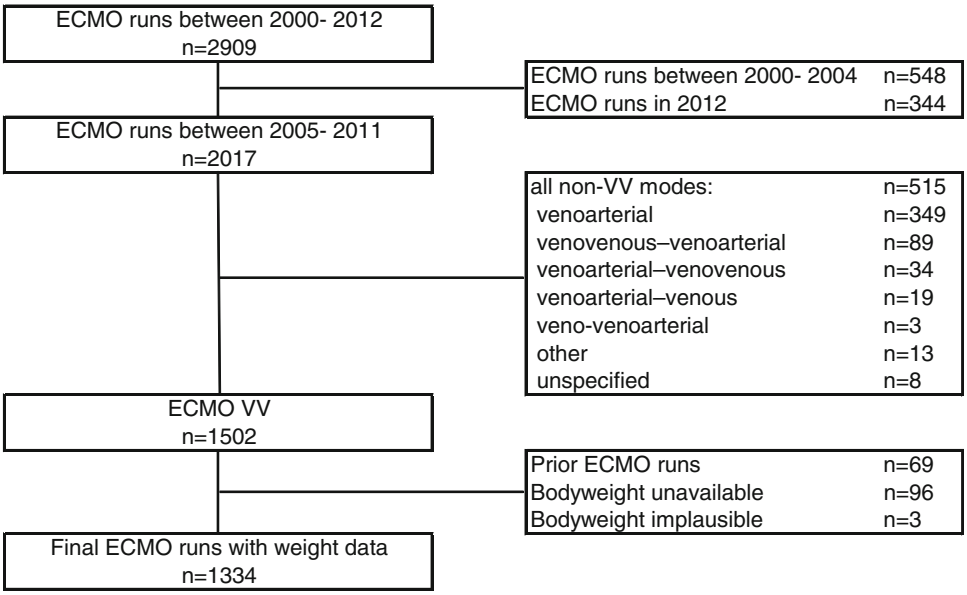

Fig. 1 Flow chart

statistically not different (81.0 vs. 80.0 kg, $P = 0.06$). The distribution of body weight did not change between 2005 and 2011. Body weights in the lower quartiles were seen more frequently in Asians whereas those in the higher quartiles were predominantly seen in the Caucasian and African–American population (Table 1). Patients in the lowest body weight quartile were more commonly female and tended to be younger compared to those in higher quartiles. Patients with body weights in the highest quartile were ventilated with significantly higher PEEP, peak inspiratory pressures and mean airway pressures. The time of mechanical ventilation prior to initiation of VV ECMO tended to be short and resulted generally in uncompensated respiratory acidosis and poor oxygenation. The VVDL + V configuration was more frequently used for patients in the highest body weight quartile who also had higher median ECMO flows in the first 24 h (Table 2). The duration of ECMO support increased with body weight and was statistically significant when the highest and lowest quartiles were compared (OR 1.8, 95 % CI 1.3–2.5). Unadjusted hospital mortality, however, was not statistically different across body weight quartiles (Table 1).

Univariate analysis identified body weight to be inversely associated with risk of death, with patients in the highest body weight quartile having the lowest mortality (Table 3). Other significant factors identified included age, primary diagnosis, blood pressure, duration of mechanical ventilation, respiratory rate, bicarbonate, pH (all prior to institution of ECMO), year, mode and duration of ECMO support (Tables 3, 4). Patients with body weight in the highest decile (121–251 kg) did not have increased risk of death (OR 0.62, 95 % CI 0.38–1.02, $P = 0.06$) either.

In multivariable analysis, only age, primary diagnosis and intubation time were independent risk factors for mortality (Table 5). Body weight was no longer significantly associated with a reduced adjusted risk of death. The lack of association of body weight with mortality was not altered when H1N1 status was included in multivariate analysis (OR 0.73, CI 95 % 0.51–1.03, $P = 0.071$).

Of the 1,334 patients in the study group, 196 (14.7 %) had a confirmed H1N1 infection, accounting for 20.0 % of all VV ECMO patients on the ELSO database for the period from 2009 to 2011. The body weight of this subgroup was significantly higher than that of the remaining study group [median (Q1, Q3) kg, 92.4 (80.0–115.7) vs. 80.0 (67.0, 97.0), respectively, $P < 0.001$]. Body weight was not significantly associated with risk of death for these patients either (univariate OR for Q4 vs. Q1: 0.75, 95 % CI 0.33–1.72, $P = 0.49$).

