Intensive Care Med (2021) 47:1440–1449
https://doi.org/10.1007/s00134-021-06528-6

ORIGINAL

The association of the COVID-19 pandemic and short-term outcomes of non-COVID-19 critically ill patients: an observational cohort study in Brazilian ICUs

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Abstract

Purpose: To assess whether intensive care unit (ICU) outcomes for patients not affected by coronavirus disease 2019 (COVID-19) worsened during the COVID-19 pandemic.

Methods: Retrospective cohort study including prospectively collected information of patients admitted to 165 ICUs in a hospital network in Brazil between 2011 and 2020. Association between admission in 2020 and worse hospital outcomes was performed using different techniques, including assessment of changes in illness severity of admitted patients, a variable life-adjusted display of mortality during 2020, a multivariate mixed regression model with admission year as both fixed effect and random slope adjusted for SAPS 3 score, an analysis of trends in performance using standardized mortality ratio (SMR) and standardized resource use (SRU), and perturbation analysis.

Results: A total of 644,644 admissions were considered. After excluding readmissions and patients with COVID-19, 514,219 patients were available for analysis. Non-COVID-19 patients admitted in 2020 had slightly lower age and SAPS 3 score but a higher mortality (6.4%) when compared with previous years (2019: 5.6%; 2018: 6.1%). Variable-adjusted life display (VLAD) in 2020 increased but started to decrease as the number of COVID-19 cases increased; this trend reversed as number of COVID cases reduced but recurred on the second wave. After logistic regression, being admitted in 2020 was associated with higher mortality when compared to previous years from 2016 and 2019. Individual ICUs standardized mortality ratio also increased during 2020 (higher SMR) while resource use remained constant, suggesting worsening performance. A perturbation analysis further confirmed changes in ICU outcomes for non-COVID-19 patients.

Conclusion: Hospital outcomes of non-COVID-19 critically ill patients worsened during the pandemic in 2020, possibly resulting in an increased number of deaths in critically ill non-COVID patients.

Keywords: ICU performance, COVID-19, Variable life-adjusted display, Standardized mortality ratio

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Introduction

The outcomes of critically ill patients have improved in the past decades [1, 2]. Higher survival rates were observed in elective surgical admission, sepsis, cancer, and immunocompromised patients, among other intensive care patients [1–5]. Reasons for better outcomes include the improvement in available treatments for the underlying diseases (such as cancer and other chronic illnesses) and advances in the management of organ dysfunctions and intensive care unit (ICU) acquired complications.

The coronavirus disease 2019 (COVID-19) pandemic has stressed the ICUs in several ways, including an abrupt increase in the need for ICU beds, a rise in the proportion of mechanically ventilated patients, the adaptation of biosafety protocols to a new disease, among others [6–8]. While much attention has been given to the outcomes of critically ill COVID-19 patients [9], it is uncertain whether the sudden changes in case-mix and the burden imposed by the pandemic had an impact on the outcomes of non-COVID-19 critically ill patients [10].

We sought to analyze trends in crude and risk-adjusted mortality and ICU performance in a 10-year cohort of patients of ICU patients in Brazil. We hypothesized that overall time trends in reduction of ICU mortality would have been impaired during the pandemic and the markers of ICU performance, including standardized mortality ratio (SMR) and standardized resource use (SRU) would have been impacted by COVID.

Take-home message

In a large cohort of hospitals in Brazil, non-COVID-19 critically ill patients had worse adjusted outcomes in 2020 when compared with previous years. This association was consistent among several different approaches. The impacts of COVID-19 pandemic extend beyond COVID-19 patients.

Methods

Design

Retrospective cohort study performed in ICUs from an integrated private hospital network (*Rede D'Or São Luiz)* present in eight Brazilian States. The use of fully anonymized cohort data for research purposes has been approved by Local Ethics Committee and the Brazilian National Ethics Committee (CAAE: 17079119.7.0000.5249) without the need for informed consent. All data was anonymized previously to extraction and analysis.

Population

Critically ill patients admitted from January 1st, 2011, until 31st December 2020. All adult (age equal or greater than 18); COVID-19 patients (confirmed or suspected) were not considered for the main analyses. We considered only the first admission to the ICU for each patient.

Data collection

Data were routinely and prospectively collected using a standardized electronic system (Epimed Monitor ICU System, Rio de Janeiro, Brazil [11]). Information collected included demographic data (age, sex at birth), comorbidities, admission type (medical, elective or urgent surgical), the Simplified Acute Physiological Score 3 (SAPS 3) [12]), organ support use at admission (mechanical ventilation, non-invasive ventilation, vasopressors, renal replacement therapy at ICU admission or up to the first hour after ICU admission), comorbidities, performance status on the week previous to ICU admission (measured by Eastern Cooperative Oncology Group classes, stratified in 0 or 1—independent or with minor performance impairment, 2—moderate performance impairment and 3 or 4—severe performance impairment or bedridden) [13], respectively), ICU and hospital length-of-stay (LOS) and ICU and hospital mortality.

