CRITICAL CARE AND RESUSCITATION

Original Article

The impact of body mass index on long-term survival after ICU admission due to COVID-19: A retrospective multicentre study

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ARTICLE INFORMATION

ABSTRACT

Objective: The impact of obesity on long-term survival after intensive care unit (ICU) admission with severe coronavirus disease 2019 (COVID-19) is unclear. We aimed to quantify the impact of obesity on time to death up to two years in patients admitted to Australian and New Zealand ICUs.

Design: Retrospective multicentre study.

Setting: 92 ICUs between 1st January 2020 through to 31st December 2020 in New Zealand and 31st March 2022 in Australia with COVID-19, reported in the Australian and New Zealand Intensive Care Society adult patient database.

Participants: All patients with documented height and weight to estimate the body mass index (BMI) were included. Obesity was classified patients according to the World Health Organization recommendations.

Interventions and main outcome measures: The primary outcome was survival time up to two years after ICU admission. The effect of obesity on time to death was assessed using a Cox proportional hazards model. Confounders were acute illness severity, sex, frailty, hospital type and jurisdiction for all patients.

Results: We examined 2,931 patients; the median BMI was 30.2 (IQR 25.6–36.0) kg/m². Patients with a BMI ≥30 kg/m² were younger (median [IQR] age 57.7 [46.2–69.0] vs. 63.0 [50.0–73.6]; p < 0.001) than those with a BMI <30 kg/m². Most patients (76.6%; 2,244/2,931) were discharged alive after ICU admission. The mortality at two years was highest for BMI categories <18.5 kg/m² (35.4%) and 18.5–24.9 kg/m² (31.1%), while lowest for BMI ≥40 kg/m² (14.5%). After adjusting for confounders and with BMI 18.5–24.9 kg/m² category as a reference, only the BMI ≥40 kg/m² category patients had improved survival up to 2 years (hazard ratio = 0.51; 95%CI: 0.34–0.76).

Conclusions: The obesity paradox appears to exist beyond hospital discharge in critically ill patients with COVID-19 admitted in Australian and New Zealand ICUs. A BMI ≥40 kg/m² was associated with a higher survival time of up to two years.

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1. Introduction

The prevalence of obesity is increasing globally, with approximately 20 % of patients admitted to the intensive care unit (ICU) obese.[1–3] While obesity is typically associated with morbidity and mortality and poses additional care challenges in managing the critically ill, emerging literature has paradoxically reported higher short-term survival for patients with critical illness who are obese, also known as the obesity paradox.[2,4–7] A large epidemiological study reporting on patients in ICUs from Australia and New Zealand observed that 35 % of the patients were obese and confirmed that some level of obesity was associated with overall lower in-hospital mortality.[8] A recent study observed the obesity paradox in survivors of critical illness up to 4 years after their ICU admission.[9]

There are however no accepted physiological mechanistic models to explain why morbid obesity could be protective. Although the causal mechanisms are unknown, some pathophysiologic mechanisms such as higher energy reserves, anti-inflammatory immune profile, the role of adipose tissue, prevention of muscle wasting and an association between increased BMI and lower risk of hypoglycaemia may all provide explanations for this obesity paradox.[4,8–10] Apart from chronic disease, sarcopenia, malnutrition and smoking status, other non-physiological methodological explanations have been postulated.[8,11,12] Furthermore, many biases such as selection bias, confounder bias, collider stratification bias, reporting bias, treatment bias and publication bias may be added to explain this phenomenon.[1,8] A large retrospective study demonstrated that the obesity paradox is more than just a simple association between body mass index (BMI) and mortality and emphasized the importance of acute illness severity.[13]

Several studies have found an association between coronavirus disease 2019 (COVID-19) severity and obesity,[14–21] such that obesity was labelled a risk factor for severe COVID-19, ICU admission and mechanical ventilation.[18] As excess body fat mass results in various hormonal, metabolic, and inflammatory changes,[22] it was hypothesized that adipose tissue may play a vital role in the mechanism of progression of COVID-19.[23,24] In patients with severe COVID-19, there is a linear association between body mass index (BMI) and hospitalization, ICU admission and the need for mechanical ventilation and death among patients with COVID-19.[14,17–20,25–39] Furthermore, the Health Outcome Predictive Evaluation for COVID-19 Registry revealed no evidence of obesity paradox in patients with COVID-19.[40] However, a recent study found that obese patients with COVID-19 admitted to hospital had lower survival, but amongst those who have been admitted to ICU, there is a higher survival associated with obesity.[25] These discrepancies in findings may be due to differences in study population characteristics, and most meta-analyses showed significant heterogeneity.[39]

To our knowledge, the impact of obesity on long-term survival after intensive care unit (ICU) admission with severe COVID-19 has never been investigated. Therefore, our primary aim was to investigate the association between BMI and long-term survival after ICU admission due to COVID-19. We hypothesized that after adjusting for confounders, increasing levels of obesity would be associated with higher survival for up to two years.

2. Methods:

2.1. Study design and participants

We performed a retrospective multicentre study of all critically ill adult (age ≥ 16 years) patients admitted to Australian and New Zealand ICUs for their index ICU admission with a diagnosis of COVID-19. The patients were identified as suspected or confirmed COVID-19 based on the diagnostic code allocated as the cause of ICU admission (Supplementary Table 1). We only included the first ICU admission per hospitalization. Patients transferred to another ICU were excluded. We also excluded patients if there were no documented height and weight to estimate BMI, if the outcome was missing or if admitted for organ donation purposes.