Discussion

In this large cohort of adult patients on veno-venous ECMO, high body weight was not associated with an increase in hospital mortality. Indeed, patients with a body weight in the highest quartile showed a trend toward a reduced adjusted risk of death when compared with those who had a body weight in the lowest quartile.

Our main intention was to investigate the validity of body weight as an independent prognostic factor on VV ECMO support. The ELSO database does not include the patient's height and, as a consequence, the body mass index (BMI) could not be calculated in this study. Therefore, caution is required in the extrapolation of our results to patients who are obese as defined by the BMI.

Amongst ambulatory cohorts, overweight and obesity are well-established risk factors for diabetes, cancer and cardiovascular diseases and related mortality [18].

Table 1 Demographic and pre-ECMO physiologic characteristics of study patients according to body weight quartile

Variable	All patients (n = 1,334)	Body weight quartiles				P value
		Q1 25.0–69.3 (n = 340)	Q2 69.3–80.4 (n = 328)	Q3 80.4–101.0 (n = 384)	Q4 101.0–251.0 (n = 282)	
Mortality (%)	38.5	42.1	33.2	40.4	33.3	0.12
Age (years)[a]	39 (27, 53)	36 (24, 52)	38 (26, 55)	42 (31, 54)	40 (30, 51)	0.002
Sex[b]						
Male	758 (56.8)	115 (33.9)	205 (62.9)	250 (65.1)	188 (67.1)	<0.001
Race[b]						
White	920 (69.0)	196 (58.3)	219 (67.4)	284 (74.3)	221 (79.5)	<0.001
Asian	177 (13.3)	90 (26.8)	46 (14.2)	29 (7.6)	12 (4.3)	
Afro-American	125 (9.4)	21 (6.3)	35 (10.8)	37 (9.7)	32 (11.5)	
Hispanic	61 (4.6)	16 (4.8)	14 (4.3)	21 (5.5)	10 (3.6)	
Other	38 (2.8)	13 (3.9)	11 (3.4)	11 (2.9)	3 (1.1)	
Diagnosis[b]						
Pneumonia	541 (40.6)	109 (32.1)	130 (39.6)	177 (46.1)	125 (44.3)	<0.001
Other	793 (59.4)	231 (67.9)	198 (60.4)	207 (53.9)	157 (55.7)	
Pre-ECMO[a]						
Intubation time (h)	62 (21, 152)	55 (19, 179)	53 (16, 126)	70 (24, 142)	67 (27, 157)	0.08
RR (/min)	20 (15, 26)	20 (16, 28)	20 (16, 25)	20 (14, 25)	20 (14, 26)	0.06
PIP (cmH_2O)	37 (32, 44)	36 (32, 42)	36 (32, 42)	37 (32, 43)	40 (35, 46)	<0.001
PEEP (cmH_2O)	14 (10, 17)	12 (10, 15)	14 (10, 16)	15 (10, 18)	15 (12, 18)	<0.001
PaO_2/FiO_2 (torr)	58 (47, 72)	60 (46, 80)	56 (46, 70)	58 (49, 71)	57 (47, 69)	0.59
pH	7.25 (7.15, 7.34)	7.24 (7.15, 7.33)	7.23 (7.12, 7.33)	7.27 (7.16, 7.36)	7.25 (7.17, 7.36)	0.013
pCO_2 (torr)	59 (47, 78)	59 (46, 83)	60 (45, 81)	59 (47, 73)	59 (48, 75)	0.88
HCO_3 (mEq/L)	25 (20, 30)	25 (20, 30)	24 (19, 29)	24 (20, 30)	25 (21, 31)	0.017
BPsys (mmHg)	104 (86, 122)	102 (82, 120)	102 (82, 120)	104 (90, 120)	104 (90, 130)	0.15
BPdias (mmHg)	55 (46, 65)	55 (45, 65)	55 (46, 64)	55 (48, 65)	56 (49, 65)	0.42

