Body Mass Index and Mortality in Subjects With ARDS: Post-hoc Analysis of the OSCILLATE Trial

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BACKGROUND: Studies on the association of obesity with mortality in subjects with ARDS have yielded inconsistent results. METHODS: In a sub-analysis of the Oscillation for ARDS Treated Early (OSCILLATE) randomized controlled trial, 451 subjects were divided into 5 strata based on their body mass index (BMI) using the World Health Organization definitions: underweight < 18.5 kg/m^2; normal weight 18.5–24.99 kg/m^2; overweight 25–29.99 kg/m^2; obese 30–39.99 kg/m^2; severely obese > 40 kg/m^2. The primary outcome was all-cause hospital mortality across BMI strata for all subjects and for the 2 study arms (high-frequency oscillatory ventilation [HFOV] vs conventional ventilation) separately using multivariable logistic regression adjusting for potential confounding variables. RESULTS: Hospital mortality was not different across the BMI strata for all subjects ($P = .86$), for the HFOV arm ($P = .94$) or for the conventional ventilation arm ($P = .59$). After risk adjustment, BMI was not associated with increased risk for hospital mortality (odds ratio 1.01, 95% CI 0.97–1.04, $P = .67$), whereas HFOV was independently associated with increased mortality (odds ratio 1.74, 95% CI 1.11–2.72, $P = .02$) with no effect modification by BMI strata (for this interaction, $P = .56$). Although there was no difference in the use of rescue therapies or in the number of days on sedation or analgesia, higher daily doses of fentanyl and midazolam were administered as BMI increased. CONCLUSION: There was no difference in adjusted hospital mortality across BMI strata in subjects with moderate to severe ARDS. Processes of care were not different across BMI strata except for higher daily doses of fentanyl as BMI increased. (ClinicalTrials.gov registration NCT0150640) *Key words: randomized; controlled trial; mechanical ventilation; high-frequency ventilation; obesity; mortality* [Respir Care 2019;64(9):1042–1048. © 2019 Daedalus Enterprises]

Introduction

The prevalence of obesity in the world is increasing dramatically. Reports indicate that two thirds of the population in the United States is overweight or obese, with a body mass index (BMI) > 25 kg/m^2.[1] Obese patients are at increased risk of comorbidities, have different adaptive mechanisms to illnesses and stresses, and altered cardiopulmonary physiology. Studies have demonstrated that hospitalized obese patients are more likely to require mechanical ventilation than non-obese patients.[2] The association

between obesity and increased all-cause mortality in the general population is well described.[3,4] Among critically ill patients, studies have shown that obesity is associated with an increased risk of developing ARDS,[5] but the association between obesity and mortality in ARDS is inconsistent.[6] A secondary analysis of the ARDS Network study comparing low tidal volumes of 6 mL/kg versus

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12 mL/kg did not show any difference in outcome between obese and normal weight subjects.[7] Other studies have suggested better survival for obese subjects with ARDS compared to subjects with normal weight.[5] Studies have also shown that being underweight is associated with increased mortality in subjects with ARDS.[8]

The Oscillation for ARDS Treated Early (OSCILLATE) study was a randomized, controlled trial that randomized adults with moderate-to-severe ARDS to high-frequency oscillatory ventilation (HFOV) or conventional mechanical ventilation. The purpose of this sub-analysis of the OSCILLATE trial was to examine the association of BMI on mortality and relevant processes of care of subjects with moderate-to-severe ARDS. We hypothesized that mortality differs across different BMI strata and that these differences may be related to variations in certain processes of care. The OSCILLATE dataset represents a unique opportunity to address this question because it includes subjects who were managed closely by protocolized conventional ventilation that was based on lung-protective strategy. It also includes subjects managed with HFOV, a group in which the relation of BMI and outcomes has not been studied before.

Methods

Study Subjects and Sample

The OSCILLATE trial randomized 548 subjects with moderate-to-severe ARDS to HFOV or conventional ventilation from 39 ICUs in Canada, the United States, Saudi Arabia, Chile, and India.[9] Institutional review boards of

QUICK LOOK

Current knowledge

Obesity has been associated with increased risk of death in the general population. In ARDS, the association of obesity with mortality has yielded inconclusive results.

