Obesity and survival in critically ill patients with acute respiratory distress syndrome: a paradox within the paradox

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See related research by Ni et al., http://ccforum.biomedcentral.com/articles/10.1186/s13054-017-1615-3.

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The incidence of obesity is steadily increasing, and its prevalence, defined as a body mass index (BMI) above 30 kg/m², is 13% in the world adult population, and rises to up to 40% in high-income countries [1]. As a consequence, around 20% of the patients admitted to the intensive care unit (ICU) are obese [2]. Obesity and overweight are associated with an increased risk of death in the general population [3], but in specific disease conditions a decrease in mortality has been reported: this is the case of patients with septic shock [4] and acute respiratory distress syndrome (ARDS), and is referred to as the obesity paradox. The association between higher BMI and lower mortality is difficult to interpret and potentially influenced by several confounding factors. In patients with ARDS, this paradox is particularly surprising, as obese patients have peculiar alterations of the respiratory function, such as increased chest wall elastance and lower total respiratory system compliance, posing specific challenges for the clinician when mechanical ventilation is required [5, 6].

The obesity paradox in ARDS patients has been investigated in several studies and two recent meta-analyses [7, 8]. Ni and co-authors [7] analysed the evidence concerning the association between BMI and clinical outcomes in ARDS patients, pooling data from 6268 patients enrolled in five studies, including three prospective observational studies [9–11], a retrospective cohort study [12] and one randomised controlled trial [13]. The authors conclude that obesity and morbid obesity were associated with a lower mortality rate in patients with ARDS, therefore supporting the concept of the obesity paradox. In another recent analysis including four additional studies, Zhi et al. [8] reported that obesity increased ARDS-associated morbidity in the ICU population; however, mortality due to ARDS in obese was lower compared to non-obese patients. An increased mortality among underweight patients was also reported, which could be explained by the worse clinical conditions and comorbidities of patients admitted to the ICU with impaired nutritional status.

In the five studies included by Ni et al., [7] obese patients were systematically younger and had lower severity scores compared to the reference group (normal weight), while the opposite was observed in the underweight patients. The analysis by Zhi et al. [8] does not report patients’ severity scores. Figure 1 illustrates the observed unadjusted mortality rates in the different obesity classes for the studies included in the meta-analyses for which severity scores (SAPS II predicted mortality or APACHE III) could be extracted: the trend in mortality in the different obesity classes is similar to that of illness severity. This could suggest that the effect of BMI on mortality might be mediated by other clinical factors.

Both meta-analyses present some limitations: 1) inclusion of retrospective studies; 2) lack of adjustment for confounders; 3) most analyses are restricted to studies in which obesity was classified according to the WHO BMI classes; and 4) the presence of heterogeneity in some analyses. The adjustment for potential confounding factors is virtually impossible in a conventional meta-analysis without access to individual patient data, especially when a limited number of studies is included [14]. Indeed, when

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correcting for confounders, BMI was no longer associated with mortality in one of the studies [10], as previously reported in mechanically ventilated patients [15].

Several pathophysiological mechanisms and clinical management-related factors could explain the decreased mortality in obese critically ill patients, including those with ARDS. Recent evidence suggests the existence of a protective response called pre-conditioning cloud where obesity induces a low-grade inflammation, generating a process that subsequently protects the lung against further insults [16]. Indeed, pre-conditioning implies that a chronic pro-inflammatory status creates a protective environment, limiting the detrimental effects of a more aggressive second hit, such as ventilator-induced lung injury or sepsis. Obesity itself increases the plasma and adipose levels of inflammatory cytokines, including in ARDS [13], and the adipose-triggered inflammatory mediators could alter peripherally the physiological responses to injury, contributing to abnormalities in systemic and pulmonary circulation [17]. Some of these mechanisms are similar to the endogenous reactive protection occurring during endotoxemia in healthy subjects [18]. Also, during critical illness adipose tissue macrophages shift from pro-inflammatory M1 to alternative or anti-inflammatory M2 phenotypes [19]. Finally, the concept of metabolically healthy obesity (MHO) has been recently proposed, referring to obese individuals without associated metabolic comorbidities [20]. Interestingly, MHO has been linked to weaker adipose-related inflammatory activity and lower mortality risk compared to individuals with metabolically unhealthy obesity [20]. Moreover, clinicians tend to consider obese patients at high risk of worse outcome; thus, this might result in earlier admission to the ICU for monitoring purposes as well as increased use of prophylactic measures such as early mobilisation, more cautious pressure ulcer prevention, stricter glycaemic control, and more attention paid to mechanical ventilation parameters [21]. Moreover, in obesity, the high chest wall elastance could redistribute regional transpulmonary pressure, possibly reducing the potential negative effects of mechanical ventilation in an inhomogeneous lung.

Meta-analyses of observational studies are a tool for generating experimental hypotheses to be tested in other experimental settings, and their results should be cautiously interpreted as an association, not necessarily implying causality. It would be extremely important to answer the question of whether the obesity paradox in ARDS is mediated by other factors: if the association is confirmed it could open new perspectives for the management of respiratory failure. A quasi-experimental setting could be achieved by performing an individual data meta-analysis, but further physiological and clinical studies are warranted to better understand the interaction between obesity and response to critical illness.

![Fig. 1](https://example.com/fig1.png) Mortality and disease severity in different BMI classes. Upper panel: unadjusted observed mortality rates in the five BMI classes. Lower panel: APACHE III severity scores. For one study [9] the APACHE III score was not reported; therefore, the SAPS II predicted mortality is plotted (blue dashed line). This figure reports data from only the studies included in the two meta-analyses [14, 15] for which disease severity was available. O’Brien 2006 [9], Morris 2007 [11], Stapleton 2010 [13], Soto 2012 [12], Gong 2010 [10], Soubani 2015 [22].
Abbreviations
APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: Acute respiratory distress syndrome; BMI: Body mass index; ICU: Intensive care unit; MHO: Metabolically healthy obesity; SAPS: Simplified Acute Physiology Score; WHO: World Health Organization.

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