RR respiratory rate, *PIP* peak inspiratory pressure, *PEEP* positive end expiratory pressure, PaO_2 partial pressure of oxygen in arterial blood, FiO_2 fraction of inspired oxygen, $PaCO_2$ partial pressure of carbon dioxide in arterial blood, HCO_3 bicarbonate, *BPsys* systolic blood pressure, *BPdias* diastolic blood pressure

[a] Median (Q1, Q3)
[b] n (%)

Table 2 ECMO characteristics of study patients according to body weight quartile

Variable	All patients (n = 1,334)	Body weight quartiles				P value
		Q1 25.0–69.3 (n = 340)	Q2 69.3–80.4 (n = 328)	Q3 80.4–101.0 (n = 384)	Q4 101.0–251.0 (n = 282)	
ECMO year[b]						
2005–2008	354 (26.5)	101 (29.7)	99 (30.2)	97 (25.3)	57 (20.2)	0.018
2009–2011	980 (73.5)	239 (70.3)	229 (69.8)	287 (74.7)	225 (79.8)	
ECMO mode						
VV	828 (62.1)	226 (66.5)	196 (59.8)	229 (59.6)	177 (62.8)	<0.001
VVDL	446 (33.4)	109 (32.1)	123 (37.5)	133 (34.6)	81 (28.7)	
VVDL + V	60 (4.5)	5 (1.5)	9 (2.7)	22 (5.7)	24 (8.5)	
ECMO pump flow[a]						
At 4 h (l/min)	3.9 (3.1, 4.5)	3.2 (2.5, 3.9)	3.8 (3.2, 4.2)	4.1 (3.3, 4.6)	4.3 (3.7, 5.0)	<0.001
At 24 h (l/min)	3.8 (3.1, 4.5)	3.2 (2.6, 3.9)	3.6 (3.1, 4.4)	4.1 (3.4, 4.7)	4.4 (3.7, 5.2)	<0.001
ECMO runs[b]						
1	1,308 (98.1)	333 (97.9)	321 (97.9)	374 (97.4)	280 (99.3)	0.36
2	25 (1.9)	6 (1.8)	7 (2.1)	10 (2.6)	2 (0.7)	
3	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	
ECMO runtime (h)[a]	179 (95, 309)	159 (88, 274)	172 (86, 324)	184 (94, 300)	193 (132, 329)	0.005

VV veno-venous, *VVDL* veno-venous double lumen, *VVDL + V* veno-venous double lumen configuration with additional venous drainage
[a] Median (Q1, Q3)
[b] n (%)

Table 3 Univariate analysis of demographic and pre-ECMO physiologic characteristics of patients for hospital mortality

Variable	OR	95 % CI		*P* value
		Lower	Upper	
Age (years)				
Q1(<27)	Reference	–	–	–
Q2 (27–39)	0.90	0.65	1.24	0.51
Q3 (39–53)	1.30	0.95	1.78	0.10
Q4 (>53)	1.92	1.40	2.63	<0.001
Body weight (kg)				
Q1 (<69)	Reference	–	–	–
Q2 (69–80)	0.82	0.60	1.11	0.20
Q3 (80–101)	0.93	0.69	1.25	0.64
Q4 (>101)	0.69	0.50	0.96	0.03
Primary diagnosis				
Pneumonia	Reference	–	–	–
Other	1.67	1.33	2.10	<0.001
Pre-ECMO				
Intubation time (days)				
<1	Reference	–	–	–
2–3	0.89	0.65	1.21	0.45
4–7	1.70	1.25	2.32	<0.001
>7	2.32	1.70	3.16	<0.001
Respiratory rate (/min)				
Q1 (<15)	Reference	–	–	–
Q2 (15–20)	0.88	0.64	1.23	0.46
Q3 (20–26)	1.16	0.81	1.65	0.42
Q4 (>26)	1.80	1.28	2.51	<0.001
pH				
Q1 (< 7.15)	Reference	–	–	–
Q2 (7.15–7.25)	1.60	1.16	2.21	0.004
Q3 (7.25–7.34)	1.02	0.73	1.44	0.89
Q4 (>7.34)	1.08	0.78	1.50	0.65
pCO_2 (torr)				
Q1 (<47)	Reference	–	–	–
Q2 (47–59)	1.14	0.82	1.59	0.43
Q3 (59–78)	1.35	0.97	1.88	0.07
Q4 (>78)	1.39	1.00	1.93	0.051
HCO_3 (mEq/L)				
Q1 (<20)	Reference	–	–	–
Q2 (20–24)	0.71	0.50	1.01	0.056
Q3 (24–30)	0.93	0.66	1.30	0.66
Q4 (>34)	1.40	1.00	1.95	0.047
BPsys (mmHg)				
Q1 (<86)	Reference	–	–	–
Q2 (86–104)	0.79	0.57	1.10	0.16
Q3 (104–122)	0.61	0.43	0.85	0.004
Q4 (>122)	0.51	0.36	0.72	<0.001
BPdias (mmHg)				
Q1 (<46)	Reference	–	–	–
Q2 (46–55)	0.91	0.66	1.26	0.58
Q3 (55–65)	0.74	0.52	1.04	0.08
Q4 (>65)	0.55	0.39	0.79	<0.001

