



The effects of performance status one week before hospital admission on the outcomes of critically ill patients

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Abstract

Purpose: To assess the impact of performance status (PS) impairment 1 week before hospital admission on the outcomes in patients admitted to intensive care units (ICU).

Methods: Retrospective cohort study in 59,693 patients (medical admissions, 67 %) admitted to 78 ICUs during 2013. We classified PS impairment according to the Eastern Cooperative Oncology Group (ECOG) scale in absent/minor (PS = 0–1), moderate (PS = 2) or severe (PS = 3–4). We used univariate and multivariate logistic regression analyses to investigate the association between PS impairment and hospital mortality.

Results: PS impairment was moderate in 17.3 % and severe in 6.9 % of patients. The hospital mortality was 14.4 %. Overall, the worse the PS, the higher the ICU and hospital mortality and length of stay. In addition, patients with worse PS were less frequently discharged home. PS impairment was associated with worse outcomes in all SAPS 3, Charlson Comorbidity Index and age quartiles as well as according to the admission type. Adjusting for other relevant clinical characteristics, PS impairment was associated with higher hospital mortality (odds-ratio (OR) = 1.96 (95 % CI 1.63–2.35), for moderate and OR = 4.22 (3.32–5.35), for severe impairment). The effects of PS on the outcome were particularly relevant in the medium range of severity-of-illness. These results were consistent in the subgroup analyses. However, adding PS impairment to the SAPS 3 score improved only slightly its discriminative capability.

Conclusion: PS impairment was associated with worse outcomes independently of other markers of chronic health status, particularly for patients in the medium range of severity of illness.

Keywords: Performance status, Critical care, Outcomes, Markers of baseline health status

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We dedicate this work to the memory of our colleague, Dr. Marcelo Lugarinho, who recently passed away.

Take-home message: Impaired performance status at 1 week prior to hospital admission is associated with worse outcomes independently of other markers of baseline health status, such as comorbidities and age. This association is more distinguishable in the mid-range severity of illness scores.

Introduction

The outcome of critically ill patients depends a priori on three major domains: patient characteristics before admission to the intensive care unit (ICU), the specific circumstances associated with ICU admission and the consequences of the acute illness in terms of physiological derangements and organ dysfunctions [1]. Among the patient characteristics, baseline health status plays a major role.

Severity-of-illness scores have been used by clinicians, researchers and administrators in the field of critical care to characterize patients in terms of severity of illness in clinical studies and evaluation of ICU performance [2]. These instruments typically measure baseline or chronic health status using age and major comorbidities [1, 3, 4]. One additional domain of chronic health status is functional capacity or performance status (PS), which estimates a patient's ability to carry on daily life activities. However, a patient's PS can not be assessed using these scoring systems [1, 3, 4]. PS impairments have been demonstrated to be associated with worse outcomes in critically ill patients [5–7]. Frailty (which shares some common factors with PS) has also been suggested to be associated with higher in-hospital and 1-year mortality [8]. Nonetheless, to our knowledge, studies carried out to date have mostly been single-centered, restricted to specific subgroups of patients (such as transplant recipients, cancer patients, patients with sepsis and elderly patients) and did not account for important confounders [5, 7, 9–11].

We have investigated the impact of PS impairments at 1 week prior to hospital admission on the hospital mortality in a large cohort of critically ill patients. We also evaluated whether the addition of a PS assessment to an illness severity-of-illness score [The Simplified Acute Physiology Score 3 (SAPS 3)] would improve the predictive accuracy of the SAPS 3. We hypothesized that the higher the degree of PS impairment, the higher the in-hospital mortality regardless of other markers of baseline health status, such as age and comorbidities.

Patients and methods

Study design and participating centers

This was a secondary post hoc analysis of the ORCHES-TRA study, a multicenter retrospective cohort study of critical care organization and outcomes in 59,693 patients admitted to 78 ICUs participating in the Brazilian Research in Intensive Care Network (BRICNet) at 51 Brazilian hospitals during 2013 [12]. The local Ethics Committee of the D'Or Institute for Research and Education (IDOR approval number: 334.835) and the Brazilian National Ethics Committee (CAAE: 19687113.8.1001.5249) approved the study and waived the need for informed consent. The complete list of investigators is given in the Electronic Supplementary Material (ESM).

