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Research article

The impact of body mass index on the prognostic performance of the Simplified Acute Physiology Score 3: A prospective cohort study

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ABSTRACT

Objective: To assess the Simplified Acute Physiology Score 3 (SAPS3) prognostic score performance across different body mass index categories.

Methods: A retrospective cohort study in a general ICU in Brazil. A secondary analysis of medical records was performed with clinical and epidemiological data. Patients were stratified according to their body mass index (BMI) category, and a binary logistic regression was then performed to identify factors independently associated with mortality. SAPS3 accuracy was determined using the area under the receiver operating characteristics curve and the Hosmer-Lemeshow test. A modified Kaplan-Meyer plot was employed to evaluate death probability according to BMI. ICU mortality was evaluated as the primary outcome.

Results: A total of 2,179 patients (mean age of 67.9 years and female predominance (53.1%)) were enrolled. SAPS3 was found accurate in all groups except in the underweight (AUC: 0.694 95% CI 0.616–0.773; HL = 0.042). The patients in the underweight group tended to be older, have longer hospital stay, have worse functional status, and have a higher value on prognostic scores. After the adjustments, no statistically significant difference between the BMI groups was noted in relation to mortality, except for the low weight that presented a likelihood of death of 3.50 (95% CI, 1.43–8.58, p = 0.006).

Conclusion: This research showed that SAPS3 had poor accuracy in predicting ICU mortality in underweight patients. This group was shown to be an independent risk factor for worse clinical outcomes.

1. Introduction

Healthcare, a dynamically evolving field, involves a broad range of complex variables, as patients characteristics and therapeutic and diagnostic tools change over time. Thus, prognostic scores need to be reassessed frequently to ensure their optimal functionality [1]. Body weight is commonly used in the composition of scores, but the body composition of the population has been changing over recent years; the prevalence of obesity almost tripled between 1975 and 2016 [2].

The World Health Organization (WHO) has reported that obesity is the abnormal or excessive accumulation of body fat that can affect health. The Body mass index (BMI) is one of the recommended tools for its

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diagnosis [2]. Following the global trend of increasing obesity rates, data collected in Brazil, from 2018 onwards, reveal that 55.7% of the country's adult population is overweight and 19.8% is obese, while the corresponding values in 2006 were 42.6% and 11.8%, respectively [3]. Excess body fat has a well-established association with increased morbidity and mortality in long-term follow-up of out-of-hospital populations. In addition, the increase in the prevalence of obesity in the general population and the burden of comorbidities associated with this disease resulted in an increase in the number of hospitalizations of obese people in intensive care units (ICU) [4].

Despite the obesity epidemic, developing countries present a double burden, in which the obese coexist with a significant population of underweight individuals [5, 6]. Several studies have demonstrated the association of low BMI with all-cause mortality and underlying pathologies in an advanced stage. However, this condition is not considered by most prognostic scores and is not widely studied in the context of ICU [7]. The Simplified Acute Physiology Score 3 (SAPS3) was developed from a multinational database of general ICU patients and is commonly used in Brazilian ICUs, as it has shown good calibration and discrimination in low- and middle-income countries [1, 8]. However, as the country's epidemiological scenario has changed over the years, this study seeks to assess the accuracy of the score in a large cohort of critically ill patients, emphasizing the differences between BMI strata.

2. Methods

2.1. Clinical study design

An observational, analytical cohort study was conducted from August 2015 through July 2018 in a general ICU at *Hospital da Cidade* in Salvador, Bahia, Brazil. A secondary analysis of admission data stored in the Epimed Monitor system was performed. All patients consecutively admitted to the ICU with the length of stay >24 h were included. Patients <18 years or those with missing data were excluded.

Covariates included were age, weight, height, sex, comorbidities, functional capacity, admission diagnosis, length of ICU and hospital stay, physiological and laboratorial data within the first six hours of admission, complications, use of supportive therapy in the ICU, Modified Frailty Index (MFI) [9], the SAPS3 [8], the Charlson Comorbidity Index (CCI) [10]. The patients were stratified based on their BMI values obtained at ICU admission into underweight (BMI <18.5 kg/m^2), normal weight (BMI range, 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), obese grade I (BMI, 30–34.9 kg/m^2) or obese grade II/III (BMI >35 kg/m^2) [2]. Our primary outcome was ICU death.

2.2. Ethics statement

This article was ethically approved by the Research Ethics Committee of Hospital Ana Nery under number 2,571,265 and CAAE 52892315.1.0000.0045. This same ethics committee approved the waiver of consent to participate in accordance with the regulatory standards of the national health council (N° 466/12), which addresses observational, analytical, or descriptive studies that use the information available in medical records; in which data is analyzed anonymously. The present study was conducted in accordance with the Declaration of Helsinki.

2.3. Data analysis

Categorical variables were expressed as frequencies and percentages and analyzed by Fisher's exact test and Z-test. Continuous variables with normal distribution were expressed as means (standard deviation, SD) and means between groups were compared with the one-way analysis of variance (ANOVA) and Tukey's HSD test. Non-normal continuous variables were expressed as median (interquartile range, IQR) and compared with the Mann-Whitney U test and the Kruskal-Wallis test. Normality was assessed by the d'Agostino-Pearson test. All tests results were two-tailed and considered statistically significant for $p < 0.05$. A binary logistic regression, the backward stepwise method, was used to identify characteristics independently associated with ICU mortality. Finally, the area under the receiver operating characteristic curve (ROC) was determined to assess the discriminative capacity of SAPS3. AUC >0.8 was considered satisfactory. Calibration was assessed using Hosmer-Lemeshow goodness-of-fit test.

The data were analyzed with Microsoft Excel suite Office 365, GraphPad Prism version 6.01, and Statistical Package for the Social Sciences, SPSS version 25.0 (IBM, SPSS, USA).

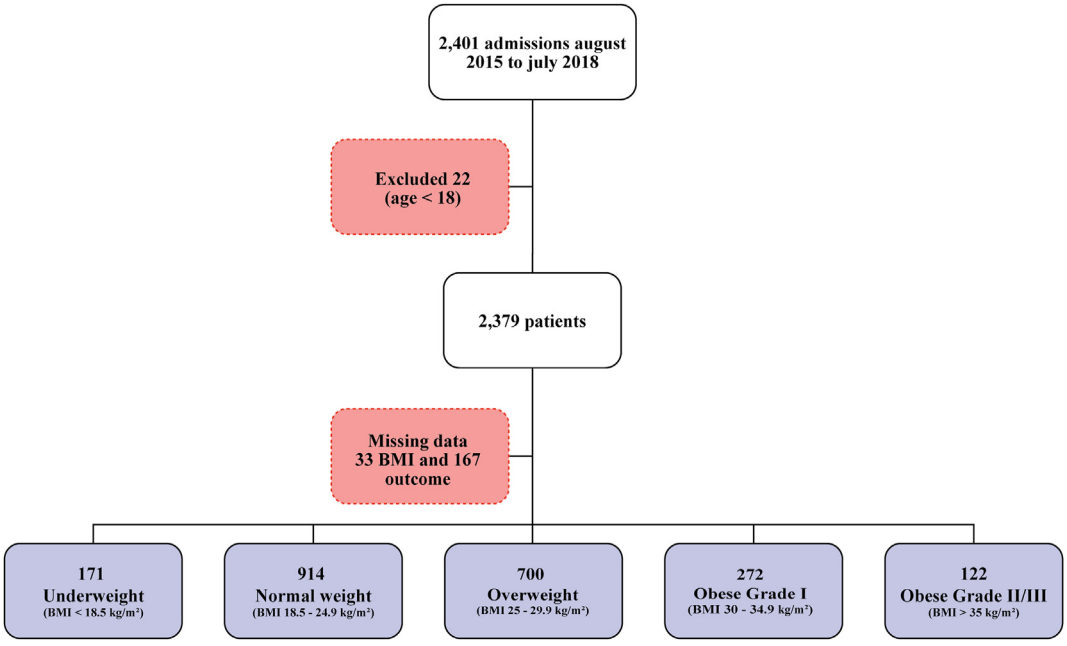

Figure 1. Study flowchart.

3. Results

During the study period, 2401 patients were admitted to the ICU. Two hundred and twenty-two subjects were excluded due to missing height, weight, or outcome data or because they did not meet the study inclusion criteria. Finally, 2179 patients were divided into five groups according to their BMI categories (Figure 1). General patient characteristics are provided in Table 1.

When comparing the BMI groups, the underweight participants had significantly different characteristics. They were older and had a longer length of stay prior to ICU admission and lower mean arterial pressure. A third of this group had an infection as the main diagnosis, in addition to a higher prevalence of comorbidities such as cancer, stroke, and dementia. In contrast, overweight and obese patients had a higher frequency of admissions for surgery and cardiovascular pathologies. No significant difference was observed regarding the need

Table 1. Characteristics of the study population.

