

Body Mass Index and clinical outcome of severe COVID-19 patients with acute hypoxic respiratory failure: unravelling the “obesity paradox” phenomenon

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Abstract

Background and aims: Although obesity have been generally shown to be an independent risk factor for poor outcomes in COVID-19 infection, some studies demonstrate a paradoxical protective effect (“obesity paradox”). This study examines the influence of obesity categories on clinical outcomes of severe COVID-19 patients admitted to an intensive care unit with acute hypoxic respiratory failure requiring either non-invasive or invasive mechanical ventilation.

Methods: This is a single centre, retrospective study of consecutive COVID-19 patients admitted to the intensive care unit between 03/2020 to 03/2021. Patients were grouped according to the NICE Body Mass Index (BMI) category. Admission variables including age, sex, comorbidities, and ICU severity indices (APACHE-II, SOFA and $\text{PaO}_2/\text{FiO}_2$) were collected. Data were compared between BMI groups for outcomes such as need for invasive mechanical ventilation (IMV), renal replacement therapy (RRT) and 28-day and overall hospital mortality.

Results: 340 patients were identified and of those 333 patients had their BMI documented. Just over half of patients (53%) had obesity. Those with extreme obesity (obesity groups II and III) were younger with fewer comorbidities, but were more hypoxaemic at presentation, than the healthy BMI group. Although non-significant, obesity groups II and III paradoxically showed a lower in-hospital mortality than the healthy weight group. However, adjusted (age, sex, APACHE-II and CCI) competing risk regression analysis showed three-times higher mortality in obese category I (sub-distribution hazard ratio = 3.32 (95% CI 1.30-8.46), $p=0.01$) and a trend to higher mortality across all obesity groups compared to the healthy weight group.

Conclusions: In this cohort, those with obesity were at higher risk of mortality after adjustment for confounders. We did not identify an “obesity paradox” in this cohort. The obesity paradox may be explained by confounding factors such as younger age, fewer comorbidities, and less

severe organ failures. The impact of obesity on indicators of morbidity including likelihood of requirement for organ support measures was not conclusively demonstrated and requires further scrutiny.

Keywords

COVID-19

Intensive care

Body mass index

Obesity

Acute hypoxic respiratory failure

Invasive mechanical ventilation

Introduction

Over the last two years, the COVID-19 pandemic, caused by a novel strain of beta coronavirus (SARS-CoV-2), has secured its place in history, infecting over 300 million people and placing unprecedented stress on the global health infrastructure [1]. The emergence of this pandemic has focused attention on individual risk stratification, in part, because constraints on healthcare resources such as immunisations have promoted a strategy of protecting the most vulnerable individuals first. The risk factors for increased severity of COVID-19 infection are well-documented and include increased age, ethnicity, presence of cardiovascular disease, chronic lung disease and diabetes mellitus [2–4].

The role of obesity in patient outcomes is of interest due to its increasing prevalence across western and now developing world. Based on global data from 2016, the it is estimated that by 2025, global obesity prevalence will reach 18% in men and surpass 21% in women [5]. There is also a large body of evidence that supports obesity as a risk factor for poorer outcome in a range of respiratory viral infections, including H1N1 influenza and the Middle East Respiratory Syndrome–Related Coronavirus (MERS-CoV) [6,7]. The impact of obesity on the disease course of COVID-19 is less clear, with outcome heterogeneity across a range of observational studies. A large multi-centre retrospective cohort study of critically ill COVID-19 patients demonstrated a linear association between BMI and the need for invasive mechanical ventilation, independent of other metabolic risk factors, and a non-linear association between increasing BMI and 28-day all-cause mortality [8]. This relationship between BMI and mortality was also investigated by several other observational studies [9–13], but the relationship was not universally observed. Some studies found increased BMI was associated with an increased risk of requiring intubation and ventilation, but with no clear relationship with mortality [14–17]. In contrast, the Intensive Care National Audit and Research Centre

(ICNARC) highlighted a paradoxical relationship within the national dataset whereby increasing BMI was associated with lower 28-day in-hospital mortality [18]. This finding is supported by the Practice of Ventilation in COVID-19 (PRoVENTCOVID) study, which enrolled patients from 22 intensive care units and found higher rates of in-hospital mortality, ICU mortality and 90-day all-cause mortality in overweight and healthy individuals than obese patients. However, this effect diminished when the analysis was adjusted for age, co-morbidities, and a range of other physiological parameters [19].