Data collection and definitions

We retrieved de-identified patients' data from the Epimed Monitor System[®] (Epimed Solutions[®], Rio de Janeiro, Brazil), a cloud-based registry for ICU quality improvement and benchmarking purposes. ICUs

using this system prospectively enter data in a standardized structured electronic case report form, most commonly by a trained case manager (usually a graduate nurse). Patient data are routinely registered in the system, including demographics, the SAPS 3 score [1], the Sequential Organ Failure Assessment (SOFA) score [13], comorbidities based on the Charlson Comorbidity Index (CCI) [14] and SAPS 3, Eastern Cooperative Oncology Group (ECOG) PS in the week prior to hospital admission, ICU admission diagnosis, invasive support use, ICU and hospital length-of-stay (LOS) and vital status at ICU and hospital discharge, respectively. The ECOG PS has six categories: with a score of 0 indicating the patient is fully active and able to carry on all pre-disease performance without restriction; 1 indicating some restriction in the performance of physically strenuous activity, but the patient is still ambulatory and able to carry out work of a light or sedentary nature; 2 indicating that the patient is ambulatory and up and about for >50 % of waking hours, capable of all self-care, but unable to carry out any work activities; 3 indicating that the patient is capable of only limited self-care and is confined to the bed or chair for >50 % of waking hours; 4 indicating that the patient is completely disabled, cannot carry out any self-care tasks and is totally confined to the bed or chair; 5 indicating death [15]. In our study, we used three pre-specified categories for the level of PS impairment that are routinely registered in the Epimed System[®] as follows: absent/minor (PS = 0–1), moderate (PS = 2) or severe (PS = 3–4) [5, 7].

Data processing and statistical analysis

Retrieved data were screened for missing information, implausible and outlying values, logical errors and insufficient details. In all of these cases, we contacted local investigators with the request to provide the missing information. There was no missing information regarding patients' core data and outcomes. Information on PS impairment was missing for 3476 patients (5.8 %), and we therefore applied a robust imputation method using random forests (missForest package [16]) to allow the inclusion of these patients in the analysis. Imputation was based on baseline patient features, as described in the ESM [16]. Missing data on other patient characteristics were minimal, and we performed single imputation using the reference or "normal" category in these cases [17]. We compared categorical variables between groups using Chi-squared tests and assessed continuous variables for normality using the Kolmogorov–Smirnov test. Parametric variables were compared using Student's *t* test and analysis of variance, and nonparametric variables were compared using Mann–Whitney rank-sum or Kruskal–Wallis test. We reported the mortality rates

for each of the PS impairment groups according to the quartiles of severity-of-illness, age, CCI and admission type. Both univariate and multivariate logistic regression analyses were used to assess the effect of PS on hospital mortality. We also performed sensitivity analyses for the following pre-specified groups of patients: medical and surgical, patients with sepsis, cancer, any major comorbidity (defined as those encompassed by SAPS 3 score; namely: acquired immunodeficiency syndrome, hematological malignancy, cirrhosis, solid tumor with metastasis; chronic heart failure class IV) and requirement for mechanical ventilation, vasopressors or renal replacement therapy. We performed two multivariate analyses. In the first model, we estimated the effects of PS impairment adjusted for SOFA score, CCI, age, presence of sepsis and admission type (“SOFA Model”). In the second multivariate analysis, the association between PS impairment on outcome was assessed after adjusting by SAPS 3 score (“SAPS 3 model”). In this model, we applied a restrictive cubic spline with four knots for SAPS 3, thereby allowing nonlinear components to be modeled. We built receiver operating characteristic (ROC) curves for two models: one including only SAPS 3 and the other including SAPS 3 + PS impairment (without interactions, thus mimicking the effects of adding PS impairment to a future severity index score) and compared their area under the ROC curves (AUROC) in order to assess differences in accuracy. For this analysis, we divided the sample size randomly into test and training groups, comprising 80 and 20 % of the total sample size, respectively. We trained the models in the training set and thereafter validated these in the test sample. We compared AUROCs using DeLong’s test. Finally, we calculated the net reclassification improvement (continuous value–NRIc) and the integrated discrimination improvement (IDI) in the whole database. NRIc can be interpreted as a measurement of how well a model reclassifies the subjects, correctly or not. NRI ranges from -1 to 1 , with positive values meaning an increase in correct reclassification and negative values meaning a decrease in correct reclassification. We also performed a categorical NRI analysis considering an arbitrary cut-off of 0.2 predicted chance of event (as suggested by Pencina [18]), since a continuous NRI may overinflate the current effect of the new marker in reclassification [19]. The IDI is the difference in discriminative slopes between two models; that is, the difference between predicted probabilities in events and non-events [20, 21]. We assessed the calibration of the models using calibration plots. We also used other accuracy predictors (Brier score and Nagelkerke’s R^2) between the two models (original SAPS 3 vs. SAPS 3 + PS) to assess for an increase in predictive accuracy, with the higher the R^2 , the more the change in variance

is explained by the model. For the Brier’s index (the mean squared error of the prediction), lower values are associated with higher predictive accuracy [20]. We also performed a sensitivity analysis including only patients for whom information on PS was available. Other sensitivity analyses were performed to confirm the results according to admission type (medical, elective surgery or emergency surgery) and to exclude a potential effect of the included centers by applying a mixed effect model. We considered a p value of <0.05 as significant for all analyses. We used R version 3.3.0 for all analysis with the following packages: rms, lme4, ggplot2, PredictABEL, missForest, funModeling, dplyr and tableone [16, 22–24].