PaCO2 partial pressure of carbon dioxide in arterial blood *HCO_3* bicarbonate, *BPsys* systolic blood pressure, *BPdias* diastolic blood pressure

Table 4 Univariate analysis of ECMO characteristics for hospital mortality

Variable	OR	95 % CI		*P* value
		Lower	Upper	
ECMO				
2005–2008	Reference	–	–	–
2009–2011	0.72	0.56	0.92	0.009
Mode				
VV	Reference	–	–	–
VVDL	0.60	0.47	0.76	<0.001
VVDL + V	0.57	0.32	1.00	0.050
ECMO pump flow at 4 h (l/min)				
Q1 (<3.1)	Reference	–	–	–
Q2 (3.1–3.9)	0.78	0.57	1.07	0.12
Q3 (3.9–4.5)	0.83	0.60	1.14	0.24
Q4 (>4.5)	0.80	0.58	1.11	0.18
ECMO pump flow at 24 h (l/min)				
Q1 (<3.1)	Reference	–	–	–
Q2 (3.1–3.8)	0.79	0.57	1.10	0.17
Q3 (3.9–4.6)	0.96	0.70	1.33	0.82
Q4 (>4.6)	0.98	0.71	1.36	0.92
ECMO runtime (h)				
Q1 (<95)	Reference	–	–	–
Q2 (95–179)	0.42	0.31	0.58	<0.001
Q3 (179–310)	0.47	0.34	0.65	<0.001
Q4 (>310)	0.91	0.67	1.24	0.56

VV veno-venous, *VVDL* veno-venous double lumen, *VVDL + V* veno-venous double lumen configuration with additional venous drainage

Table 5 Multivariable analysis for hospital mortality

Variable	OR	95 % CI		*P* value
		Lower	Upper	
Age (years)				
Q1 (<27)	Reference	–	–	–
Q2 (27–39)	1.01	0.72	1.41	0.96
Q3 (39–53)	1.50	1.08	2.08	0.015
Q4 (>53)	2.17	1.56	3.02	<0.0001
Body weight (kg)				
Q1 (<69)	Reference	–	–	–
Q2 (69–80)	0.86	0.62	1.19	0.37
Q3 (80–101)	0.96	0.70	1.32	0.81
Q4 (>100)	0.73	0.52	1.04	0.08
Primary diagnosis				
Pneumonia	Reference	–	–	–
Other	1.7	1.33	2.16	<0.0001
Intubation time (days)				
<1	Reference	–	–	–
2–3	0.98	0.71	1.35	0.91
4–7	1.93	1.4	2.66	<0.0001
>7	2.71	1.97	3.75	<0.0001

Counter-intuitively, several meta-analyses have demonstrated that overweight and obesity, in contrast to the deleterious effects in the general population, were associated with similar or even lower mortality rates in critically ill patients [19–23]. This so-called obesity paradox has also been reported for patients undergoing non-bariatric surgery [24] or coronary revascularization [25] and trauma patients [26]. Similarly, obesity has not been associated with higher mortality in mechanical ventilated patients [27, 28] or those with acute lung injury or ARDS [3, 29–31]. It has been speculated that the obesity paradox is caused by a larger nutritional reserve of overweight patients with critical illness [21, 23]. Some studies suggest that adipose tissue

releases factors such as leptin and IL-10, which may favourably modulate the inflammatory response [32, 33].

