Severity of Illness Scores May Misclassify Critically Ill Obese Patients*

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Objective: Severity of illness scores rest on the assumption that patients have normal physiologic values at baseline and that patients with similar severity of illness scores have the same degree of deviation from their usual state. Prior studies have reported differences in baseline physiology, including laboratory markers, between obese and normal weight individuals, but these differences have not been analyzed in the ICU. We compared deviation from baseline of pertinent ICU laboratory test results between obese and normal weight patients, adjusted for the severity of illness.

Design: Retrospective cohort study in a large ICU database.

Setting: Tertiary teaching hospital.

Patients: Obese and normal weight patients who had laboratory results documented between 3 days and 1 year prior to hospital admission.

Interventions: None.

Measurements and Main Results: Seven hundred sixty-nine normal weight patients were compared with 1,258 obese patients. After adjusting for the severity of illness score, age, comorbidity index, baseline laboratory result, and ICU type, the following deviations were found to be statistically significant: WBC 0.80 (95% CI, 0.27–1.33) × 10^9/L; $p = 0.003$; log (blood urea nitrogen) 0.01 (95% CI, 0.00–0.02); $p = 0.014$; log (creatinine) 0.03 (95% CI, 0.02–0.05), $p < 0.001$; with all deviations higher in obese patients. A logistic regression analysis suggested that after adjusting for age and severity of illness at least one of these deviations had a statistically significant effect on hospital mortality ($p = 0.009$).

Conclusions: Among patients with the same severity of illness score, we detected clinically small but significant deviations in WBC, creatinine, and blood urea nitrogen from baseline in obese compared with normal weight patients. These small deviations are likely to be increasingly important as bigger data are analyzed in increasingly precise ways. Recognition of the extent to which all critically ill patients may deviate from their own baseline may improve the objectivity, precision, and generalizability of ICU mortality prediction and severity adjustment models. (*Crit Care Med* 2018; 46:394–400)

Key Words: critical care; obesity; outcome; severity of illness score

***See also p. 484.**

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Obesity is currently a global pandemic, responsible for 3–4 million deaths per year (1), with an increasing prevalence in adults as well as children and adolescents (2). Obesity is overrepresented in the ICU, comprising approximately one-third of patients (3), compared with the 20% prevalence of being overweight or obese worldwide. ICUs commonly use severity of illness scores, such as Acute Physiology and Chronic Health Evaluation (APACHE), Simplified

Acute Physiology score version II (SAPS-II), or Sequential Organ Failure Assessment (SOFA) to predict mortality (4–6), but none of these scoring systems incorporates obesity into their risk adjustment variables.

These scores rely on the assumptions that patients have the same normal physiologic values at baseline and that similar severity of illness scores represent the same degree of deviation from the baseline state. However, this may not always hold true for different population groups in different intensive care settings. In obese patients, prior studies have shown abnormal laboratory markers including WBC and liver enzymes (7, 8), platelet counts (9), and respiratory physiological values (10, 11).

Therefore, although obese and normal weight patients may present to the ICU with a similar physiological "snapshot or phenotype" as reflected by the same severity of illness scores, these identical scores may actually represent inherently different levels of deviation from the prior baseline state. This may inadvertently result in misclassification, leading to potential errors in mortality prediction and severity adjustment. The case of obese ICU patients is made more complex in that, despite their higher prevalence of chronic diseases that would be expected to result in generally higher all-cause mortality compared with normal weight individuals (2), critically ill obese patients have been reported to paradoxically have better clinical outcomes than nonobese patients (12).

We postulated that prognostic severity misclassification may be an artifact of applying the same scoring system to these two diverse populations without regard to divergences in evolving anomalies. This question is critical in determining whether the use of conventional scoring systems produce reliable predictions in conditions associated with diverse physiologies, including obesity.

To investigate this question, we analyzed a large ICU database (which included baseline laboratory results prior to hospital admission) to compare the deviation of laboratory tests utilized in scoring systems from baseline to ICU admission in both obese and normal weight patients.

