Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHEST

Trends in Intensive Care Admissions and Outcomes of Stroke Patients Over 10 Years in Brazil

Impact of the COVID-19 Pandemic

Pedro Kurtz, MD, PhD; Leonardo S. L. Bastos, PhD; Fernando G. Zampieri, MD, PhD; Gabriel R. de Freitas, MD, PhD; Fernando A. Bozza, MD, PhD; Marcio Soares, MD, PhD; and Jorge I. F. Salluh, MD, PhD

BACKGROUND: The coronavirus 2019 (COVID-19) pandemic affected stroke care worldwide. Data from low- and middle-income countries are limited.

RESEARCH QUESTION: What was the impact of the pandemic in ICU admissions and outcomes of patients with stroke, in comparison with trends over the last 10 years?

STUDY DESIGN AND METHODS: Retrospective cohort study including prospectively collected data from 165 ICUs in Brazil between 2011 and 2020. We analyzed clinical characteristics and mortality over a period of 10 years and evaluated the impact of the pandemic on stroke outcomes, using the following approach: analyses of admissions for ischemic and hemorrhagic strokes and trends in in-hospital mortality over 10 years; analysis of variable life-adjusted display (VLAD) during 2020; and a mixed-effects multivariable logistic regression model.

RESULTS: A total of 17,115 stroke admissions were analyzed, from which 13,634 were ischemic and 3,481 were hemorrhagic. In-hospital mortality was lower after ischemic stroke as compared with hemorrhagic (9% vs 24%, respectively). Changes in VLAD across epidemiological weeks of 2020 showed that the rise in COVID-19 cases was accompanied by increased mortality, mainly after ischemic stroke. In logistic regression mixed models, mortality was higher in 2020 compared with 2019, 2018, and 2017 in patients with ischemic stroke, namely, in those without altered mental status. In hemorrhagic stroke, the increased mortality in 2020 was observed in patients 50 years of age or younger, as compared with 2019.

INTERPRETATION: Hospital outcomes of stroke admissions worsened during the COVID-19 pandemic, interrupting a trend of improvements in survival rates over 10 years. This effect was more pronounced during the surge of COVID-19 ICU admissions affecting predominantly patients with ischemic stroke without coma, and young patients with hemorrhagic stroke.

CHEST 2023; 163(3):543-553

KEY WORDS: coronavirus 2019; COVID-19 pandemic; hemorrhagic; ischemic; outcomes; stroke

FOR EDITORIAL COMMENT, SEE PAGE 471

ABBREVIATIONS: IQR = interquartile range; SAPS 3 = Simplified Acute Physiological Score 3; VLAD = variable life-adjusted display

AFFILIATIONS: From the D'Or Institute for Research and Education (IDOR) (P. K., G. R. de F., F. A. B., M. S., and J. I. F. S.), Rio de Janeiro, RJ, Brazil; the Hospital Copa Star (P. K.), Rio de Janeiro, RJ, Brazil; Paulo Niemeyer State Brain Institute (IECPN) (P. K.), Rio de Janeiro, RJ, Brazil; the Department of Industrial Engineering (DEI) (L. S. L. B.), Pontifical Catholic University of Rio de Janeiro (PUC-Rio), Rio de Janeiro, RJ, Brazil; the Intensive Care Unit (F. G. Z.), Hospital Vila Nova Star, São Paulo, Brazil; the Department of Critical Care Medicine (F. G. Z.), Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada; the Department of Neurology (G. R. de F.), Universidade Federal Fluminense, Rio de Janeiro, Brazil; the National Institute of Infectious Disease Evandro Chagas (INI) (F. A. B.), Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, RJ, Brazil; and the Postgraduate Program of Internal Medicine (J. I. F. S.), Federal University of Rio de Janeiro, (UFRJ), Rio de Janeiro, Brazil.

CORRESPONDENCE TO: Pedro Kurtz, MD, PhD; email: kurtzpedro@mac.com

DOI: https://doi.org/10.1016/j.chest.2022.10.033

Take-home Points

Study Question: Did the pandemic impact ICU admissions and outcomes of patients with stroke, in comparison with historical trends?

Results: The rise in COVID-19 cases was followed by increased mortality of stroke patients, mainly after ischemic stroke. Adjusted models showed increased mortality in 2020 compared with 2019, 2018, and 2017, in patients with ischemic stroke, especially in those without altered mental status. After hemorrhagic stroke, increased mortality in 2020 was observed in patients 50 years of age or younger, as compared with 2019.

Interpretation: The COVID-19 pandemic in Brazil during 2020 was associated with an overall decrease in ICU admissions for stroke and disrupted the trends of improvement in outcomes of those patients observed over a decade. The effect on increased mortality in 2020 was observed across all ages in noncomatose ischemic stroke patients but only in those younger than 50 years with hemorrhagic stroke.

Large national registries and stroke care networks from high-income countries reported a reduction in hospitalizations for stroke and increased mortality during the COVID-19 pandemic in 2020.[1,2] Data also suggest an increase in severity in hospitalized patients with stroke, including a higher rate of large vessel occlusions and a more frequent indication of mechanical thrombectomy.[3] The reasons for these observed patterns remain unclear but potentially include limited access to emergency care during mobility restrictions and lockdowns, increased prothrombotic risk factors caused by viral infection, organizational changes in stroke care, and reduced access to the stroke unit and ICU beds.[4-7] However, data on this topic from large multicenter studies representing low and middle-income countries are still scarce.

We sought to analyze trends in crude and risk-adjusted mortality for stroke in a 10-year cohort of ICU patients in Brazil. We hypothesized that the pandemic would be associated with worse outcomes and impact the secular trend of ICU hospitalizations for stroke.

Study Design and Methods

Design

A retrospective cohort study was performed in 165 ICUs from 45 hospitals of an integrated private hospital network (Rede D'Or São Luiz). The use of fully anonymized cohort data for research purposes has been approved by the Local Ethics Committee and the Brazilian National Ethics Committee (CAAE: 17079119.7.0000.5249) without the need for informed consent. All data were anonymized previously for extraction and analysis.

Population

Patients admitted to an ICU with a main diagnosis of stroke from January 1, 2011, until December 31, 2020 were studied. 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[8]). Information collected included demographic data (age, sex at birth), comorbidities, performance status on the week before 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),[9] admission stroke type (ischemic vs hemorrhagic), Simplified Acute Physiological Score 3 (SAPS 3), the presence of altered mental status at admission (defined as the presence of delirium, stupor, or coma), neurological deficits, use of IV thrombolysis, the presence of cerebral mass effect in neuroimaging studies, indication of intracranial pressure monitoring or neurosurgery, the use of mechanical ventilation, ICU and hospital length-of-stay, and ICU and hospital mortality.

Primary Outcome

The primary outcome was in-hospital mortality from any cause of patients admitted to the ICU with ischemic or hemorrhagic stroke. Adjusted mortality rates in 2020 were compared with those in previous years.