Variable	General (n = 2179)	Non-survivors (n = 343)	Survivors (n = 1836)	p-value
Age (years)	68 ± 18	77 ± 15	66 ± 18	<0.0001
Gender, female	1158 (53.1)	172 (50.1)	986 (53.7)	0.239
BMI	25.6 ± 5.7	23.1 ± 5.5	26.0 ± 5.6	<0.0001
Eutrophic	914 (41.9)	172 (50.1)	742 (40.4)	0.001
Underweight	171 (7.8)	64 (18.7)	107 (5.8)	<0.0001
Overweight	700 (32.1)	76 (22.2)	624 (34.0)	<0.0001
Obese Grade I	272 (12.5)	21 (6.1)	251 (13.7)	<0.0001
Obese Grade II/III	122 (5.6)	10 (2.9)	112 (6.1)	0.015
Congestive heart failure	132 (6.1)	16 (4.7)	116 (6.3)	0.268
Chronic renal failure	251 (11.5)	45 (13.1)	206 (11.2)	0.311
Cirrhosis	28 (1.3)	6 (1.7)	22 (1.2)	0.430
Cancer	302 (13.9)	71 (20.7)	231 (12.6)	<0.0001
Immune deficiency	27 (1.2)	7 (2.0)	20 (1.1)	0.177
Diabetes	817 (37.5)	132 (38.5)	685 (37.3)	0.716
Coronary Artery Disease	241 (11.1)	31 (9.0)	210 (11.4)	0.223
Chronic Atrial Fibrillation	137 (6.3)	32 (9.3)	105 (5.7)	0.015
Stroke	340 (15.6)	77 (22.4)	263 (14.3)	<0.0001
Dementia	125 (5.7)	48 (14.0)	77 (4.2)	<0.0001
Tobacco	164 (7.5)	19 (5.5)	145 (7.9)	0.147
Alcoholism	119 (5.5)	22 (6.4)	97 (5.3)	0.436
Psychiatric disease	169 (7.8)	23 (6.7)	146 (8.0)	0.509
Dyslipidemias	201 (9.2)	24 (7.0)	177 (9.6)	0.128
Systolic arterial pressure (mmHg)	138 ± 29	130 ± 30	139 ± 28	0.846
Diastolic Blood Pressure (mmHg)	79 ± 20	75 ± 21	80 ± 20	<0.0001
Mean Arterial Pressure (mmHg)	99 ± 21	93 ± 22	100 ± 20	<0.0001
HR (bpm)	86 ± 20	94 ± 22	84 ± 20	<0.0001
RR (bpm)	20 ± 4	21 ± 5	20 ± 4	<0.0001
Temperature (°C)	36 ± 1	36 ± 1	36 ± 1	0.692
Urea (mmol/L)	57 ± 47	86 ± 64	51 ± 42	<0.0001
Creatinine (mg/dL)	1.44 ± 2	1.86 ± 2	1.36 ± 2	<0.0001
Platelets (x103)	235 ± 113	230 ± 130	236 ± 109	0.420
Hematocrit (%)	34 ± 7	32 ± 8	35 ± 7	<0.0001
Leukocytes total (x103; /uL)	11 ± 11	13 ± 7	11 ± 11	0.011
Bands (/uL)	176.1 ± 511.6	304.6 ± 666.5	152.1 ± 473.5	<0.0001
Segmented (x103; /uL)	9.26 ± 5.74	11.05 ± 6.40	8.92 ± 5.54	<0.0001
Eosinophils (/uL)	123.5 ± 246.5	112.6 ± 286.0	125.5 ± 238.4	0.404
Basophils (/uL)	18.6 ± 48.7	8.58 ± 27.55	20.47 ± 51.55	<0.0001
Lymphocytes (x103; /uL)	1.69 ± 8.84	1.27 ± 1.04	1.77 ± 9.61	0.360
Atypical (/uL)	9.78 ± 172.8	28.58 ± 390.26	6.26 ± 83.38	0.034
Monocytes (/uL)	562.6 ± 390.2	521.38 ± 410.73	570.34 ± 385.85	0.040
Na (mEq/L)	139.3 ± 7.11	138.86 ± 9.56	139.4 ± 6.53	0.211
K (mEq/L)	4.32 ± 0.85	4.56 ± 1.07	4.28 ± 0.79	<0.0001
Use of vasoactive drug	201 (9.2)	93 (27.1)	108 (5.9)	<0.0001
Use of mechanical ventilation	347 (15.9)	149 (43.4)	198 (10.8)	<0.0001
C-reactive Protein (mg/L)	84.64 ± 69.73	136.75 ± 63.45	74.37 ± 66.25	<0.0001
Length of stay prior to ICU admission (days)	2.37 ± 11.31	4.12 ± 11.20	2.05 ± 11.30	0.002
ICU Duration (days)	8.04 ± 13.30	16.08 ± 24.20	6.54 ± 9.31	<0.0001
ICU readmission	200 (9.2)	49 (2.2)	151 (8.2)	<0.0001

Results expressed by number (%), mean ± standard deviation (SD). MAP = Mean arterial pressure; HR = heart rate; RR = Respiratory rate.

for organic support in ICU (Table 2). There were 343 (15.7%) deaths reported in the ICU during the study period. Especially among the underweight group, there was a higher mortality rate, accompanied by higher scores on the modified Frailty Index (MFI), CCI, and SAPS3 (Table 2). Multiple comparisons between each BMI group are represented in Tables 3 and 4.

The ability of SAPS3 to predict intra-unit mortality was assessed for each BMI group. Its accuracy was excellent in all groups except in the underweight group, with an AUC of 0.69 (95% CI 0.61–0.77; $p < 0.001$), reflecting a significantly decreased sensitivity in its performance and Hosmer-Lemeshow goodness of fit test significance of 0.042 (Figure 2). A model including BMI and SAPS3 showed an association of the two variables with mortality, however, with poor goodness-of-fit (Hosmer-Lemeshow p-value: 0.102), suggesting incompleteness of the model (Table 5).

Univariable analysis showed a significantly higher probability of death (OR 3.71; 95% CI 2.65–5.18), for underweight patients, in contrast to overweight, obese, and obese II/III (Figure 3). A binary regression model was performed to assess factors that could confound the assessment of mortality. The highest chance of death persisted in the underweight group, with an OR of 3.50 (95% CI 1.43–8.58, $p = 0.006$), while the overweight and obese groups were no longer associated with mortality. The need for mechanical ventilation or vasopressors on admission (OR 3.11 [95% CI, 4.90–8.24, $p < 0.0001$] and OR 2.69 [95% CI, 1.74–4.18, $p < 0.0001$], respectively), were the variables that represented the highest independent risk in our model (Figure 3). Greater dependence on performing daily activities was also an independent predictor of mortality in our population (OR: 2.84 [95%CI: 1.76–4.57]). The model presented good fit with a Hosmer-Lemeshow goodness-of-fit p-value of 0.102. No difference was observed between the BMI groups for the use of these supports. Moreover, when evaluated as a continuous variable, the BMI presented statistical significance on both the univariate and multivariate analysis with a decrease of 0.04% in the odds of mortality for each additional 1 kg/m^2 (Figure 4).

Table 2. Comparison between BMI groups.

Characteristics	Underweight (n = 171)	Normal weight (n = 914)	Overweight (n = 700)	Obese Grade I (n = 272)	Obese Grade II/III (n = 122)	p-value
Age (years; mean, SD)	76.06 ± 16.39	69.48 ± 18.51	66.10 ± 16.73	64.67 ± 16.19	62.40 ± 18.78	<0.0001
Gender, female (n, %)	98 (57.3)	438 (47.9)	356 (50.9)	176 (64.7)	90 (73.8)	<0.0001
SAPS3 (mean, SD)	54.06 ± 11.49	48.52 ± 12.68	44.63 ± 11.49	43.01 ± 11.87	44.02 ± 12.39	<0.0001
CCI (mean, SD)	2.06 ± 1.90	1.75 ± 1.84	1.55 ± 1.68	1.28 ± 1.63	1.24 ± 1.50	<0.0001
MFI (mean, SD)	1.94 ± 1.30	1.62 ± 1.30	1.68 ± 1.21	1.67 ± 1.06	1.75 ± 1.08	0.040
Admission Diagnosis (n, %)						<0.0001
Cardiovascular	25 (14.6)	152 (16.6)	160 (22.9)	81 (29.8)	34 (27.9)	
Respiratory	13 (7.6)	55 (6.0)	40 (5.7)	13 (4.8)	5 (4.1)	
Neurological	22 (12.9)	171 (18.7)	115 (16.4)	41 (15.1)	11 (9.0)	
Infectious	57 (33.3)	184 (20.1)	96 (13.7)	30 (11.0)	25 (20.5)	
Surgical	10 (5.8)	141 (15.4)	143 (20.4)	65 (23.9)	21 (17.2)	
Other	44 (25.7)	211 (23.1)	146 (20.9)	42 (15.4)	26 (21.3)	
Use of VAD (n, %)	21 (12.3)	86 (9.4)	60 (8.6)	27 (9.9)	7 (5.7)	0.375
Use of MV (n, %)	32 (18.7)	157 (17.2)	110 (15.7)	38 (14.0)	10 (8.2)	0.081
Length of stay prior to ICU (days)	4.95 ± 16.70	2.95 ± 14.58	1.65 ± 6.28	1.22 ± 4.77	1.08 ± 3.47	0.001
ICU length of stay (days)	9.77 ± 12.86	9.34 ± 15.85	6.84 ± 10.74	6.79 ± 12.07	5.58 ± 5.51	<0.0001
Congestive Heart Failure (n, %)	11 (6.4)	59 (6.5)	44 (6.3)	13 (4.8)	5 (4.1)	0.257
Chronic Kidney Disease (n, %)	17 (9.9)	119 (13.0)	82 (11.7)	26 (9.6)	7 (5.7)	0.021
Cirrhosis (n, %)	1 (0.6)	9 (1.0)	14 (2.0)	3 (1.1)	1 (0.8)	0.453
Cancer (n, %)	29 (17.0)	149 (16.3)	90 (12.9)	23 (8.5)	11 (9.0)	0.004
Immunodeficiency (n, %)	2 (1.2)	17 (1.9)	4 (0.6)	3 (1.1)	1 (0.8)	0.056
Diabetes Mellitus (n, %)	61 (35.7)	315 (34.5)	277 (39.6)	108 (39.7)	56 (45.9)	0.003
Coronary Artery Disease (n, %)	12 (7.0)	86 (9.4)	106 (15.1)	23 (8.5)	14 (11.5)	0.098
Stroke (n, %)	41 (24.0)	157 (17.2)	96 (13.7)	35 (12.9)	11 (9.0)	0.002
Dementia (n, %)	29 (17.0)	60 (6.6)	25 (3.6)	7 (2.6)	4 (3.3)	<0.0001
Performance status (n, %)						<0.0001
Completely independent	113 (66.1)	778 (85.1)	641 (91.6)	245 (90.1)	109 (89.3)	
Partially independent	18 (10.5)	65 (7.1)	39 (5.6)	18 (6.6)	8 (6.6)	
Fully dependent	40 (23.4)	71 (7.8)	20 (2.9)	9 (3.3)	5 (4.1)	
Clinical and Laboratory (mean, SD)						
Mean arterial pressure (mmHg)	91.88 ± 21.22	97.45 ± 20.80	99.73 ± 20.22	102.45 ± 20.71	101.32 ± 21.53	<0.0001
Heart rate (bpm)	89.70 ± 21.04	86.31 ± 20.83	84.46 ± 19.55	82.57 ± 19.17	87.90 ± 21.52	0.001
Respiratory rate (ipm)	21.21 ± 4.98	20.10 ± 4.43	20.23 ± 4.34	19.83 ± 4.55	20.45 ± 4.21	0.021
Creatinine (mg/dL)	1.40 ± 2.27	1.49 ± 2.28	1.52 ± 2.63	1.26 ± 1.82	1.08 ± 1.10	0.249
Platelets ($x10^3$)	252.5 ± 136.0	239.7 ± 113.7	227.3 ± 110.3	221.1 ± 76.0	259.8 ± 149.3	0.001
Hematocrit (%)	32.34 ± 6.75	34.17 ± 7.58	35.20 ± 7.38	36.75 ± 6.65	36.10 ± 5.94	<0.0001
Na (mEq/L)	140.2 ± 8.87	138.7 ± 7.68	139.7 ± 6.25	140.0 ± 6.48	139.1 ± 5.40	0.014
C Reactive Protein (mg/dL)	96.77 ± 64.73	91.38 ± 70.15	79.53 ± 70.15	72.48 ± 67.35	73.09 ± 68.99	<0.0001
ICU deaths (n, %)	64 (37.4)	172 (18.8)	76 (10.9)	21 (7.7)	10 (8.2)	<0.0001

Results expressed by number (%), mean ± standard deviation (SD). CCI = Charlson Comorbidity Index, MFI = Modified Frailty Index, ICU = Intensive care unit; VAD = Vasoactive drug; MV = Mechanical ventilation; bpm = beats per minute; incursions per minute.

