Internal and Emergency Medicine
https://doi.org/10.1007/s11739-022-03118-2

RESEARCH LETTER TO THE EDITOR

Reporting and representation of obesity in randomized controlled trials of noninvasive oxygenation strategies in hypoxemic respiratory failure

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Received: 13 August 2022 / Accepted: 29 September 2022

Keywords Obesity · Noninvasive oxygen · Acute hypoxemic respiratory failure

Dear Editor,

Hypoxemic respiratory failure is a common cause of critical illness and is associated with high rates of mortality [1]. Obesity is a major risk factor for developing hypoxemic respiratory failure, an association that has been highly visible within the coronavirus pandemic, where nearly half of patients needing intensive care have had obesity [2–4].

Noninvasive oxygen is an initial respiratory support that may preserve spontaneous breathing and prevent tracheal intubation. There are several devices available to clinical providers that deliver oxygen with variable positive airway pressure and subsequent effectiveness depending on the etiology of hypoxemia [5]. Obese patients are prone to alveolar collapse from high pleural pressure and cranial displacement of the diaphragm, resulting in impairments in gas exchange [6]. End expiratory lung volume may improve with use of strategies that create more inspiratory recruitment and higher levels of positive end expiratory pressure to overcome the effect of excessive adiposity. A favorable physiologic response when using these strategies in obese individuals has been seen in invasive ventilation for acute respiratory distress syndrome and in postoperative management after bariatric surgery [7, 8]. There is likely sufficient rationale to think that obese individuals represent a source for heterogeneity of treatment effect in trials of noninvasive oxygenation strategies. While noninvasive oxygenation strategies have been compared in prior randomized controlled trials, it is unclear how evidence applies to individuals with obesity [9].

To provide applicable information to treating clinicians, randomized controlled trials focused on noninvasive oxygen support must ensure adequate enrollment of obese patients and be transparent in their reporting of obesity. Our objective was to determine the available reporting of information about the eligibility and enrollment of obese participants in trials of noninvasive oxygen support in hypoxemic respiratory failure.

Methods

Selection of trials

We selected all trials that were included in a high impact systematic review and meta-analysis assessing the comparative effectiveness of different noninvasive oxygenation strategies in hypoxemic respiratory failure [9]. In summary, the meta-analysis identified 25 trials from 1995 through 2020 that enrolled adult patients (aged ≥ 18 years) with hypoxemic respiratory failure comparing high flow nasal oxygen, facemask ventilation, helmet noninvasive ventilation and standard oxygen therapy evaluating either mortality, endotracheal intubation, or both. These trials included critically ill patients from 10 different countries.

Data collection

We reviewed the manuscript, registration record and protocol when available for each trial. Trial authors were not contacted for study data. We documented if the trial inclusion or exclusion criteria restricted enrollment based on

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Published online: 14 October 2022

body mass index (BMI) or other markers of weight. We then reviewed each trial to determine if BMI was reported. If available, we collected summary statistics (e.g., mean, standard deviation) for BMI as well as the proportion of enrolled obese participants. We defined obesity based on the conventional standard of a BMI ≥ 30 kg/m^2 and morbid obesity as a BMI ≥ 40 kg/m^2.

Data analysis

In cases where the proportion of obese participants was not reported yet summary statistics on BMI were available, we estimated the obese proportion under the assumption that BMI followed a normal distribution and summarized the proportions across trials using median and interquartile range (IQR) [10].

Results

We included 25 RCTs (3804 participants enrolled in 10 countries) that compared noninvasive oxygenation strategies in hypoxemic respiratory failure. Detailed characteristics of the trials are previously reported [9]. The main etiology of hypoxemic respiratory failure was community-acquired pneumonia in 16 (64%) trials and 14 (56%) trials included immunocompromised patients. We found a registration record in 17 (68%) and a protocol in 7 (28%) trials.

Available reporting of BMI and obesity

From review of available trial information, no trials specifically targeted obese participants for enrollment. 2 (8%) trials excluded patients with a BMI ≥ 40 kg/m^2 and 3 (12%) excluded patients with a history of sleep disorders such as obstructive sleep apnea. Information on BMI was provided in 7 (28%) trials. No trial performed subgroup analyses based on BMI.

Representation of obesity

Only 1 (4%) trial reported the proportion of obese participants. Of the 7 trials that reported BMI data, 6 provided the mean and standard deviation of BMI and 1 trial provided the median and IQR. BMI data for these trials were provided for each intervention but did not report that BMI and distribution for the total study cohort.

Of the 1336 participants enrolled in trials that provided BMI data, we estimated that 337 (25.2%) were obese and 59 (4.4%) were morbidly obese. As shown in Fig. 1, the median proportion of obese participants in the 7 trials that reported BMI information was 21.7 (IQR 2.6, 21.7) and the median proportion of morbidly obese participants was 0.5 (IQR 0, 7.8).