METHODS

Data Sources

For this study, we used the Medical Information Mart for Intensive Care (MIMIC-III) database, a large, open-access dataset of patients admitted to the Beth Israel Deaconess Medical Center (Boston, MA). This database contains data for more than 60,000 deidentified patient admissions to ICUs between 2001 and 2012 and is hosted by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology. MIMIC-III contains data that were downloaded from different sources, including archives from critical care information systems, hospital electronic health record databases, and out-of-hospital records of patient mortality. Such data include high resolution vital signs, laboratory results, prescribed medications, fluid balance, procedure codes, diagnostic codes, imaging reports, provider notes, and hospital administrative data. All these data were collected during routine clinical care and data collection was not visible to caregivers, which means there was no interference with their workflow (13). The use of the MIMIC-III database has been approved by Institutional Review Boards of Beth Israel Deaconess Medical Center (2001-P-001699/14) and MIT (No. 0403000206).

Study Population

Study inclusion criteria were first ICU admission of patients 16 years and older and available documentation of height and weight, as well laboratory test results at baseline and at ICU admission. We excluded data from subsequent admissions if patients were admitted to ICU more than once. We defined baseline laboratory values as the mean laboratory result of all readings available between 3 days before to 1 year prior to ICU admission. ICU values were defined as the most abnormal laboratory result in the first 24 hours of ICU admission, similar to the analysis in the calculation of the SAPS-II and SOFA scores (5, 6).

Obesity was determined according to World Health Organization classification. The height measured during the hospital admission and the average of weights measured 24 hours before and 24 hours after the ICU admission were used. Only obese (body mass index [BMI], ≥ 30) and normal weight patients (BMI, ≥ 18.5 and < 25) were included as comparison groups to maximize the difference between study groups.

Study Variables

The following baseline patient level characteristics were collected: age, gender, ethnicity, marital status, insurance coverage, and comorbidities as defined by Elixhauser et al (14) combined in a composite score by van Walraven et al (15), here after referred to as the comorbidity index. Smoking status was identified using Natural Language Processing searches for history of active smoking in the provider notes. Hospital characteristics, procedures in the first 24 hours of the ICU admission, as well as SAPS-II and SOFA score on ICU admission were also included (5, 6).

The exposure variable was BMI status, comparing obese to normal weight individuals, and the primary outcome was the deviation in laboratory results between that measured at baseline and during ICU admission. We selected laboratory results that were used in the SAPS-II or SOFA scores in our analyses, except for bilirubin, which was not included due to a significant fraction of missing baseline data.

Statistical Analyses

We used quantile-quantile normal plots to assess the appropriateness of assuming normality. Continuous variables were summarized using the mean and SD while those with a nonnormal distribution were summarized with the median and interquartile range. For the continuous variables, mean values were compared using two-sample *t* tests, and median values were assessed using the Mann-Whitney test. Tests for association between categorical variables and BMI status were assessed using a chi-square test.

Absolute values at baseline as well as deviations from baseline were compared between normal weight and obese individuals. The differences in deviation from baseline between

both groups were compared using multivariable linear regression adjusted for age, gender, comorbidity index (15), SAPS-II score (5) or SOFA score (6), and type of ICU, and the relevant baseline laboratory result. A full model comprising the BMI status and all the covariates was initially fit and subjected to stepwise backward elimination retaining BMI status in the model, until a final model was obtained with only statistically significant variables. Statistical significance was assessed at the 0.05 level. For variables violating the modeling assumptions of linear regression models, the logarithm (base 10) of the baseline and ICU laboratory results were calculated and the regression analysis performed on the log transformed values.