2.2. Data sources and measurement

Data were extracted from the Australian and New Zealand Intensive Care Society (ANZICS) adult patient database, a bi-national clinical quality registry dataset, collected by the ANZICS Centre for Outcomes and Resources Evaluation, that contains information on all admissions to 98 % of adult ICUs in Australia and 67 % of ICUs in New Zealand. ICU admission records between 1st January 2020 through 31st December 2020 in New Zealand and 31st March 2022 in Australia, were linked to the date of death recorded in the national death registers in each country using an encoded linkage key. This provided a maximum follow-up of 27 months. Data collectors receive regular training and quality assurance reviews and data is collected using a standardized data dictionary. In addition, regular automated data checks further ensure the validity of recorded data.[41] Apart from each patient's demographic details, the registry also captures their diagnostic, biochemical, physiological, and chronic health parameters from the first 24 h of ICU admission as required to calculate illness severity

scores. The definitions are described in the ANZICS adult patient database data dictionary.[42]

2.3. Variables

We extracted data on patient demographics (age, sex, comorbidities, ethnicity, ICU admission source, smoking status), frailty status using the clinical frailty scale (CFS), BMI (based on patient's weight and height which could have been estimated at ICU admission), ICU organ supports (receipt of invasive mechanical ventilation, non-invasive ventilation, vasopressors, extracorporeal membrane oxygenation, and/or renal replacement therapy), ICU and hospital mortality, ICU and hospital length of stay and discharge destinations (home, chronic care facility or rehabilitation).

2.4. BMI definition

BMI was classified according to the World Health Organization recommendations:[43] BMI <18.5 kg/m^2 'underweight'; BMI between $18.5 \leq 24.9$ kg/m^2 'healthy weight'; BMI 25.0 and ≤ 29.9 kg/m^2 'overweight' and BMI$\geq$30 kg/m^2 'obese'. Obesity was further classified into three severity categories: class-I (BMI 30.0–34.9 kg/m^2), class-II (BMI 35.0–39.9 kg/m^2) and class-III (BMI $\geq$40 kg/m^2).[44] BMI was calculated based on the available weight and height in the ANZICS adult patient database (body weight (kg) divided by height squared (m^2)).

2.5. Confounding variables

Based on a previous study, the confounding variables included in the model pertain to the ICU (location, type, and size), patient (frailty, age, gender, and comorbidities), ICU admission (care type, source, treatment limitations and pre-ICU length of stay) and patient acute illness severity.[45] Illness severity was determined using the ANZROD which is a highly predictive mortality prediction model used for benchmarking ICU performance in Australia and New Zealand.[46,47] ANZROD includes components of the APACHE IV scoring system, such as age, chronic illnesses, acute physiological disturbance and diagnosis, and the presence of treatment limitation on admission to ICU and provides an accurate estimate of the severity of illness in the first 24 h of ICU admission. Recent studies demonstrated that ANZROD was predictive of longer-term outcomes.[48,49] Frailty was included as a confounder as 20 % of patients with COVID-19 admitted to ICU were frail.[49–51]

2.6. Outcomes

The primary outcome was a survival time of up to two years and is reported as observed mortality at one and two years after ICU admission. Secondary outcomes included ICU and hospital mortality, ICU and hospital length of stays, and discharge destinations.

2.7. Subgroup analysis

Predefined subgroup analyses based on those who survived hospitalisation, and those receiving mechanical ventilation were performed.

2.8. Statistical analysis

For categorical variables, we reported counts with percentage (*n* (%)) and made comparisons between BMI categories using Chi-squared tests. For continuous data, we report normally distributed data using means (standard deviation) and non-parametric data using median (interquartile range [IQR]). We made

comparisons using the student's t-test for normally distributed data and the Mann–Whitney U test otherwise. All analyses were performed with the BMI 18.5–24.9 kg/m^2 category as the reference. We treated BMI both as a continuous and categorical variable in separate regression models. As estimates can cluster around centres, we used a robust-variance sandwich-type estimator to derive the standard errors and account for this clustering.[52] Overall survival estimates are displayed using Kaplan–Meier curve plots. The effect of BMI on time to death was assessed using a Cox proportional hazards model, adjusting for ANZROD, male sex, CFS, hospital type (tertiary, metropolitan, rural/regional, and private) and jurisdiction (Australian states and New Zealand), clustered by site, and site treated as a random effect. The results were reported using hazard ratios (HR, 95%CI). We assigned CFS and ANZROD as nonlinear predictors in the regression analysis where the estimation algorithm arranges the predictors based on significance to determine the best fitting fractional-polynomial function for each predictor while assuming all other predictors are linear using the mfp package on R. We conducted an additional post hoc analysis looking at an interaction effect of age*obesity treated both as continuous and categorical variables while adjusting for illness severity, hospital type, jurisdiction, and frailty. We performed data analysis using R4.2.2 (The R Foundation).[53] We used a two-sided p-value of <0.05 to indicate statistical significance.

2.9. Ethics approval

All experimental protocols were approved by The Alfred Hospital Ethics Committee (local reference 413/19).

3. Results

During the study period, the ANZICS adult patient database listed 5834 patients with COVID-19 hospitalizations which were linked with the National Death Index. After excluding: 64 patients from New Zealand admitted in 2021; 413 patients who were transferred from another ICU; and 2423 patients who had insufficient information to estimate BMI, the final study population comprised 2931 patients from 87 Australian and 5 New Zealand ICUs (Supplementary Fig. 1). Compared to patients with estimated BMI, those without BMI were of similar age, frailty status and illness severity, less commonly were mechanically ventilated and had lower 2-year mortality after ICU admission (Supplementary Table 2).

Of the total 2931 patients, 50.9 % (n = 1493) had a BMI of $\geq$ 30 kg/m^2 (median [IQR] BMI 30.2 [25.6–36.0]) kg/m^2). Patients with obesity were younger (median [IQR] age 57.7 [46.2–69.0] vs. 63.0 [50.0–73.6]; p < 0.001), a higher proportion had diabetes mellitus and a lower proportion of solid organ or haematological malignancies or immunosuppressive conditions or treatment limitations at ICU admission. Patients with obesity were more likely to receive invasive and non-invasive ventilatory and vasopressor supports than those without obesity. No difference in the receipt of other organ supports was observed. The baseline characteristics of patients with COVID-19 based on BMI categories are summarized in Table 1, while Supplementary Table 3 summarizes the comparison based on obesity status.