Table 3. Multiple comparisons between BMI categories.

Variable	BMI Reference category	BMI comparison group	Mean difference (95% CI)	Error[2]	p-value
Age	**Underweight**	**Normal weight**	6,58 (2,48; 10,69)	1.46	**0.001**
		Overweight	9,97 (5,77; 14,17)	1.5	**0.001**
		Obese grade I	11,39 (6,58; 16,2)	1.71	**0.001**
		Obese grade II/III	13,66 (7,82; 19,5)	2.08	**0.001**
	Normal weight	**Underweight**	-6,58 (-10,69; -2,48)	1.46	**0.001**
		Overweight	3,39 (0,91; 5,86)	0.88	**0.001**
		Obese grade I	4,81 (1,41; 8,21)	1.21	**0.001**
		Obese grade II/III	7,08 (2,33; 11,83)	1.69	**0.001**
	Overweight	**Underweight**	-9,97 (-14,17; -5,77)	1.5	**0.001**
		Normal weight	-3,39 (-5,86; -0,91)	0.88	**0.001**
		Obese grade I	1,42 (-2,1; 4,94)	1.25	0.787
		Obese grade II/III	3,7 (-1,14; 8,53)	1.72	0.2
	Obese grade I	**Underweight**	-11,39 (-16,2; -6,58)	1.71	**0.001**
		Normal weight	-4,81 (-8,21; -1,41)	1.21	**0.001**
		Overweight	-1,42 (-4,94; 2,1)	1.25	0.787
		Obese grade II/III	2,27 (-3,1; 7,64)	1.91	0.758
	Obese grade II/III	**Underweight**	-13,66 (-19,5; -7,82)	2.08	**0.001**
		Normal weight	-7,08 (-11,83; -2,33)	1.69	**0.001**
		Overweight	-3,7 (-8,53; 1,14)	1.72	0.2
		Obese grade I	-2,27 (-7,64; 3,1)	1.91	0.758
SAPS3	**Underweight**	**Normal weight**	5,55 (2,71; 8,38)	1.01	**0.001**
		Overweight	9,43 (6,53; 12,33)	1.03	**0.001**
		Obese grade I	10,96 (7,64; 14,28)	1.18	**0.001**
		Obese grade II/III	10,04 (6,01; 14,07)	1.43	**0.001**
	Normal weight	**Underweight**	-5,55 (-8,38; -2,71)	1.01	**0.001**
		Overweight	3,88 (2,18; 5,59)	0.61	**0.001**
		Obese grade I	5,42 (3,07; 7,77)	0.84	**0.001**
		Obese grade II/III	4,5 (1,22; 7,77)	1.17	**0.001**
	Overweight	**Underweight**	-9,43 (-12,33; -6,53)	1.03	**0.001**
		Normal weight	-3,88 (-5,59; -2,18)	0.61	**0.001**
		Obese grade I	1,53 (-0,9; 3,96)	0.87	0.39
		Obese grade II/III	0,61 (-2,72; 3,95)	1.19	0.986
	Obese grade I	**Underweight**	-10,96 (-14,28; -7,64)	1.18	**0.001**
		Normal weight	-5,42 (-7,77; -3,07)	0.84	**0.001**
		Overweight	-1,53 (-3,96; 0,9)	0.87	0.39
		Obese grade II/III	-0,92 (-4,63; 2,78)	1.32	0.957
	Obese grade II/III	**Underweight**	-10,04 (-14,07; -6,01)	1.43	**0.001**
		Normal weight	-4,5 (-7,77; -1,22)	1.17	**0.001**
		Overweight	-0,61 (-3,95; 2,72)	1.19	0.986
		Obese grade I	0,92 (-2,78; 4,63)	1.32	0.957
CCI	Underweight	Normal weight	0,31 (-0,1; 0,72)	0.15	0.205
		Overweight	0,51 (0,09; 0,93)	0.15	**0.006**
		Obese grade I	0,78 (0,29; 1,26)	0.17	**0.001**
		Obese grade II/III	0,82 (0,24; 1,4)	0.21	**0.001**
	Normal weight	Underweight	-0,31 (-0,72; 0,1)	0.15	0.205
		Overweight	0,2 (-0,05; 0,45)	0.09	0.153
		Obese grade I	0,46 (0,12; 0,8)	0.12	**0.001**
		Obese grade II/III	0,51 (0,03; 0,98)	0.17	**0.022**
	Overweight	**Underweight**	-0,51 (-0,93; -0,09)	0.15	**0.006**
		Normal weight	-0,2 (-0,45; 0,05)	0.09	0.153
		Obese grade I	0,26 (-0,09; 0,61)	0.13	0.222
		Obese grade II/III	0,31 (-0,18; 0,79)	0.17	0.38
	Obese grade I	**Underweight**	-0,78 (-1,26; -0,29)	0.17	**0.001**
		Normal weight	-0,46 (-0,8; -0,12)	0.12	**0.001**
		Overweight	-0,26 (-0,61; 0,09)	0.13	0.222
		Obese grade II/III	0,05 (-0,49; 0,58)	0.19	0.999
	Obese grade II/III	**Underweight**	-0,82 (-1,4; -0,24)	0.21	**0.001**
		Normal weight	-0,51 (-0,98; -0,03)	0.17	**0.022**

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Table 3 (*continued*)

Variable	BMI Reference category	BMI comparison group	Mean difference (95% CI)	Error[2]	p-value
		Overweight	-0,31 (-0,79; 0,18)	0.17	0.38
		Obese grade I	-0,05 (-0,58; 0,49)	0.19	0.999
MFI	**Underweight**	**Normal weight**	0,32 (0,03; 0,61)	0.01	**0.016**
		Overweight	0,26 (-0,03; 0,56)	0.01	0.091
		Obese grade I	0,27 (-0,07; 0,61)	0.01	0.168
		Obese grade II/III	0,2 (-0,22; 0,61)	0.01	0.665
	Normal weight	**Underweight**	-0,32 (-0,61; -0,03)	0.01	**0.016**
		Overweight	-0,06 (-0,23; 0,12)	0.01	0.893
		Obese grade I	-0,05 (-0,29; 0,19)	0.01	0.976
		Obese grade II/III	-0,12 (-0,46; 0,21)	0.01	0.839
	Overweight	Underweight	-0,26 (-0,56; 0,03)	0.01	0.091
		Normal weight	0,06 (-0,12; 0,23)	0.01	0.893
		Obese grade I	0,01 (-0,24; 0,25)	0.01	1
		Obese grade II/III	-0,07 (-0,41; 0,27)	0.01	0.982
	Obese grade I	Underweight	-0,27 (-0,61; 0,07)	0.01	0.168
		Normal weight	0,05 (-0,19; 0,29)	0.01	0.976
		Overweight	-0,01 (-0,25; 0,24)	0.01	1
		Obese grade II/III	-0,07 (-0,45; 0,3)	0.01	0.983
	Obese grade II/III	Underweight	-0,2 (-0,61; 0,22)	0.01	0.665
		Normal weight	0,12 (-0,21; 0,46)	0.01	0.839
		Overweight	0,07 (-0,27; 0,41)	0.01	0.982
		Obese grade I	0,07 (-0,3; 0,45)	0.01	0.983
Length of stay prior to ICU	Underweight	Normal weight	0,43 (-2,67; 3,54)	0.94	0.211
		Overweight	2,93 (-0,24; 6,11)	0.96	**0.006**
		Obese grade I	2,98 (-0,65; 6,61)	1.1	**0.007**
		Obese grade II/III	4,19 (-0,22; 8,6)	1.34	**0.031**
	Normal weight	Underweight	-0,43 (-3,54; 2,67)	0.94	0.211
		Overweight	2,5 (0,63; 4,37)	0.57	0.15
		Obese grade I	2,55 (-0,02; 5,12)	0.79	0.179
		Obese grade II/III	3,76 (0,17; 7,34)	1.09	0.422
	Overweight	**Underweight**	-2,93 (-6,11; 0,24)	0.96	**0.006**
		Normal weight	-2,5 (-4,37; -0,63)	0.57	0.15
		Obese grade I	0,05 (-2,61; 2,71)	0.81	0.985
		Obese grade II/III	1,26 (-2,4; 4,91)	1.11	0.986
	Obese grade I	**Underweight**	-2,98 (-6,61; 0,65)	1.1	**0.007**
		Normal weight	-2,55 (-5,12; 0,02)	0.79	0.179
		Overweight	-0,05 (-2,71; 2,61)	0.81	0.985
		Obese grade II/III	1,21 (-2,85; 5,26)	1.23	1
	Obese grade II/III	**Underweight**	-4,19 (-8,6; 0,22)	1.34	**0.031**
		Normal weight	-3,76 (-7,34; -0,17)	1.09	0.422
		Overweight	-1,26 (-4,91; 2,4)	1.11	0.986
		Obese grade I	-1,21 (-5,26; 2,85)	1.23	1
ICU length of stay	Underweight	Normal weight	2 (-0,65; 4,64)	1.1	0.995
		Overweight	3,3 (0,59; 6)	1.13	0.071
		Obese grade I	3,72 (0,62; 6,82)	1.29	0.143
		Obese grade II/III	3,87 (0,11; 7,62)	1.57	0.059
	Normal weight	Underweight	-2 (-4,64; 0,65)	1.1	0.995
		Overweight	1,3 (-0,3; 2,9)	0.67	**0.002**
		Obese grade I	1,73 (-0,48; 3,93)	0.92	**0.043**
		Obese grade II/III	1,87 (-1,19; 4,93)	1.28	**0.027**
	Overweight	Underweight	-3,3 (-6; -0,59)	1.13	0.071
		Normal weight	-1,3 (-2,9; 0,3)	0.67	**0.002**
		Obese grade I	0,43 (-1,85; 2,7)	0.95	1
		Obese grade II/III	0,57 (-2,54; 3,68)	1.3	0.87
	Obese grade I	Underweight	-3,72 (-6,82; -0,62)	1.29	0.143
		Normal weight	-1,73 (-3,93; 0,48)	0.92	**0.043**
		Overweight	-0,43 (-2,7; 1,85)	0.95	1
		Obese grade II/III	0,14 (-3,32; 3,6)	1.44	0.919
	Obese grade II/III	Underweight	-3,87 (-7,62; -0,11)	1.57	0.059