We also assessed the effect on hospital mortality of any statistically significant deviations found comparing the obese and normal weight groups using logistic regression. A null (baseline) model was fit composed of SAPS-II, SOFA, age, and the ICU values of the laboratory tests, which were found to be statistically significant when comparing the deviations from baseline between obese and normal weight subjects. A model fit using all variables in the null model, in addition to any laboratory deviation variables found to have a statistically significant difference between the normal weight and obese patients, was compared with the null model using a likelihood ratio test.

Information about the number of missing laboratory values is provided in detail in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/D72). All analyses were performed with R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). We have made all our data extraction and modeling queries and codes available online: https://github.com/deliberato/Obesity-project.

RESULTS

Of the 61,532 admissions in the MIMIC-III database, 38,367 were unique patients greater than 16 years old. Of these, 3,205 (8.35%) had laboratory results available prior to hospital admission and also had height and weight data available during admission. After excluding underweight and overweight individuals, a total of 2,027 patients were included in the final cohort (**Fig. 1**).

A total of 769 normal weight patients and 1,258 obese patients were compared. Baseline characteristics are summarized in **Table 1**. The obese patients were slightly younger (median age of 64.3 vs. 66.9; $p = 0.01$), less likely to be white (74% vs. 76%; $p < 0.001$) and more likely to have private insurance (41% vs. 32%; $p < 0.001$). In addition, obese patients had a lower comorbidity index (median of 2 vs. 5; $p < 0.001$), and comprised a higher proportion of cardiac surgery recovery unit (CSRU) patients (58% vs. 39%; $p < 0.001$) and a smaller proportion of medical ICU patients (22% vs. 38%; $p < 0.001$). During the first 24 hours of ICU stay, the obese patients were more likely to require mechanical ventilation (74% vs. 59%; $p < 0.001$) and vasopressor therapy (58% vs. 45%; $p < 0.001$).