What this paper contributes to our knowledge

Death in hospital was not different among BMI strata in the whole study cohort, nor for the high-frequency oscillatory ventilation and conventional ventilation groups. High-frequency oscillatory ventilation was independently associated with increased mortality.

the participating centers approved the study. Patients were eligible for inclusion if they had had an onset of pulmonary symptoms within the previous 2 weeks, had undergone tracheal intubation, had hypoxemia ($P_{aO_2}/F_{IO_2} \leq 200$, with an $F_{IO_2} \geq 0.5$), and had bilateral air-space opacities on chest radiography. Written informed consent was obtained from all the subjects or their legal representatives. After enrollment, a standardized assessment of hypoxemia was performed using pressure control mode, a tidal volume of 6 mL/kg, and an F_{IO_2} of 0.60 with a PEEP level of 10 cm H_2O or higher. After 30 min, if the P_{aO_2}/F_{IO_2} ratio remained at or below 200, the subject was randomized. The trial excluded patients weighing < 35 kg, obese patients with actual body weight > 1 kg per centimeter in height, and patients with documented chronic CO_2 retention (P_{aCO_2} > 50 mm Hg). For this secondary analysis, 451/548 (82%) of subjects had available baseline weight data and were divided into 5 strata of BMI using baseline study data. The enrollment measured weight and height provided the data for BMI calculations for each subject. BMI was calculated by dividing subjects' body weight by the square of their height in meters (kg/m^2).[10] The strata were categorized based on the World Health Organization classification:[10] underweight < 18.5 kg/m^2; normal weight 18.5–24.99 kg/m^2; overweight 25–29.99 kg/m^2; obese 30–39.99 kg/m^2; severely obese > 40 kg/m^2.

Subject demographics, processes of care, and outcomes data were obtained from the original trial database. We extracted data on the following processes of care, which may affect outcome: the doses of intravenous infusions of sedatives and analgesics, the use of neuromuscular blockade, fluid balance (calculated as the average daily balance for the first 3 d), and oxygenation rescue therapies (eg, nitric oxide, prone positioning, HFOV in the subjects in the conventional ventilation group). The primary outcome was hospital mortality. Secondary outcomes were ICU and 28-d mortality, mechanical ventilation settings, ICU and

hospital length of stay (reported from the time of randomization), and incidence of barotrauma (pneumothorax, pneumomediastinum, pneumopericardium, or subcutaneous emphysema occurring spontaneously or after a recruitment maneuver).

Statistical Analysis

We reported categorical and continuous variables using means and standard deviation, medians and interquartile ranges, or counts and percentages, as appropriate. We compared demographic data, processes of care, and outcomes across BMI strata using chi-square and analysis of variance, as appropriate. We examined the independent association of BMI and hospital mortality by constructing a multivariate logistic regression model adjusting for the following variables: age (in 10-y increments), acute physiology score (in 5-unit increments), days in hospital prior to randomization, sepsis, and treatment group (HFOV vs conventional ventilation). Results are expressed as odds ratios (ORs) with 95% CI. We implemented the above analyses for the whole cohort and for the 2 study arms (ie, HFOV and conventional ventilation) separately. To examine whether HFOV compared to conventional ventilation has a differential effect across BMI on mortality, we compared mortality between HFOV and conventional ventilation for each BMI strata. We tested whether BMI is an effect modifier of the association between the mode of ventilation and mortality by an interaction term in the model. Tests were 2-sided, and a P value < .05 was considered significant. SAS v. 9.3 (SAS Institute, Cary, North Carolina) was used to analyze the data.

Results

Baseline Characteristics

Table 1 shows the baseline characteristics of subjects across the BMI strata. There were no differences in the baseline characteristics of subjects by BMI strata for age, severity of illness, ARDS etiology, pre-enrollment ventilator settings, or severity of hypoxemia. Sex distribution was different across the BMI strata (P = .005), with a higher proportion of females among the 2 highest BMI strata.

The pre-enrollment ventilator settings and the severity of hypoxemia were similar across the BMI strata (Table 1). Specifically, tidal volume, PEEP, plateau pressure, driving pressure, P_{aO_2}/F_{IO_2}, and pH were similar.

Processes of Care

Subjects received higher doses of midazolam and fentanyl as BMI increased (Table 2); however, there was no difference in the average daily dose of propofol or morphine. There was no difference in the number of days on sedation or analgesia or neuromuscular blockade, in cumulative fluid balance for the first 3 d, or in the use of rescue therapies across BMI strata (Table 2). Process of care among subjects in the HFOV and conventional ventilation groups are shown in supplemental Table 2 (see the supplementary materials at http://www.rcjournal.com).