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Table 3 (*continued*)

Variable	BMI Reference category	BMI comparison group	Mean difference (95% CI)	Error[2]	p-value
		Normal weight	-1,87 (-4,93; 1,19)	1.28	**0.027**
		Overweight	-0,57 (-3,68; 2,54)	1.3	0.87
		Obese grade I	-0,14 (-3,6; 3,32)	1.44	0.919
Hospital length of stay	Underweight	Normal weight	1,33 (-3,63; 6,29)	1.77	0.944
		Overweight	6,5 (1,42; 11,58)	1.81	**0.003**
		Obese grade I	7,95 (2,14; 13,76)	2.07	**0.001**
		Obese grade II/III	7,58 (0,53; 14,64)	2.51	**0.022**
	Normal weight	Underweight	-1,33 (-6,29; 3,63)	1.77	0.944
		Overweight	5,17 (2,18; 8,16)	1.06	**0.001**
		Obese grade I	6,62 (2,51; 10,74)	1.46	**0.001**
		Obese grade II/III	6,25 (0,51; 11,99)	2.04	**0.019**
	Overweight	**Underweight**	-6,5 (-11,58; -1,42)	1.81	**0.003**
		Normal weight	-5,17 (-8,16; -2,18)	1.06	**0.001**
		Obese grade I	1,45 (-2,8; 5,71)	1.51	0.873
		Obese grade II/III	1,08 (-4,76; 6,92)	2.08	0.985
	Obese grade I	**Underweight**	-7,95 (-13,76; -2,14)	2.07	**0.001**
		Normal weight	-6,62 (-10,74; -2,51)	1.46	**0.001**
		Overweight	-1,45 (-5,71; 2,8)	1.51	0.873
		Obese grade II/III	-0,37 (-6,86; 6,11)	2.31	1
	Obese grade II/III	**Underweight**	-7,58 (-14,64; -0,53)	2.51	**0.022**
		Normal weight	-6,25 (-11,99; -0,51)	2.04	**0.019**
		Overweight	-1,08 (-6,92; 4,76)	2.08	0.985
		Obese grade I	0,37 (-6,11; 6,86)	2.31	1
Mean arterial pressure	**Underweight**	**Normal weight**	-5,57 (-10,41; -0,72)	1.72	**0.011**
		Overweight	-7,85 (-12,81; -2,89)	1.77	**0.001**
		Obese grade I	-10,56 (-16,24; -4,89)	2.02	**0.001**
		Obese grade II/III	-9,44 (-16,34; -2,53)	2.46	**0.001**
	Normal weight	**Underweight**	5,57 (0,72; 10,41)	1.72	**0.011**
		Overweight	-2,28 (-5,21; 0,65)	1.04	0.185
		Obese grade I	-5 (-9,01; -0,98)	1.43	**0.004**
		Obese grade II/III	-3,87 (-9,49; 1,76)	2	0.3
	Overweight	**Underweight**	7,85 (2,89; 12,81)	1.77	**0.001**
		Normal weight	2,28 (-0,65; 5,21)	1.04	0.185
		Obese grade I	-2,72 (-6,87; 1,44)	1.48	0.353
		Obese grade II/III	-1,59 (-7,31; 4,14)	2.04	0.936
	Obese grade I	**Underweight**	10,56 (4,89; 16,24)	2.02	**0.001**
		Normal weight	5 (0,98; 9,01)	1.43	**0.004**
		Overweight	2,72 (-1,44; 6,87)	1.48	0.353
		Obese grade II/III	1,13 (-5,23; 7,48)	2.26	0.988
	Obese grade II/III	**Underweight**	9,44 (2,53; 16,34)	2.46	**0.001**
		Normal weight	3,87 (-1,76; 9,49)	2	0.3
		Overweight	1,59 (-4,14; 7,31)	2.04	0.936
		Obese grade I	-1,13 (-7,48; 5,23)	2.26	0.988
Heart rate	Underweight	Normal weight	3,39 (-1,36; 8,14)	1.69	0.262
		Overweight	5,24 (0,38; 10,11)	1.73	**0.021**
		Obese grade I	7,14 (1,57; 12,7)	1.98	**0.003**
		Obese grade II/III	1,8 (-4,97; 8,57)	2.41	0.945
	Normal weight	Underweight	-3,39 (-8,14; 1,36)	1.69	0.262
		Overweight	1,85 (-1,02; 4,71)	1.02	0.368
		Obese grade I	3,74 (-0,2; 7,68)	1.4	0.059
		Obese grade II/III	-1,59 (-7,11; 3,92)	1.96	0.927
	Overweight	**Underweight**	-5,24 (-10,11; -0,38)	1.73	**0.021**
		Normal weight	-1,85 (-4,71; 1,02)	1.02	0.368
		Obese grade I	1,9 (-2,18; 5,97)	1.45	0.687
		Obese grade II/III	-3,44 (-9,05; 2,17)	2	0.421
	Obese grade I	**Underweight**	-7,14 (-12,7; -1,57)	1.98	**0.003**
		Normal weight	-3,74 (-7,68; 0,2)	1.4	0.059
		Overweight	-1,9 (-5,97; 2,18)	1.45	0.687
		Obese grade II/III	-5,34 (-11,56; 0,89)	2.22	0.114

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Table 3 (*continued*)

Variable	BMI Reference category	BMI comparison group	Mean difference (95% CI)	Error[2]	p-value
	Obese grade II/III	Underweight	-1,8 (-8,57; 4,97)	2.41	0.945
		Normal weight	1,59 (-3,92; 7,11)	1.96	0.927
		Overweight	3,44 (-2,17; 9,05)	2	0.421
		Obese grade I	5,34 (-0,89; 11,56)	2.22	0.114
Respiratory rate	**Underweight**	**Normal weight**	1,12 (0,07; 2,16)	0.37	**0.023**
		Overweight	0,98 (-0,08; 2,05)	0.38	0.073
		Obese grade I	1,38 (0,16; 2,61)	0.44	**0.013**
		Obese grade II/III	0,76 (-0,73; 2,25)	0.53	0.606
	Normal weight	**Underweight**	-1,12 (-2,16; -0,07)	0.37	**0.023**
		Overweight	-0,13 (-0,76; 0,5)	0.22	0.977
		Obese grade I	0,27 (-0,6; 1,13)	0.31	0.907
		Obese grade II/III	-0,36 (-1,57; 0,86)	0.43	0.925
	Overweight	Underweight	-0,98 (-2,05; 0,08)	0.38	0.073
		Normal weight	0,13 (-0,5; 0,76)	0.22	0.977
		Obese grade I	0,4 (-0,5; 1,29)	0.32	0.72
		Obese grade II/III	-0,22 (-1,46; 1,01)	0.44	0.987
	Obese grade I	**Underweight**	-1,38 (-2,61; -0,16)	0.44	**0.013**
		Normal weight	-0,27 (-1,13; 0,6)	0.31	0.907
		Overweight	-0,4 (-1,29; 0,5)	0.32	0.72
		Obese grade II/III	-0,62 (-2; 0,75)	0.49	0.707
	Obese grade II/III	Underweight	-0,76 (-2,25; 0,73)	0.53	0.606
		Normal weight	0,36 (-0,86; 1,57)	0.43	0.925
		Overweight	0,22 (-1,01; 1,46)	0.44	0.987
		Obese grade I	0,62 (-0,75; 2)	0.49	0.707
Temperature	Underweight	Normal weight	-0,13 (-0,38; 0,12)	0.09	0.598
		Overweight	-0,11 (-0,37; 0,15)	0.09	0.755
		Obese grade I	-0,14 (-0,44; 0,15)	0.1	0.64
		Obese grade II/III	-0,11 (-0,46; 0,25)	0.13	0.917
	Normal weight	Underweight	0,13 (-0,12; 0,38)	0.09	0.598
		Overweight	0,02 (-0,13; 0,17)	0.05	0.996
		Obese grade I	-0,02 (-0,22; 0,19)	0.07	1
		Obese grade II/III	0,02 (-0,27; 0,31)	0.1	1
	Overweight	Underweight	0,11 (-0,15; 0,37)	0.09	0.755
		Normal weight	-0,02 (-0,17; 0,13)	0.05	0.996
		Obese grade I	-0,03 (-0,25; 0,18)	0.08	0.991
		Obese grade II/III	0 (-0,29; 0,3)	0.1	1
	Obese grade I	Underweight	0,14 (-0,15; 0,44)	0.1	0.64
		Normal weight	0,02 (-0,19; 0,22)	0.07	1
		Overweight	0,03 (-0,18; 0,25)	0.08	0.991
		Obese grade II/III	0,04 (-0,29; 0,36)	0.12	0.998
	Obese grade II/III	Underweight	0,11 (-0,25; 0,46)	0.13	0.917
		Normal weight	-0,02 (-0,31; 0,27)	0.1	1
		Overweight	0 (-0,3; 0,29)	0.1	1
		Obese grade I	-0,04 (-0,36; 0,29)	0.12	0.998
Creatinine	Underweight	Normal weight	-0,08 (-0,65; 0,49)	0.2	0.994
		Overweight	-0,11 (-0,7; 0,47)	0.21	0.983
		Obese grade I	0,14 (-0,52; 0,81)	0.24	0.974
		Obese grade II/III	0,32 (-0,48; 1,12)	0.28	0.793
	Normal weight	Underweight	0,08 (-0,49; 0,65)	0.2	0.994
		Overweight	-0,03 (-0,37; 0,31)	0.12	0.999
		Obese grade I	0,23 (-0,24; 0,69)	0.17	0.646
		Obese grade II/III	0,4 (-0,24; 1,04)	0.23	0.393
	Overweight	Underweight	0,11 (-0,47; 0,7)	0.21	0.983
		Normal weight	0,03 (-0,31; 0,37)	0.12	0.999
		Obese grade I	0,26 (-0,23; 0,74)	0.17	0.565
		Obese grade II/III	0,43 (-0,22; 1,09)	0.23	0.339
	Obese grade I	Underweight	-0,14 (-0,81; 0,52)	0.24	0.974
		Normal weight	-0,23 (-0,69; 0,24)	0.17	0.646
		Overweight	-0,26 (-0,74; 0,23)	0.17	0.565