COVID-19 status

Since February 2020, all admitted patients were categorized according to confirmed COVID-19 (through polymerase chain reaction—PCR), suspected COVID-19 (unavailable PCR diagnosis but high clinical suspicion) and non-COVID-19 patients (PCR negative and without suspicion of COVID-19).

Primary outcome

Primary outcome was in-hospital mortality. Pre-specified subgroup analysis included patients stratified according to admission type, infection as main diagnosis for admission, performance status impairment, and use of mechanical ventilation at admission. As secondary outcomes, we also assessed trends in SMR and SRU (as proxies of ICU performance) among participating units (see details below).

Missing data policy

We excluded patients with missing hospital outcomes for the main analysis. Relevant variables with missing values were imputed in a single process using a multiple chain equation using mice R package [14]; the average of 5 imputation sets or the commonest result (for categorical variables) was used. Imputation was performed for missing values on admission type, performance status, and use of mechanical ventilation and vasopressors at admission.

Statistical analysis

We used standard descriptive methods to report main patients' characteristics features over time. We assessed the association between admission year and outcome using a sequential approach:

1. An exploratory unadjusted analysis showing trends of admission SAPS3 score, age, admission type, number of admissions and mortality.
2. A SAPS 3 calibration analysis based on SAPS3 standard equation to check fluctuation, in the whole sample of non-COVID patients, between actual and predicted SAPS3 mortality.
3. An analysis of trends in variable life-adjusted display (VLAD) for non-COVID patients in 2020 coupled with number of COVID admissions according to admission week during 2020. VLAD is an accumulated sum of adjusted risks. In brief, for each surviving patient a value equal to predicted probability of dying by SAPS 3 score was added and for each dying patient, the probability of survival was subtracted from the cumulative sum. For example, if a patient with a predicted mortality of 0.4 survives, 0.4 is added to the cumulative VLAD sum; if the patient dies, 0.6 is removed from the sum. VLAD, therefore, increases if the system is outperforming the predicted mortality, and decreases in VLAD suggest a decrease in overall performance [15]. VLAD was designed to allow frequent assessment of performance of a unit over time and has been shown to be sensible to changes in performance [15].
4. A mixed regression model with SAPS3 score, admission year and their interaction as fixed effects and a random intercept for unit and random slope for year for non-COVID patients. This analysis was further enhanced for a specific secondary analysis comparing specific moments in the 2020 pandemic versus 2019.
5. An assessment of changes in ICU performance over time measured as their SMR and SRU for bimesters during 2016–2019 considering only non-COVID patients.
6. A perturbation analysis of SMR in 2020 versus previous years (2016–2019), again considering only non-COVID patients.

We used mixed regression models in analysis (4) for subgroup analyses.

Analyses (1) and (2) were designed to provide a broad evaluation of trends over time. The third analysis (3) was used to assess whether the burden of COVID-19 cases in the participating units would track changes in outcome measured by SAPS3 adjusted VLAD in 2020. The fourth analysis (4) is a traditional regression model designed to account for sites and illness severity in a comparison between 2020 and all the other years in the cohort at the patient level; it is further enhanced by an ancillary analysis that considers phases of the pandemic (see ESM for details). Analysis (5) was designed to provide a graphical representation of performance for selected units considering ICUs with full information available from 2016 to 2020. In this analysis, we evaluated bimonthly temporal changes in SMR and SRU from 2016 to 2020 considering only ICUs that had admissions in all bimesters between 2016 and 2020 inserted in the database. SRU was calculated as the observed-to-expected use of resources, we used the ICU LOS as a surrogate measure of resource use and the average LOS per survivor as the expected resource use [16]. We assessed structural changes in the progression of SMR and SRU before and during 2020 using Chow's Test [17].

The last analysis (6) was based on the same set of ICUs for analysis (5) and was performed through estimating the potential degree instability in the system induced by the pandemic in 2020 [18, 19] (see ESM for details). This analysis is a broad representation on how SMR and SRU changed in two different periods (2020 versus 2016–2019) considering not only shift in crude SMR and SRU values but also change in the dispersion of SMR and SRU values in the participating units. In this specific case, the SMR and SRU values in 2020 were compared to the respective average SMR or SRU values from 2016 to 2019 for each unit using violin plots and dot plots. Additionally, each bimester in 2020 was compared to previous baseline values of 2016–2019.

We performed all analyses in R project version 4.04 [20] with packages *lme4* [21], *emmeans* [22] and *mdp* [19]. We considered a p-value lower than 0.05 to be significant in the mixed model result, with post-hoc comparisons of mortality over time (year to year comparison) being performed using Tukey adjusted p-values for multiple comparisons within the logistic regression model for mortality (therefore not accounting for all possible comparisons between all models performed). A $p<0.05$ was considered significant for Chow test. Comparison between perturbation scores in 2020 bimesters versus 2016–2019 was made using Mann–Whitney U test with Bonferroni adjustment.