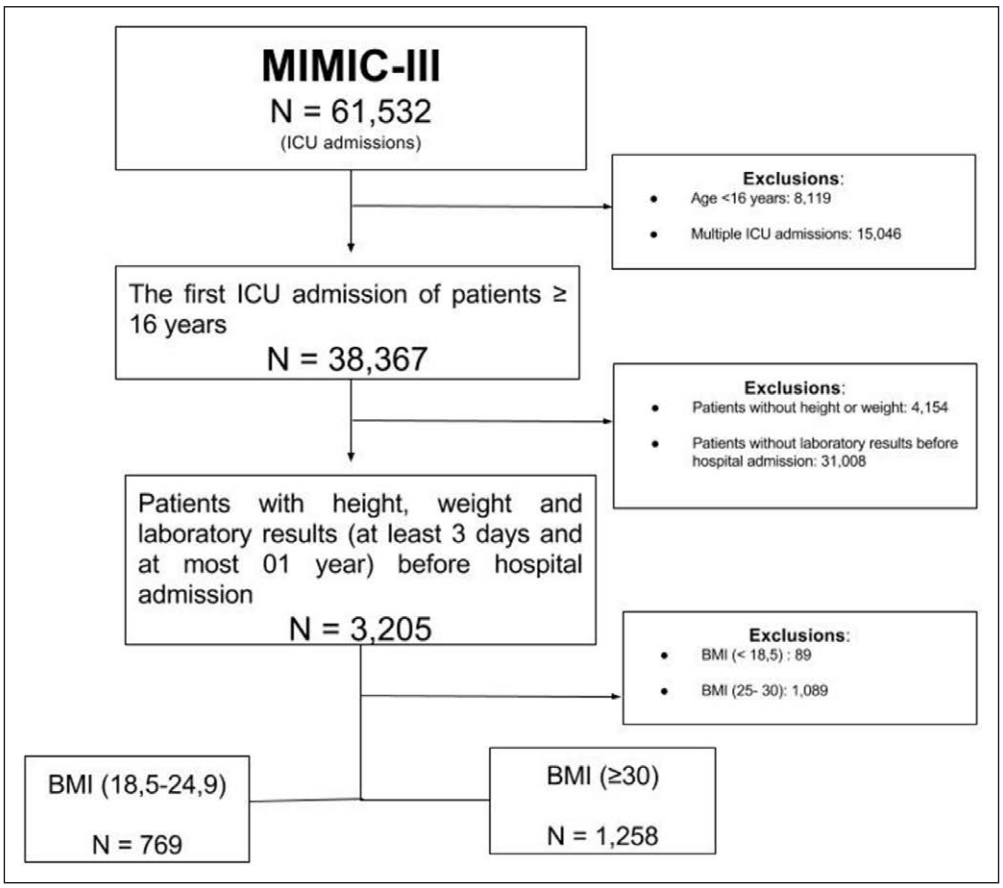

Figure 1. Patient fluxogram. BMI = body mass index, MIMIC-III = Medical Information Mart for Intensive Care III.

A crude comparison of laboratory results at baseline showed that the obese patient group had lower platelet counts (231 vs. 245×10^9/L; $p < 0.001$) and higher sodium (140 vs. 139; $p < 0.001$) than normal weight individuals (**Table 2**). The deviation in WBC (6.4 vs. 5×10^9/L; $p < 0.001$), sodium (–3.2 vs. –2.6; $p = 0.003$) and potassium (1 vs. 0.8; $p = 0.001$) in ICU from each individual's baseline was also significantly greater in obese individuals (Table 2).

The laboratory parameters included in SAPS-II scoring were adjusted for SAPS-II score as well as baseline laboratory result, ICU type, age, gender, and comorbidity index (**Table 3**). The WBC deviation was 0.80 (95% CI, 0.27–1.33) ×10^9/L and the log(BUN) deviation was 0.01 (95% CI, 0.00–0.02), both were statistically significant higher in obese patients. There were no statistically significant differences in the deviation in

TABLE 1. Baseline Demographic Characteristics

Variables	Normal Weight (BMI, 18.5–24.9), *n* = 769	Obese (BMI, > 30), *n* = 1,258	*p*
Age (yr), (median, IQR)	66.9 (53–78.5)	64.3 (55.5–72.7)	0.01
Male, *n* (%)	431 (56)	741 (59)	0.22
Ethnicity: white, *n* (%)	583 (76)	935 (74)	< 0.001
Marital status, *n* (%)			0.11
Married	415 (54)	738 (59)	
Single/divorced/separated	227 (30)	352 (28)	
Other/unknown	127 (16)	168 (13)	
Insurance, *n* (%)			< 0.001
Medicare/Medicaid	497 (65)	709 (56)	
Private/other	272 (35)	549 (44)	
Comorbidity index (median, IQR)	5 (0–10)	2 (0–7)	< 0.001
BMI (kg/m^2), (median, IQR)	23.1 (21.3–24.1)	34.3 (31.9–38.2)	< 0.001
Smoker, yes, *n* (%)	379 (49)	649 (52)	0.20
Admission type, *n* (%)			< 0.001
Elective	321 (42)	752 (60)	
Emergency	433 (56)	491 (39)	
Urgent	15 (2)	15 (1)	
Source of admission, *n* (%)			< 0.001
Emergency room	310 (40)	319 (25)	
Physician referral	367 (48)	822 (65)	
Other, *n* (%)	92 (12)	117 (10)	
ICU admission type, *n* (%)			< 0.001
Cardiac surgery recovery unit	300 (39)	726 (58)	
Medical ICU	286 (38)	272 (22)	
Surgical ICU/trauma ICU/coronary care unit	183 (23)	260 (20)	
Primary International Classification of Disease version 9 diagnosis, *n* (%)			0.01
Sepsis, including pneumonia	110 (14)	188 (15)	
Cardiovascular disease	357 (46)	528 (42)	
Other respiratory condition	49 (7)	50 (4)	
Neurological condition	47 (6)	88 (7)	
Other	206 (27)	404 (32)	
Procedures in the first 24 hr of ICU admission, *n* (%)			
Mechanical ventilation	453 (59)	937 (74)	< 0.001
Vasopressors	346 (45)	731 (58)	< 0.001
Renal replacement therapy	32 (4)	35 (3)	0.12
Severity of illness			
Simplified Acute Physiology score version II (median, IQR)	35 (27–45)	32 (25.2–40)	< 0.001
Sequential Organ Failure Assessment score (median, IQR)	4 (2–6)	4 (2–6)	0.02

BMI = body mass index, IQR = interquartile range.