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Table 3 (*continued*)

Variable	BMI Reference category	BMI comparison group	Mean difference (95% CI)	Error[2]	p-value
		Obese grade II/III	0,18 (-0,55; 0,9)	0.26	0.96
	Obese grade II/III	Underweight	-0,32 (-1,12; 0,48)	0.28	0.793
		Normal weight	-0,4 (-1,04; 0,24)	0.23	0.393
		Overweight	-0,43 (-1,09; 0,22)	0.23	0.339
		Obese grade I	-0,18 (-0,9; 0,55)	0.26	0.96
Platelets	Underweight	Normal weight	12,75 (-14,8; 40,29)	9.8	0.691
		Overweight	25,15 (-3,07; 53,38)	10.04	0.09
		Obese grade I	31,41 (-0,81; 63,62)	11.46	**0.049**
		Obese grade II/III	-7,35 (-46,3; 31,59)	13.86	0.984
	Normal weight	Underweight	-12,75 (-40,29; 14,8)	9.8	0.691
		Overweight	12,41 (-4,11; 28,92)	5.88	0.216
		Obese grade I	18,66 (-4,01; 41,33)	8.07	0.141
		Obese grade II/III	-20,1 (-51,61; 11,41)	11.21	0.378
	Overweight	Underweight	-25,15 (-53,38; 3,07)	10.04	0.09
		Normal weight	-12,41 (-28,92; 4,11)	5.88	0.216
		Obese grade I	6,26 (-17,23; 29,75)	8.36	0.945
		Obese grade II/III	-32,51 (-64,61; -0,4)	11.43	**0.036**
	Obese grade I	**Underweight**	-31,41 (-63,62; 0,81)	11.46	**0.049**
		Normal weight	-18,66 (-41,33; 4,01)	8.07	0.141
		Overweight	-6,26 (-29,75; 17,23)	8.36	0.945
		Obese grade II/III	-38,76 (-74,42; -3,1)	12.69	**0.019**
	Obese grade II/III	Underweight	7,35 (-31,59; 46,3)	13.86	0.984
		Normal weight	20,1 (-11,41; 51,61)	11.21	0.378
		Overweight	32,51 (0,4; 64,61)	11.43	**0.036**
		Obese grade I	38,76 (3,1; 74,42)	12.69	**0.019**
Hematocrit	**Underweight**	**Normal weight**	-1,83 (-3,6; -0,06)	0.63	**0.031**
		Overweight	-2,86 (-4,68; -1,04)	0.65	**0.001**
		Obese grade I	-4,41 (-6,48; -2,34)	0.74	**0.001**
		Obese grade II/III	-3,75 (-6,26; -1,25)	0.89	**0.001**
	Normal weight	**Underweight**	1,83 (0,06; 3,6)	0.63	**0.031**
		Overweight	-1,03 (-2,09; 0,03)	0.38	0.051
		Obese grade I	-2,58 (-4,04; -1,12)	0.52	**0.001**
		Obese grade II/III	-1,92 (-3,95; 0,1)	0.72	0.059
	Overweight	**Underweight**	2,86 (1,04; 4,68)	0.65	**0.001**
		Normal weight	1,03 (-0,03; 2,09)	0.38	0.051
		Obese grade I	-1,55 (-3,06; -0,04)	0.54	**0.032**
		Obese grade II/III	-0,89 (-2,96; 1,17)	0.74	0.742
	Obese grade I	**Underweight**	4,41 (2,34; 6,48)	0.74	**0.001**
		Normal weight	2,58 (1,12; 4,04)	0.52	**0.001**
		Overweight	1,55 (0,04; 3,06)	0.54	**0.032**
		Obese grade II/III	0,66 (-1,64; 2,95)	0.82	0.929
	Obese grade II/III	**Underweight**	3,75 (1,25; 6,26)	0.89	**0.001**
		Normal weight	1,92 (-0,1; 3,95)	0.72	0.059
		Overweight	0,89 (-1,17; 2,96)	0.74	0.742
		Obese grade I	-0,66 (-2,95; 1,64)	0.82	0.929
Leukocytes	Underweight	Normal weight	0,55 (-2,18; 3,28)	0.97	0.98
		Overweight	0,53 (-2,27; 3,32)	0.99	0.984
		Obese grade I	0,84 (-2,35; 4,03)	1.14	0.946
		Obese grade II/III	-0,48 (-4,34; 3,37)	1.37	0.997
	Normal weight	Underweight	-0,55 (-3,28; 2,18)	0.97	0.98
		Overweight	-0,02 (-1,66; 1,62)	0.58	1
		Obese grade I	0,3 (-1,95; 2,54)	0.8	0.996
		Obese grade II/III	-1,03 (-4,15; 2,09)	1.11	0.886
	Overweight	Underweight	-0,53 (-3,32; 2,27)	0.99	0.984
		Normal weight	0,02 (-1,62; 1,66)	0.58	1
		Obese grade I	0,32 (-2,01; 2,64)	0.83	0.996
		Obese grade II/III	-1,01 (-4,19; 2,17)	1.13	0.899
	Obese grade I	Underweight	-0,84 (-4,03; 2,35)	1.14	0.946
		Normal weight	-0,3 (-2,54; 1,95)	0.8	0.996

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Table 3 (*continued*)

Variable	BMI Reference category	BMI comparison group	Mean difference (95% CI)	Error[2]	p-value
		Overweight	-0,32 (-2,64; 2,01)	0.83	0.996
		Obese grade II/III	-1,33 (-4,86; 2,21)	1.26	0.829
	Obese grade II/III	Underweight	0,48 (-3,37; 4,34)	1.37	0.997
		Normal weight	1,03 (-2,09; 4,15)	1.11	0.886
		Overweight	1,01 (-2,17; 4,19)	1.13	0.899
		Obese grade I	1,33 (-2,21; 4,86)	1.26	0.829
Segmented neutrophils	Underweight	Normal weight	498,96 (-898,42; 1896,34)	497.27	0.854
		Overweight	1178,21 (-253,81; 2610,23)	509.59	0.141
		Obese grade I	1036,11 (-597,74; 2669,96)	581.42	0.384
		Obese grade II/III	-244,51 (-2219,86; 1730,84)	702.94	0.997
	Normal weight	Underweight	-498,96 (-1896,34; 898,42)	497.27	0.854
		Overweight	679,25 (-159,73; 1518,23)	298.56	0.153
		Obese grade I	537,15 (-612,92; 1687,22)	409.26	0.683
		Obese grade II/III	-743,47 (-2341,97; 855,02)	568.84	0.687
	Overweight	Underweight	-1178,21 (-2610,23; 253,81)	509.59	0.141
		Normal weight	-679,25 (-1518,23; 159,73)	298.56	0.153
		Obese grade I	-142,1 (-1334,02; 1049,82)	424.15	0.997
		Obese grade II/III	-1422,72 (-3051,59; 206,14)	579.64	0.102
	Obese grade I	Underweight	-1036,11 (-2669,96; 597,74)	581.42	0.384
		Normal weight	-537,15 (-1687,22; 612,92)	409.26	0.683
		Overweight	142,1 (-1049,82; 1334,02)	424.15	0.997
		Obese grade II/III	-1280,62 (-3089,49; 528,24)	643.7	0.271
	Obese grade II/III	Underweight	244,51 (-1730,84; 2219,86)	702.94	0.997
		Normal weight	743,47 (-855,02; 2341,97)	568.84	0.687
		Overweight	1422,72 (-206,14; 3051,59)	579.64	0.102
		Obese grade I	1280,62 (-528,24; 3089,49)	643.7	0.271
Band neutrophils	Underweight	Normal weight	75,96 (-48,73; 200,65)	44.37	0.427
		Overweight	105,63 (-22,15; 233,41)	45.47	0.138
		Obese grade I	140,73 (-5,06; 286,52)	51.88	0.052
		Obese grade II/III	66,52 (-109,75; 242,78)	62.72	0.827
	Normal weight	Underweight	-75,96 (-200,65; 48,73)	44.37	0.427
		Overweight	29,67 (-45,19; 104,54)	26.64	0.799
		Obese grade I	64,77 (-37,85; 167,39)	36.52	0.389
		Obese grade II/III	-9,44 (-152,08; 133,19)	50.76	1
	Overweight	Underweight	-105,63 (-233,41; 22,15)	45.47	0.138
		Normal weight	-29,67 (-104,54; 45,19)	26.64	0.799
		Obese grade I	35,1 (-71,26; 141,45)	37.85	0.886
		Obese grade II/III	-39,12 (-184,46; 106,23)	51.72	0.943
	Obese grade I	Underweight	-140,73 (-286,52; 5,06)	51.88	0.052
		Normal weight	-64,77 (-167,39; 37,85)	36.52	0.389
		Overweight	-35,1 (-141,45; 71,26)	37.85	0.886
		Obese grade II/III	-74,21 (-235,62; 87,19)	57.44	0.696
	Obese grade II/III	Underweight	-66,52 (-242,78; 109,75)	62.72	0.827
		Normal weight	9,44 (-133,19; 152,08)	50.76	1
		Overweight	39,12 (-106,23; 184,46)	51.72	0.943
		Obese grade I	74,21 (-87,19; 235,62)	57.44	0.696
Lymphocytes	Underweight	Normal weight	-28,93 (-2185,57; 2127,71)	767.45	1
		Overweight	-796,2 (-3006,3; 1413,9)	786.48	0.85
		Obese grade I	-360,33 (-2881,92; 2161,25)	897.32	0.995
		Obese grade II/III	-274,81 (-3323,44; 2773,83)	1084.88	0.999
	Normal weight	Underweight	28,93 (-2127,71; 2185,57)	767.45	1
		Overweight	-767,27 (-2062,09; 527,56)	460.77	0.456
		Obese grade I	-331,4 (-2106,35; 1443,55)	631.63	0.985
		Obese grade II/III	-245,88 (-2712,9; 2221,15)	877.91	0.999
	Overweight	Underweight	796,2 (-1413,9; 3006,3)	786.48	0.85
		Normal weight	767,27 (-527,56; 2062,09)	460.77	0.456
		Obese grade I	435,87 (-1403,67; 2275,4)	654.61	0.964
		Obese grade II/III	521,39 (-1992,5; 3035,29)	894.59	0.978
	Obese grade I	Underweight	360,33 (-2161,25; 2881,92)	897.32	0.995