Results

A total of 644,644 admissions were available in the whole data set. We excluded non-adult patients (8314 patients—1.3%), ICU readmissions (91,623—16.8%), and patients with missing hospital outcome (8865 patients—1.6%), leaving 535,842 patients for analysis. Of those, 21,550 were patients with confirmed or suspected COVID-19; therefore, our main analysis focuses on 514,292 patients included in 165 ICUs from 45 different hospitals (flowchart is shown in sFigure 1). There were no missing data for SAPS 3 score for all patients; missing values for other variables are shown in ESM, sFigure 2, sFigure 3 and a comparison between imputed and not imputed datasets is provided in sTable 1. A summary of patient's features according to admission year is shown in Table 1. An overview of SAPS 3, age, mortality, number of admissions and admission type over time is shown in Fig. 1. SAPS3 and age slightly decreased in 2020 compared to 2019 and mortality slightly increased. Crude mortality was higher in 2020 than in 2019 (Table 1), despite the discrete reductions in SAPS 3 and age. Calibration of predicted SAPS3 mortality using global equation over the 10 years in the cohort in shown in sFigure 4; a plot of SAPS 3 calibration for the whole sample and specific years (2011, 2018, 2019, all patients from 2011 to 2019, and 2020) is shown in sFigure 5.

Changes in VLAD for non-COVID patients in each epidemiological week in 2020 is shown in Fig. 2A and the number of cases of COVID-19 admitted to the participating units in the corresponding weeks are shown in Fig. 2B. The rise in COVID-19 cases after the 11th week in 2020 was accompanied by a decrease in VLAD; after the peak of number of COVID-19 cases in weeks 17–20, the decrease in COVID-19 admissions was accompanied by an increase in VLAD. A second increase in COVID-19 cases after week 43 was further followed by another decrease in VLAD for non-COVID patients.

In logistic regression mixed model, the odds ratio for mortality in non-COVID patients was higher in 2020 versus 2019, 2018 and 2017, but like 2016 and lower for 2011–2015 (with the exception of very severe patients—SAPS 3 above 90 points—for the comparison between 2020 and 2019). Results of the logistic regression model are shown in Fig. 3 (numeric raw values are shown in sTable 2 and subgroup analysis are shown in sFigures 6–12). A similar pattern to the main analysis was seen for most subgroups. For very sick patients (SAPS 3 above 70) the association was less pronounced in patients with moderate or severe performance status impairment and elective surgery patients. In the ancillary analysis comparing specific periods of 2020 versus 2019, there were no differences in SAPS 3 adjusted mortality in early 2020 (before COVID-19) and 2019. The first peak was associated with an important increase in mortality, which was less clear in the second peak (sFigure 13).

Finally, trends in SMR and SRU for 65 ICUs that included patients in all bimesters from 2016 until end 2020 are shown in Fig. 4A and B, respectively. There was a trend towards reduction in overall and average SMR for these units over time until March 2020, when SMR started to rise. Changes in SRU over time were of lower magnitude and not grossly affected by the pandemic. A representation of SMR and SRU for all units is shown in sFigure 14. Fluctuations in SMR were confirmed on the perturbation analysis shown in Fig. 4C; similarly, even though average SRU was not clearly modified, it was also perturbed in 2020 (Fig. 4D). The aggregated SMR or SRU values for these 65 ICUs from 2016 to 2019 are shown in blue with the perturbation index in the y-axis in Fig. 4C and D, with 2020 values shown in purple. The increase in perturbation score suggests that the system was exposed to a different factor that affected the trends of SMR and SRU scores, but that perturbation on SMR was probably more important.

Discussion

In this large prospective cohort of critically ill patients admitted to 165 Brazilian ICUs between 2011 and 2020, a decrease in overall and risk-adjusted (SAPS3) mortality was consistently observed until 2020 when a reversal of this trend of mortality coincided with the beginning of COVID-19 pandemic. Different analysis methods as well as subgroup analysis provided similar results. In addition, the visual life-adjusted display (VLAD) and a perturbation analysis reinforced the conclusion that the system was somehow disturbed after March 2020. Markers of ICU performance, especially SMR, were modified during 2020. The association was consistent in most subgroups.

Assessing causality between COVID-19 burden and worse outcomes in non-COVID-19 patients is cumbersome. While there is an environmental rationale for our findings, it is pivotal to provide further evidence of the phenomena and strengthen the possible causal link. Several methods were applied to do so. First, the increase in mortality for non-COVID patients could not be directly attributed to an increase in baseline illness severity or need for organ support at ICU admission or to a major shift in age, performance status or admission type in 2020 (as shown in Fig. 1). This increase in mortality shifted the SAPS3 calibration curve upwards, reducing the tendency of SAPS3 predicted mortality to overestimate deaths that was becoming prominent in the previous years (shown in sFigure 2 and sFigure 3). Second, during 2020, the increase in COVID-19 cases was accompanied by worsening of outcomes of non-COVID-19 critically ill patients during the two peaks of ICU admission (shown in Fig. 2A). The fact that VLAD for non-COVID-19 patients inversely "tracked" the number of COVID-19 admissions during 2020 (shown in Fig. 2B) may suggest that both a "dose–effect" and reversibility events were present during 2020. Third, the strength of the association was estimated in a mixed effect regression model that accounted not only for ICU but also for the year effect within each ICU during a large period. The observed trends in improving