Outcomes

Death in hospital was not different among BMI strata in the whole study cohort (Fig. 1, Table 3). Running the analysis separately by group did not materially change any associations (Table 3 in the supplementary materials at http://www.rcjournal.com). After risk adjustment, BMI was not associated with increased risk for hospital mortality (OR 1.01, 95% CI 0.97–1.04, P = .67), whereas HFOV was independently associated with increased mortality (OR 1.74, 95% CI 1.11–2.72, P = .02) (Table 4). The association between HFOV and hospital mortality was not modified by BMI strata (P value for interaction = .56, Fig. 1). There was no difference in mechanical ventilator days, ICU length of stay, or barotrauma across all BMI strata (Table 3).

Discussion

In the OSCILLATE trial, there was no difference in hospital mortality across BMI strata. BMI was not an effect modifier of the association between mode of ventilation and mortality. Subjects received higher doses of midazolam and fentanyl with increasing BMI strata, but this did not appear to translate to better or worse outcomes for increasing BMI levels.

Excess body weight has been associated with increased risk of developing ARDS. In a prospective study of 1,795 ICU subjects at risk for ARDS, obesity was associated with ARDS compared with normal weight (OR 1.66, 95% CI 1.21–2.28 for obese; OR 1.78, 95% CI 1.12–2.92 for severely obese).[11] However, the effect of BMI on survival outcomes in subjects with ARDS is not clear.[5,9] O'Brien et al[6] examined the outcome of subjects enrolled in the ARMA trial and reported that the adjusted 28-d mortality was not affected by BMI (adjusted OR 0.80, 95% CI 0.30–2.13, P > .2), and the benefits of lower tidal volume were similar for all BMI categories. In a related prospective cohort study, the mortality of 825 subjects with ARDS was lower in the severely obese subjects (25.9%) compared to subjects with normal weight. The adjusted mortality, however, was not significantly different between all BMI categories.[5] In a large (N = 1,488 subjects) retrospective ARDS database study, lower BMIs

Table 1. The Baseline Characteristics of Subjects Across the BMI Strata Before Randomization

	BMI Strata					*P*
	< 18.5 (*n* = 14)	18.5–24.99 (*n* = 118)	25–29.99 (*n* = 146)	30–39.99 (*n* = 137)	≥ 40 (*n* = 36)	
Age, y	55.9 (44.3–73.8)	52.2 (42.4–65.9)	55.4 (43.3–64.8)	56.9 (47.6–67.1)	57.4 (39.0–63.8)	.38
Female sex	5 (35.7)	53 (44.9)	44 (30.1)	65 (47.5)	21 (58.3)	.005
APACHE II score	31.5 (24–36)	28 (24–35)	28 (24–34)	29 (24–33)	28.5 (23–33.5)	.82
Time in hospital prior to study, d	4.5 (2–12)	3 (1–6)	3 (1–5)	2 (1–6)	1 (1–4)	.02
Duration of mechanical ventilation prior to study, d	2 (2–3)	1 (1–3)	1 (1–3)	2 (1–3)	1 (1–2.5)	.55
Risk factors for ARDS						
Sepsis	8 (57.1)	52 (44.1)	66 (45.2)	62 (45.3)	21 (58.3	.54
Pneumonia	6 (42.9)	76 (64.4)	88 (60.3)	92 (67.2)	17 (47.2)	.11
Gastric aspiration	4 (28.6)	24 (20.3)	22 (15.1)	17 (12.4)	6 (16.7)	.29
Trauma	0 (0)	2 (1.7)	5 (3.4)	7 (5.1)	0 (0)	.51
H1N1	0 (0)	4 (3.4)	10 (6.9)	5 (3.7)	1 (2.8)	.66
Other	2 (14.3)	23 (19.5)	25 (17.1)	24 (17.5)	7 (19.4)	.98
Ventilator mode on enrollment						.16
Pressure assist control	9 (64.3)	49 (41.5)	84 (57.5)	71 (51.8)	22 (61.1)	NA
Volume assist control	5 (35.7)	35 (29.7)	32 (21.9)	34 (24.8)	5 (13.9)	NA
Volume-targeted pressure control	0 (0)	21 (17.8)	16 (10.9)	25 (18.3)	5 (13.9)	NA
Pressure support	0 (0)	12 (10.2)	11 (7.5)	7 (5.1)	4 (11.1)	NA
Other	0 (0)	1 (0.9)	3 (2.1)	0 (0)	0 (0)	NA
Tidal volume, mL/kg predicted body weight	5.9 (5.5–6.5)	6.17 (5.9–6.9)	6.14 (5.9–6.9)	6.14 (5.9–7.4)	6.25 (5.66–7.5)	.38
Plateau pressure, cm H_2O	32 (28–35)	28.5 (25–33)	30 (24–34)	30 (26–34)	30 (28–34)	.41
Set PEEP, cm H_2O	13 (10–15)	12 (10–15)	12 (10–15)	14 (10–16)	15 (12–17.5)	.09
Driving pressure, cm H_2O	18 (15–23)	15 (12–19)	16 (12–20)	16 (12–20)	15 (12,20)	.60
Minute ventilation, L/min	11.8 (9.3–13.3)	10.04 (8.4–13.1)	11 (8.8–12.3)	10.8 (9.2–13)	10.89 (8.8–12.4)	.54
Oxygenation index	15.6 (14.1–29.3)	17.48 (11.3–25.8)	16.5 (11.8–23.6)	19.91 (12.5–25.9)	21.76 (16.8–25.7)	.11
P_{aO_2}/F_{IO_2}	125.2 (109.3–150)	108.33 (78.8–141.7)	120.83 (93.5–148.1)	109.17 (82–136.7)	110 (86–125.3)	.19
P_{aCO_2}, mm Hg	42 (40–46)	45 (39–53)	44 (38.5–52)	44 (40–53)	44 (36.5–54.5)	.98
Arterial pH	7.3 (7.3–7.4)	7.31 (7.2–7.4)	7.31 (7.3–7.4)	7.33 (7.3–7.4)	7.32 (7.3–7.4)	.25
Use of HFOV	8 (57.1)	65 (55.1)	79 (54.1)	73 (53.3)	16 (44.4)	.84