Missing Data Policy

We excluded patients with missing hospital outcomes for the main analysis. No imputation of data was performed. In multivariable models, individuals with missing data on predictor variables were excluded.

Statistical Analysis

We used standard descriptive methods to report the main patients' features over the 10-year period of analysis. We assessed the association between admission year and outcome, using the following approach: An unadjusted exploratory analysis showing characteristics of the overall cohort and patients with each stroke type (ischemic or hemorrhagic) was performed, including premorbid conditions, admission severity measures, neurological status in the first 24 hours of admission, length of stay, and in-hospital mortality. We also performed an exploratory analysis to evaluate trends in characteristics and outcomes over the 10 years studied.

A subsequent analysis was performed with the trends in variable life-adjusted display (VLAD) for ischemic and hemorrhagic stroke patients in 2020, coupled with the number of COVID-19 admissions according to admission week during the same year. VLAD is an accumulated sum of adjusted mortality risks. In brief, for each surviving patient, a value equal to the predicted probability of dying by SAPS 3 score was added,[10,11] 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. VLAD was designed to allow frequent assessment of the performance of a unit over time and has been shown to be sensitive to changes in performance.[12]

Finally, we developed mixed-effects regression models to perform an adjusted analysis of in-hospital mortality risk from 2020 compared with previous years. We included age, altered mental status, admission year, the interaction of age × admission year, and the interaction of altered mental status × admission year as fixed effects, a random intercept for unit, and random slopes for the year of admission. Models were developed separately for patients with ischemic and hemorrhagic stroke. These regression models were designed to account for sites (random intercept in hospitals) and either age or stroke severity, comparing 2020 with all other years in the cohort at the patient level.

We performed all analyses in R project version 4.0.2 with packages lme4[13] and emmeans.[14] We considered a *P* lower than .05 significant in the mixed-model results, with comparisons of mortality in 2020 in relation to previous years, and reported adjusted ORs and CIs of these pairwise comparisons.

Results

Overall, 17,115 stroke admissions were analyzed, from which 13,634 (79.7%) were ischemic and 3,481 (20.3%) were hemorrhagic. A summary of stroke patients' characteristics is shown in Table 1, including comorbidities, acute systemic and neurologic severity, and hospital outcomes, stratified by ischemic and hemorrhagic stroke. A similar description according to admission year is shown in e-Table 1. The median age was 70 (interquartile range [IQR], 55-81) years, 32% of patients had moderate to severe performance status impairment before the stroke, median SAPS-3 at admission was 47 (IQR 40-53) points, and 9% were mechanically ventilated on the first day of ICU admission. Five thousand three hundred five (31%) had altered mental status, and 32% had a focal neurological deficit. Seven hundred forty-nine (4%) had brain mass effect on neuroimaging, 3% received intracranial pressure monitoring, and 3% underwent neurosurgery on the first day of admission. Hospital length of stay was 8 (IQR, 4-16) days, and in-hospital mortality was 12%. Ischemic etiology was four times

TABLE 1] Characteristics of Included Patients With Ischemic or Hemorrhagic Stroke

Characteristic	No.	Overall, N = 17,115[a]	Hemorrhagic, N = 3,481[a]	Ischemic, N = 13,634[a]
Age, y	17,115	70 (55-81)	65 (51-79)	71 (57-81)
Female, No. (%)	17,115	9,089 (53)	1,862 (53)	7,227 (53)
Charlson comorbidity index, points	17,070	1 (0-2)	0 (0-2)	1 (0-2)
Performance impairment (ECOG), No. (%)	16,846			
None/minor		11,510 (68)	2,493 (73)	9,017 (67)
Moderate		4,009 (24)	609 (18)	3,400 (25)
Severe		1,327 (7.9)	321 (9.4)	1,006 (7.5)
MFI, points	14,586	2 (1-3)	2 (1-2)	2 (1-3)
SAPS 3, points	17,115	47 (40-53)	47 (38-56)	46 (41-52)
SOFA score ≥ 1, No. (%)	14,821	7,279 (49)	1,744 (58)	5,535 (47)
MV on first day, No. (%)	17,095	1,576 (9.2)	876 (25)	700 (5.1)
Altered mental status, No. (%)	17,081	5,305 (31)	1,364 (39)	3,941 (29)
Neurological deficit, No. (%)	17,081	5,459 (32)	793 (23)	4,666 (34)
Glasgow ≤ 13, No. (%)	15,409	3,018 (20)	962 (31)	2,056 (17)
Brain mass effect, No. (%)	17,095	749 (4.4)	527 (15)	222 (1.6)
ICP monitoring, No. (%)	16,956	458 (2.7	337 (9.8)	121 (0.9)
Thrombolytics, No. (%)	16,956	386 (2.3)	…	386 (2.8)
Neurosurgery, No. (%)	17,081	460 (2.7)	201 (5.8)	259 (1.9)
Tracheostomy, No. (%)	16,956	644 (3.8)	305 (8.8)	339 (2.5)
ICU LOS, d	17,115	3 (2-7)	5 (2-11)	3 (2-6)
Hospital LOS, d	17,115	8 (4-16)	10 (5-22)	7 (4-14)
In-hospital mortality, No. (%)	17,115	2,109 (12)	837 (24)	1,272 (9.3)

ECOG = Eastern Cooperative Oncology Group; Glasgow = Glasgow coma score; ICP = intracranial pressure; LOS = length of stay; MFI = modified fragility index; MV = mechanical ventilation; SAPS = Simplified Acute Physiology Score; SOFA = sequential organ failure assessment.
[a]Continuous variables are expressed in median (25-75 interquartile range).

more frequent than hemorrhagic stroke during the study period. In general, patients with ischemic stroke were older (71 [57-81] years vs 65 [51-79] years) and were less likely to be mechanically ventilated at admission (5% vs 25%) or to require neurosurgery (2% vs 6%) as compared with those with hemorrhagic stroke. Hospital length of stay was shorter (7 [4-14] days vs 10 [5-22] days), and crude in-hospital mortality was lower after ischemic stroke compared with hemorrhagic (9% vs 24%, respectively).