Table 1 Characteristics of included patients over cohort years

	All years $N=514{,}292$[1]	2011 $N=16{,}360$	2012 $N=26{,}069$	2013 $N=34{,}459$	2014 $N=41{,}747$	2015 $N=48{,}592$	2016 $N=54{,}189$	2017 $N=65{,}010$	2018 $N=75{,}072$	2019 $N=84{,}803$	2020 $N=67{,}991$
Age, years, mean (SD)	61 (20)	64 (19)	64 (19)	63 (19)	62 (20)	62 (20)	61 (20)	61 (20)	61 (20)	61 (21)	60 (20)
SAPS 3, points, mean (SD)	42 (12)	43 (13)	42 (13)	42 (12)	42 (12)	42 (13)	42 (13)	42 (13)	42 (12)	41 (12)	40 (13)
CCI, points[2], mean (SD)	1.20 (1.77)	1.36 (1.82)	1.27 (1.74)	1.26 (1.77)	1.14 (1.67)	1.15 (1.67)	1.17 (1.68)	1.19 (1.70)	1.18 (1.7)	1.20 (1.83)	1.24 (1.98)
Performance impairment, *n* (%)											
Absent/minor	386,391 (75%)	12,681 (78%)	20,595 (79%)	26,874 (78%)	32,642 (78%)	37,296 (77%)	41,074 (76%)	46,450 (71%)	55,828 (74%)	61,331 (72%)	51,620 (76%)
Moderate	94,962 (18%)	2334 (14%)	3604 (14%)	5119 (15%)	5867 (14%)	8252 (17%)	9951 (18%)	14,619 (22%)	14,389 (19%)	18,065 (21%)	12,762 (19%)
Severe	32,939 (6.4%)	1345 (8.2%)	1870 (7.2%)	2466 (7.2%)	3238 (7.8%)	3044 (6.3%)	3164 (5.8%)	3941 (6.1%)	4855 (6.5%)	5407 (6.4%)	3609 (5.3%)
Admission type, *n* (%)											
Elective surgery	91,242 (18%)	3,395 (21%)	5,309 (20%)	6,493 (19%)	7,441 (18%)	8,595 (18%)	9,917 (18%)	11,493 (18%)	12,132 (16%)	13,044 (15%)	13,423 (20%)
Medical	405,611 (79%)	12,279 (75%)	19,965 (77%)	26,657 (77%)	33,059 (79%)	38,707 (80%)	42,577 (79%)	51,422 (79%)	60,511 (81%)	68,858 (81%)	51,576 (76%)
Urgent surgery	17,439 (3.4%)	686 (4.2%)	795 (3%)	1309 (3.8%)	1247 (3.0%)	1290 (2.7%)	1695 (3.1%)	2095 (3.2%)	2429 (3.2%)	2901 (3.4%)	2992 (4.4%)
Presence of infection[3], *n* (%)	103,039 (20%)	2765 (17%)	4699 (18%)	6555 (19%)	8214 (20%)	10,746 (22%)	11,784 (22%)	13,090 (20%)	15,293 (20%)	17,458 (21%)	12,435 (18%)
Mechanical ventilation at admission, *n* (%)	20,336 (4%)	1319 (8.1%)	1671 (6.4%)	1948 (5.7%)	2178 (5.2%)	2236 (4.6%)	2135 (3.9%)	2315 (3.6%)	2125 (2.8%)	2371 (2.8%)	2038 (3%)
Vasopressor at admission, *n* (%)	21,106 (4.1%)	932 (5.7%)	1286 (4.9%)	1893 (5.5%)	1910 (4.6%)	2312 (4.8%)	2206 (4.1%)	2621 (4%)	2526 (3.4%)	3022 (3.6%)	2398 (3.5%)
ICU length-of-stay (days), mean (SD)	4.7 (9.6)	4.7 (15.6)	4.9 (17.4)	4.8 (10.7)	4.9 (11.2)	4.9 (9.5)	4.9 (9.1)	4.8 (8.6)	4.6 (8.2)	4.4 (7.2)	4.2 (7)
Hospital mortality, *n* (%)	39,161 (7.6%)	1847 (11%)	2941 (11%)	3583 (10%)	4040 (9.7%)	4332 (8.9%)	4286 (7.9%)	4448 (6.8%)	4558 (6.1%)	4768 (5.6%)	4358 (6.4%)

[1] Mean (SD); *n* (%)

[2] Charlson Comorbidity Index

[3] Presence of infection at enrollment. COVID-19 patients are not included in the table