The “Obesity Paradox”, where higher BMI can appear protective in individual datasets, has been previously observed in end-stage renal disease [20], chronic obstructive pulmonary disease (COPD) [21], and pulmonary embolism [22]. If there is an “obesity paradox” in the context of COVID-19 [23], its root cause is not universally agreed upon. Consequently, we explored the relationship between body mass index (BMI) and outcomes in a retrospective cohort of critically ill COVID-19 patients admitted to our intensive care unit with acute hypoxic respiratory failure.

Methods

All adults (≥ 18 years old) in whom SARS-CoV-2 positivity was confirmed by RT-PCR (Reverse-Transcriptase Polymerase Chain Reaction) admitted to the General Intensive Care Unit (GICU) at University Hospital Southampton NHS Foundation Trust between 19th March 2020 and 12th March 2021, a period that covered two distinct waves of the pandemic in the UK, were included in this study. Patients were sub-categorized into five BMI classes according to National Institute of clinical Excellence (NICE) BMI classification: healthy weight (BMI 18.5 - 24.9 kg/m²), overweight (25 - 29.9 kg/m²), Obesity I (30 - 34.9 kg/m²), Obesity II (35 - 39.9 kg/m²) and Obesity III (>40 kg/m²) [24]. This study has ethical approval as part of "a longitudinal cohort study to facilitate better understanding and management of SARS-CoV-2

infection from hospital admission to discharge across all levels of care (REACT-COVID19)” (North West Research Ethics Committee (REC 17/NW/0632), and Specific Review Board (REC 20/HRA/2986)) [25]. Taking of consent was waived due to the nature of the study. Collected data were anonymised and handled according to the local institutional and national policies. The study used STROBE guidelines for reporting observational studies [26].

Demographic data including age, sex, clinical frailty score (CFS), and comorbidities (type-I diabetes, type-II diabetes, asthma, COPD, hypertension, ischemic heart disease, congestive cardiac failure, arrhythmia, chronic kidney disease, immunosuppression, and pre-existing steroid use) were all collected. Comorbidities are quantitatively presented as Charlson’s Comorbidity Index (CCI) [27]. Admission severity indices including Acute Physiology and Chronic Health Evaluation (APACHE-II), Sequential Organ Failure Assessment (SOFA) scores, oxygenation indices with laboratory variables were documented during the first 24 hours of admission. The ICU organ support measures including the use of non-invasive ventilation (NIV), invasive mechanical ventilation and renal replacement therapy were collected. The outcomes assessed were 28-day and overall hospital mortality and were available for all patients. Clinical management of patients was in accordance with local guidelines. Most patients admitted to the ICU required ventilatory support either in the form of NIV or mechanical ventilation. Our local guidance suggests the initiation of NIV in all patients with severe acute hypoxic respiratory failure needing inspired oxygen of $\text{FiO}_2 > 60\%$. The type of NIV initiated was at the discretion of the treating physician. Deteriorating patients were subsequently intubated and mechanically ventilated.

Continuous variables are reported as median and interquartile range (IQR) and the group comparisons are made using Kruskal-Wallis test. Categorical variables are reported as number

and percentage and analysed using Fisher's exact test. Significance was defined at $p < 0.05$. Pearson's correlation coefficient was used to assess the relationship of demographic variables and BMI. Logistic regression analysis was used to assess the risk of invasive mechanical ventilation and renal replacement therapy according to the BMI categories. Unadjusted and adjusted competing risk regression analyses (adjusted for age, sex, CCI and APACHE II score) were carried out to assess the effect of BMI categories on 28-day and overall hospital mortality and presented as the sub-distribution hazard ratio (SHR). Statistical analysis was performed using SPSS version 27, Stata version 17.0, R version 1.2.5042 and MedCalc version 20.008.