Results

Characteristics of the participating centers and the study population

A total of 59,693 patients admitted to 78 ICUs were evaluated. Participating ICUs were mostly medical/surgical ($n = 62$, 79 %) and located in private hospitals ($n = 72$, 92 %). The main characteristics of the ICUs are given in ESM Table 1. The median number of patients per ICU was 589 (interquartile range (25–75%) 419–890). PS impairment was absent/minor in 43,020 (72.0 %) patients, moderate in 9511 (16.0 %) and severe in 3684 (6.2 %); information on PS was missing for 3476 (5.8 %) patients. A comparison of the characteristics of patients with and without information on the PS is shown in ESM Table 2. A missing map (visual representation of missing values for each variable in every row of the database) is provided in ESM Fig. 1. In brief, patients with missing PS impairment information showed a tendency to be more commonly admitted to medical–surgical ICUs located in public hospitals and hospitals with training programs in critical care than to other ICUs (ESM Table 2). These patients were also more frequently surgical patients, had a somewhat lower SAPS 3 score, a similar SOFA score and higher ICU and hospital mortality rates, as well as longer length of hospital stay, than patients for whom PS impairment information was available. After imputing for missing values, there were 45,223 (75.8 %) patients with absent/minor PS impairment, 10,354 (17.3 %) with moderate PS impairment and 4116 (6.9 %) with severe PS impairment. Table 1 presents the main patient characteristics stratified according to PS impairment. Approximately 66.8 % of the admissions were medical and 33.2 % were surgical. The ICU mortality was 9.6 % ($n = 5723$), and the hospital mortality was 14.4 % ($n = 8581$).

Effect of PS impairments on patient outcomes

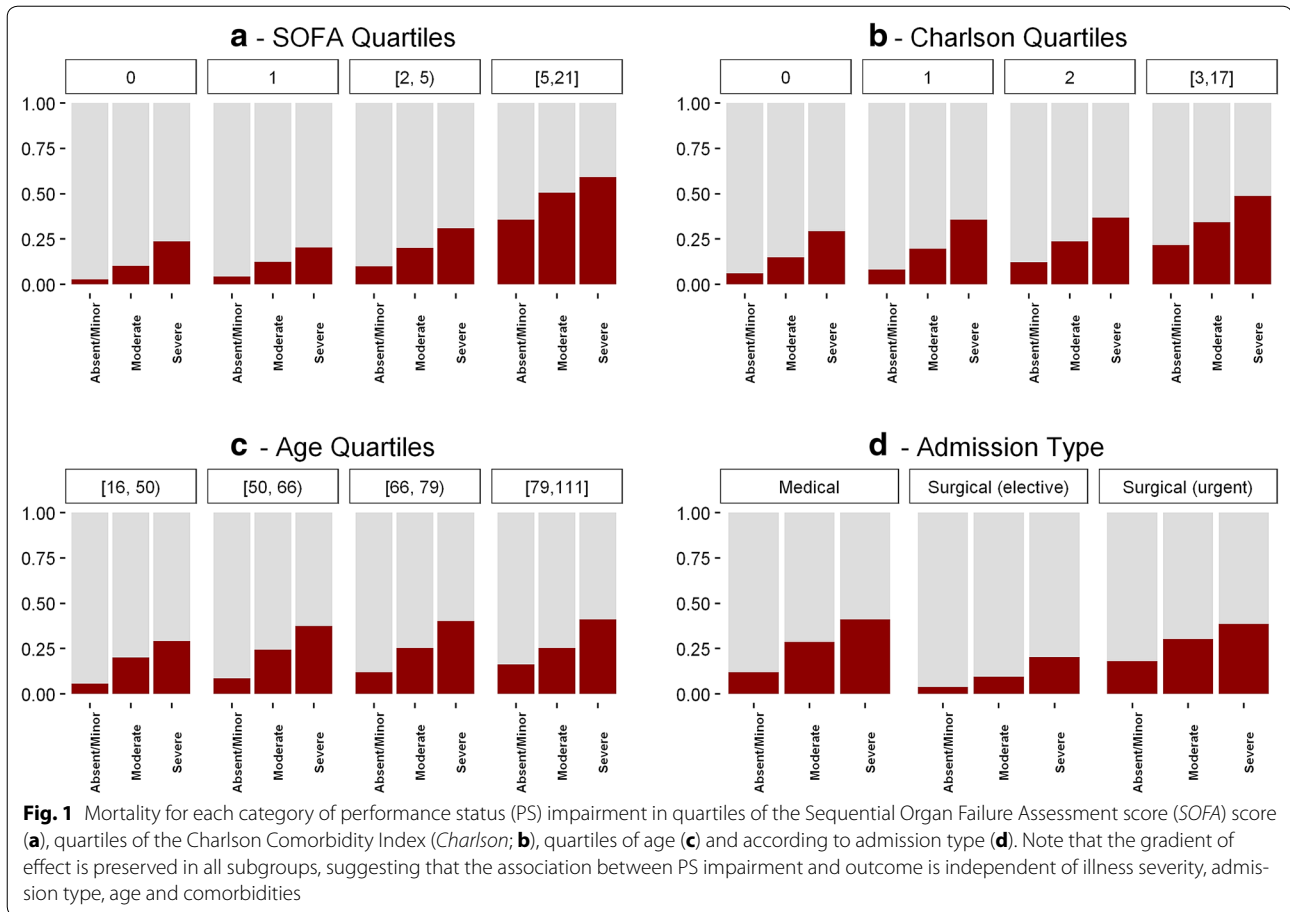
Overall, the worse the PS, the higher both the ICU and hospital mortality rates and LOS (Table 1). In addition, patients with worse PS were less frequently discharged