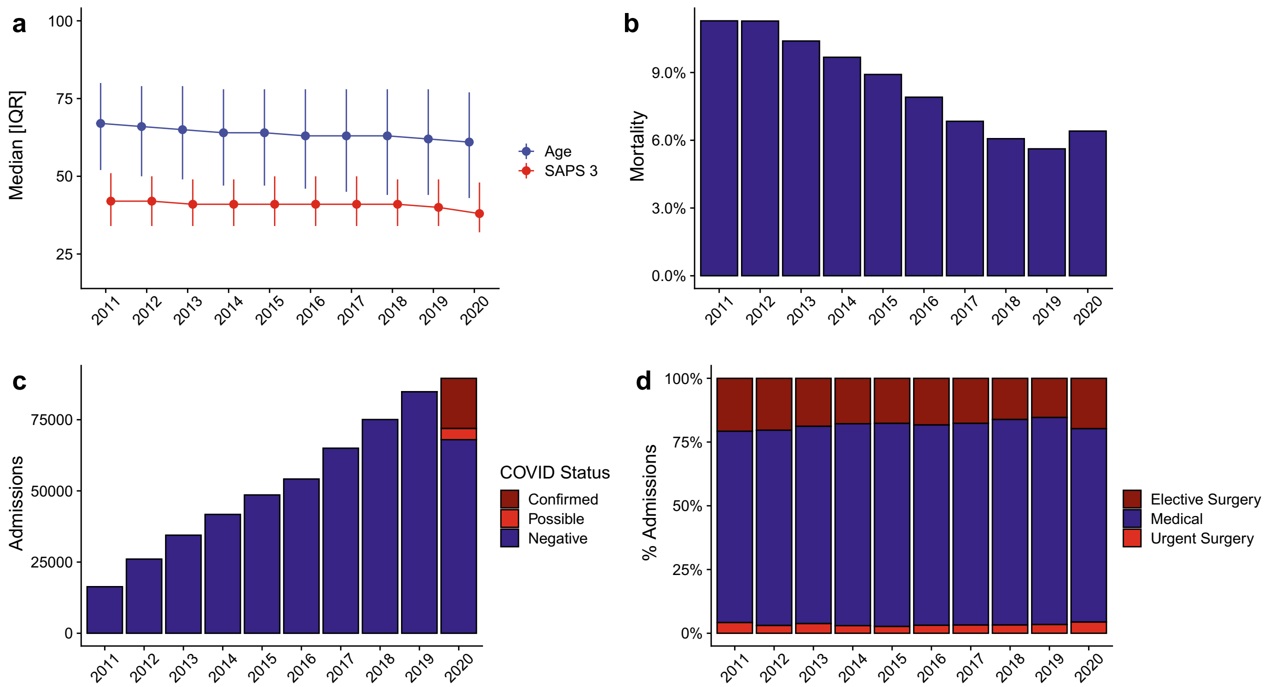

Fig. 1 Trends in SAPS 3 score (**a**), age (**a**), hospital mortality (**b**), number of admissions (**c**), with COVID-19 confirmed and suspected admissions shown in red, and admission type (**d**) during the cohort. Continuous values are displayed as mean and standard deviation

outcomes for the past years were reversed in 2020, with admission to the ICU in 2020 being a risk factor for mortality. We also considered possible interactions between illness severity and year of admission; results were compatible with a higher odd for mortality in 2020 versus previous years, with performance matching 2016. Finally, trends in SMR over time and the perturbation analysis are compatible with an abrupt change in ICU performance during 2020. SRU remained largely unchanged but was also disturbed by the pandemic to a certain degree. A reasonably constant standardized resource use coupled by an increase in standardized mortality provides indirect evidence that no "early discharges" (which would be accompanied by a decrease in SRU) were responsible for this higher mortality.

While these results provide the rationale for a causal association between the pandemic and worse outcomes of critically ill non-COVID patients, they lack mechanistic information on the possible reasons for the effect. We can hypothesize several unmeasured factors such as late hospital referral, disruption of organization and process of care due to reduced staff (burnout, sickness leave, increased number of ICU beds), and ICU strain are frequently associated with reduced in the adherence to process of care measures and consequently associated with increased morbidity and mortality. Regardless of the mechanistic pathway, it is reasonable to assume that COVID-19 impacted the outcome of non-COVID-19 critically ill patients, perhaps resulting in excess deaths in our setting. Therefore, solely considering COVID-19 deaths as a measurement of the impact of the pandemic may underestimate its effect on patients with different diagnosis, including critically ill surgical patients, patients with infection, among other groups.

Despite many studies assessing the effect of COVID-19 on the presentation of other conditions [23–25], there are few reports on the effect of COVID-19 on the outcomes of non-COVID critically ill patients or assessing the impact on ICU performance. A recent nationwide study in Denmark reported that outcomes of several acute conditions on hospitalized patients, including those with sepsis and cancer, were worst during COVID-19 pandemic [26]. Although not focused specifically on critically ill patients, conditions whose outcomes were more impaired during COVID-19 were unsurprisingly those requiring more urgent care. The present report presents recent data from a large Brazilian cohort that corroborates with the idea that care for non-COVID acute patients was somehow impaired during the pandemic. The overall increase in mortality is relevant considering the large number of admissions and should prompt a discussion on how to optimize care for non-COVID patients during the present outbreak. Specifically, future efforts in this subject should include other relevant information on