Results

During the period between March 2020 and March 2021, there were 340 patients admitted to the General Intensive Care Unit due to COVID-19 related pneumonia. SARS-CoV-2 infection was confirmed by RT-PCR in all patients. Of those admitted, 66% were male with a median age of 59 years (IQR 49, 69) and 77% of white ethnic origin. The median days between symptom onset to hospitalization was seven (IQR 4, 10). Patients were categorized according to the National Institute of Clinical Excellence, UK (NICE) obesity classification groups as healthy, overweight, obesity I, obesity II and obesity III, accounting for 17.6%, 27.4%, 25.6%, 15.6% and 11.8% of patients respectively (Figure 1). The median BMI was 31 kg/m^2 (IQR 26,35). The admission demographics for individual BMI categories are presented in Table 1.

Those in obesity groups II and III were younger than the healthy BMI group. The proportional distribution of obesity categories between sexes is pictorially presented as Figure 2. There were no differences in the timing of symptomatic presentation to hospital between groups. The weighted composite score for comorbidities (Charlson's Comorbidity Index) was lower in obesity groups II and III in comparison to the overweight or healthy categories with individual differences in the presence of congestive cardiac failure and ischemic heart disease. Although

there were no differences in the SOFA scores at admission between groups, the APACHE-II scores were significantly lower in the obesity II and III groups compared to the healthy BMI group. Moreover, the admission oxygen index defined by the ratio of arterial oxygen (PaO_2) to inspired fractional oxygen (FiO_2) was lower in patients in obesity group III, suggesting more severe hypoxemia at presentation in this group. Admission laboratory variables were similar except for ferritin, D-Dimer, and cardiac troponin levels between groups (Table 1).

We assessed the relationship between BMI and admission variables (age, APACHE-II and $\text{PaO}_2/\text{FiO}_2$ ratio) which demonstrated group differences. There was a negative correlation between BMI and age (Pearson $r = -0.24$, $p < 0.001$), BMI and APACHE-II score (Pearson $r = -0.23$, $p < 0.001$), and BMI and $\text{PaO}_2/\text{FiO}_2$ ratio (Pearson $r = -0.25$, $p < 0.001$). This suggests that patients with a higher BMI are more likely to be young, with single organ failure/less chronic comorbidity (defined by lower APACHE II score) but with increased severity of hypoxemia at presentation (Figure 3). Overall, 54.1% of patients required mechanical ventilation and 15.6% developed acute kidney injury and needed renal replacement therapy (RRT). We performed logistic regression analysis for these outcomes of requirement for mechanical ventilation or RRT using the BMI groups adjusting for covariates including age, sex, CCI and APACHE-II scores. There were no significant differences in the need for mechanical ventilation or RRT between BMI category groups in this analysis (Table 2).

Of those patients with BMI measurements ($N=333$) and subdivided according to the BMI category, there were no significant differences in the duration of ICU or hospital length of stay between the groups. The 28-day and overall hospital mortality were 18.3% and 23.7% respectively. The 28-day hospital mortality for the groups healthy, overweight, obesity I, obesity II, obesity III was 21.7%, 28.0%, 21.8%, 17.0% and 12.5% respectively. A similar trend was also seen for the overall hospital mortality which was 21.7%, 30.1%, 26.4%, 17.0%

and 15.0% respectively (Table 3). Competing-risks regression models were used to assess the impact of obesity categories on mortality outcomes, 28-day in-hospital mortality and overall hospital mortality with discharge from hospital specified as a competing risk. Both unadjusted and adjusted (age, sex, APACHE-II, and CCI) models were utilised. Although it appeared that obesity groups II and III had lower 28-day and overall hospital mortality, these were not statistically significant (Table 4 and Figure 4). In each analysis, the sub-distribution hazard ratio (SHR) determines the risk of death for each BMI category comparing to the healthy-weight category after adjusting for the confound covariates. All obesity groups had greater 28-day and overall hospital mortality, but it was only statistically significant for BMI group I [SHR 3.31 (p=0.01) and SHR 2.82 (p=0.009)] respectively than healthy BMI patients.