From 2011 to 2015, the number of patients admitted to the ICU with stroke per hospital in the network increased from 43 to 59 and remained relatively stable from 2015 until 2019—59 per hospital in both years (e-Table 1). The trends in absolute numbers are shown in Figure 1 and e-Figures 1, 2, and 3. This was reversed in 2020, when a sharp reduction in the absolute number of patients (e-Figs 2, 3) with ischemic (from 1,827 in 2019 to 1,505 in 2020—18% reduction) and hemorrhagic stroke (from 397 in 2019 to 294 in 2020—26% reduction) was observed (Fig 1A and 1B). During the same period, we observed a trend toward reduced unadjusted in-hospital mortality rates for patients with ischemic stroke until 2019 (from 12% in 2014 to 7.2% in 2019), which was also interrupted in 2020, when an increase in mortality was demonstrated (from 7.2% in 2019 to 9.1% in 2020—26% increase [Fig 1C]). No such trend over the years or any evident change in 2020 was found in patients with hemorrhagic stroke (Fig 1D). We analyzed age, SAPS-3, mechanical ventilation rates, and altered mental status at admission over the 10 years evaluated and found no

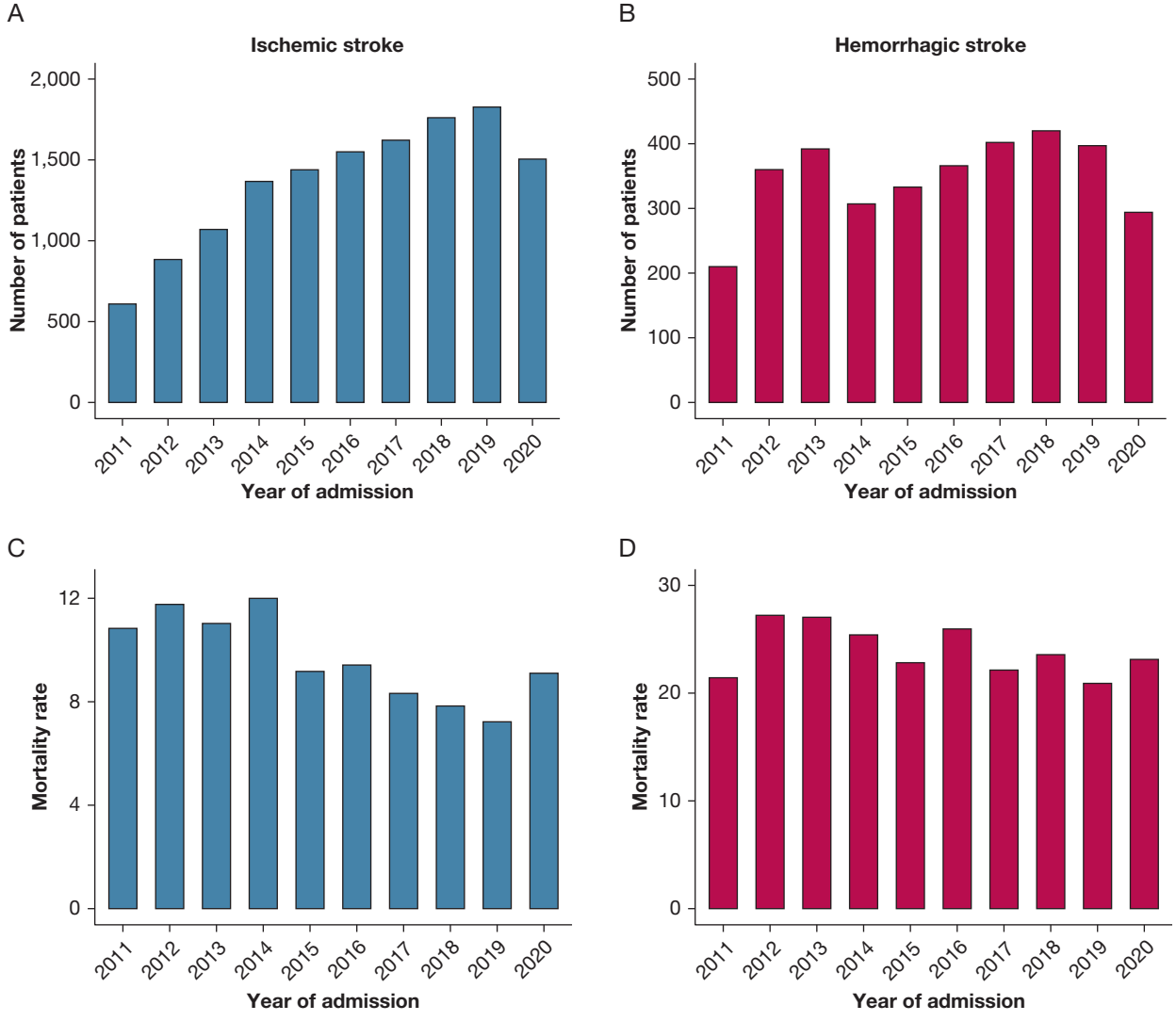

Figure 1 – *Trends in number of admissions and in-hospital mortality for patients with ischemic (A and C) and hemorrhagic stroke (B and D).*