Patients in our analysis, who were supported with VV ECMO between 2005 and 2011, had a median body weight of 80 kg (IQR 69–101 kg). This needs to be compared to the median body weight of only 61 kg (IQR 50–75 kg) of patients on ECMO for severe respiratory failure reported to the ELSO database in the early 1990s [13]. This increase may not only reflect a rising prevalence of overweight in the general population and critical ill patients with respiratory failure, but possibly also a change in the risk assessment of ECMO utilisation over the last two decades despite scarce published evidence. Mongero et al. [34] reported on two patients with a BMI of more than 50 kg/m^2 and ARDS who were successfully managed with veno-venous ECMO. Brogan et al. [13], who undertook a multivariable analysis of data on adults with severe respiratory failure supported with various ECMO modes in 2002–2006, reported a statistically significantly higher body weight in survivors. Their study, however, included a large number of patients on other modes than VV ECMO from the early years of the last decade and provided no further details of the association of body weight and death.

About half of the adults requiring ICU admission in the USA for the management of H1N1 pandemic influenza were obese [6, 7, 35, 36]. More than a quarter of patients with confirmed critical illness related to H1N1 admitted to ICUs in Australia and New Zealand had a BMI greater than 35 kg/m^2 [37]. The median BMI of those on ECMO support for severe hypoxia related to H1N1 pandemic influenza ranged between 26 and 33 kg/m^2 in various international reports [10–12]. Not surprisingly, our analysis found that the body weight of patients with H1N1 infection on VV ECMO was higher than those without confirmed H1N1 infection.

Obesity and morbid obesity were frequently identified as risk factors for death [6, 8, 38–42] in patients hospitalized with confirmed H1N1. In contrast, our analysis shows that hospital mortality was independent of body weight in patients with H1N1 infection who were supported with VV ECMO. Interestingly, Kok et al. [43] reported recently that the mortality rate of patients admitted to Australian ICUs during the first wave of pandemic H1N1 was not increased in the group of obese patients (mean body weight of 116 kg), which was supported with ECMO in 10 % of cases.

Some methodological factors need to be considered for the interpretation of our study results. Selection bias may have influenced the decision to initiate ECMO for obese patients. The severity of respiratory illness in this group may have been less than that perceived because of the difficulty in interpreting chest radiographs or atelectasis related to the body habitus thus lowering the threshold to initiate ECMO. Similarly, selection bias might have favoured only the "fittest" obese patients being selected for initiation of ECMO support, causing an inverse association of body weight and mortality. Furthermore, high body weight could solely be indicative of a large muscle compartment in patients with an athletic body habitus while unintentional weight loss due to smoking and chronic illness may have contributed to increased mortality in patients with low body weight.

We were not able to adjust for some factors that may be associated with mortality that were not reported such as co-morbidities, severity of illness, ECMO centre, tidal volume and plateau pressures of ventilation before ECMO support and procedures of care (e.g. thrombosis prophylaxis or nutrition). We did not adjust for specific diagnostic groups other than the presence or absence of pneumonia as in a majority of cases diagnoses belonged either to a multitude of infrequent miscellaneous categories or remained altogether unclear. Criteria for the institution and mode of ECMO are centre specific and neither standardized nor included in the ELSO database thus potentially limiting the external validity of our analysis. However, we believe that this outcome analysis, which includes data of the largest number of patients supported with VV ECMO published to date, is a fair representation of recent worldwide practice.

In summary, we have shown that increased body weight was not a risk factor for hospital mortality of adult patients who required support with VV ECMO and may even be protective. Even though obesity has been previously identified as a risk factor for death of hospitalised patients with confirmed H1N1 infection, body weight was not independently associated with increased mortality of those on VV ECMO.

In view of our results, high body weight should not be regarded as a contraindication to initiation of VV ECMO in adult patients. We further recommend that data collection and reporting should include patient height in addition to body weight to facilitate future research into the association of obesity with outcome of ECMO patients.

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