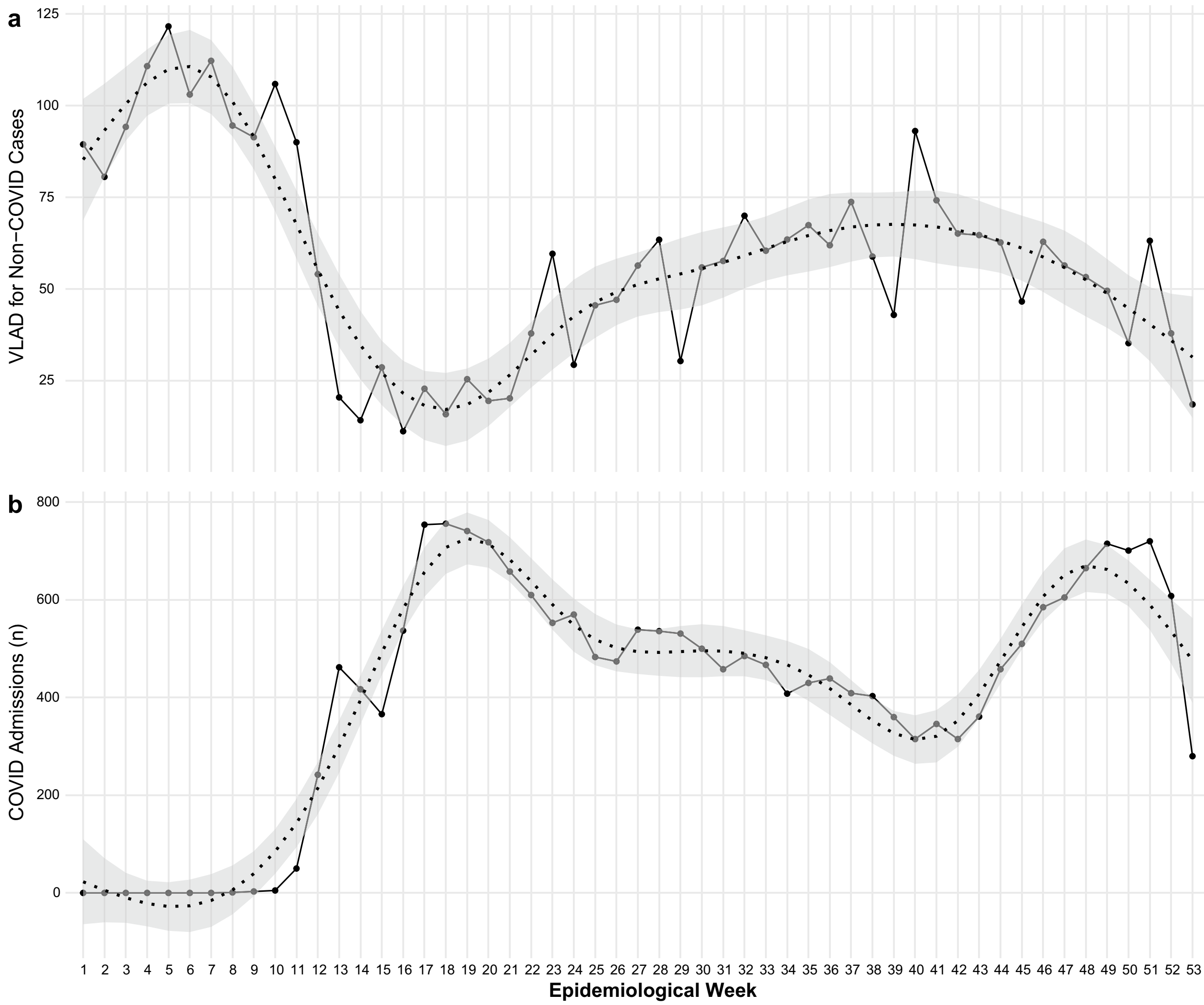

Fig. 2 (**a**) Weekly cumulative Variable-adjusted life display (VLAD) during all weeks in 2020. Increases in VLAD suggest a lower-than-expected mortality, while downwards shifts suggest the inverse trend. (**b**) Number of COVID-19 cases admitted to the participating ICUs during the epidemiological weeks of 2020

staff density, wellness, and other markers of both hospital and ICU strain, among other variables to elucidate the mechanisms behind a possible worsening in outcomes of critically ill patients during situations of high demand.