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Table 3 (*continued*)

Variable	BMI Reference category	BMI comparison group	Mean difference (95% CI)	Error[2]	p-value
		Normal weight	331,4 (-1443,55; 2106,35)	631.63	0.985
		Overweight	-435,87 (-2275,4; 1403,67)	654.61	0.964
		Obese grade II/III	85,53 (-2706,16; 2877,22)	993.44	1
	Obese grade II/III	Underweight	274,81 (-2773,83; 3323,44)	1084.88	0.999
		Normal weight	245,88 (-2221,15; 2712,9)	877.91	0.999
		Overweight	-521,39 (-3035,29; 1992,5)	894.59	0.978
		Obese grade I	-85,53 (-2877,22; 2706,16)	993.44	1
Atypical lymphocytes	Underweight	Normal weight	-4,12 (-46,25; 38,01)	14.99	0.999
		Overweight	-3,93 (-47,11; 39,25)	15.37	0.999
		Obese grade I	-33,62 (-82,87; 15,64)	17.53	0.308
		Obese grade II/III	0,12 (-59,43; 59,67)	21.19	1
	Normal weight	Underweight	4,12 (-38,01; 46,25)	14.99	0.999
		Overweight	0,19 (-25,12; 25,51)	9.01	1
		Obese grade I	-29,5 (-64,17; 5,18)	12.34	0.118
		Obese grade II/III	4,24 (-43,95; 52,43)	17.15	0.999
	Overweight	Underweight	3,93 (-39,25; 47,11)	15.37	0.999
		Normal weight	-0,19 (-25,51; 25,12)	9.01	1
		Obese grade I	-29,69 (-65,63; 6,25)	12.79	0.138
		Obese grade II/III	4,05 (-45,07; 53,16)	17.48	0.999
	Obese grade I	Underweight	33,62 (-15,64; 82,87)	17.53	0.308
		Normal weight	29,5 (-5,18; 64,17)	12.34	0.118
		Overweight	29,69 (-6,25; 65,63)	12.79	0.138
		Obese grade II/III	33,74 (-20,8; 88,27)	19.41	0.41
	Obese grade II/III	Underweight	-0,12 (-59,67; 59,43)	21.19	1
		Normal weight	-4,24 (-52,43; 43,95)	17.15	0.999
		Overweight	-4,05 (-53,16; 45,07)	17.48	0.999
		Obese grade I	-33,74 (-88,27; 20,8)	19.41	0.41
Monocytes	Underweight	Normal weight	-47,81 (-142,96; 47,33)	33.86	0.62
		Overweight	-16,02 (-113,52; 81,48)	34.7	0.991
		Obese grade I	-40,29 (-151,53; 70,96)	39.59	0.847
		Obese grade II/III	-96,22 (-230,71; 38,28)	47.86	0.261
	Normal weight	Underweight	47,81 (-47,33; 142,96)	33.86	0.62
		Overweight	31,8 (-25,33; 88,92)	20.33	0.521
		Obese grade I	7,53 (-70,77; 85,83)	27.86	0.999
		Obese grade II/III	-48,4 (-157,24; 60,43)	38.73	0.722
	Overweight	Underweight	16,02 (-81,48; 113,52)	34.7	0.991
		Normal weight	-31,8 (-88,92; 25,33)	20.33	0.521
		Obese grade I	-24,27 (-105,42; 56,89)	28.88	0.918
		Obese grade II/III	-80,2 (-191,1; 30,7)	39.47	0.251
	Obese grade I	Underweight	40,29 (-70,96; 151,53)	39.59	0.847
		Normal weight	-7,53 (-85,83; 70,77)	27.86	0.999
		Overweight	24,27 (-56,89; 105,42)	28.88	0.918
		Obese grade II/III	-55,93 (-179,09; 67,23)	43.83	0.706
	Obese grade II/III	Underweight	96,22 (-38,28; 230,71)	47.86	0.261
		Normal weight	48,4 (-60,43; 157,24)	38.73	0.722
		Overweight	80,2 (-30,7; 191,1)	39.47	0.251
		Obese grade I	55,93 (-67,23; 179,09)	43.83	0.706
Basophils	Underweight	Normal weight	-1,16 (-13,03; 10,71)	4.22	0.999
		Overweight	-9 (-21,16; 3,17)	4.33	0.23
		Obese grade I	-6,38 (-20,26; 7,5)	4.94	0.697
		Obese grade II/III	-9,9 (-26,68; 6,88)	5.97	0.46
	Normal weight	Underweight	1,16 (-10,71; 13,03)	4.22	0.999
		Overweight	-7,84 (-14,96; -0,71)	2.54	**0.017**
		Obese grade I	-5,21 (-14,98; 4,56)	3.48	0.563
		Obese grade II/III	-8,74 (-22,32; 4,84)	4.83	0.369
	Overweight	Underweight	9 (-3,17; 21,16)	4.33	0.23
		Normal weight	7,84 (0,71; 14,96)	2.54	**0.017**
		Obese grade I	2,62 (-7,5; 12,75)	3.6	0.95
		Obese grade II/III	-0,9 (-14,74; 12,94)	4.92	1

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Table 3 (*continued*)

Variable	BMI Reference category	BMI comparison group	Mean difference (95% CI)	Error[2]	p-value
	Obese grade I	Underweight	6,38 (-7,5; 20,26)	4.94	0.697
		Normal weight	5,21 (-4,56; 14,98)	3.48	0.563
		Overweight	-2,62 (-12,75; 7,5)	3.6	0.95
		Obese grade II/III	-3,53 (-18,89; 11,84)	5.47	0.968
	Obese grade II/III	Underweight	9,9 (-6,88; 26,68)	5.97	0.46
		Normal weight	8,74 (-4,84; 22,32)	4.83	0.369
		Overweight	0,9 (-12,94; 14,74)	4.92	1
		Obese grade I	3,53 (-11,84; 18,89)	5.47	0.968
Eosinophils	Underweight	Normal weight	42,95 (-17,15; 103,05)	21.39	0.262
		Overweight	35,87 (-25,72; 97,46)	21.92	0.474
		Obese grade I	54,64 (-15,63; 124,91)	25.01	0.186
		Obese grade II/III	69,19 (-15,77; 154,14)	30.23	0.149
	Normal weight	Underweight	-42,95 (-103,05; 17,15)	21.39	0.262
		Overweight	-7,08 (-43,16; 29,01)	12.84	0.982
		Obese grade I	11,68 (-37,78; 61,15)	17.6	0.964
		Obese grade II/III	26,23 (-42,52; 94,98)	24.47	0.821
	Overweight	Underweight	-35,87 (-97,46; 25,72)	21.92	0.474
		Normal weight	7,08 (-29,01; 43,16)	12.84	0.982
		Obese grade I	18,76 (-32,5; 70,03)	18.24	0.842
		Obese grade II/III	33,31 (-36,75; 103,37)	24.93	0.669
	Obese grade I	Underweight	-54,64 (-124,91; 15,63)	25.01	0.186
		Normal weight	-11,68 (-61,15; 37,78)	17.6	0.964
		Overweight	-18,76 (-70,03; 32,5)	18.24	0.842
		Obese grade II/III	14,55 (-63,25; 92,35)	27.68	0.985
	Obese grade II/III	Underweight	-69,19 (-154,14; 15,77)	30.23	0.149
		Normal weight	-26,23 (-94,98; 42,52)	24.47	0.821
		Overweight	-33,31 (-103,37; 36,75)	24.93	0.669
		Obese grade I	-14,55 (-92,35; 63,25)	27.68	0.985
Na	Underweight	Normal weight	1,47 (-0,28; 3,22)	0.62	0.128
		Overweight	0,47 (-1,32; 2,26)	0.64	0.948
		Obese grade I	0,2 (-1,86; 2,25)	0.73	0.999
		Obese grade II/III	1,04 (-1,43; 3,51)	0.88	0.761
	Normal weight	Underweight	-1,47 (-3,22; 0,28)	0.62	0.128
		Overweight	-1 (-2,05; 0,05)	0.37	0.056
		Obese grade I	-1,27 (-2,72; 0,18)	0.52	0.099
		Obese grade II/III	-0,43 (-2,42; 1,56)	0.71	0.974
	Overweight	Underweight	-0,47 (-2,26; 1,32)	0.64	0.948
		Normal weight	1 (-0,05; 2,05)	0.37	0.056
		Obese grade I	-0,27 (-1,77; 1,23)	0.53	0.987
		Obese grade II/III	0,57 (-1,46; 2,6)	0.72	0.934
	Obese grade I	Underweight	-0,2 (-2,25; 1,86)	0.73	0.999
		Normal weight	1,27 (-0,18; 2,72)	0.52	0.099
		Overweight	0,27 (-1,23; 1,77)	0.53	0.987
		Obese grade II/III	0,84 (-1,42; 3,1)	0.81	0.835
	Obese grade II/III	Underweight	-1,04 (-3,51; 1,43)	0.88	0.761
		Normal weight	0,43 (-1,56; 2,42)	0.71	0.974
		Overweight	-0,57 (-2,6; 1,46)	0.72	0.934
		Obese grade I	-0,84 (-3,1; 1,42)	0.81	0.835
K	Underweight	Normal weight	0,01 (-0,2; 0,22)	0.08	1
		Overweight	0,05 (-0,17; 0,27)	0.08	0.966
		Obese grade I	0,11 (-0,14; 0,36)	0.09	0.707
		Obese grade II/III	-0,03 (-0,33; 0,27)	0.11	0.998
	Normal weight	Underweight	-0,01 (-0,22; 0,2)	0.08	1
		Overweight	0,04 (-0,08; 0,17)	0.04	0.881
		Obese grade I	0,1 (-0,07; 0,28)	0.06	0.444
		Obese grade II/III	-0,04 (-0,28; 0,2)	0.09	0.99
	Overweight	Underweight	-0,05 (-0,27; 0,17)	0.08	0.966
		Normal weight	-0,04 (-0,17; 0,08)	0.04	0.881
		Obese grade I	0,06 (-0,12; 0,24)	0.06	0.869