3.1. Primary outcome

The mortality at two years progressively decreased with increasing BMI, highest for BMI <18.5 kg/m^2 (35.4 %) and lowest for BMI $\geq$40 kg/m^2 (14.5 %; p < 0.001) (Table 2, Fig. 1, Supplementary Table 4). The median [IQR] survival time for patients with obesity was 6.4 [4.5–16.8] months when compared to 7.1 [4.0–20.6] months for patients with a BMI <30 kg/m^2 (p < 0.001). After adjusting for

Table 1

Baseline characteristics, illness severity and ICU management of patients with COVID-19 based on BMI categories.

BMI	<18.5 kg/m² (Underweight)	18.5–24.9 kg/m² (Healthy)	25.0–29.9 kg/m² (Overweight)	30.0–34.9 kg/m² (Class 1 obesity)	35.0–39.9 kg/m² (Class 2 obesity)	≥40.0 kg/m² (Class 3 obesity)	p-value
Number	48 (1.6 %)	595 (20.3 %)	793 (27.1 %)	659 (22.5 %)	375 (12.8 %)	459 (15.7 %)	–
Male sex	20 (41.7 %)	370 (62.2 %)	534 (67.3 %)	390 (59.2 %)	206 (54.9 %)	212 (46.2 %)	**< 0.001**
Indigenous status	4 (8.9 %)	34 (5.9 %)	27 (3.6 %)	18 (2.8 %)	9 (2.5 %)	20 (4.7 %)	**0.030**
CFS score	5 (4, 6)	3 (2, 4)	3 (2, 4)	3 (2, 4)	3 (2, 4)	3 (3, 4)	**< 0.001**
Age (years)	63.5 (50.1, 76.4)	63.0 (49.0, 73.6)	62.7 (50.7, 73.5)	60.0 (49.7, 70.1)	58.0 (45.9, 70.0)	52.7 (41.7, 64.4)	**< 0.001**
Hospital classification							
- Public Tertiary	16 (33.3 %)	312 (52.4 %)	430 (54.2 %)	347 (52.7 %)	205 (54.7 %)	216 (47.1 %)	**< 0.001**
- Public Metropolitan	17 (35.4 %)	167 (28.1 %)	250 (31.5 %)	231 (35.1 %)	118 (31.5 %)	177 (38.6 %)	
- Public rural/regional	13 (27.1 %)	100 (16.8 %)	100 (12.6 %)	77 (11.7 %)	48 (12.8 %)	63 (13.7 %)	
- Private	2 (4.2 %)	16 (2.7 %)	13 (1.6 %)	4 (0.6 %)	4 (1.1 %)	5 (1.1 %)	
ICU admission source							
- Emergency department	29 (60.4 %)	372 (62.5 %)	420 (53.0 %)	341 (51.7 %)	186 (49.6 %)	250 (54.5 %)	**< 0.001**
- Ward	12 (25.0 %)	187 (31.4 %)	329 (41.5 %)	282 (42.8 %)	164 (43.7 %)	189 (41.2 %)	
- Other hospital	4 (8.3 %)	29 (4.9 %)	38 (4.8 %)	33 (5.0 %)	22 (5.6 %)	16 (3.5 %)	
- Operating theatre/ Recovery	0 (0 %)	1 (0.2 %)	1 (0.1 %)	0 (0 %)	1 (0.3 %)	1 (0.2 %)	
- Direct admit	3 (6.3 %)	6 (1.0 %)	5 (0.6 %)	3 (0.5 %)	2 (0.5 %)	4 (0.9 %)	
Documented co-morbidities							
- Chronic respiratory condition	24 (50.0 %)	95 (16.0 %)	88 (11.1 %)	82 (12.4 %)	46 (12.3 %)	80 (17.4 %)	**< 0.001**
- Chronic cardiovascular condition	5 (10.4 %)	55 (9.2 %)	57 (7.2 %)	57 (8.6 %)	29 (7.7 %)	40 (8.7 %)	0.83
- Chronic renal failure	1 (2.1 %)	19 (3.2 %)	24 (3.0 %)	18 (2.7 %)	13 (3.5 %)	14 (3.1 %)	**0.017**
- Chronic liver disease	4 (8.3 %)	4 (0.7 %)	2 (0.3 %)	8 (1.2 %)	5 (1.3 %)	6 (1.3 %)	**< 0.001**
- Diabetes mellitus	8 (16.7 %)	126 (21.2 %)	199 (25.1 %)	228 (34.6 %)	120 (32.0 %)	148 (32.2 %)	**< 0.001**
- Cancer	2 (4.2 %)	33 (5.5 %)	30 (3.8 %)	14 (2.1 %)	8 (2.1 %)	7 (1.5 %)	**0.003**
- Immunosuppression	5 (10.0 %)	40 (7.1 %)	51 (6.1 %)	35 (5.3 %)	14 (3.6 %)	9 (1.8 %)	**< 0.001**
- Lymphoma	0 (0 %)	7 (1.2 %)	5 (0.6 %)	2 (0.3 %)	3 (0.8 %)	1 (0.2 %)	0.44
- Leukaemia	0 (0 %)	11 (1.8 %)	15 (1.9 %)	8 (1.2 %)	2 (0.5 %)	2 (0.4 %)	0.19
Miscellaneous							
- ICU admission post-MET call	8 (16.7 %)	129 (21.9 %)	238 (30.1 %)	198 (30.3 %)	127 (34.0 %)	133 (29.2 %)	**< 0.001**
- Treatment limitations	16 (33.3 %)	103 (17.3 %)	102 (12.9 %)	70 (10.6 %)	42 (11.2 %)	44 (9.6 %)	**< 0.001**
- Cardiac arrest 24 h prior	2 (4.2 %)	14 (2.4 %)	11 (1.4 %)	6 (0.9 %)	4 (1.1 %)	2 (0.4 %)	**0.004**
- Pre-ICU (hours)	9.0 (3.7, 19.4)	7.3 (4.0, 24.0)	9.8 (4.5, 40.4)	10.6 (4.5, 39.3)	10.0 (4.1, 46.2)	8.6 (4.4, 42.4)	**0.033**
Organ failure scores							
- APACHE-II	17.7 [6.1]	16.5 [7.7]	15.9 [6.7]	15.8 [6.4]	15.2 [6.6]	15.0 [6.3]	**< 0.001**
- APACHE-III	56.4 [21.0]	53.7 [15.7]	53.2 [21.8]	51.9 [20.1]	50.0 [20.0]	48.3 [19.0]	**< 0.001**
- ANZROD (%)	8.6 (4.4, 18.4)	6.3 (2.5, 14.3)	5.8 (2.5, 13.2)	5.0 (2.6, 11.9)	4.8 (2.3, 9.7)	3.9 (2.0, 8.7)	**< 0.001**
Organ supports							
- Mechanical ventilation	6 (12.5 %)	158 (27.0 %)	277 (35.4 %)	239 (36.5 %)	144 (38.6 %)	190 (42.4 %)	**< 0.001**
- MV duration (hours)	326 (85, 548)	105 (26, 226)	128 (27, 308)	152 (49, 315)	167 (42, 290)	142 (42, 256)	0.09
- Non-invasive ventilation	15 (31.3 %)	162 (28.0 %)	284 (36.4 %)	289 (44.4 %)	152 (41.0 %)	235 (52.6 %)	**< 0.001**
- Vasopressor and inotropes	13 (27.1 %)	209 (35.7 %)	307 (39.1 %)	270 (41.3 %)	158 (42.2 %)	187 (41.6 %)	**0.047**
- Renal replacement therapy	2 (4.3 %)	23 (4.0 %)	52 (6.7 %)	38 (5.9 %)	20 (5.5 %)	17 (3.9 %)	**0.018**
- ECMO	0 (0 %)	5 (0.9 %)	10 (1.3 %)	12 (1.9 %)	3 (0.8 %)	8 (1.8 %)	0.61
- Tracheostomy	2 (4.3 %)	14 (2.4 %)	35 (4.6 %)	26 (4.0 %)	19 (5.2 %)	15 (3.4 %)	0.40