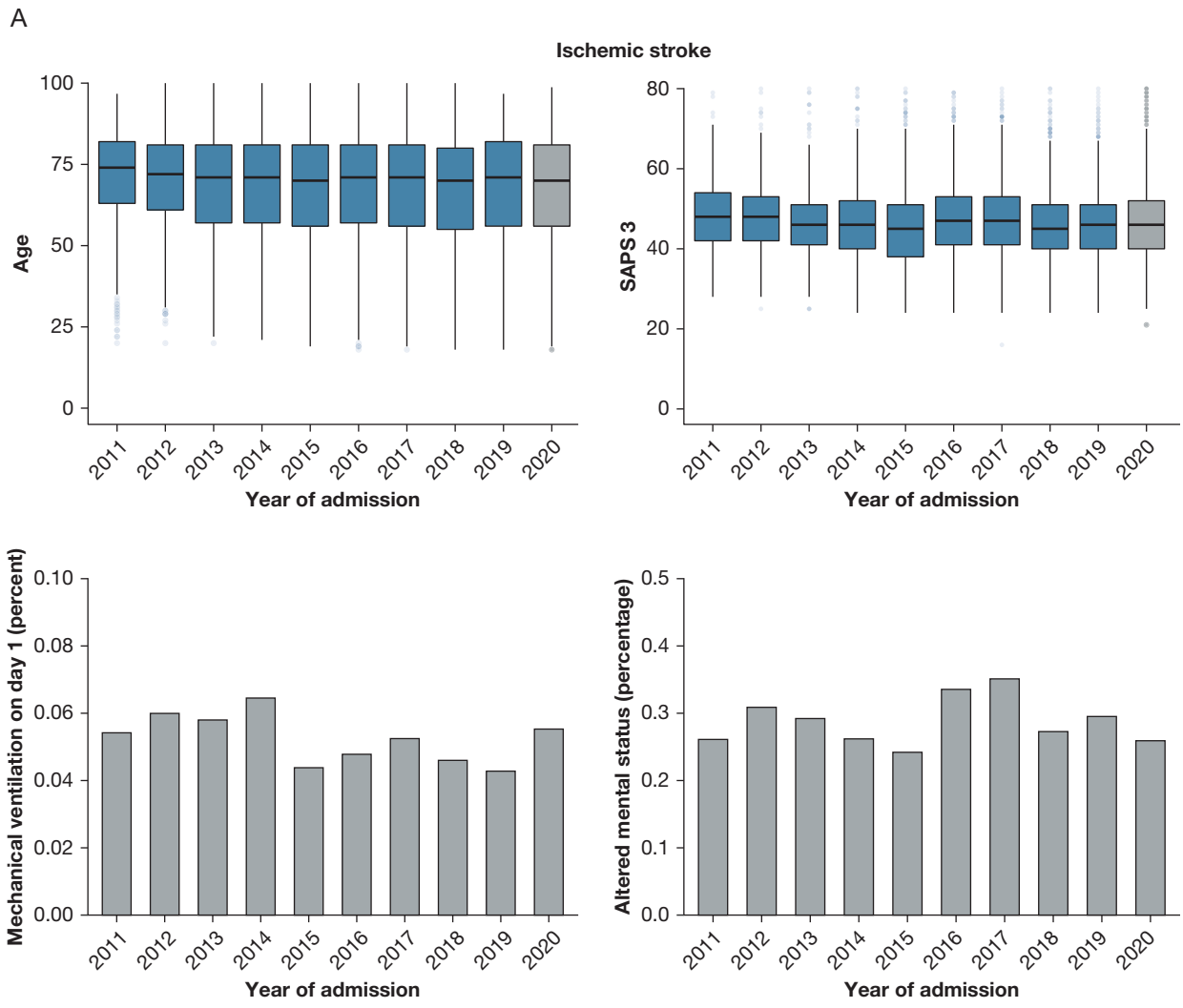

Figure 2 – *Trends in systemic and neurological severity measures on admission for patients with ischemic (A) and hemorrhagic stroke (B).*

clear trend toward increased severity of stroke patients admitted in 2020 compared with previous years (Fig 2A, 2B).

Changes in VLAD for stroke patients across epidemiological weeks of 2020 are shown in Figure 3A and stratified by ischemic and hemorrhagic in Figure 3B. The number of COVID-19 cases admitted to the participating units in the corresponding weeks is shown in Figure 3C. The rise in COVID-19 cases after the 11th week in 2020 was accompanied by a decrease in VLAD, mainly in patients with ischemic stroke. Similarly, the reduction of COVID-19 admissions after the peak in week 17 was followed by an increase in VLAD, again, namely, in ischemic stroke patients.

In logistic regression mixed models, the OR for mortality in ischemic stroke was higher in 2020 vs 2019, 2018, and 2017, but similar to years 2016 through 2011 (except for those older than 80 and 90 years) (Fig 4, e-Table 2). In patients with hemorrhagic stroke, the OR for mortality was higher in 2020 only in those younger than 50 years, compared with 2019 (Fig 5 and e-Table 3). When we stratified patients according to the presence of altered mental status on admission, the OR for mortality was higher in 2020 vs 2019, 2018, and 2017 only in those with ischemic stroke and with preserved mental status at admission (e-Tables 4, 5, Fig 6). Model results are detailed in e-Tables 6, 7, 8, and 9.

Discussion

Our study found that the COVID-19 pandemic in Brazil during 2020 was associated with an overall decrease in the total number of ICU admissions with stroke, with a 19% reduction from 2019 to 2020. In addition, it

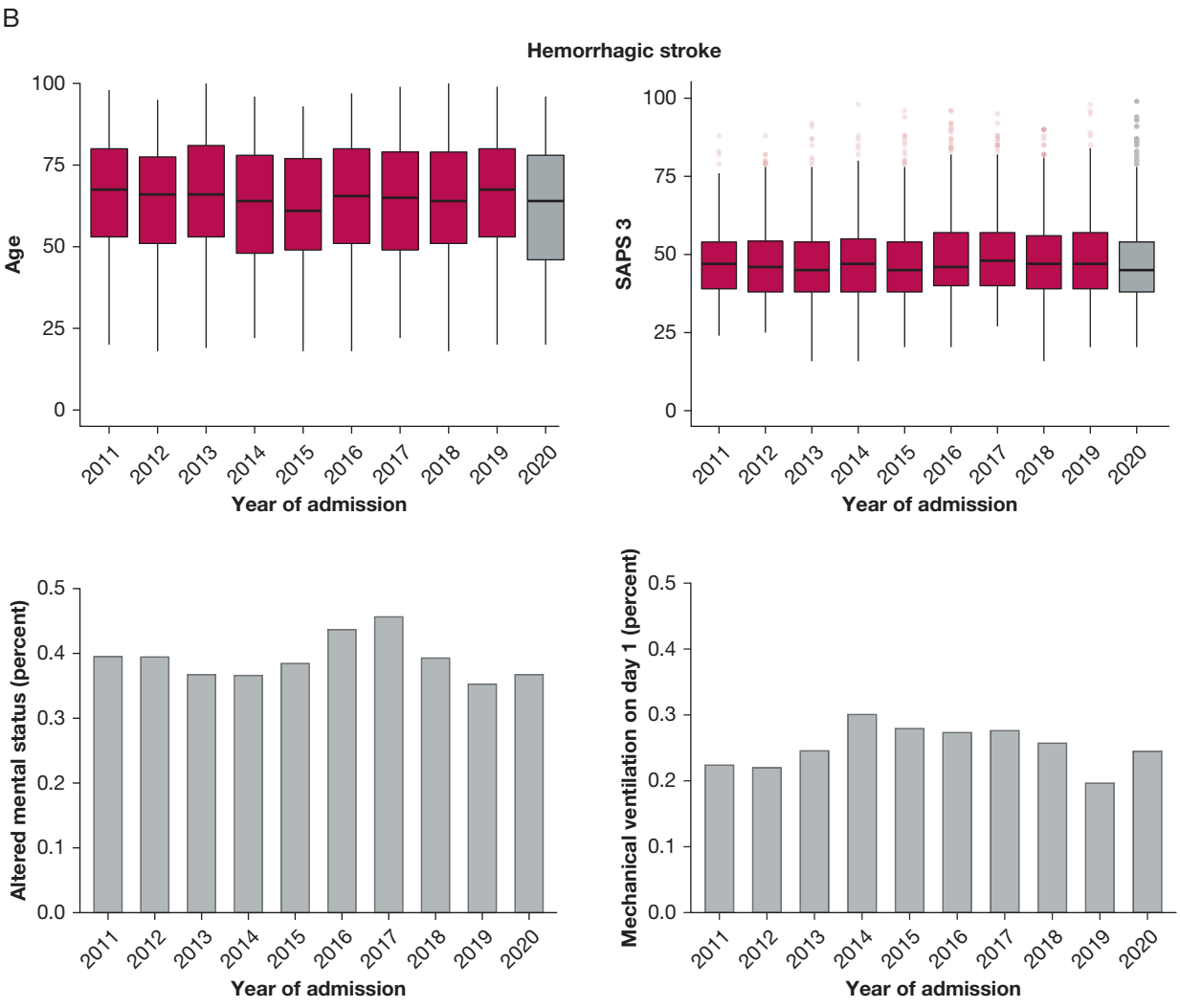

Figure 2 – *Continued*

disrupted the trends of improvement in outcomes of patients with ischemic stroke observed over a decade. The effect of increased mortality in 2020 was observed across all ages in ischemic stroke but only in those younger than 50 years with hemorrhagic stroke. Moreover, we demonstrated through the VLAD that surges in hospital admissions for COVID-19 were followed by worsening outcomes, especially among patients with ischemic stroke.