Table 1 Main patient characteristics

Patient characteristics	All patients	Patient categories based on severity of performance status impairment			p
		Absent/minor	Moderate	Severe	
n (%)	59,693	45,223 (75.8 %)	10,354 (17.3 %)	4116 (6.9 %)	–
Age (years)	62.3 ± 19.3	58.93 ± 18.8	72.3 ± 16.6	74.34 ± 17.4	<0.001
Gender (female/male)	29,921/29,772 (50.1%/49.9 %)	22,171/23,052 (49.0%/51.0 %)	5527/4827 (53.4%/46.6 %)	2223/1893 (54.0%/46.0 %)	<0.001
Simplified Acute Physiology Score 3	43.0 ± 14.9	40.0 ± 13.5	50.87 ± 15.3	56.19 ± 14.5	<0.001
Sequential Organ Failure Assessment score	2.3 ± 3.0	2.0 ± 2.8	3.18 ± 3.4	4.1 ± 3.6	<0.001
Charlson Comorbidity Index	1.0 [0.0, 2.0]	0.0 [0.0, 2.0]	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	<0.001
Length of stay in hospital before ICU stay ≥ 1 day	10,521 (17.6 %)	6598 (14.6 %)	2835 (27.4 %)	1088 (26.4 %)	<0.001
Admission type (%)					<0.001
Medical	39,863 (66.8 %)	28,653 (63.4 %)	7605 (73.4 %)	3605 (87.6 %)	
Elective surgery	16,652 (27.9 %)	14,101 (31.2 %)	2190 (21.2 %)	361 (8.8 %)	
Emergency surgery	3178 (5.3 %)	2469 (5.5 %)	559 (5.4 %)	150 (3.6 %)	
Sepsis	11,121 (18.6 %)	6682 (14.8 %)	2582 (24.9 %)	1857 (45.1 %)	<0.001
Heart failure Class 4	437 (0.7 %)	210 (0.5 %)	183 (1.8 %)	44 (1.1 %)	<0.001
Acquired immunodeficiency syndrome	435 (0.7 %)	334 (0.7 %)	86 (0.8 %)	15 (0.4 %)	0.011
Cirrhosis	1082 (1.8 %)	750 (1.7 %)	260 (2.5 %)	72 (1.7 %)	<0.001
Chronic kidney disease	5152 (8.6 %)	3130 (6.9 %)	1501 (14.5 %)	521 (12.7 %)	<0.001
Diabetes	14,692 (24.6 %)	10,260 (22.7 %)	3233 (31.2 %)	1199 (29.1 %)	<0.001
Hypertension	31,536 (52.8 %)	22,631 (50.0 %)	6589 (63.6 %)	2316 (56.3 %)	<0.001
Dementia	3357 (5.6 %)	906 (2.0 %)	1238 (12.0 %)	1213 (29.5 %)	<0.001
Hematological malignancy	1008 (1.7 %)	641 (1.4 %)	302 (2.9 %)	65 (1.6 %)	<0.001
Solid tumor metastatic	2647 (4.4 %)	1415 (3.1 %)	910 (8.8 %)	322 (7.8 %)	<0.001
Solid tumor non-metastatic	6641 (11.1 %)	4651 (10.3 %)	1507 (14.6 %)	483 (11.7 %)	<0.001
Major comorbidity ^a	5433 (9.1 %)	3243 (7.2 %)	1688 (16.3 %)	502 (12.2 %)	<0.001
Need for renal replacement therapy	2959 (5.1 %)	1728 (4.0 %)	849 (8.3 %)	382 (9.3 %)	<0.001
Need for Mechanical ventilation	10,951 (19.0 %)	6867 (15.8 %)	2557 (25.1 %)	1527 (37.2 %)	<0.001
Need for vasopressors	8544 (14.8 %)	5025 (11.6 %)	2230 (21.9 %)	1289 (31.4 %)	<0.001
ICU mortality	5723 (9.6 %)	3100 (6.9 %)	1639 (15.8 %)	984 (23.9 %)	<0.001
Hospital mortality	8581 (14.4 %)	4418 (9.8 %)	2552 (24.6 %)	1611 (39.1 %)	<0.001
ICU LOS (days)	2.0 [1.0, 5.0]	2.0 [1.0, 4.0]	3.0 [2.0, 6.0]	5.0 [2.0, 11.0]	<0.001
Hospital LOS (days)	8.0 [4.0, 16.0]	7.0 [3.0, 13.0]	11.0 [6.0, 24.0]	17.0 [8.0, 39.0]	<0.001
Location at discharge					<0.001
No discharge (death)	8581 (14.4 %)	4418 (9.8 %)	2552 (24.6 %)	1611 (39.1 %)	
Home	47,450 (79.5 %)	38,166 (84.4 %)	7165 (69.2 %)	2119 (51.5 %)	
Home-care/hospice	372 (0.6 %)	134 (0.3 %)	83 (0.8 %)	155 (3.8 %)	
Other/unknown	3290 (5.5 %)	2505 (5.5 %)	554 (5.4 %)	231 (5.6 %)	