Data are n (%), mean [SD] or median (IQR).

CFS – clinical frailty scale, SD – standard deviation, IQR – interquartile range, BMI – body mass index, MET – medical emergency team, APACHE – Acute Physiology and Chronic Health Evaluation, ICU – intensive care unit, ANZROD – Australia New Zealand risk of death, MV - mechanical ventilation, NIV – non-invasive ventilation, ECMO – extracorporeal membrane oxygenation.

Table 2
Raw outcomes of patients with COVID-19 based on BMI categories.

BMI	<18.5 kg/m² (Underweight)	18.5–24.9 kg/m² (Healthy)	25.0–29.9 kg/m² (Overweight)	30.0–34.9 kg/m² (Class 1 obesity)	35.0–39.9 kg/m² (Class 2 obesity)	≥40.0 kg/m² (Class 3 obesity)	p-value
Primary outcome							
- Mortality at one year	14/48 (29.2 %)	156/595 (26.2 %)	179/793 (22.6 %)	134/659 (20.3 %)	68/375 (18.1 %)	57/461 (12.4 %)	**< 0.001**
- Mortality at two years	17/48 (35.4 %)	185/595 (31.1 %)	196/793 (24.7 %)	145/659 (22.0 %)	77/375 (20.5 %)	67/461 (14.5 %)	**< 0.001**
Secondary outcomes							
ICU mortality	2/48 (4.2 %)	65/595 (10.9 %)	78/793 (9.8 %)	66/658 (10.0 %)	31/375 (8.3 %)	31/461 (6.7 %)	0.15
Hospital outcomes							**< 0.001**
- Died in-hospital	5/48 (10.4 %)	89/595 (15.0 %)	113/793 (14.2 %)	77/659 (11.7 %)	39/375 (10.4 %)	37/461 (8.0 %)	
- Discharged home	36 (75.0 %)	403 (67.7 %)	512 (64.6 %)	438 (66.5 %)	240 (64.0 %)	311 (67.5 %)	
- Transferred to other hospital	5 (10.4 %)	57 (9.6 %)	60 (7.6 %)	55 (8.3 %)	25 (6.7 %)	38 (8.2 %)	
- Rehabilitation facility	1 (2.1 %)	21 (3.5 %)	40 (5.0 %)	32 (4.9 %)	24 (6.4 %)	16 (3.5 %)	
- Chronic care facility or nursing home	1 (2.1 %)	4 (0.7 %)	3 (0.4 %)	9 (1.4 %)	4 (1.1 %)	5 (1.1 %)	
- Other[a]	0 (0)	21 (3.5 %)	65 (8.1 %)	48 (7.3 %)	43 (11.5 %)	54 (11.7 %)	
Length of stay							
- ICU length of stay	2.1 (0.9, 5.0)	2.7 (1.2, 5.7)	4.2 (2.0, 8.8)	4.2 (2.0, 8.8)	3.7 (1.7, 9.0)	4.6 (2.1, 9.9)	**< 0.001**
- Hospital length of stay	8.1 (4.5, 15.0)	9.0 (4.8, 17.1)	11.4 (6.2, 20.0)	11.1 (6.3, 18.9)	10.4 (5.8, 18.1)	10.7 (6.1, 18.0)	**< 0.001**

Data are n (%), mean [SD] or median (IQR).
COVID-19 – Coronavirus disease 2019, ICU – intensive care unit, IQR – interquartile range.
[a] Includes discharge to other ICU, mental health facility or hospital in the home.

confounders, the Cox proportional hazards regression demonstrated higher survival time up to two years only for patients with BMI ≥40 kg/m² (HR = 0.51; 95%CI: 0.34–0.76) (Table 3). When BMI was modelled as a continuous variable, a non-linear relationship with time to death was noted. Patients with BMIs between BMI 32 and 60 kg/m² had the best survival (Fig. 2).