Our findings corroborate data from other cohorts that showed reductions in hospitalizations for ischemic stroke during the pandemic[1,15,16] In some countries, this was associated with severe movement restrictions and lockdowns. This was not the reality in Brazil,[17] which suggests that other causes drove these reductions. Another potential explanation would be the limited access to ICU beds, occupied by patients with COVID-19. However, previously published data from our group showed that, despite the severe collapse of the public health care system,[18] the private hospital network that contributed to this study underwent preparedness with increases in ICU bed and resource availability, which resulted in almost unrestricted access to ICU care.[19] Thus, unmeasured factors are probably related to the observed reduction in hospitalizations for stroke, such as the fear of being infected with COVID-19 and the reduced awareness of signs and symptoms of mild stroke, as well as changes in workplace relations. Interestingly, ICU admissions for hemorrhagic stroke were not reduced during the pandemic as compared with previous years.

In contrast to previous reports, we were not able to demonstrate a higher severity of stroke in 2020, as measured by the need for mechanical ventilation or

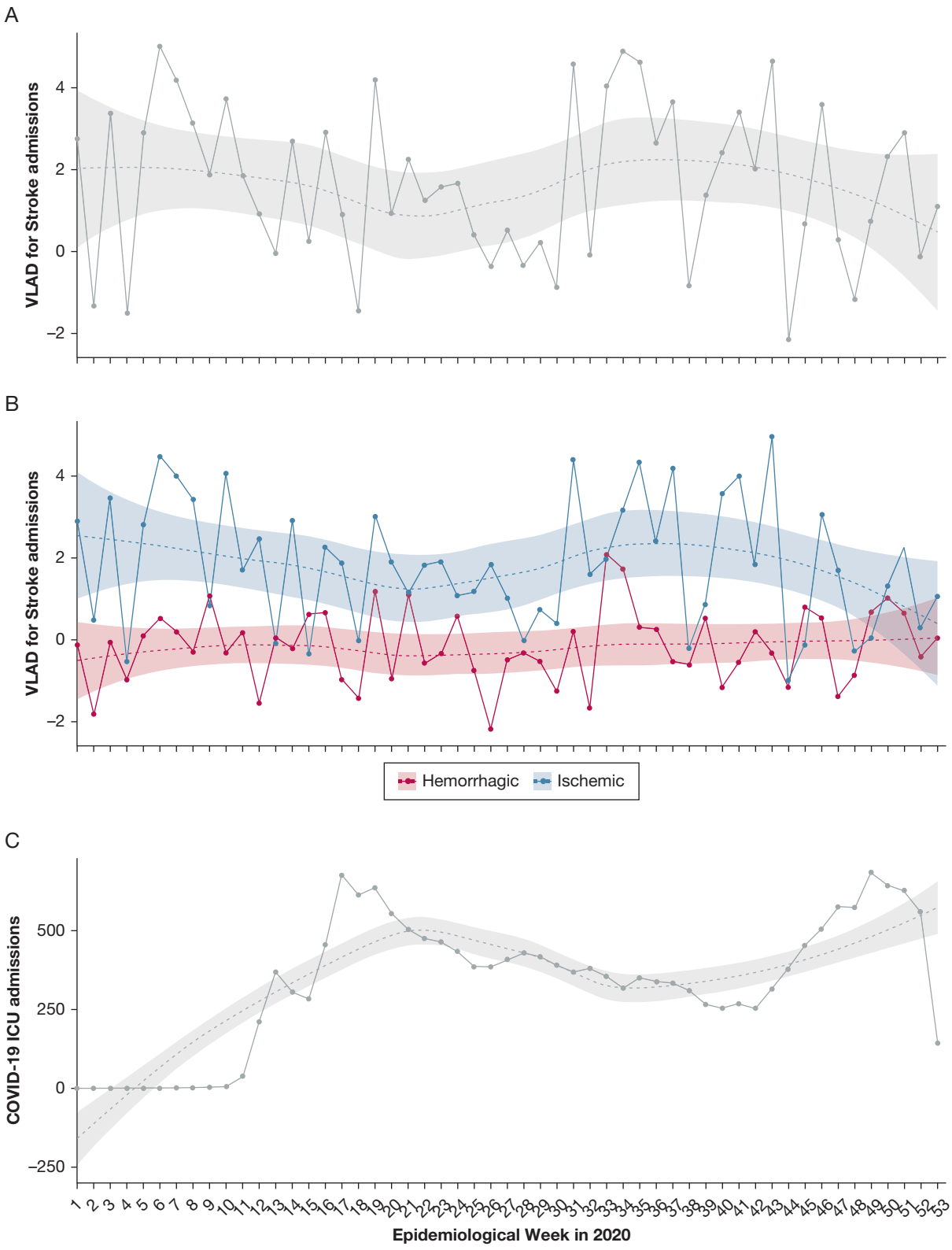

Figure 3 – *(A) Weekly cumulative Variable-adjusted life display (VLAD) for all stroke patients during 2020, shown per week. Increases in VLAD suggest a lower-than-expected mortality, whereas downward shifts suggest the inverse trend. (B) Weekly cumulative VLAD, stratified by ischemic and hemorrhagic stroke. (C) Number of COVID-19 cases admitted to the participating ICUs according to the epidemiological weeks of 2020. Solid lines represent absolute values for VLAD (A and B) or n of COVID-19 admissions (C) per epidemiological week. Dotted lines and shaded areas represent smoothed averages and 95% CI.*