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Table 3 (*continued*)

Variable	BMI Reference category	BMI comparison group	Mean difference (95% CI)	Error[2]	p-value
		Obese grade II/III	-0,08 (-0,33; 0,16)	0.09	0.879
	Obese grade I	Underweight	-0,11 (-0,36; 0,14)	0.09	0.707
		Normal weight	-0,1 (-0,28; 0,07)	0.06	0.444
		Overweight	-0,06 (-0,24; 0,12)	0.06	0.869
		Obese grade II/III	-0,14 (-0,42; 0,13)	0.1	0.569
	Obese grade II/III	Underweight	0,03 (-0,27; 0,33)	0.11	0.998
		Normal weight	0,04 (-0,2; 0,28)	0.09	0.99
		Overweight	0,08 (-0,16; 0,33)	0.09	0.879
		Obese grade I	0,14 (-0,13; 0,42)	0.1	0.569
C Reactive Protein	Underweight	Normal weight	5,4 (-11,94; 22,74)	6.17	0.906
		Overweight	17,24 (-0,54; 35,02)	6.33	0.051
		Obese grade I	24,29 (4,09; 44,49)	7.19	**0.007**
		Obese grade II/III	23,69 (-1,14; 48,52)	8.84	0.057
	Normal weight	Underweight	-5,4 (-22,74; 11,94)	6.17	0.906
		Overweight	11,84 (1,49; 22,19)	3.68	**0.012**
		Obese grade I	18,89 (4,79; 33)	5.02	**0.002**
		Obese grade II/III	18,29 (-1,9; 38,48)	7.18	0.081
	Overweight	Underweight	-17,24 (-35,02; 0,54)	6.33	0.051
		Normal weight	-11,84 (-22,19; -1,49)	3.68	**0.012**
		Obese grade I	7,05 (-7,59; 21,69)	5.21	0.657
		Obese grade II/III	6,45 (-14,12; 27,01)	7.32	0.904
	Obese grade I	**Underweight**	-24,29 (-44,49; -4,09)	7.19	**0.007**
		Normal weight	-18,89 (-33; -4,79)	5.02	**0.002**
		Overweight	-7,05 (-21,69; 7,59)	5.21	0.657
		Obese grade II/III	-0,61 (-23,29; 22,08)	8.07	1
	Obese grade II/III	Underweight	-23,69 (-48,52; 1,14)	8.84	0.057
		Normal weight	-18,29 (-38,48; 1,9)	7.18	0.081
		Overweight	-6,45 (-27,01; 14,12)	7.32	0.904
		Obese grade I	0,61 (-22,08; 23,29)	8.07	1

Bonferroni post hoc analysis was used, after ANOVA, to compare the study variables between each BMI category. In bold are the variables with statistical significance ($p < 0.05$).

4. Discussion

While SAPS3 performed well in the obese, overweight, and normal weight groups, there was a significant lack of accuracy in underweight patients. Similarly, Deliberato et al. demonstrated that the performance of others severity scores was inconsistent across BMI categories [11]. We assume that the clinical differences observed between the groups may impact the performance of the score; therefore, it should be accessed and readjusted.

We found clinically significant differences between the BMI groups in our study that may be compromising SAPS3 predictive performance in patients with low weight. These patients were older and had a higher

Table 4. Differences in proportions between each BMI category.

Variables		Underweight	Normal weight	Overweight	Obese grade I	Obese grade II/III
Gender	**Female**	98a, b (57, 31%)	438b (47, 92%)	356b (50, 86%)	176a, c (64, 71%)	90c (73, 77%)
	Male	73a, b (42, 69%)	476b (52, 08%)	344b (49, 14%)	96a, c (35, 29%)	32c (26, 23%)
Admission Diagnosis	**Cardiovascular**	25a, b (14, 62%)	152b (16, 63%)	160a, c (22, 86%)	81c (29, 78%)	34a, c (27, 87%)
	Respiratory	13a (7, 6%)	55a (6, 02%)	40a (5, 71%)	13a (4, 78%)	5a (4, 1%)
Neurological	Neurological	22a (12, 87%)	171a (18, 71%)	115a (16, 43%)	41a (15, 07%)	11a (9, 02%)
	Infectious	57a (33, 33%)	184b (20, 13%)	96c (13, 71%)	30c (11, 03%)	25a, b, c (20, 49%)
	Surgical	10a (5, 85%)	141b (15, 43%)	143b, c (20, 43%)	65c (23, 9%)	21b, c (17, 21%)
	Other	44a (25, 73%)	211a (23, 09%)	146a (20, 86%)	42a (15, 44%)	26a (21, 31%)
Use of VAD	Yes	21a (12, 28%)	86a (9, 41%)	60a (8, 57%)	27a (9, 93%)	7a (5, 74%)
	No	150a (87, 72%)	828a (90, 59%)	640a (91, 43%)	245a (90, 07%)	115a (94, 26%)
Use of MV	Yes	32a (18, 71%)	157a (17, 18%)	110a (15, 71%)	38a (13, 97%)	10a (8, 2%)
	No	139a (81, 29%)	757a (82, 82%)	590a (84, 29%)	234a (86, 03%)	112a (91, 8%)
Congestive Heart Failure	Yes	11a (6, 43%)	59a (6, 46%)	44a (6, 29%)	13a (4, 78%)	5a (4, 1%)
	No	160a (93, 57%)	855a (93, 54%)	656a (93, 71%)	259a (95, 22%)	117a (95, 9%)
Chronic Renal Failure	Yes	17a (9, 94%)	119a (13, 02%)	82a (11, 71%)	26a (9, 56%)	7a (5, 74%)
	No	154a (90, 06%)	795a (86, 98%)	618a (88, 29%)	246a (90, 44%)	115a (94, 26%)

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Table 4 (*continued*)

Variables		Underweight	Normal weight	Overweight	Obese grade I	Obese grade II/III
Cirrhosis	Yes	1a (0, 58%)	9a (0, 98%)	14a (2%)	3a (1, 1%)	1a (0, 82%)
	No	170a (99, 42%)	905a (99, 02%)	686a (98%)	269a (98, 9%)	121a (99, 18%)
Cancer	Yes	29a, b (16, 96%)	149b (16, 3%)	90a, b (12, 86%)	23a (8, 46%)	11a, b (9, 02%)
	No	142a, b (83, 04%)	765b (83, 7%)	610a, b (87, 14%)	249a (91, 54%)	111a, b (90, 98%)
Immunodeficient	Yes	2a (1, 17%)	17a (1, 86%)	4a (0, 57%)	3a (1, 1%)	1a (0, 82%)
	No	169a (98, 83%)	897a (98, 14%)	696a (99, 43%)	269a (98, 9%)	121a (99, 18%)
Diabetes Mellitus	Yes	61a (35, 67%)	315a (34, 46%)	277a (39, 57%)	108a (39, 71%)	56a (45, 9%)
	No	110a (64, 33%)	599a (65, 54%)	423a (60, 43%)	164a (60, 29%)	66a (54, 1%)
Coronary Artery Disease	Yes	12a, b (7, 02%)	86b (9, 41%)	106a (15, 14%)	23a, b (8, 46%)	14a, b (11, 48%)
	No	159a, b (92, 98%)	828b (90, 59%)	594a (84, 86%)	249a, b (91, 54%)	108a, b (88, 52%)
Stroke	Yes	41a (23, 98%)	157a, b (17, 18%)	96b (13, 71%)	35b (12, 87%)	11b (9, 02%)
	No	130a (76, 02%)	757a, b (82, 82%)	604b (86, 29%)	237b (87, 13%)	111b (90, 98%)
Dementia	Yes	29a (16, 96%)	60b (6, 56%)	25b (3, 57%)	7b (2, 57%)	4b (3, 28%)
	No	142a (83, 04%)	854b (93, 44%)	675b (96, 43%)	265b (97, 43%)	118b (96, 72%)
Performance status	Completely independent	113a (66, 08%)	778b (85, 12%)	641c (91, 57%)	245b, c (90, 07%)	109b, c (89, 34%)
	Partially independent	18a (10, 53%)	65a (7, 11%)	39a (5, 57%)	18a (6, 62%)	8a (6, 56%)
	Fully dependent	40a (23, 39%)	71b (7, 77%)	20c (2, 86%)	9b, c (3, 31%)	5b, c (4, 1%)
ICU deaths	Yes	64a (37, 43%)	172b (18, 82%)	76c (10, 86%)	21c (7, 72%)	10c (8, 2%)
	No	107a (62, 57%)	742b (81, 18%)	624c (89, 14%)	251c (92, 28%)	112c (91, 8%)
ICU readmission	Yes	20a, b (11, 7%)	105b (11, 49%)	51a (7, 29%)	14a (5, 15%)	10a, b (8, 2%)
	No	151a, b (88, 3%)	809b (88, 51%)	649a (92, 71%)	258a (94, 85%)	112a, b (91, 8%)

Z-test with Bonferroni correction of clinical and epidemiological characteristics between BMI groups. In Bold, variables with significant difference ($p < 0.05$). Each subscript letter denotes a subset whose columns proportions do not differ significantly from each other.

burden of comorbidities that were independently associated with worse outcomes. Overweight and obese patients had a higher prevalence of diabetes and a lower mean SAPS3 score. The absence of significance between the creatinine values according to BMI groups may be associated with the presence of acute kidney injury at admission in underweight patients, since a lower proportion of lean mass is expected in this group [12]. In earlier studies, even after adjusting for significant comorbidities, low weight showed an association with mortality [13, 14, 15, 16]. However, in the current study, obese and overweight patients showed no protective factors, despite findings on previous research [17, 18, 19].