3.2. Subgroup analyses

Patients who survived hospitalization: 2570 patients were discharged alive from the hospital; 52.2 % (n = 1342) were obese. Kaplan Meier survival curves estimated that patients with BMI ≥ 40 kg/m² had the highest survival compared to other BMI categories (p < 0.001; Supplementary Fig. 2, Supplementary Table 5). Similar findings of higher survival time up to two years only for patients with BMI ≥40 kg/m² were observed in the adjusted Cox proportional hazards regression (Supplementary Table 6). The log hazards 2-year survival demonstrated a non-linear survival advantage for patients with BMI >25 kg/m² (Supplementary Fig. 3).

Patients receiving mechanical ventilation: 1015 patients received mechanical ventilation, of which 56.6 % (n = 574) were obese. The duration of mechanical ventilation was also similar across BMI categories (Supplementary Table 7). Kaplan Meier survival curves estimated that patients with BMI category <18.5 kg/m² had the lowest 2-year survival, while BMI ≥40 kg/m² had the highest (Supplementary Fig. 2). The adjusted Cox proportional hazards regression demonstrated a higher survival time of up to 2 years for all patients with BMI ≥25 kg/m² (Supplementary Table 8). The log hazards' 2-year survival demonstrated a non-linear survival advantage beyond BMI 25 kg/m² (Supplementary Fig. 3).

3.3. Secondary outcomes

The hospital mortality was highest for BMI 18.5–24.9 kg/m² (15 %, n = 89), and lowest for patients with BMI ≥40 kg/m² (8.0 %, n = 37). Compared to patients with BMI <18.5 and 18.5–24.9 kg/m², patients with BMI 25.0–29.9 kg/m² and patients with all three obesity classes had longer ICU and hospital length of stays (p < 0.001 and p = 0.015, respectively). There was no difference in the discharge destinations between BMI categories among patients discharged to their usual residence, to rehabilitation or a nursing home, respectively. The raw secondary outcomes are summarized in Table 2.

3.4. Post hoc analysis

When the mortality was standardised by age and obesity in the population, there was no interaction effect between age and obesity ($p_{interaction}$ = 0.32), when both were treated as continuous variables, adjusted for confounders (Supplementary Table 9). However, when BMI was categorised, age significantly interacted with only BMI<18.5 kg/m2 ($p_{interaction}$ = 0.004) and BMI 35.0–35.9 kg/m2 ($p_{interaction}$ = 0.026) categories, when adjusted for the same confounders (Supplementary Table 10).

4. Discussion

4.1. Executive summary

This retrospective study examined the impact of obesity (defined via BMI) on long-term survival time up to two years after ICU admission among patients with severe COVID-19 in Australia and New Zealand. We found that more than half the patients had obesity, which was higher than pre-pandemic. Patients with obesity were younger and had lower illness severity scores than

Fig. 1. Kaplan Meier up to 2-year survival curves based on BMI categories for all patients.
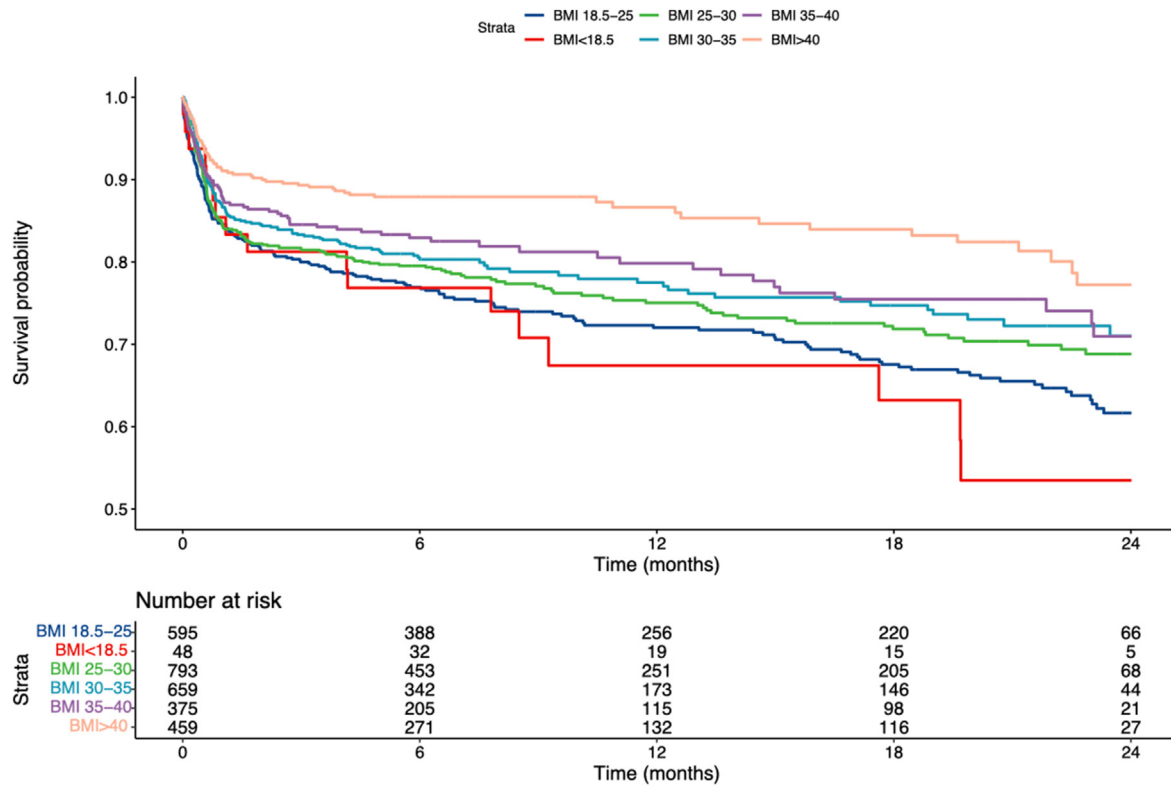
BMI <18.5 kg/m² = Underweight, BMI 18.5-24.9 kg/m² = Healthy, BMI 25.0-29.9 kg/m² = Overweight, BMI 30.0-34.9 kg/m² = Class 1 obesity, BMI 35.0-39.9 kg/m² = Class 2 obesity, BMI ≥40 kg/m² = Class 3 obesity