Data are presented as the number with the percentage in parenthesis, the mean ± standard deviation or the median with the interquartile range in square brackets, as appropriate. Multiple imputation was used for 3476 patients with missing information regarding the performance status

^a Major comorbidities: acquired immunodeficiency syndrome, hematological malignancy, cirrhosis, solid tumor with metastasis; chronic heart failure class IV

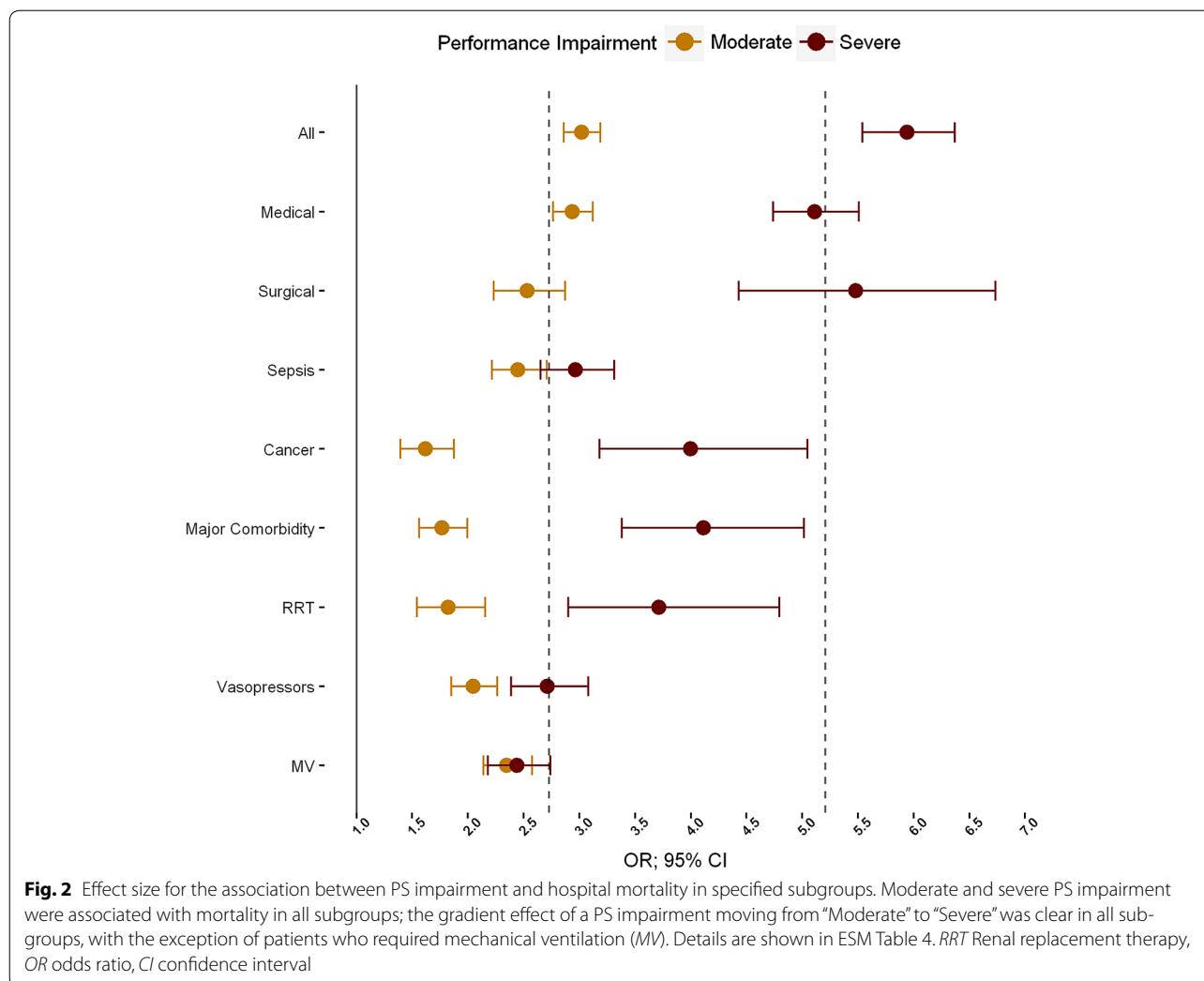


home. PS impairment was associated with worse outcomes in all SOFA quartiles (Fig. 1a), CCI quartiles (Fig. 1b) and age quartiles (Fig. 1c) and according to admission type (Fig. 1d), suggesting that the effect of PS impairment on outcome was independent of other common markers of baseline health status (age and CCI) and also of markers of illness severity (SAPS 3) and type of admission. Higher PS impairment was associated with higher mortality even in matrix quartiles of CCI and age (ESM Fig. 2) and in quartiles of SAPS 3 without assessment scores for age, comorbidities and admission type (ESM Fig. 3). ESM Table 3 shows the main patient characteristics according to hospital survival. In the univariate analysis, a worse PS was associated with higher mortality in an incremental manner in all subgroups, with the exception of those on mechanical ventilation where no difference was found between patients with moderate or severe PS impairment (Fig. 2; ESM Table 4).

In both of the constructed logistic regression models (SOFA and SAPS 3 models), PS impairment was independently associated with higher hospital mortality (Figs. 3, 4). A plot of the association between SAPS 3 and PS impairment with survival (Fig. 3) shows that the association