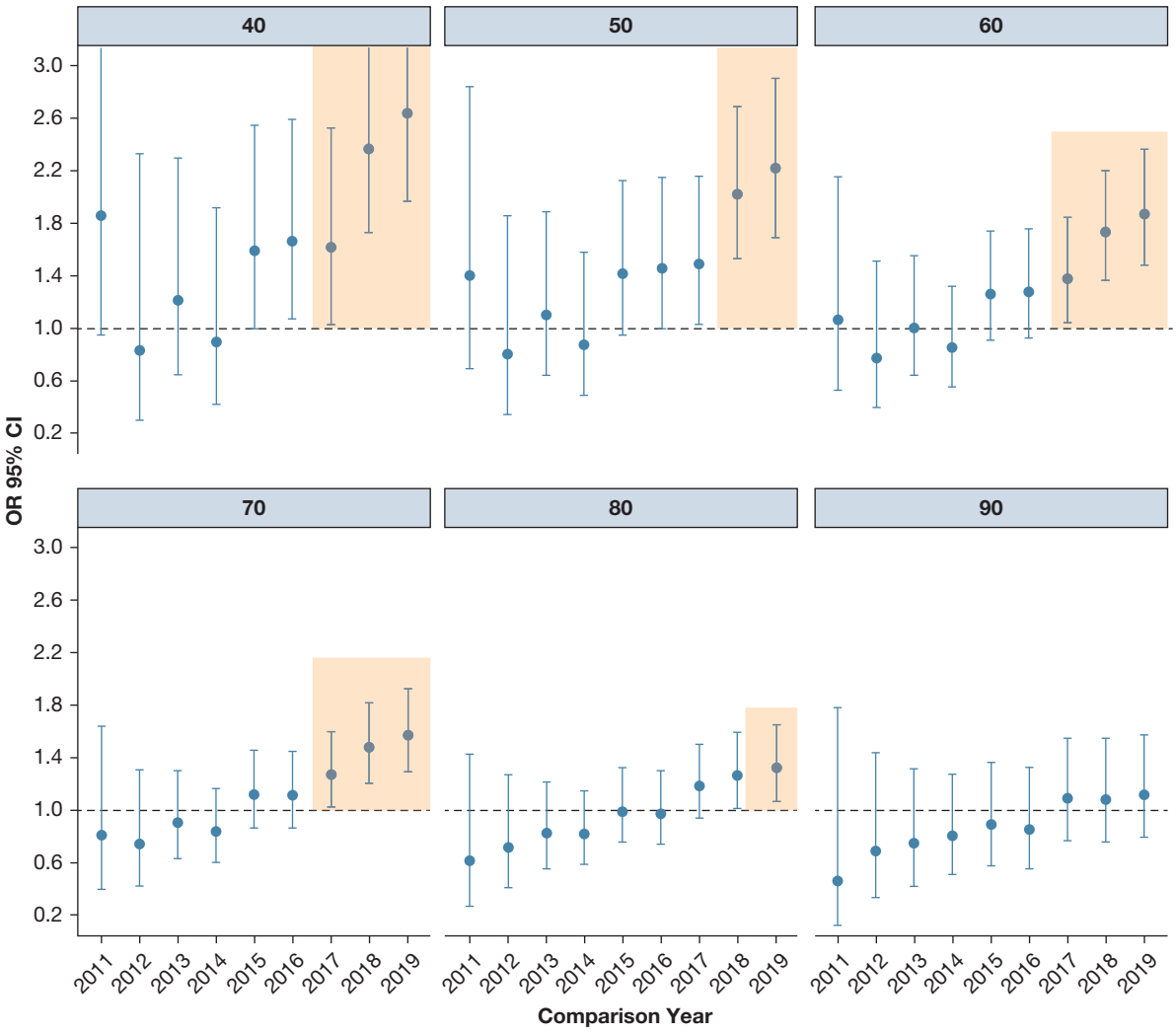

Figure 4 – *OR and their corresponding 95% CI for mortality in 2020 vs other years (references in x-axis) for fixed age (panels) obtained through marginal means, in patients with ischemic stroke (n = 13,634). The dashed line marks OR = 1.00.*

presentation with altered mental status. Other studies evaluated ischemic stroke severity using more specific measures, such as increased National Institutes of Health Stroke Scale or more frequent need of mechanical thrombectomy for large vessel occlusion, which were unavailable in our database.[1,3,20] In patients with hemorrhagic stroke, data are also conflicting. As opposed to our findings of no changes in either volume of hospitalizations or severity of stroke during the pandemic, previous studies have shown increases in hemorrhagic stroke rates and milder clinical presentations,[21,22] whereas a population-based study in Brazil also found no differences during the pandemic compared with previous years.[20]

Despite unchanged neurological severity for both ischemic and hemorrhagic stroke hospitalizations in 2020 as compared with previous years, our study found an interruption in the trend of improved hospital outcomes observed from 2011 to 2019. For ischemic stroke, adjusted mortality rates in 2020 were worse than those observed in the previous 3 years. This effect was seen across all age groups up to 80 years. For hemorrhagic stroke, in-hospital mortality increased in 2020 only in those younger than 50 years. Moreover, when analyzing patients with or without altered mental status, comparative mortality increases during the pandemic were seen only in those admitted for ischemic stroke with preserved consciousness. These data suggest that the impact of the pandemic on hospital outcomes was more pronounced among patients with less severe stroke. We can hypothesize that several unmeasured factors such as late hospital referral, disruption of stroke care organization, increased ICU strain, and reduced

