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LETTER

Variants of concern and clinical outcomes in critically ill COVID-19 patients

The DP-EFFECT-BRAZIL investigators*

Dear Editor,

The emergence of variants of concern (VOC), particularly their virulence and ability to evade the immune system, has challenged intensive care units (ICUs) managing patients with coronavirus disease 2019 (COVID-19) [1]. Gamma and Delta VOC have been associated with increased severity in critically ill [2]. Although data suggest that the Omicron VOC is associated with milder disease and fewer hospitalizations, unchanged ICU mortality has been reported [1, 3, 4]. We aimed to define the clinical profiles of ICU COVID-19-patients during the Omicron wave and compare their clinical characteristics and outcomes to those from previous periods.

We evaluated a multicenter cohort of COVID-19 patients whose diagnosis was confirmed by real-time polymerase chain reaction (RT-PCR) and admitted to 231 Brazilian ICUs from February 27th, 2020 to March 29th, 2022. Assessing genomic data, we defined patients from three time periods: epoch 1 (Nonvariant VOC dominance), epoch 2 (Gamma/Delta VOC dominance), and epoch 3 (Omicron VOC dominance) [5] (Fig. 1A). We evaluated the association of epoch of admission (exposure of interest) with a 60-day in-hospital mortality (primary outcome) using random-effects multivariable logistic regression. We tested potential effect modification of the epoch on mortality according to the requirement of mechanical ventilation. We estimated the adjusted odds ratio (adjOR) and its corresponding 95% confidence interval using marginal means. Sensitivity analyses included those with COVID-19 as primary admission diagnosis and a subset excluding those admitted within periods of transition of VOC dominance.

Of 47,465 ICU admissions, 21,996 were in Nonvariant, 21,183 in Gamma/Delta, and 4286 in Omicron VOC dominance epochs. During epoch 3 (Omicron VOC dominance), patients were older (68 years [IQR 46–81] vs 52 [IQR 41–66] in epoch 2 and 55 [IQR 42–69] in epoch 1, respectively), more frail (24% vs 11% vs 13%), required less mechanical ventilation (10% vs 26% vs 19%), and had more brain dysfunction (13% vs 8.5% vs 9.1%). Overall, after adjustment, epoch 3 (Omicron dominance) was associated with lower 60-day mortality compared to previous epochs 1 and 2 (adjOR 0.51, 95% CI [0.29–0.90] and adjOR 0.32, 95% CI [0.18–0.56], respectively). In addition, interaction revealed that ventilated patients had similar odds of mortality during epoch 3 (Omicron dominance) compared to both epochs 1 and 2 (adjOR 0.87, 95% CI [0.44–1.71] and adjOR 0.73, 95% CI [0.37–1.44], respectively) (Fig. 1C, D). Limitations of our work include the absence of information on patient-level genomic data, vaccination status, and specific treatments targeted at COVID-19. To mitigate these, we adjusted our analyses for pandemic periods, performed sensitivity analyses that confirmed the main findings, and demonstrated that by the end of 2021, more than 60% of adults had received the first vaccination dose, 30% a second dose, and more than 90% of those aged > 60 years had complete vaccination (Fig. 1B).

We found a distinct clinical profile of COVID-19-ICU patients during the epoch with Omicron VOC dominance: older, frail, with less respiratory impairment, and more acute brain dysfunction. We also observed that nonventilated patients during Omicron had lower adjusted mortality compared to previous epochs with Gamma/Delta and Nonvariant dominance. In addition, similar outcomes were observed in those