between PS impairment and outcome was more relevant in the mid-range of illness severity, especially in the second and third quartiles of SAPS 3 (area between dashed vertical lines). No clear association between PS impairment and mortality was observed for patients with a high SAPS 3 score. The effect size of PS impairment in the univariate analysis and in both the SAPS 3 and SOFA models is shown in Fig. 4 and ESM Table 5.

We observed a small improvement in the accuracy by adding the PS to the original SAPS 3 (ESM Fig. 4). The AUROC increased slightly (0.857–0.86; $p = 0.001$; ESM Fig. 3), the Brier score (0.088–0.087) decreased and the R^2 increased (0.376–0.383) with the addition of PS impairment to SAPS 3 score. ESM Fig. 5 shows the box-plot of predicted probability for survivors and non-survivors using SAPS 3 values and SAPS 3 + PS impairment. The IDI after adding PS impairment to SAPS 3 was 3.7 % ($p < 0.001$) and the NRIc was 0.56 (95 % confidence interval 0.54–0.58; $p < 0.001$). Results for the NRIc are given in the ESM and these remained significant even when an arbitrary 20 % cutoff was used, although the magnitude was lower [18, 20]. The calibration was mostly unchanged after PS was added to the SAPS 3 score (ESM Fig. 6).



Comparable results were obtained when the analyses were performed with only patients for whom PS information was available (ESM Table 6; ESM Fig. 7).

Other sensitivity analyses

Sensitivity analysis according to admission type highlighted the association of PS impairment with a higher odds for mortality; however, the association was more robust and had higher magnitude in medical admissions (ESM Table 7; ESM Figs. 8–10). For surgical admissions (both elective and emergency), we found a clear association between worse PS and higher mortality only for those patients with severe PS impairment (ESM Table 7; ESM Figs. 8–10). Results for the mixed effect models confirmed the association of PS impairment and higher hospital mortality while accounting for potential individual ICU effects (ESM Table 8; ESM Fig. 11).