Table 3

Cox Proportional Hazards Regression Analysis, for up to 2-year survival, adjusted for ANZROD, male sex, frailty (CFS), hospital type and jurisdiction for all patients with COVID-19. BMI was treated as a categorical variable.

Predictor	HR (95%CI)	p-value
BMI categories		
− <18.5 kg/m2	0.69 (0.41−1.19)	0.18
− 18.5−24.9 kg/m2	Reference	
− 25.0−29.9 kg/m2	0.90 (0.67−1.20)	0.46
− 30.0−34.9 kg/m2	0.84 (0.66−1.05)	0.13
− 35.0−39.9 kg/m2	0.95 (0.65−1.36)	0.78
− ≥40.0 kg/m2	0.51 (0.34−0.76)	**0.001**
Sex		
− Male sex	1.17 (0.99−1.39)	0.06
Patient factors		
− log (ANZROD/10)	2.02 (1.79−2.27)	**< 0.001**
− log (CFS/10)	6.30 (5.19−7.26)	**< 0.001**
Hospital classification		
− Metropolitan	Reference	
− Private	1.12 (0.67−1.88)	0.65
− Rural/Regional	0.86 (0.68−1.09)	0.21
− Tertiary	0.90 (0.73−1.12)	0.39
Jurisdiction		
− New South Wales	Reference	
− Northern Territory	0.88 (0.07−2.09)	0.27
− New Zealand	1.55 (0.58−4.15)	0.39
− Queensland	0.60 (0.37−0.98)	**0.041**
− South Australia	0.26 (0.19−0.34)	**< 0.001**
− Tasmania	0.00 (0.00−0.00)	**< 0.001**
− Victoria	0.81 (0.67−0.99)	**0.035**
− Western Australia	0.98 (0.30−3.20)	0.98

CFS − Clinical Frailty Scale, BMI − body mass index, ANZROD − Australia New Zealand risk of death.

those who were within the normal or underweight range. Secondly, in the adjusted analysis, only patients with BMI ≥40 kg/m² were associated with higher survival times up to two years. Third, most of the patients who survived hospitalization were alive at 2 years, the highest for patients with BMI ≥40 kg/m². Fourth, all three obesity classes had higher two-year survival among those needing mechanical ventilation. Finally, our findings suggest that the obesity paradox exists beyond hospital discharge and up to 2 years in critically ill patients with COVID-19 admitted to Australian and New Zealand ICUs.

4.2. Relationship to previous studies

The in-hospital mortality rates for patients with COVID-19 in Australia and New Zealand were lower than in other countries.[50,54] Recent studies from Australia have found that in-hospital mortality rates in patients with severe COVID-19 reached nearly 15 %[51,54] and that this was highest in the third wave of COVID-19 (26th June to 1st November 2021).[54] While one study reported that 6-month survival was less than 50 % following ICU admission,[55] others have found that more than 50 % of patients receiving mechanical ventilation for COVID-19 survived to 180 days.[56] However, no studies reported long-term outcomes while taking BMI into account.

Previous evidence suggests that being overweight and moderately obese was protective with lower mortality when compared with underweight BMI, normal BMI, or more severe obesity.[25] Our
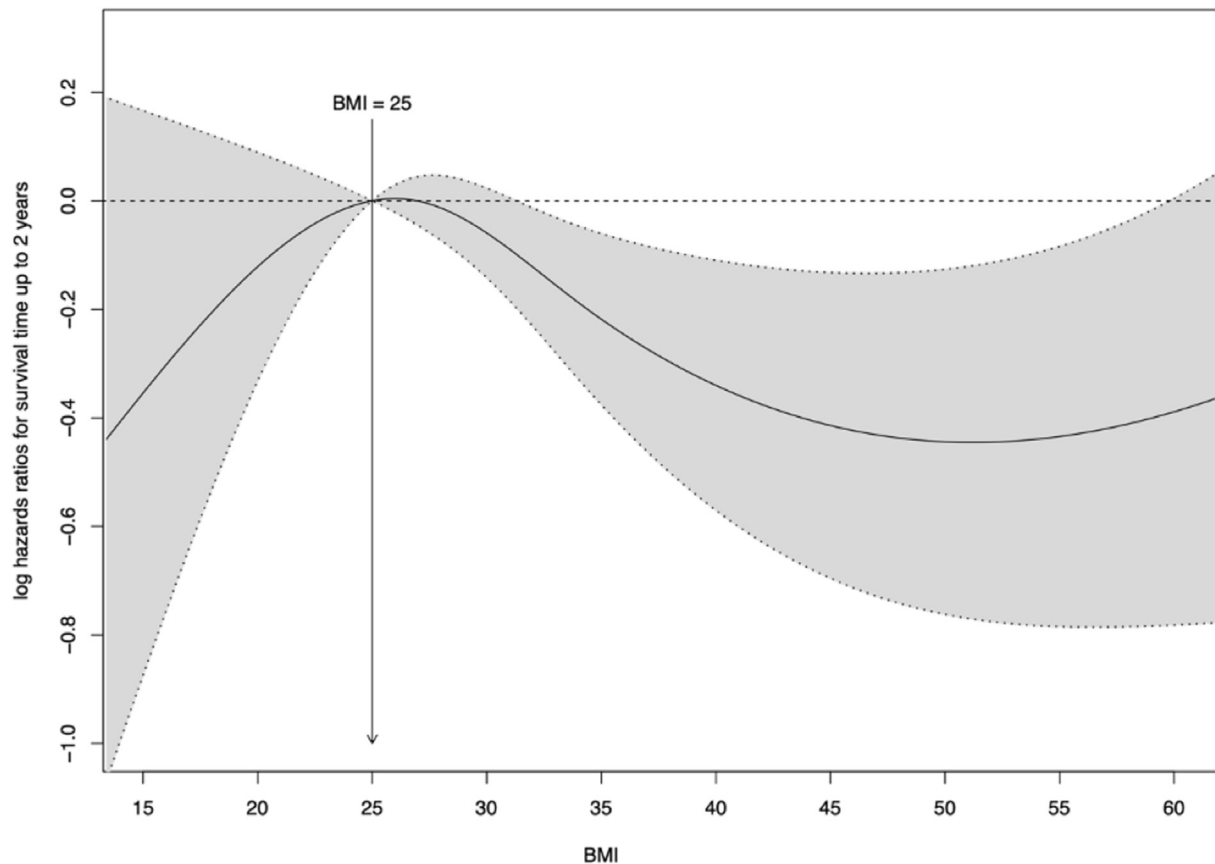
Fig. 2. Relationship between obesity and up to 2-year survival in patients with severe COVID-19 admitted to Australian and New Zealand intensive care units.