This study has several limitations. As with any observational study, a definitive causal pathway cannot be fully established. However, the analysis was built to reinforce several key elements of causality (time dependency, reversibility, "dose–effect", strength of the association). It remains conceivable that residual confounding may explain our results or that other unmeasured aspects such as triage and admission criteria, unavailable in our data, could explain the results. Model adjustment relied mainly on a single illness severity score, which, in turn, is accurate and well-calibrated in our setting. We applied several models and we did not control for all possible multiple comparisons; therefore much (but not all) of the remaining multiplicity relates to use of different analytical approaches which were specifically chosen to provide a wide range of views on the question being asked. The correspondence of all of them strengthens (rather than weakens) the overall conclusion. We had no data on ICU or staff characteristics, including age experience workload or years of practice, neither on human factors, such as fatigue or burnout, which may be of importance in this context. Our cohort has an exceptionally low hospital mortality rate for critically ill patients, which reflects local ICU

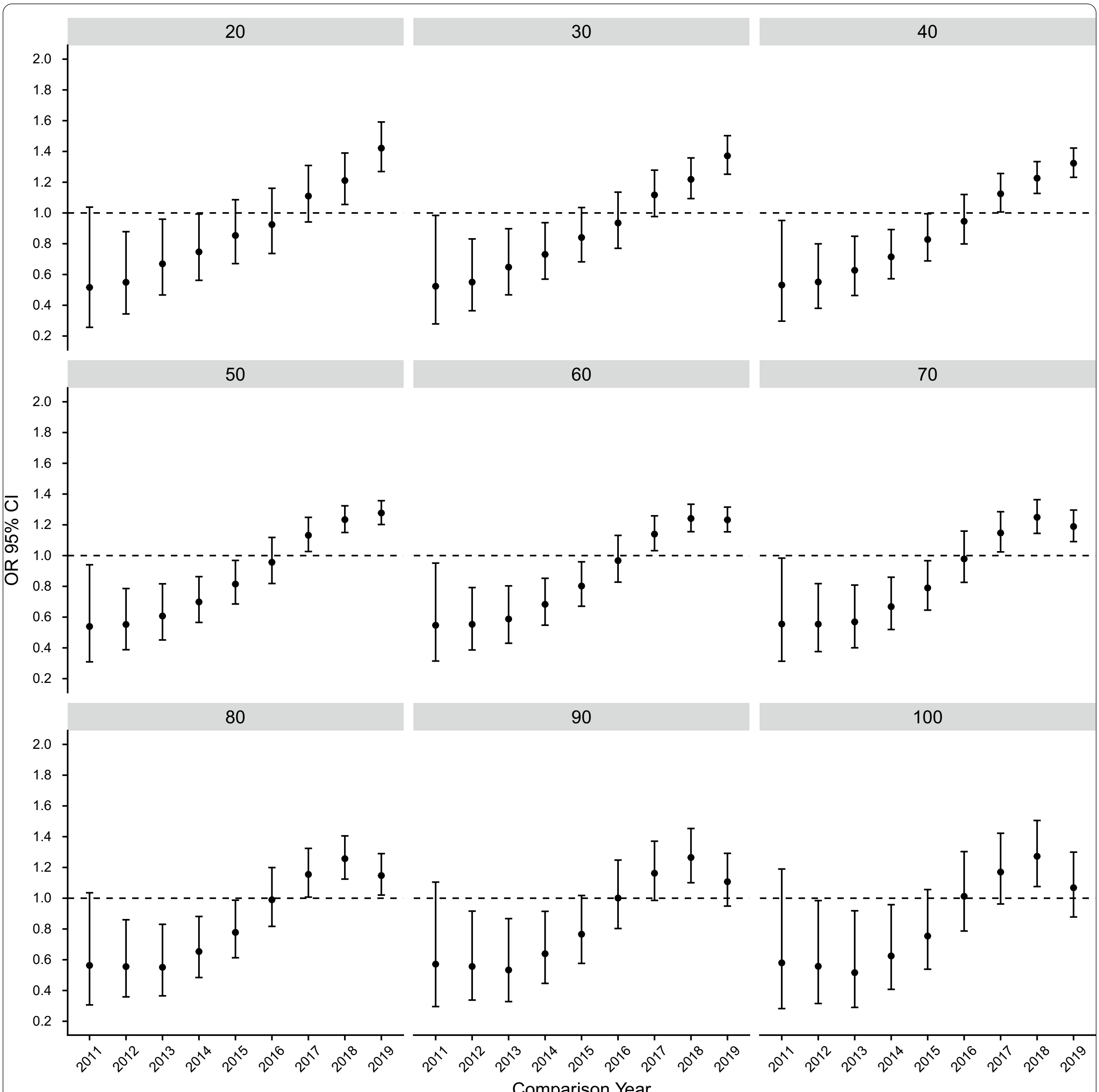

Fig. 3 Odds ratio and their corresponding 95% confidence intervals for mortality in 2020 versus other years (*x*-axis) for fixed SAPS-3 scores (panels) obtained through marginal means. The dashed line marks OR = 1.00

admission policies; this may limit extrapolation of these findings to other settings; however, the increase in mortality occurred in both low and high illness severity patients. In addition, we were not available to provide information on the process of care or staffing before and during the pandemic, as well as its potential disruption in standards of care. We also lack information on the number of ICU beds during COVID-19 surge; it is conceivable that some units increased their capacity and that this could be related to our findings. Finally, some subgroups were defined based on information with missing values that were imputed. While the percentage of missing values was low, this may have resulted in some imprecision in subgroup analyses.