Discussion

This study explores the relationship between BMI and clinical outcomes in a selective cohort of patients with severe COVID-19 pneumonia with acute hypoxic respiratory failure admitted to an intensive care unit. Raised BMI was a common finding, with 80% of patients being overweight, 53% obese and a median BMI of 31 (IQR 26,35) kg/m² in the overall cohort. Our study, principally studying the most severe group of COVID-19 patients, within a predominantly Caucasian population (76.5%), suggests that extreme obesity in severe COVID-19 was associated with younger age, less comorbidity and lower disease severity as quantified by cumulative CCI and APACHE-II scores. However, the obesity group III had more pronounced hypoxemia at presentation. There were no differences in the need for invasive mechanical ventilation or RRT between groups. Despite a trend towards lower unadjusted proportionate mortality among the obesity groups II (17%) and III (15%) compared to the healthy group (21.7%), the adjusted (according to age, sex, APACHE-II and CCI) hospital mortality was higher among all obesity groups. However, statistical significance was only reached for BMI group I (BMI 30-34.9 kg/m²), who had nearly three times greater 28-day and

overall hospital mortality than the healthy group. Thus, we did not identify the “obesity paradox” phenomenon in this population.

Others have uncovered varying extents of Obesity Paradox in ICU cohorts. A recent study showed that the moderate obesity cohort had a lower mortality rate (13.8%) than healthy-weight patients, or those with overweight or severe obesity (17.6%, 21.7%, and 50%, respectively) [28]. In addition, this study also showed that those with severe obesity tended to develop severe ARDS more frequently with a higher rate of mechanical ventilation [28]. In contrast, our study demonstrated that moderate obesity (BMI 30-34.9 kg/m²) rather than severe obesity (BMI >40 kg/m²) in the context of COVID-19 was independently associated with increased hospital mortality. The discrepancy in the finding could be due to number of reasons including variations in patient demographics and ICU interventions such as the proportion of patients requiring mechanical ventilation. A similar study in an Italian ICU cohort showed no association between BMI and increased risk of 30-day mortality after similar adjustments. Only severe obesity was found to be associated with an increased risk of mortality in invasively ventilated patients [29]. A New York based study concurs with our findings that BMI and length of stay, and BMI and need for mechanical ventilation, were not significantly associated [30]. However, in contrast, they did not observe a relationship between increased BMI and mortality in hospital, postulating that increased mortality for patients with obesity may be as a result of higher comorbidity burden in these patient groups at a population level. Their cohort of patients was also larger (n=1337) and while there were some similarities with our study in terms of age and comorbidity distribution, this New York cohort was substantially more ethnically diverse, particularly across higher BMI categories.

Meta-analyses have used myriad approaches to isolating obesity as an independent predictor of COVID disease severity and mortality. In two recent meta-analyses [8, 9], use of multi-

variable analysis to adjust for predefined confounding variables including prevalence of known risk factors did not prohibit the finding that the risk of intubation and ventilation was increased in people with obesity, and that mortality was associated with increasing BMI. Our study used APACHE-II scores and CCI, both validated for their ability to predict mortality in critically ill patients [31,32], to provide validated assessment of the comorbidity burden and to mitigate the risk of bias arising from inherent differences between subgroups. However, our sample size was modest compared to some other studies and so our study perhaps lacked the power to demonstrate the same findings as the larger metaanalyses. Nonetheless, our study adds weight to the growing body of evidence that obesity is an independent risk factor for morbidity and mortality from COVID-19.

Severe COVID-19 infection primarily causes respiratory failure and advanced age is one of the main risk factors associated with poorer clinical outcomes [33]. Moreover, comorbidities such as diabetes mellitus, chronic respiratory, cardiovascular and kidney diseases and immunosuppression are all negatively associated with clinical outcomes in hospitalised patients [34–37]. Obesity imposes a significant additional burden during COVID-19. Obesity increases the risk of infection, hospitalisation and the severity of disease [17, 38, 39]. However, ICU studies have identified contradictory findings where some postulate the existence of a concept where obesity appears to be protective. This has been demonstrated in ICU conditions such as acute respiratory distress syndrome, heart failure and cancer [40–42]. However, this is often confounded by several mitigating factors such as age, presence of other comorbidities and number of organ failures present during ICU admission. Our finding is comparable with non-COVID-19 ARDS patients, where the obesity paradox is associated with younger age with lower disease severity [43].