study observed that patients with obesity were younger, had fewer comorbidities, and had lower CFS and acute illness severity scores when compared to the underweight group who were relatively older patients, had more comorbidities, frailer with higher acute illness severity scores. A recent study found that ICU survivors demonstrated greater annual increases in lean and fat mass.[57] Contrarily, although the point estimates for the other obese groups were also in the same direction, raising the possibility that this an overall trend to greater survival with progressively increasing BMI, our study found that survival time up to 2 years was independently associated only for patients with BMI ≥40 kg/m2. Our findings, therefore, suggest that an obesity paradox exists among survivors of COVID-19 beyond hospital discharge up to two years. Furthermore, a study that looked at the mortality trends between three COVID-19 surges among 1868 patients in the USA found that low BMI was associated with higher hospital mortality in patients admitted to ICU.[58] In contrast, our study did not identify any not independent association with long-term survival.

Previous evidence suggests that COVID-19 patients with a BMI of ≥30 kg/m^2 were independently associated with needing mechanical ventilation.[19,59] In contrast to the findings of a pre-pandemic large multicentre study which found that patients with class-II and class-III obesity had longer durations of mechanical ventilation and ICU care, we found similar durations of mechanical ventilation across all BMI categories.

4.3. Study implications

We found an over-representation of patients with severe COVID-19 who were obese in Australian and New Zealand ICUs when compared to the large Australian epidemiological study pre-COVID-19.[8] Our findings suggest the existence of obesity paradox existed beyond hospitalization for up to two years in critically ill patients. These findings will help determine the mortality risk associated with obesity in patients with severe COVID-19 to individualize patient intervention, such as healthy eating, minimizing ultra-processed foods and lifestyle modification.[60] Furthermore, the COVID-19 vaccine's effectiveness in inducing protective humoral immunity is possibly reduced among obese individuals, therefore will require timely booster doses to improve their neutralizing immunity.[61] Furthermore, priority should be given to exploring the reasons why there is a survival advantage for morbidly obese patients with COVID-19.

4.4. Strengths

Our study has several notable strengths. Firstly, our study spans numerous ICUs that enrolled patients across Australia and New Zealand. Secondly, the relatively larger sample of high-quality data increased the precision of our estimates. Thirdly, we incorporated several pre-specified secondary analyses to assess the association of obesity with survival of up to two years.

4.5. Limitations

There are a few limitations to this study. First, the retrospective study design meant that data collection was reliant on existing datasets and medical records. As a result, patients who did not have a recorded height or weight were excluded, reducing the sample size of our study. However, despite some group differences compared to those without BMI, the illness severity was similar, suggesting that our study is representative. In addition, there is a

possibility of data coding inaccuracy, and without site-based auditing of diagnostic codes, we cannot be certain about the degree of misclassification if any, and what its effects are on our findings. While we believe that our cohort is broadly representative of the larger population, this cannot be confirmed. Moreover, as a retrospective registry-based study, it is only possible to highlight associations and no causal inferences can be drawn. Furthermore, pre-ICU factors used to estimate illness severity may be colliders or confounders. This is an inherent limitation of the registry which does not capture pre-ICU factors that may influence ICU admission. Second, we did not have any information regarding the number of patients that were referred for and denied ICU admission. Third, the Australian and New Zealand healthcare system has been very fortunate with the magnitude of COVID-19 infections being largely under control, therefore the results may not be generalizable in resource-constrained healthcare systems. Fourth, the BMI was estimated only once at ICU admission. Although the median time spent outside the ICU was 7−10 h, fluid management acutely and the loss of lean mass (over days to weeks in the hospital) could have affected the weight and BMI. Fifth, although there is evidence that patients with obesity were more prone to have pathological pulmonary limitation and pulmonary gas exchange impairment to exercise compared with nonobese COVID-19 patients,[62] we did not have the functional outcome following hospitalisation. Sixth, after discharge, the database did not record any ongoing healthcare needs following discharge. As a result, it is challenging to determine the precise impact of BMI after discharge on long-term survival. Seventh, COVID-19, its treatments, and in many places the composition of patients admitted to the ICU with COVID-19 rapidly evolved during the pandemic. Although this could have accounted for era effects in their analyses, a recent study from Australia did not show any difference based on the year of admission.[50] Eighth, although many biases are related to the obesity paradox,[1,8] collider stratification bias could be highly likely to underlie our study's findings and the decreased risk of mortality associated with obesity when in fact there is no biological basis for this relationship.[63] Finally, the results from this dataset cannot be translated to a non-critically ill population. The existing public health message that the healthy-weight BMI is 18.5−24.9 kg/m^2 has evidential support, including an association with a range of chronic diseases and early death, and the over-representation of patients with obesity and above in this dataset may speak to the increased burden of disease associated with obesity.[8]

5. Conclusion

In a large bi-national retrospective study, we confirmed the existence of the obesity paradox existed beyond hospital discharge in critically ill patients with COVID-19 admitted in Australian and New Zealand ICUs. Patients with BMI ≥40 kg/m^2 were associated with a higher survival time of up to two years. Future studies should explore reasons why there is a survival advantage for morbidly obese patients with COVID-19.