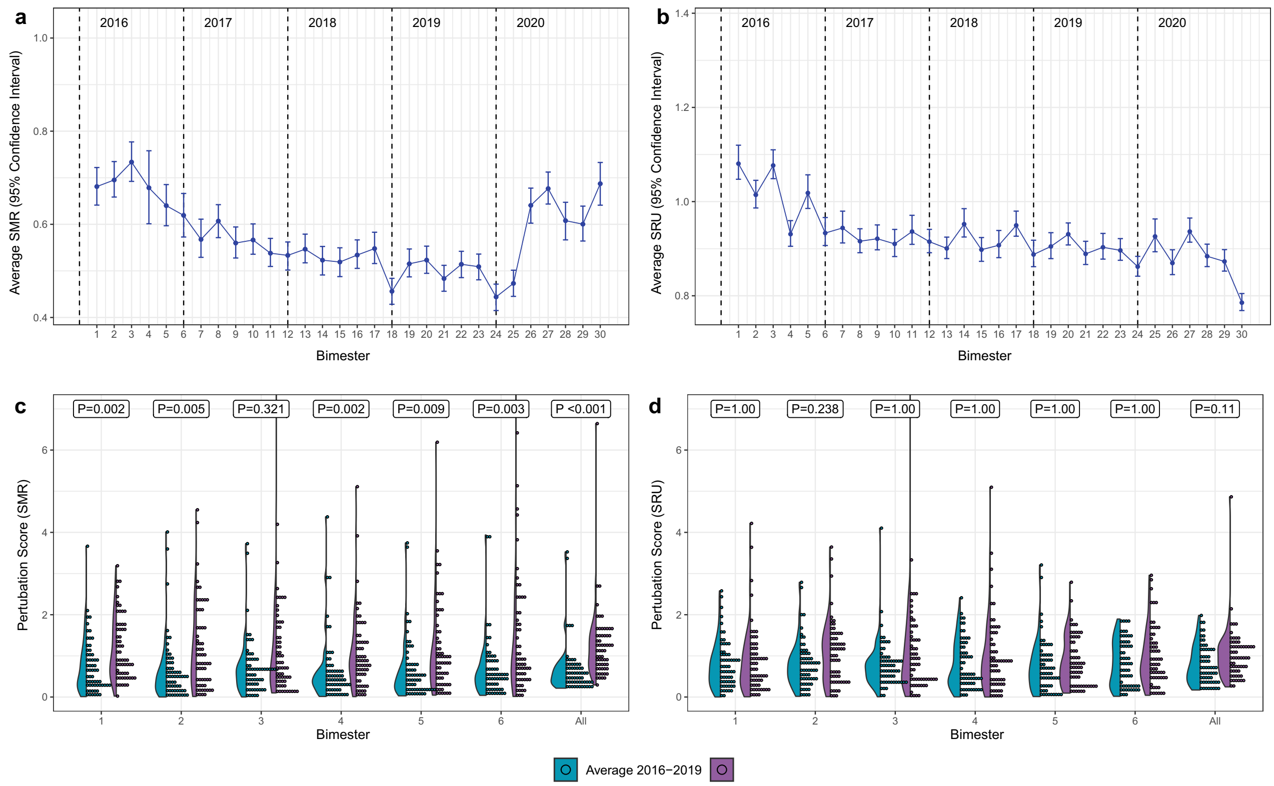

Fig. 4 Trends in SMR (**a**) and SRU (**b**) for 61 ICUs with data available from 2016 to 2020. Error bars represent 95% confidence intervals obtained from 1000 replications bootstrap. The slope of changes in SMR, but not for SRU, in 2020 is different for 2016–2019 (*p* value for Chow test < 0.001 and 0.113, respectively). Results of the perturbation analysis for SMR (**c**) and SRU (**d**) for values before 2020 (blue) and 2019–2019 (purple). Perturbation scores represents how relatively far SMR and SRU values were from to the baseline. A comparison between each bimester in 2020 and baseline, as well as an averaged comparison between 2020 and 16-2019 is shown. *p*-values for Mann–Whitney *U* test after Bonferroni correction are shown in boxes

Conclusion

Hospital outcomes of non-COVID-19 critically ill patients worsened during the pandemic in 2020, possibly resulting in an increased number of deaths in critically ill non-COVID patients. The indirect effects of the pandemic, including a disruption of the ICU performance, should be considered when measuring its toll on critically ill patients and healthcare systems.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-021-06528-6.

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Funding

FAB, JIS and MS are supported in part by individual research grants from CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) and FAPERJ (Fundação Carlos Chagas Filho de Amparo à Pesquisa do Rio de Janeiro). LSLB reports grant from CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior)—Finance Code 001.

Declarations

Conflict of interest

JIS and MS are founders of Epimed Monitor®, an electronic healthcare system used to collect data and track ICU quality metrics. FGZ has received grants for investigator-initiated studies from Ionis Pharmaceuticals (USA), Bactiguard (Sweden) and Brazilian Ministry of Health, none related to the scope of this study.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 5 June 2021 Accepted: 3 September 2021
Published online: 13 September 2021

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