Discussion

The results of this study demonstrate that PS impairment in the week before hospital admission was independently associated with increased hospital mortality in the critically ill patients enrolled in the study, regardless of other proxies for chronic health status (age and comorbidities), the type of admission and severity of illness. Importantly, the association between moderate or severe PS impairments on hospital mortality appeared to be particularly relevant in the upper mid-range of illness severity (third SAPS 3 quartile). The association between higher PS impact and higher hospital mortality was more pronounced and consistent for medical admissions and was independent of potential effects of participating ICUs. To the contrary, the simple addition of PS impairment to the SAPS 3 score improved its discriminative capability only slightly (assessed both by an increase in AUROC and cNRI/IDI).

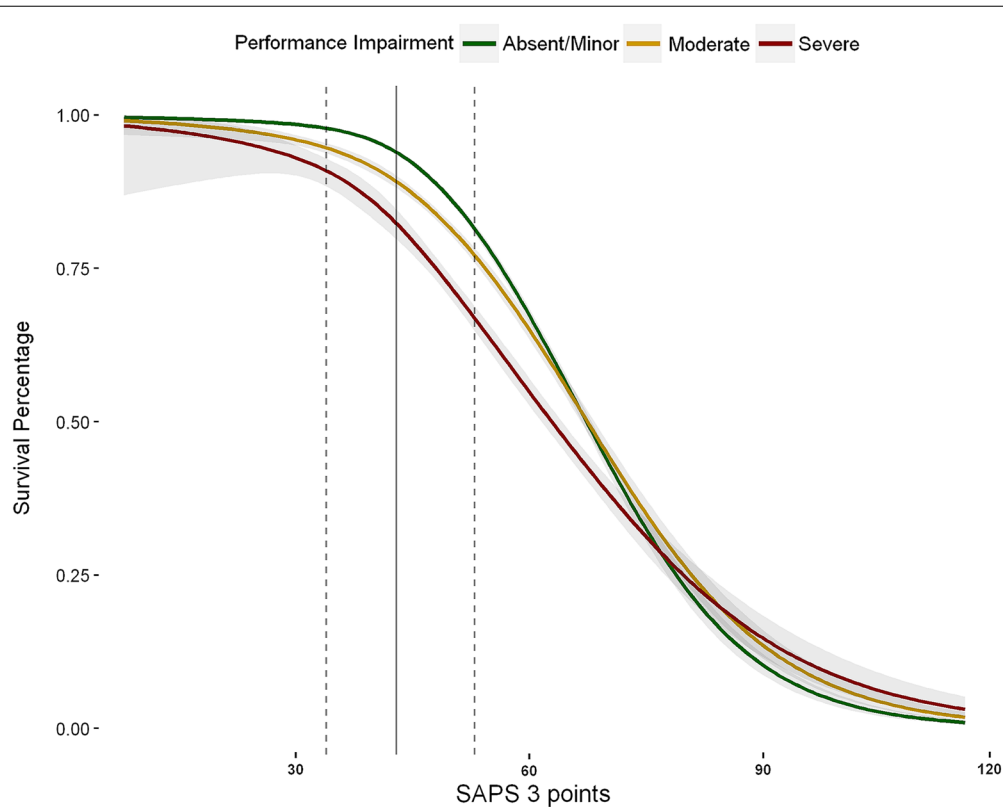
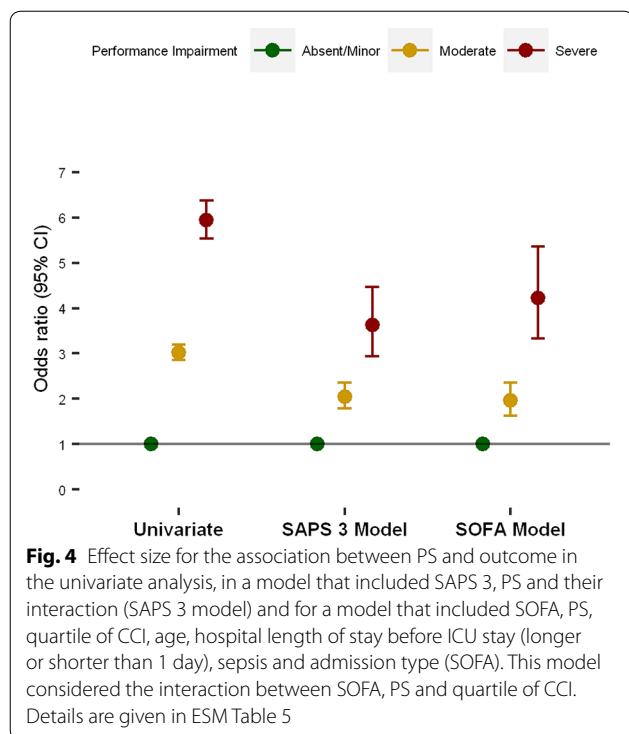