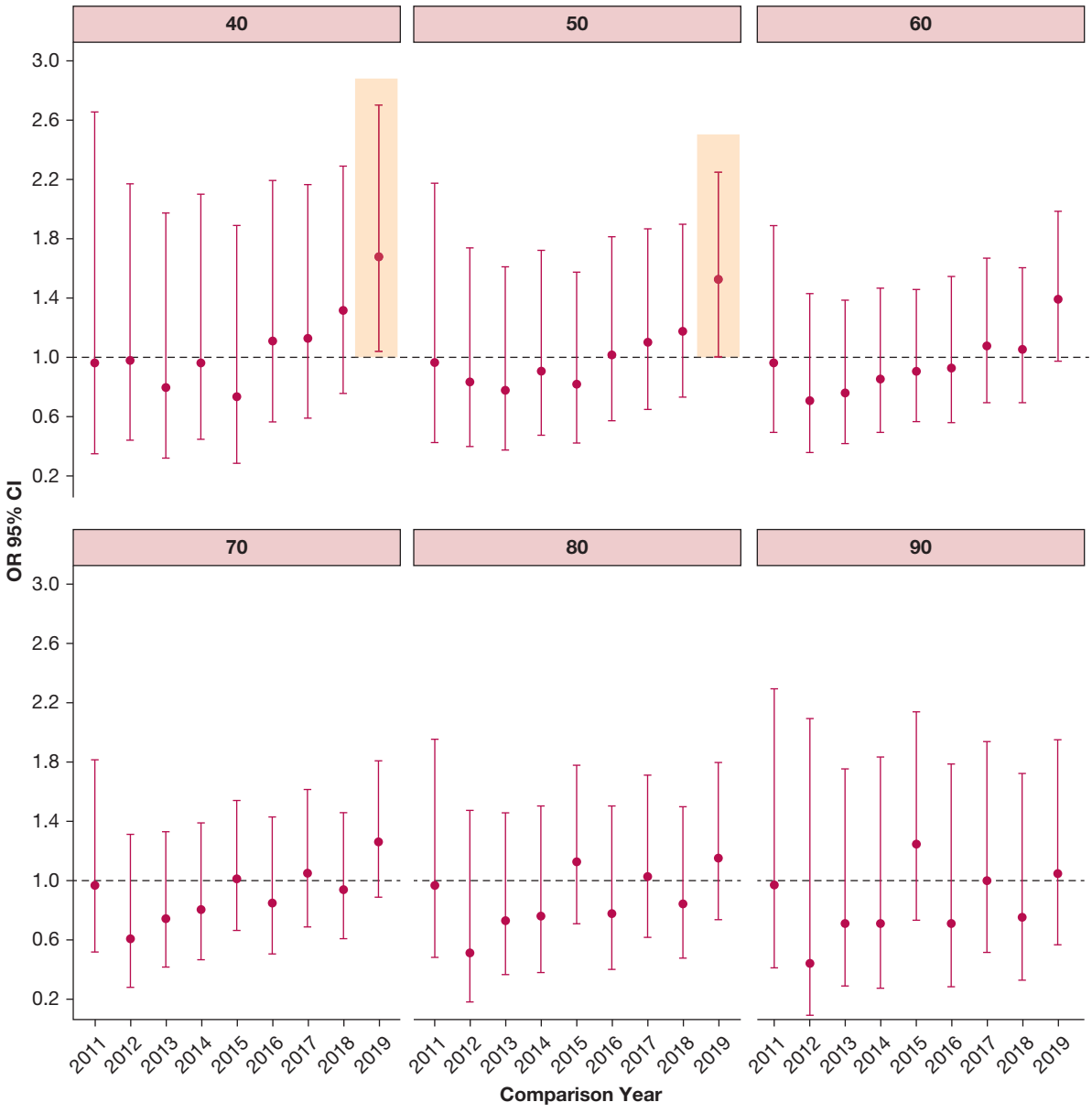

Figure 5 – *OR and their corresponding 95% CIs for mortality in 2020 vs other years (references in x-axis) for fixed age (panels) obtained through marginal means, in patients with hemorrhagic stroke (n = 3,481). The dashed line marks OR = 1.00.*

adherence to processes of care and clinical stroke protocols may have been associated with increased morbidity and mortality.[23] Regardless of the mechanistic pathway, it is reasonable to assume that COVID-19 impacted the outcome of critically ill stroke patients, perhaps resulting in excess deaths. Therefore, solely considering COVID-19 admissions as a measurement of the impact of the pandemic may underestimate its effect on patients with a different diagnosis.

Our study has some limitations. First, our database did not provide stroke-specific data to evaluate neurological severity and interventions, such as reperfusion therapies implemented, onset-to-treatment, and door-to-imaging times. Second, no postdischarge functional evaluation was performed, which is a commonly used outcome after stroke. Third, the VLAD analysis used SAPS 3 to calculate the probability of dying in the hospital. Although validation of this measure for stroke are limited, we did not have other disease-specific scales available. In addition, we acknowledge that our results were sensitive to corrections for multiple hypotheses and therefore should be seen as exploratory. Finally, we were not able to analyze structure and organizational hospital

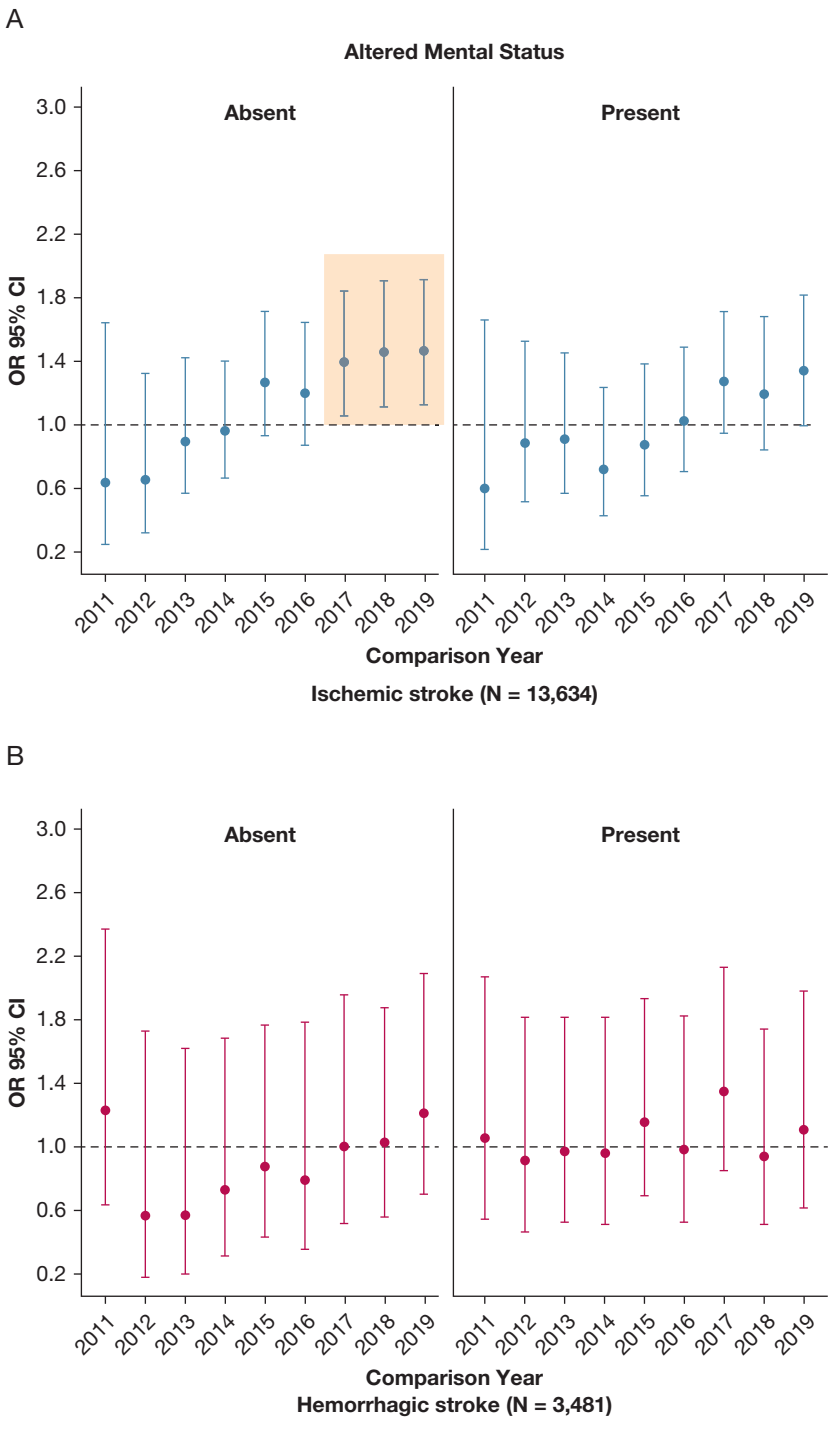

Figure 6 – *OR and their corresponding 95% CIs for mortality in 2020 vs other years (references in x-axis) for the presence or absence of altered mental status obtained through marginal means, in patients with ischemic (A, n = 13,604) and hemorrhagic stroke (b, n = 3,477). The dashed line marks OR = 1.00.*

data that could contribute to a better understanding of the disruption caused by the pandemic and the potential consequences in patient outcomes.