Obesity has become a global health concern with a rising prevalence and increased association with other chronic diseases. It is an independent risk factor for pandemic viral infections [44,45]. Obesity is linked with an increased risk of COVID-19 infection and severity. Multiple dysregulated systems may contribute to this association. In obesity, there is an accumulation of abdominal and thoracic adipose tissue, leading to restricted thoracic expansion and compromised ventilation at the lung bases worsening hypoxaemia [46]. Obesity also disrupts innate and adaptive immune responses [47, 48]. Low-grade inflammation associated with obesity can contribute to the recruitment of inflammatory cells and overt inflammatory response contributing to the “cytokine storm” often seen in severe COVID-19 patients [49–51]. Obese patients are also more susceptible to the coagulopathy induced by COVID-19 because adipose tissues produce excess plasminogen activator inhibitor-1 (PAI-1), which impairs fibrinolysis. Chronic inflammation in obesity drives procoagulant factors such as P-selectin and adhesion molecules and inhibits anticoagulant regulatory proteins, such as antithrombin and protein C, which leads to fewer checks on the procoagulant effects of SARS-CoV-2. It has been suggested that ACE2 receptors may be disproportionately present in adipose tissue [52], permitting viral entry via the spike protein and allowing adipose stores to act as a viral reservoir. Obesity is also associated with overexpression of angiotensin II at the systemic level [53], resulting in pulmonary vasoconstriction and enhanced microvascular permeability, both hallmarks of acute lung injury [54, 55]. These multiple pathophysiological processes in combination may explain the association between the increased severity of COVID-19 and obesity.

Our study has several limitations. This is from a single centre and has a retrospective observational design. The sample size is modest with a lower mortality rate compared to internationally published studies and inclusive of only few non-obese patients. As population characteristics and ICU interventions may vary between centres, the findings may not be

transferable universally. Nevertheless, our study adds to the growing literature on outcomes for obese patients with severe COVID-19 pneumonia requiring respiratory support in the intensive care setting. Our findings are consistent with several studies of similar design that have demonstrated that there are multiple confounding factors which may influence overall patient outcome.

Conclusions

The relationship between BMI and morbidity and mortality in our dataset was not straightforward. Our data do not confirm that obesity is paradoxically protective in the highest BMI subgroups with these patients at lower risk of mortality; however, higher BMI patients are more likely to be young, with single organ failure, less chronic comorbidity but with increased severity of hypoxemia at presentation. Once adjusted for these variables, obesity was associated with significant increase in mortality only among obesity group I. We have been cautious not to extend the scope of our conclusions beyond the setting in which our cohort has been recruited. The impact of obesity on indicators of disease severity with requirement for organ support measures including invasive mechanical ventilation and renal replacement therapy was not conclusively demonstrated and will require further scrutiny.

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Detail of authors contribution

Literature search – MJ, AD

Data collection – MB, LH, EH, CM

Study design – AD, CM

Data analysis – AD, HM

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Captions for figures

Figure 1 Prisma flow chart displaying the proportion of patients according to BMI category.

Figure 2. Population pyramid displaying number of male vs female patients according to their BMI

Figure 3. Scatter plots for correlation between BMI with Age (A), APACHE-II score (B) and oxygenation ($\text{PaO}_2/\text{FiO}_2$) on admission (C).

Figure 4. Competing risk regression charts. These charts show the probability of an event (28-day hospital mortality or overall hospital mortality) in the presence of a competing other event (hospital discharge). Unadjusted 28-day mortality (A) adjusted 28-day mortality (B), unadjusted overall hospital mortality (C), adjusted overall hospital mortality (D). Adjusted for age, sex, Charlson's comorbidity index and APACHE-II score.