Data are presented as median (interquartile range) or *n* (%). BMI strata are as defined by the World Health Organization.
BMI = body mass index
APACHE II = Acute Physiology and Chronic Health Evaluation
HFOV = high-frequency oscillatory ventilation

were associated with higher odds of death, whereas overweight and obese BMIs were associated with lower odds (overweight adjusted OR 0.72, 95% CI 0.51–1.02; obese adjusted OR 0.67, 95% CI 0.46–0.97; severely obese adjusted OR 0.78, 95% CI 0.44–1.38).[2]

We considered several explanations as to why the outcomes of patients with ARDS could differ across BMI strata and why studies have yielded inconsistent results regarding this association. First, there may be variations in case identifications across BMI strata, especially in nonprotocolized observational studies. For instance, very high BMI can confound chest radiograph interpretations with the appearance of lower lung volumes and thus can potentially lead to an overestimate of the extent of air-space disease. This is less likely in the OSCILLATE trial because the identification of cases was protocolized and included a standardized hypoxemia assessment. Second, very high BMI can confound estimates of disturbance in oxygenation as a result of effects on transpulmonary pressure.

Third, differences in mortality between obese and nonobese patients reported in some studies may be explained by other residual confounding ventilator parameters.[7] However, this was not the case in our study because tidal volumes were not different across different BMI strata.[12] Fourth, our study showed that obese subjects received higher doses of midazolam and fentanyl. Excessive use of sedation has been linked to poorer outcome in critically ill patients. This is further cofounded by the fact that most of these drugs are lipophilic[13] and their volume of distribution is increased in obese individuals, further increasing the possibility of prolonged and excessive sedation in obese patients with ARDS[14,15]; however, we did not observe longer ICU or hospital lengths of stay among subjects with higher BMI. Higher doses of sedation may have facilitated lung-protective strategies and decreased risk of ventilator-induced lung injury from patient-ventilator asynchrony by avoiding large swings of pleural pressure and thus high tidal volumes.[16] Fifth, other aspects of general ICU man-

Table 2. Processes of Care for Subjects Across the BMI Strata During the Study Period