Interpretation

Our study found a reduction in ICU admissions with stroke during the first year of the pandemic in the largest hospital network in Latin America. We also demonstrated an interruption in the trend of improved outcomes observed in the past years up to 2019, with an increase in adjusted mortality in 2020. This effect was more pronounced during the surge of ICU admissions for COVID-19 and affected predominantly patients with ischemic stroke without coma, and young patients with hemorrhagic stroke.

Funding/Support

This study was supported by the National Council for Scientific and Technological Development (CNPq), the Coordination for the Improvement of Higher Education Personnel (CAPES)—Finance Code 001, Carlos Chagas Filho Foundation for Research Support of the State of Rio de Janeiro (FAPERJ), the Pontifical Catholic University of Rio de Janeiro, and by departmental funds from the D'Or Institute for Research and Education. Authors were not paid to contribute to this manuscript. Authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication. The funding sources had no role in the analysis, interpretation of results, or drafting of the manuscript.

Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following: M. S. and J. I. F. S. are founders and equity shareholders of Epimed Solutions, which commercializes the Epimed Monitor System, a cloud-based software for ICU management and benchmarking. None declared (P. K., L. S. L. B., F. G. Z., G. R. de F., F. A. B.).

Acknowledgments

Author contributions: P. K. is the full guarantor of this manuscript. F. A. B., P. K., L. S. L. B., M. S., and J. I. F. S. contributed to the study conception and design, and data interpretation. L. S. L. B., P. K., and F. G. Z. performed data processing and statistical analysis. P. K. and J. I. F. S. drafted the first version of the manuscript. F. A. B., M. S., and J. I. F. S. supervised the study. All authors had full access to data, participated in data interpretation, revised the manuscript, and approved the final version of the manuscript.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Availability of data and material: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Additional information: The e-Figures and e-Tables are available online under "Supplementary Data."

References

1. Richter D, Eyding J, Weber R, et al. Analysis of nationwide stroke patient care in times of COVID-19 pandemic in Germany. *Stroke*. 2021;52(2):716-721.
2. Douiri A, Muruet W, Bhalla A, et al. Stroke care in the United Kingdom during the COVID-19 pandemic. *Stroke*. 2021;52(6):2125-2133.
3. Ortega-Gutierrez S, Farooqui M, Zha A, et al. Decline in mild stroke presentations and intravenous thrombolysis during the COVID-19 pandemic: The Society of Vascular and Interventional Neurology multicenter collaboration. *Clin Neurol Neurosurg*. 2021;201:106436.
4. Sharma R, Kuohn LR, Weinberger DM, et al. Excess cerebrovascular mortality in the United States during the COVID-19 pandemic. *Stroke*. 2021;52(2):563-572.
5. Ghoreishi A, Arsang-Jang S, Sabaa-Ayoun Z, et al. Stroke care trends during COVID-19 pandemic in Zanjan Province, Iran: from the CASCADE Initiative: statistical analysis plan and preliminary results. *J Stroke Cerebrovasc Dis*. 2020;29(12):105321.
6. Bahouth MN, Venkatesan A. Acute viral illnesses and ischemic stroke: pathophysiological considerations in the era of the COVID-19 pandemic. *Stroke*. 2021;52(5):1885-1894.
7. Elkind MSV, Boehme AK, Smith CJ, Meisel A, Buckwalter MS. Infection as a stroke risk factor and determinant of outcome after stroke. *Stroke*. 2020;51(10):3156-3168.
8. Zampieri FG, Soares M, Borges LP, Salluh JIF, Ranzani OT. The Epimed monitor ICU database(R): a cloud-based national registry for adult intensive care unit patients in Brazil. *Rev Bras Ter Intensiva*. 2017;29(4):418-426.
9. Zampieri FG, Bozza FA, Moralez GM, et al. The effects of performance status one week before hospital admission on the outcomes of critically ill patients. *Intensive Care Med*. 2017;43(1):39-47.
10. Nassar AP, Malbouisson LM, Moreno R. Evaluation of simplified acute physiology score 3 performance: a systematic review of external validation studies. *Crit Care*. 2014;18(3):R117.
11. Moreno RP, Metnitz PG, Almeida E, et al. SAPS 3: from evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med*. 2005;31(10):1345-1355.
12. Lovegrove J, Valencia O, Treasure T, Sherlaw-Johnson C, Gallivan S. Monitoring the results of cardiac surgery by variable life-adjusted display. *Lancet*. 1997;350(9085):1128-1130.
13. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Statistical Software*. 2015;67(1):1-48.
14. emmeans: Estimated Marginal Means, aka Least-Squares Means. [computer program]. Version R package version 1.6.0.
15. Pujol-Lereis VA, Flores A, Barboza MA, et al. COVID-19 lockdown effects on acute stroke care in Latin America. *J Stroke Cerebrovasc Dis*. 2021;30(9):105985.
16. Mariet AS, Giroud M, Benzenine E, et al. Hospitalizations for stroke in France during the COVID-19 pandemic before, during, and after the national lockdown. *Stroke*. 2021;52(4):1362-1369.
17. Nicolelis MAL, Raimundo RLG, Peixoto PS, Andreazzi CS. The impact of super-spreader cities, highways, and intensive care availability in the early stages of the COVID-19 epidemic in Brazil. *Sci Rep*. 2021;11(1):13001.
18. Ranzani OT, Bastos LSL, Gelli JGM, et al. Characterisation of the first 250,000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. *Lancet Respir Med*. 2021;9(4):407-418.
19. Kurtz P, Bastos LSL, Dantas LF, et al. Evolving changes in mortality of 13,301 critically ill adult patients with COVID-19 over 8 months. *Intensive Care Med*. 2021;47(5):538-548.
20. Diegoli H, Magalhaes PSC, Martins SCO, et al. Decrease in hospital admissions for transient ischemic attack, mild, and moderate stroke during the COVID-19 era. *Stroke*. 2020;51(8):2315-2321.
21. You Y, Niu Y, Sun F, et al. Impact of COVID-19 pandemic on haemorrhagic stroke admissions: a systematic review and meta-analysis. *BMJ Open*. 2021;11(12):e050559.
22. Chen Y, Xia F, Li Y, et al. Changes in characteristics, treatment and outcome in patients with hemorrhagic stroke during COVID-19. *J Stroke Cerebrovasc Dis*. 2021;30(3):105536.
23. Logroscino G, Beghi E. Stroke epidemiology and COVID-19 pandemic. *Curr Opin Neurol*. 2021;34(1):3-10.