Studies exploring the effect of BMI on ICU outcomes have reported controversial results. Three meta-analyses have already demonstrated a J-shaped relationship between BMI and mortality, with overweight and moderate obesity being protective when compared to a normal BMI [18, 19]. This remains poorly understood, but some hypotheses are currently being discussed. Obese patients tend to be younger at the time of ICU admission, a population generally at lower risk of mortality [20]. This was evident in our findings with a lower mean age among those with higher BMI. Alternatively, medical staff, anticipating possible risks and complications, may admit obese patients earlier to the ICU in relatively stable condition to initiate aggressive interventions [4]. In support of this hypothesis, obese subjects in our study were admitted with lower SAPS3 and CCI while underweight patients presented higher mean SAPS3 and MFI scores (Table 2), albeit with poor predictive performance. Despite our study was not specifically designed for this purpose, others have suggested that obese individuals have a greater nutritional reserve, thereby offering protection against hypercatabolic states experienced during critical illness

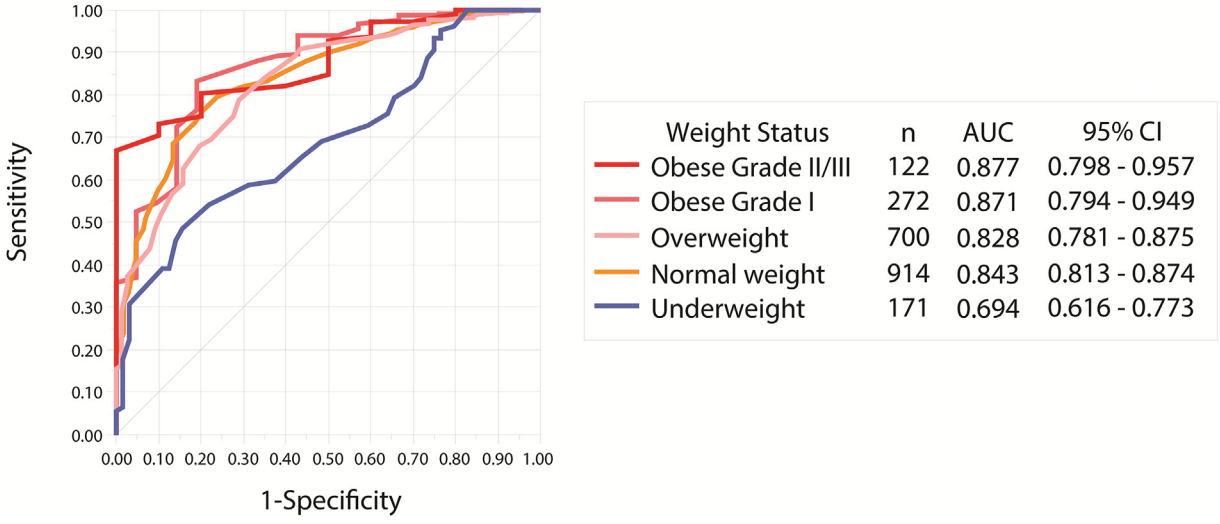

Figure 2. Performance of SAPS3 Mortality Prediction According to BMI Category. The area under the receiver operating characteristics curve was calculated for each BMI stratum. SAPS3 performance was adequate in all BMI groups except for the underweight group, in which a significantly poor discriminant function was observed. P-value for all curves <0.001.

Variable	Model	Odds Ratio (95% CI)	p-value
Surgical	Unadjusted	0.14 (0.23 - 0.37)	0.0001
	Adjusted	0,14 (0,07 - 0,28)	0.0001
Heart Rate	Unadjusted	1,02 (1,02 - 1,03)	0.0001
	Adjusted	1,01 (1.00 - 1,02)	0.0001
Segmented	Unadjusted	1.00 (1.00 - 1.00)	0.0001
	Adjusted	1.00 (1.00 - 1.00)	0.011
Atypicals	Unadjusted	1,01 (1,01 - 1,01)	0.143
	Adjusted	1.00 (1.00 - 1.00)	0.018
Leukocytes	Unadjusted	1,01 (0.99 - 1,03)	0.120
	Adjusted	0,87 (0,78 - 0,97)	0.013
CRP	Unadjusted	1,01 (1,01 - 1,02)	0.0001
	Adjusted	1,01 (1,01 - 1,01)	0.0001
Age	Unadjusted	1,04 (1,03 - 1,05)	0.0001
	Adjusted	1,04 (1,03 - 1,05)	0.0001
K	Unadjusted	1,42 (1,25 - 1,62)	0.0001
	Adjusted	1,37 (1,15 - 1,63)	0.0001
Neurological	Unadjusted	0,82 (0,59 - 1,13)	0.236
	Adjusted	1,87 (1,21 - 2,89)	0.005
Cancer	Unadjusted	1,81 (1,35 - 2,44)	0.0001
	Adjusted	2,12 (1,38 - 3,27)	0.001
Underweight	Unadjusted	3,70 (2,65 - 5,18)	0.0001
	Adjusted	2,21 (1,37 - 3,56)	0.001
Dependence	Unadjusted	6.00 (4,22 - 8,55)	0.0001
	Adjusted	2,84 (1,76 - 4,57)	0.0001
Use of MV	Unadjusted	6,35 (4,90 - 8,34)	0.0001
	Adjusted	4,41 (2,99 - 6,51)	0.0001
Use of VAD	Unadjusted	5,95 (4,38 - 8,09)	0.0001
	Adjusted	3,38 (2,07 - 5,50)	0.0001

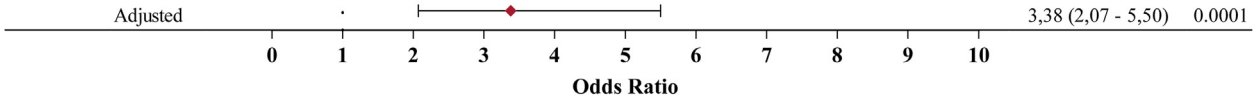

Figure 3. Risk assessment model for intra-unit mortality. The white prism represents the OR in the univariate analysis, while the black prism represents the OR after adjustment in the binary logistic regression. The variables that presented statistical significance at the end of the binary logistic regression were represented. CRP (C-reactive protein); K (potassium level); MV (mechanical ventilation); VAD (vasopressor drug).

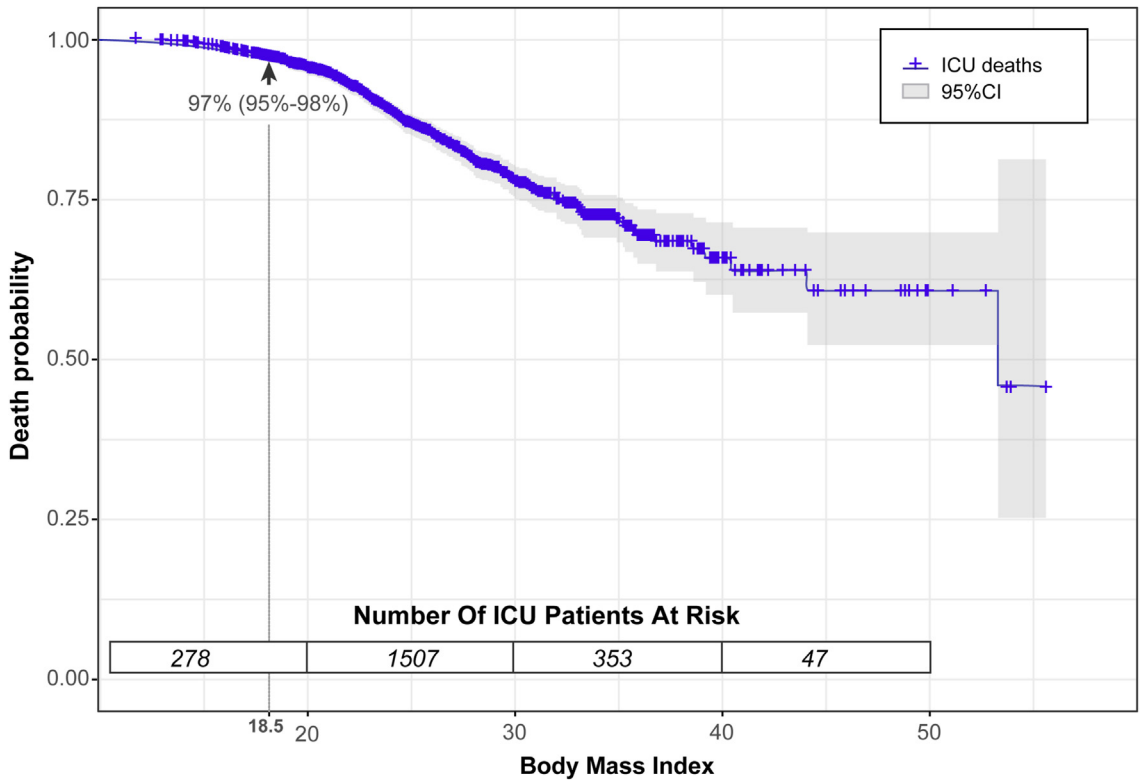

Figure 4. Death Probability According to BMI. A modified Kaplan-Meier curve to estimate the probability of death by BMI level. For every 1 additional kg/m^2, there is a 0.04% reduction in the probability of death.

Table 5. Binary logistic regression of BMI and SAPS3 association with mortality.

Parameters	B	S.E.	Exp (B)	95% C.I. for EXP(B)	P-value
Saps3Points	0,117	0,007	1,124	(1,109–1,14)	0,0001
BMI	-0,07	0,014	0,932	(0,908–0,958)	0,0001
Constant	-6,036	0,514	0,002		

as compared to their underweight counterparts [4, 13]. Still, others hypothesize that the adipokine profile in obese patients may modulate and dampen the immunological response to severe acute illness which may be absent in the underweight population [4]. While we did not confirm obesity as a protective factor when adjusting for comorbidities, the mortality risk for underweight critically ill patients found in our study supports prior findings from the developed world [13, 14, 15, 16].

Our study has certain limitations. First, as a single-center study, there may be unmeasured local confounders that could impact the analyses performed. Also, in this study, only variables obtained at admission of patients were considered. The use of BMI as a parameter for obesity diagnosis, while useful at the population level, does not distinguish between lean mass and fat mass, thus being less precise in elderly and muscular individuals [21]. Moreover, BMI may not accurately assess visceral fat, a risk factor for disease independent of total body fat [22]. Future studies using BMI together with accurate methods of assessing body fat are suggested to address this limitation.

5. Conclusion

Overall, the SAPS3 is inaccurate for predicting mortality in critically ill underweight patients, even with this group presenting a greater chance of death. Recalibration of this tool may aid in the clinical management of these patients.

Declarations

Author contribution statement

Isabella B B Ferreira and Rodrigo C Menezes: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Kevan M Akrami: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Nivaldo Filgueiras Filho: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Bruno B Andrade: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Matheus L Otero: Performed the experiments; Wrote the paper.

Thomas A Carmo: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Gabriel A Agareno, Gabriel P Telles and Bruno V B Fahel: Performed the experiments.

María B Arriaga and Kiyoshi F Fukutani: Analyzed and interpreted the data.

Licurgo Pamplona Neto and Sydney Agareno: Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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