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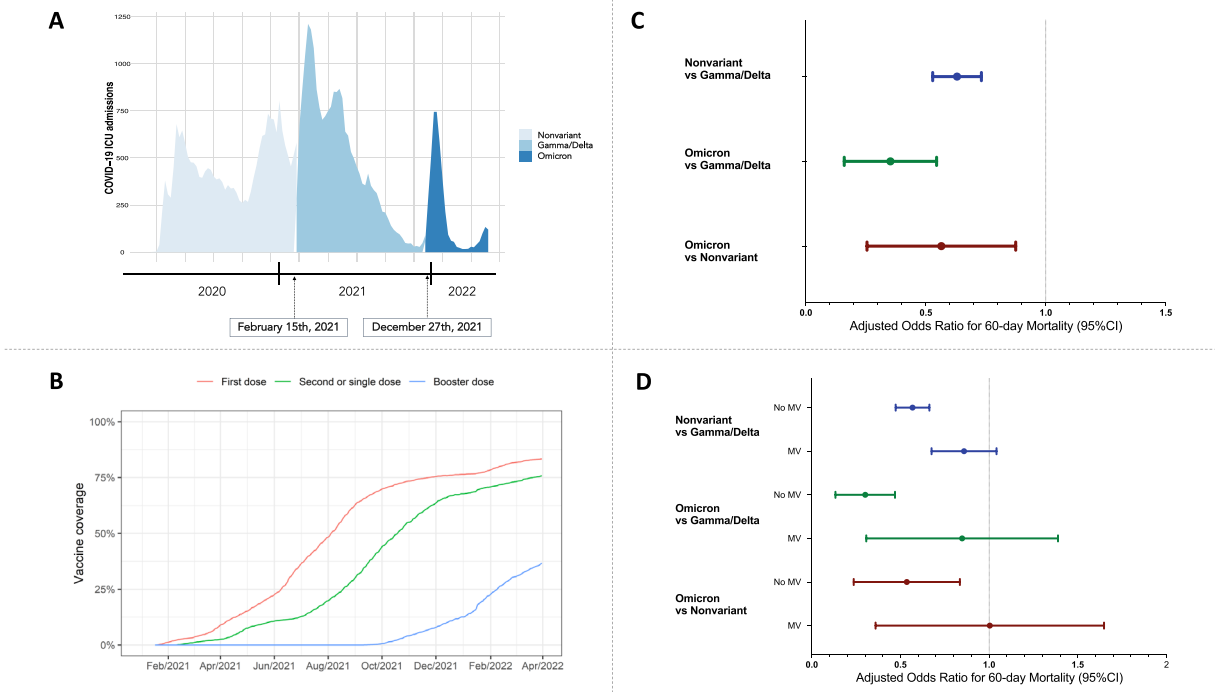

Fig. 1 **A** Density plot of COVID-19 ICU admissions according to period of variant dominance in Brazil in 231 study ICUs. **B** Vaccination coverage rates for COVID-19 in the Brazilian population (https://coronavirusbra1.github.io/sobre). **C**, **D** Multivariable mixed logistic regression model with 60-day in-hospital mortality as the binary outcome variable. Adjusted for age, sex, frailty, performance status, COVID-19 as the primary diagnosis, source of admission to ICU, pandemic period, and clinical profile at admission, including organ dysfunction and support. **C** Adjusted odds ratios obtained through marginal means in multivariable model with no interaction terms. **D** Adjusted odds ratios obtained through marginal means in multivariable model that included the interaction between variants of concern periods (Nonvariant, Gamma/Delta, and Omicron) and the requirement of invasive mechanical ventilation at the first ICU day (Yes/No)

undergoing invasive mechanical ventilation for the same comparisons.

Supplementary Information

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Author contributions

All authors contributed to the study conception and design, and data interpretation. PK, OTR, LSB, FGZ performed data processing and statistical analysis. PK, OTR, LSB, FAB drafted the first version of the manuscript. MS, JS, SH, FAB 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. PK and LSLB contributed equally to this manuscript.

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Availability of data and materials

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

Code availability
The programming code of data analysis is available in a GitHub repository (https://github.com/noispuc/ICODA_COVID_ICU_Variants).

Declarations

Conflicts of interest
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. MS and JS are founders and equity shareholders of Epimed Solutions®, which commercializes 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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References

1. Sigal A, Milo R, Jassat W (2022) Estimating disease severity of Omicron and Delta SARS-CoV-2 infections. Nat Rev Immunol 22(5):267–269
2. Kurtz P, Bastos LSL, Dantas LF, Zampieri FG, Soares M, Hamacher S et al (2021) Evolving changes in mortality of 13,301 critically ill adult patients with COVID-19 over 8 months. Intensive Care Med 47(5):538–548
3. Vieillard-Baron A, Flicoteaux R, Salmona M, Chariot A, De Maupeou DB, Darmon M et al (2022) Omicron variant in the critical care units of Paris metropolitan area the reality research group. Am J Respir Crit Care Med. https://doi.org/10.1164/rccm.202202-0411LE
4. de Prost N, Audureau E, Heming N, Gault E, Pham T, Chaghouri A et al (2022) Clinical phenotypes and outcomes associated with SARS-CoV-2 variant Omicron in critically ill French patients with COVID-19. Nat Commun 13(1):6025
5. Giovanetti M, Slavov SN, Fonseca V, Wilkinson E, Tegally H, Patane JSL et al (2022) Genomic epidemiology of the SARS-CoV-2 epidemic in Brazil. Nat Microbiol 7(9):1490–1500