TABLE 2. Laboratory Results at Baseline and Change in Results Between ICU and Baseline

Baseline[a]				Δ (ICU – baseline)[a]			
Variables	Normal Weight	Obese	*p*	Variables	Normal Weight	Obese	*p*
SAPS-II laboratory parameters				SAPS-II laboratory parameters			
WBC × 10^9/L, median (IQR)	7.3 (5.6–9.5)	7.4 (6–9.1)	0.39	WBC × 10^9/L, mean ± SD	5 ± 5.9	6.4 ± 5.9	< 0.001
Sodium, mmol/L, median (IQR)	139 (136–141)	140 (137–141)	< 0.001	Sodium, mmol/L, mean ± SD	−2.6 ± 4.3	−3.2 ± 3.6	0.003
Potassium, mmol/L, median (IQR)	4.2 ± 0.5	4.2 ± 0.4	0.63	Potassium, mmol/L, mean ± SD	0.8 ± 1.1	1 ± 0.9	0.001
BUN, mg/dL, median (IQR)	18.5 (14–25)	18.4 (15–24.4)	0.49	Log (BUN, mg/dl), mean ± SD	0.02 ± 0.2	0.01 ± 0.2	0.26
BIC, mg/dL, median (IQR)	27 (25–28.7)	27 (25–28.5)	0.73	BIC, mg/dL, mean ± SD	−4 ± 4.1	−4 ± 3.6	0.8
SOFA laboratory parameters				SOFA laboratory parameters			
Creatinine, mg/dL, median (IQR)	0.9 (0.7–1.2)	1 (0.8–1.2)	0.06	Log (creatinine, mg/dL), mean ± SD	0.01 ± 0.2	0.03 ± 0.2	0.05
Platelets × 10^9/L, median (IQR)	245 (189–315)	231 (186–284)	< 0.001	Platelets × 10^9/L, mean ± SD	−75 ± 119	−70.6 ± 79	0.37

BIC = bicarbonate, BUN = blood urea nitrogen, IQR = interquartile range, SAPS-II = Simplified Acute Physiology Score version II, SOFA = Sequential Organ Failure Assessment score.

[a]Information about the number of missing laboratory values might be found in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/D72).

values in both groups with respect to sodium, potassium, and bicarbonate. The laboratory parameters included in SOFA scoring were adjusted for SOFA score as well as baseline laboratory result, ICU type, age, gender, and comorbidity index (Table 3). The deviation in log (creatinine) was 0.03 (95% CI, 0.02–0.05) higher in obese patients ($p < 0.001$); there was no statistically significant difference in the deviation of platelets.

In the logistic regression analysis of hospital mortality, a comparison of the null model and the model which incorporated all variables in the null model, in addition to the deviation from patient baseline of WBC, log-BUN and log-creatinine (found to be the statistically significant variables in Table 3) was performed. In this three degree of freedom test, we found that we would reject the null model ($p = 0.009$), suggesting that one or more of log (BUN), log (creatinine), or WBC deviation variables had a statistically significant effect on mortality after adjusting for the variables in the null model.