	BMI Strata					P
	< 18.5 (n = 14)	18.5–24.99 (n = 118)	25–29.99 (n = 146)	30–39.99 (n = 137)	≥ 40 (n = 36)	
Average daily dose of sedative or narcotics administered						
Midazolam, mg	95.6 (40.4–203.4)	142.3 (79–264.5)	135.3 (63.6–290.3)	195.3 (100.22–394.1)	169 (79.5–262.7)	.04
Propofol, mg	1,448 (114–1,814)	1,238 (693–2,635)	1,499 (480–2,816)	1,443 (622–3,084)	1,450 (170–3,088)	.71
Fentanyl, μg	1,228 (213–2,453)	2,525 (1,328–3,670)	2,600 (1,374–4,555)	3,142 (1,937–5,031)	3,977 (2,477–5,038)	< .001
Morphine, mg	52.7 (35.2–175.9)	62.8 (5.8–185.3)	63.5 (5–156.3)	60.6 (8–170)	130.7 (8–240)	.90
Duration of sedative or narcotic, d	8.5 (6–19)	9 (5–18)	10 (6–17)	10 (7–16)	10 (6–16)	.86
Neuromuscular blockade	11 (78.6)	83 (70.3)	91 (62.3)	94 (68.6)	30 (83.3)	.13
Duration of neuromuscular blockade, d	2 (1–3)	2 (1–5)	2 (0–5)	3 (1–6)	4 (1–5)	.39
Average cumulative fluid balance for the first 3 d, mL	3,230 (−2,822 to 5,865)	1,540 (−1,649 to 5,160)	1,920 (−1,859 to 6,344)	1,146.5 (−2,054 to 5,813.5)	−2,359 (−4,625 to 4,054)	.12
Oxygen rescue therapy						
Inhaled nitric oxide	0 (0)	18 (15.3)	15 (10.3)	16 (11.7)	2 (5.6)	.37
Prone positioning	0 (0)	1 (0.9)	4 (2.7)	4 (2.9)	0 (0)	.68
Other rescue therapy	1 (7.1)	8 (6.9)	7 (4.8)	8 (5.8)	4 (11.1)	.61

Data are presented as median (interquartile range) or n (%). BMI strata are as defined by the World Health Organization.
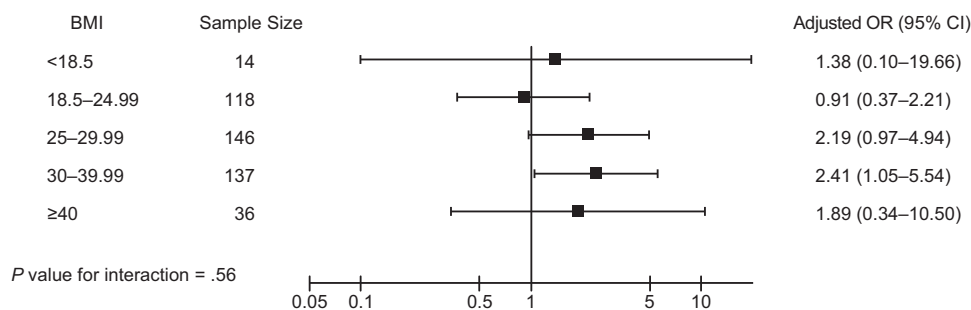BMI = body mass index

Fig. 1. In-hospital death according to BMI. BMI = body mass index; OR = odds ratio.

Table 3. Outcomes of Subjects Across the BMI Strata

	BMI Strata					P
	< 18.5 (n = 14)	18.5–24.99 (n = 118)	25–29.99 (n = 146)	30–39.99 (n = 137)	≥ 40 (n = 36)	
Death in hospital	6 (42.9)	51 (43.2)	57 (39.0)	56 (40.9)	12 (33.3)	.86
Death in ICU	6 (42.9)	46 (39.0)	53 (36.3)	50 (36.5)	12 (33.3)	.96
New barotrauma	4 (28.6)	28 (23.7)	29 (19.9)	20 (14.6)	5 (13.9)	.28
New tracheostomy	5 (35.7)	30 (25.4)	35 (24.0)	28 (20.4)	4 (11.1)	.25
Refractory hypoxemia	1 (7.1)	22 (18.6)	13 (8.9)	18 (13.1)	2 (5.6)	.12
Refractory acidosis	0 (0)	3 (2.5)	6 (4.1)	5 (3.7)	2 (5.6)	.85
Duration of mechanical ventilation, d	7 (6–14.5)	10 (5–19)	11 (7–17)	13 (8–20)	9 (7–1)	.29
Duration of mechanical ventilation in survivors, d	7 (6–14.5)	10 (5–18.5)	11 (7–17)	12.5 (8–22)	9 (7–14.5)	.24
ICU length of stay, d	16 (6–33)	13 (6–26)	13 (7–21)	13 (9–22)	12 (9–17)	.79
ICU length of stay in survivors, d	16 (7.5–31.5)	15 (7.5–26)	14 (9–24)	16 (11–28)	11.5 (9–18.5)	.38
Hospital length of stay, d	27 (16.5–63.5)	24.5 (15–42)	30 (14–41)	30 (16–48)	22 (15–31)	.58
Hospital length of stay in survivors, d	27 (16.5–63.5)	23 (14–40)	29 (14–40)	30 (16–45)	22 (15–31)	.51