Discussion

In our systematic review of randomized controlled trials on noninvasive oxygenation strategies in hypoxemic respiratory failure, we found that the majority of trials underreported information on obesity. Only 28% of trials reported participant BMI and only 4% of trials reported the proportion of obese participants. The estimated proportion of obesity in trials with available BMI data was 21.7.

The majority of trials on noninvasive oxygenation fail to report vital information on participant BMI. Obesity is a highly prevalent co-morbidity in critical illness and a

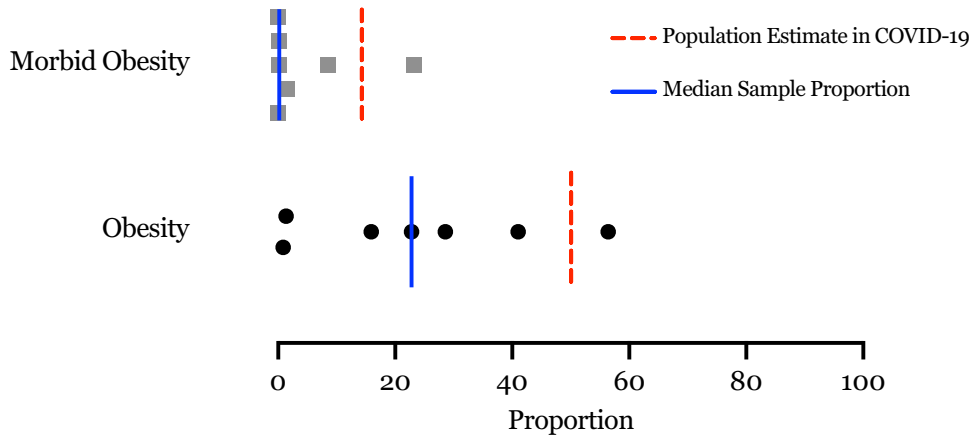

Fig. 1 Representation of Obesity in Clinical Trials of Non-Invasive Oxygenation Support. Proportion of obese (black circle) and morbidly obese (gray square) participants in the 7 randomized controlled trials with available body mass index data. Median proportion for obesity and morbid obesity for the 7 trials (blue line). Centers for Disease Control and Prevention estimates of obesity and morbid obesity in individuals admitted to the intensive care unit with COVID-19 pneumonia (dashed red line)

major risk factor for acute respiratory failure and the need for invasive ventilation. Obese individuals have worse clinical outcomes from acute respiratory failure including ventilator dependence compared to non-obese individuals [2]. Respiratory mechanics in obesity are distinctly impaired, in part due to reductions in transpulmonary pressure and subsequent alveolar collapse [6]. Reassuringly, impairments in gas exchange can be prevented and/or corrected with appropriate ventilation strategies. In other clinical contexts, use of ventilation strategies that maximize positive end expiratory pressure and recruitment have improved oxygenation and lung aeration in obese individuals and may lower mortality [7, 8]. As noninvasive oxygenation strategies deliver variable airway pressure, obese individual are likely to have different physiologic responses depending on the choice of the device and its settings. Without reporting of BMI and with potential under-representation of obesity, treatment effects estimated from these trials may be misleading when applied to obese individuals. Of concern, noninvasive strategies may be selected that that do not adequately counteract the elevated pleural pressure in obesity and can lead to worsening alveolar collapse and impairments in gas exchange. Moreover, the current state of reporting limits applicability to coronavirus infection where the prevalence of obesity in intensive care settings exceeds 50% in certain countries [3, 4].

The reasons for under-reporting and under-representation require exploration. While the prevalence of obesity has increased globally, clinicians and researchers may be less aware of obesity's adverse effects on respiratory mechanics, leading to unintentional omission of obesity data. Negative stereotypes and prejudice toward obesity is common in medical settings and decreases enrollment of obese individuals into clinical research [11]. Furthermore, racial and ethnic minorities are already poorly represented in critical care trials and are disproportionately affected by obesity [12]. Our study has limitations. We only included trials that assessed mortality and tracheal intubation, yet this captures trials over 20 years and from multiple countries. Due to the lack of reporting and that we did not contact trial authors, we estimated the proportion of obesity from summary statistics which may not reflect the true number of obese patients enrolled.

In summary, we found that randomized controlled trials on noninvasive oxygenation strategies in hypoxemic respiratory failure vastly underreport BMI and may underrepresent the obese population. Future trials assessing noninvasive oxygenation strategies in the context of acute hypoxemic respiratory failure should explicitly report the proportion of obese patients and consider targeted enrollment and analyses.

Funding No funding was received for conducting this study.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Consent for publication This research does not involve human participants and/or animals.

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