TABLE 3. Multivariable Linear Regression of Laboratory Deviation (Δ = ICU – Baseline)

Variables	Adjusted Difference[a] in Deviation Δ (ICU – Baseline) Between Obese and Normal Weight Individuals (95% CI)	*p*
Simplified Acute Physiology Score version II laboratory parameters		
Δ WBC, × 10^9/L	0.80 (0.27–1.33)	0.003
Δ Sodium, mmol/L	−0.06 (−0.40 to 0.28)	0.712
Δ Potassium, mmol/L	0.01 (−0.07 to 0.09)	0.857
Δ log (blood urea nitrogen, mg/dL)	0.01 (0.00–0.02)	0.014
Δ Bicarbonate, mg/dL	−0.19 (−0.50 to 0.13)	0.254
Sequential Organ Failure Assessment score laboratory parameters		
Δ log (creatinine, mg/dL)	0.03 (0.02–0.05)	< 0.001
Δ Platelets, ×10^9/L	4.94 (−2.48 to 12.36)	0.192

[a]Effect while keeping all other model covariates constant: models were fit via stepwise backward elimination with the full model composed of relevant score (Simplified Acute Physiology Score version II or Sequential Organ Failure Assessment score), baseline laboratory result, ICU type, age, gender, and comorbidity index.

Δ: laboratory deviation = ICU laboratory result − baseline laboratory result.

DISCUSSION

Our results suggest that the deviations in WBC, creatinine, and BUN from baseline to the most abnormal value in the first 24 hours of ICU stay are significantly higher in obese patients, adjusting for the severity of illness score. This supports the hypothesis that within the same severity of illness category, obese patients may have inherently different degrees of deviation from their usual state during critical illness. The existing

literature has reported differences in physiological and laboratory parameters between obese and nonobese patients in stable settings such as prior to and after surgery (7, 8), or in outpatient settings (9–11, 16), but our study is the first to describe this phenomenon in the setting of critical illness.

The instinctual response of a clinician to these small differences in laboratory results is that they are clinically insignificant. However, we feel that such small changes are incredibly important. As electronic health records of larger patient populations are secondarily analyzed in a context of medicine that is increasingly precise and personal, even small differences that are consistent and statistically significant, will compound and impact data analysis. As such analysis assumes an increasing role in assisting clinicians with decision making that is less susceptible to cognitive bias, the accumulation of many small changes that may seem trivial to a clinician's eye, may affect models for classification, prediction, and/or prognostication. Small changes may shift segments of populations across classes, such as disease severity from mild to moderate, or moderate to severe, for example. Furthermore, established scoring systems, as opposed to practicing clinicians, operate on nonfuzzy, fixed thresholds from transitioning from nonpoint assignments to awarding a point (such as moving from a score of 1 to 2). Therefore, even very small changes in values, for example, in the new Sepsis-3 definitions (17) where an increase in SOFA score of 2 or more points (with other criteria) defines sepsis, may produce modifications that could change the classification of a patient from "not septic" to "septic." In our attempts toward precision and personalized medicine, if an identifiable subset of patients has a consistent difference that marks that as unique, it behooves us to attempt to capture this information so that it can be applied in any predictive, real time, or retrospective analysis of clinical information.

The traditional approach to severity of illness scoring assumes a normal baseline, and hence, similar degrees of deviation among those values belonging to the same category. Such assumptions may contribute to an inaccurate representation of actual severity of illness or organ dysfunction. We believe that any prior differences do carry over into the critical care time period and must be addressed in order to certify that severity stratification methods are robust, research that uses critical care data bases is reliable, and that data driven clinical decision support applications are safe and useful.

Although our study is not designed to elucidate why the deviation in laboratory values differ between obese and nonobese patients, others have suggested that excess adiposity is associated with proliferation of macrophages and other immune cells in response to adipocyte apoptosis, which in turn secretes proinflammatory cytokines (18, 19). The differences in physiological response to a state of critical illness may account for these small differences in deviations from baseline. In addition, an abnormal baseline value, in obese patients even in the absence of apparent comorbidities, may be indicative of reduced physiological reserves, which may be associated with poorer outcomes.