Disclaimer

Ethics approval and consent to participate:

- All experimental protocols were approved by The Alfred Hospital Ethics Committee (Project No: 413/19, Project Title BMI and frailty in Critical Illness, approved 11/01/2022) approved this study with a waiver of informed consent. This was a sub-study of the larger study titled "BMI and frailty in Critical Illness".

- ANZICS Centre for Outcome and Resource Evaluation Management Committee granted access to the ANZICS-APD following standing protocols on 11/16/2022.
- All methods were carried out following the relevant guidelines and regulations of the Declaration of Helsinki.
- Consent for publication − Not applicable

Statement of authors' contributions to the manuscript

1. Designed Research:

- Study conception: AS
- Study design: AS, RRL, ER, DP
- Development of overall research plan: AS, RRL, ER, DP
- Study oversight: AS

2. Conducted research: n/a.
3. Provided essential reagents/materials: DP is the custodian of the ANZICS dataset.
4. Analysis of data:

- Data analysis, performed statistical analysis: AS, RRL
- Long-term survival statistical analysis and interpretation: DP
- Tables and figures: RRL, AS

5. Wrote paper:

- Original drafting of the manuscript: AS
- Critical revision of the manuscript for intellectually important content: AS, RRL, ER, DP

6. Primary responsibility for final content: AS.
7. Other: AS and DP were responsible for the decision to submit the manuscript.
8. All authors provided critical conceptual input, interpreted the data analysis, and read, and approved the final draft.

Conflict of interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: n/a If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2023.10.004.

Australian Capital Territory		
Calvary Hospital (Canberra) ICU	Canberra Hospital ICU	
New South Wales		
Bankstown-Lidcombe Hospital ICU	Hornsby Ku-ring-gai Hospital ICU	Shoalhaven Hospital ICU
Bathurst Base Hospital ICU	John Hunter Hospital ICU	St George Hospital (Sydney) ICU
Blacktown Hospital ICU	Lismore Base Hospital ICU	St Vincent's Hospital (Sydney) ICU
Calvary Mater Newcastle ICU	Maitland Hospital ICU	Goulburn Base Hospital ICU
Campbelltown Hospital ICU	Nepean Hospital ICU	Sydney Adventist Hospital ICU
Coffs Harbour Health Campus ICU	Northern Beaches Hospital ICU	Tamworth Base Hospital ICU
Concord Hospital (Sydney) ICU	Orange Base Hospital ICU	The Chris O'Brien Lifehouse ICU
Dubbo Base Hospital ICU	Port Macquarie Base Hospital ICU	Tweed Heads District Hospital ICU
Fairfield Hospital ICU	Prince of Wales Hospital ICU	Westmead Hospital ICU
Gosford Hospital ICU	Royal North Shore Hospital ICU	Wyong Hospital ICU
Sutherland Hospital & Community Health Services ICU	Royal Prince Alfred Hospital ICU	Wollongong Hospital ICU
Northern Territory		
Alice Springs Hospital ICU	Royal Darwin Hospital ICU	
Queensland		
Caboolture Hospital ICU	Mater Adults Hospital (Brisbane) ICU	Redcliffe Hospital ICU
Cairns Hospital ICU	Mater Health Services North Queensland ICU	Royal Brisbane and Women's Hospital ICU
Gold Coast University Hospital ICU	The Prince Charles Hospital ICU	St Vincent's Private Hospital Northside ICU
Hervey Bay Hospital ICU	Mater Private Hospital (Brisbane) ICU	St Vincent's Private Hospital (Toowoomba) ICU
Logan Hospital ICU	Noosa Hospital ICU	Sunshine Coast University Hospital ICU
Mackay Base Hospital ICU	Princess Alexandra Hospital ICU	Toowoomba Hospital ICU
South Australia		
Calvary Adelaide Hospital ICU	Flinders Medical Centre ICU	Royal Adelaide Hospital ICU
Tasmania		
Launceston General Hospital ICU	Royal Hobart Hospital ICU	
Victoria		
Alfred Hospital ICU	Epworth Freemasons Hospital ICU	Mulgrave Private Hospital ICU
Austin Hospital ICU	Epworth Geelong ICU	Royal Melbourne Hospital ICU
Box Hill Hospital ICU	Footscray Hospital ICU	St John of God Hospital (Bendigo) ICU
Cabrini Hospital ICU	Frankston Hospital ICU	St Vincent's Hospital (Melbourne) ICU
Casey Hospital ICU	Goulburn Valley Health ICU	Sunshine Hospital ICU
Central Gippsland Health Service ICU	Holmesglen Private Hospital ICU	The Northern Hospital ICU
Dandenong Hospital ICU	Knox Private Hospital ICU	University Hospital Geelong ICU
Bendigo Health Care Group Hospital ICU	Monash Medical Centre—Clayton Campus ICU	
Western Australia		
Fiona Stanley Hospital ICU	Joondalup Health Campus ICU	Royal Perth Hospital ICU
Sir Charles Gairdner Hospital ICU		
New Zealand		
Christchurch Hospital ICU	Nelson Hospital ICU	Waikato Hospital ICU
Middlemore Hospital ICU	Whangarei Area Hospital ICU, Northland Health	

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