Fig. 3 Logistic regression plot for predicted survival according to the Simplified Acute Physiology Score 3 (SAPS 3) values and PS impairment. The model applied a restricted cubic spline for SAPS 3 values and allowed interactions with PS. *Solid vertical line* Median, *dashed vertical lines* interquartile (25–75 %) range. The escalating effect of worse PS and lower survival was reduced after the third quartile, although patients with severe PS impairment still had lower survival when compared to the other groups. For very severely ill patients, PS impairment had a minimum impact on predicted mortality

Published studies on the investigation of the impact of PS in critically ill patients remain relatively scarce, particularly in comparison to other medical specialties. Of note, in oncology, PS is routinely assessed to assist not only the outcome evaluation but also to facilitate the selection of anticancer treatments, such as chemotherapy, major surgical resections or radiation therapy [25]. Studies in critically ill cancer patients have demonstrated that impairments in the PS before hospital admission are associated with worse short-to-medium-term outcomes [10, 26, 27], and they place limitations on the provision of the most recommended anticancer treatments in ICU survivors [26]. In addition to cancer patients, there are also studies suggesting that PS impairment is associated with worse outcomes in septic, liver transplant and elderly patients requiring critical care [5, 6, 11, 26]. To our knowledge, there are little data in general on critically ill patients. Park et al. reported an association between PS and outcome and found that worse PS was associated with higher in-hospital mortality even when illness severity and type of admission were accounted

for [9]. In a single-center retrospective analysis, Zampieri and Colombari found that PS impairment was associated with higher in-hospital mortality in very elderly (>80 years) patients [5]. Measuring PS impairment could therefore aid prognostication and provide an additional, as yet underappreciated, risk factor for worst prognosis that should be considered in future research.

In our study, we also demonstrated that the full picture of a patient's chronic health status is not entirely captured by the variables commonly included in the illness severity scores, such as age and major comorbidities. As shown in Fig. 1 and ESM Fig. 2, higher PS impairment was associated with worse outcome in all quartiles of age and CCI. Therefore, by not including PS in the calculation of severity scores, researchers and clinicians may miss an opportunity to acquire additional relevant information on a patient's baseline health status. In the study by Zampieri and Colombari, the addition of PS to the SAPS 3 score reasonably improved the SAPS 3 in terms of both the calibration and discrimination capabilities, a result which was not



fully corroborated by our findings. Although concerns related to selection biases can certainly be raised when the results between these two studies are compared, in our opinion the simply addition of the PS to an existing severity of illness score is not the most appropriate approach to investigate whether information on prior PS can result in eventual improvements in the accuracy of these instruments. The small increase in AUROC observed in our study should not be considered to be an irrelevant marker of PS [28]. Important predictors with large effect sizes can have a small impact on c statistics in several scenarios, especially when the baseline model accuracy is high, as was the case for the SAPS 3 values in our sample [28]. In fact, it has been suggested that logistic regression may be a sufficient (and more adequate) strategy than AUROC testing by which to assess the role of a new predictor [29].

Our work has several limitations. First, we retrieved data from an administrative database for quality improvement purposes in which PS was registered using three pre-specified categories, in contrary to the original description of the score. While this approach has been used under other conditions [5, 30, 31], it may not capture the subtleties of PS. In addition, we cannot guarantee that the PS was uniformly assessed in all of the participating ICUs. However, the ECOG scale is a valid, simple and widely used instrument to assess the PS, as well as quite easy to incorporate routinely in

patient evaluation [30]. Second, as we used the ECOG scale to assess the PS for only the 1 week preceding hospital admission, the full picture of chronic health status or frailty in critically ill patients may be overrepresented, since the disease that triggered ICU admission could have already started (and impacted PS) a few days before admission. Third, end-of-life policies are not assessed in the database, and therefore we were unable to account for this factor in the analysis. It is conceivable that PS impairment may play a role in the end-of-life decision-making process even though physicians in Brazil are prone to sustain treatment with advanced life support devices even in patients with very poor PS [32]. However, the impact of PS on end-of-life discussion in critically ill patients should be assessed in further research. Finally, this study may not also be fully representative of the panorama of critically ill patients in Brazil, since most of the included ICUs were in private hospitals and medical institutions.

Conclusion

Impairment of PS during the week prior to hospital admission was associated with higher in-hospital mortality in critically ill patients, particularly in the mid-range of the severity of illness. These findings remained consistent in the several subgroup analyses. We therefore conclude that the full picture of chronic health status is not captured by assessing only age and comorbidities.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4563-5) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

Dr. Soares and Dr. Salluh are founders and equity shareholders of Epimed Solutions®, which markets the Epimed Monitor System®, a cloud-based software for ICU management and benchmarking. The other authors declare that they have no conflict of interest.

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