Data are presented as median (interquartile range) or n (%). BMI strata are as defined by the World Health Organization.
New barotrauma = pneumothorax, pneumomediastinum, pneumopericardium, or subcutaneous emphysema occurring spontaneously or after a recruitment maneuver. Excluded from this category were patients who had barotrauma at baseline.
Refractory hypoxemia = $P_{O_2} < 60$ mm Hg or $S_{pO_2} < 88\%$ on F_{IO_2} of 1.0 for 60 min despite a trial of paralysis.
Refractory acidosis = pH < 7.05, despite a trial of paralysis and other measures to correct acidosis described for study group.
BMI = body mass index

agement may be different across different BMI strata. In an observational study, obese subjects were more likely to receive pharmacologic prophylaxis for thromboembolism.[5] Finally, the extent of lung-protective strategies may be different across different BMI strata. In our study, subjects had similar plateau pressures across all BMI strata, but because obese patients tend to have lower transpulmonary pressures because of higher pleural pressure, they may have had additional lung protection or, to the contrary, they may have had more atelectotrauma from cyclic opening and closure of the alveolar units. There was no measurement of the pleural pressure by esophageal probes in our subjects. Offsetting this phenomenon, excessive use narcotics and midazolam in obese subjects might have negated any benefit that could have resulted from lower transpulmonary pressure and negative fluid balance.

Obesity affects chest wall mechanics; therefore, ventilation strategies may lead to different outcomes in obese subjects compared to non-obese subjects.[17] HFOV, which delivers high mean airway pressure with small tidal volumes at very high frequencies has been recently examined in the OSCILLATE trial, which demonstrated that HFOV was associated with increased risk of death. This subanalysis indicates that the association of ventilation strategy and mortality was not modified by BMI strata. This is consistent with the findings of a recent individual-subject meta-analysis.[18]

Strengths of our study include prospective data collection, protocolized mechanical ventilation, and multicenter involvement. Unlike observational reports, the OSCILLATE trial included explicit clinical protocols that help reduce provider bias and practice variation in each BMI strata. Subjects in the trial had similar tidal volumes upon enrollment. Because outcomes may be different at both extremes of weight, we chose to categorize subjects according to BMI groups rather than use BMI as a con-

Table 4. Logistic Regression Adjusted Analysis of Hospital Mortality With BMI

	Odds Ratio (95% CI)	P
Age, 10-y increase	1.40 (1.21–1.64)	< .001
Acute physiology score, 5-unit increase	1.66 (1.37–2.01)	< .001
Time in hospital prior to randomization, d	1.10 (1.05–1.16)	< .001
Sepsis, yes vs. no	0.85 (0.46–1.61)	.64
BMI	1.01 (0.97–1.04)	.67
HFOV versus conventional ventilation	1.74 (1.11–2.72)	.02

182 of 451 subjects (40.4%) died during hospital stay.
BMI = body mass index
HFOV = high-frequency oscillation ventilation

tinuous variable. Weaknesses include being a post hoc analysis. The OSCILLATE trial excluded obese patients with actual body weight > 1 kg per centimeter in height, which means that extremely obese patients are underrepresented in our cohort. In addition, we included only 82% of the OSCILLATE cohort because weight data were not available. Because the cohort was stratified into 5 strata, some of the analyses may have been underpowered, and true differences may not have been detected. Some studies have suggested that the association of mortality with BMI may follow a J-shaped or U-shaped curve, with increasing mortality in severe obesity and in very low BMI. Because the OSCILLATE trial excluded both extremes of weight, our study is not designed to address the associations at both extremes of BMI.

Conclusions

In the OSCILLATE Trial, there was no difference in adjusted hospital mortality across all BMI strata in subjects with moderate-to-severe ARDS. Processes of care were not different between the BMI strata except for higher daily doses of fentanyl as BMI increased.

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