Another related and more general issue is whether dynamic score changes represent the same severity and prognostic states as more static ones. For example, does a SOFA score of 6 in someone who came in the ICU with a score of zero represent the same severity and prognostic state as a patient who also has a score of 6, but had it before admission due to chronic obstructive pulmonary disease, liver and kidney disease, decreased platelets, and maybe a touch of encephalopathy or dementia? Ideally, an optimal scoring system can be developed that represents a true measure of biological severity and is immune to the effects of prior states and nonstandardized interventions (e.g., use of vasoactive drugs).

The use of an individual patient's baseline for scoring would be a step toward more personalized and precision medicine and may contribute to mortality prediction models with better calibration. SAPS-II was developed based on mortality outcomes of a North American and European cohort and may be vulnerable not only to unique factors of the sociodemographic makeup of that particular population but also external factors such as cultural preferences, variations in practice, and differing quality of care. The impact of these contextual factors may account for the poor performance of severity of illness scores in particular populations such as the elderly (20) or in other countries—for example, a validation study of SAPS-II in a cohort of patients from 11 countries showed poorer performance than the original SAPS-II validation sample (21). Recognizing that some of these factors may be uncontrollable, consideration of the extent to which critically ill patients deviate from their own baseline may represent one way to increase the objectivity, precision, and generalizability of mortality prediction and severity adjustment models.

Our study has several limitations. First, our study was confined to those patients who had pre-ICU baseline values available, which comprised only 8.35% of the entire database. This subset may be sicker as the need for these laboratory tests may signal the presence of more comorbidities that require follow-up in the outpatient setting. Exclusion of otherwise healthy patients in the study cohort who did not have any outpatient follow-up and are more likely to have normal weight, may underestimate the difference in deviation from baseline between the two groups of patients. Second, the differences in the composition of the obese and normal weight groups may contribute to selection bias. There was a higher proportion of obese patients who were electively admitted to the ICU, comprising 60% of admissions, or 27% excluding those admitted to the CSRU; compared with nonobese patients. Although we adjusted for these differences in the regression model, there may be residual confounders between these groups that we were unable to adjust for. Third, BMI may not be the best measure of obesity and may not be reflective of the physiological processes that we try to model. However, it is the most frequently used indicator of obesity in current clinical context and would be the most generalizable. Fourth, our data were from a single center, which may also limit generalizability. Fifth, we were unable to add deviations in vital signs into our model due to absence of baseline data, which may account for some residual confounding. Finally, as our analysis only compared normal

weight individuals to obese individuals, we may not be able to extrapolate our findings to overweight individuals.

Our study does not reveal whether obese patients behave, with respect to clinical outcome, like other patient types with similarly higher scores, or have better outcomes than those scores would have indicated. This is a topic for a future study—this article represents a starting point in this regard where such differences are duly noted and analyzed to form a basis for such studies. In fact, this kind of unavoidable heterogeneity in prior conditions and physiological states is not unique to the issue of obesity and poses a general problem in the formulation of valid and reliable scoring systems. APACHE deals with this issue at a high level by assigning weights to selected historical conditions.

Future directions include examining for differences in deviations of physiological parameters such as heart rate, blood pressure, or partial pressure of oxygen (Pao_2), which are included in SOFA and SAPS-II. As with previous studies that demonstrated differences in cardiac autonomic activity and heart rate (16), and respiratory physiology (10, 11), between obese and normal weight individuals, it may well be that deviations in such parameters are also different in obese and normal weight patients with similar severity of illness scores. Further studies are required to assess if severity of illness scores based on deviations from usual state rather than assumed normal baseline values will be superior in mortality predictions. Finally, while we have done this for obese adults, other such populations may also be identified for whom the "one scoring system for all" principle may not apply.

CONCLUSION

In conclusion, our findings suggest that for the same severity of illness scores, obese and normal weight patients have different deviations of laboratory markers from baseline. This could potentially lead to severity of illness score misclassification. We encourage others to develop severity of illness scores based on deviation from usual physiologic state in order to maximize the personalization of the scores and minimize the impact of uncontrollable local factors external to the patient.

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