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Clinical outcomes associated with Mu variant infection during the third epidemic peak of COVID-19 in Colombia

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ABSTRACT

Background: The higher number of cases and deaths caused by COVID-19 in Colombia occurred during the third epidemic peak, where the Mu variant was associated with 50% of the cases.
Objective: To evaluate the association between the clinical outcome of COVID-19 with health conditions and SARS-CoV-2 lineages.
Methods: In this study, clinical metadata and SARS-CoV-2 lineages from 535 patients with different degrees of COVID-19 severity were obtained after the SARS-CoV-2 genomic surveillance in Colombia. Then, the associations between these variables were determined using a multidimensional unfolding analysis.
Results: Asymptomatic, symptomatic, severe, and deceased outcomes represented 15.2%, 29.7%, 7.3%, and 47.8% of the cases, respectively. Males tend to develop more serious COVID-19, and severe or fatal outcomes were typically observed in patients aged >60 years with comorbidities, including chronic obstructive pulmonary disease, heart disease, kidney disease, obesity, asthma, and smoking history. The SARS-CoV-2 Mu and Gamma variants dominated the third epidemic peak and accounted for most fatal cases with odd ratio values of 128.2 (CI 53.0-310.1) and 18.6 (CI 8.294-41.917).
Conclusion: This study shows the high impact of SARS-CoV-2 lineages with higher prevalence on public health and the importance of monitoring COVID-19 risk factors to control the associated mortality.

Background

By July 2022, four COVID-19 epidemic peaks and 210 lineages have been registered in Colombia, including several variants of interest and concern (INS, 2022). However, a higher number of cases and deaths occurred during the third epidemic peak, when the B.1.621 (Mu) variant was associated with 50% of the cases in the country (Álvarez-Díaz *et al.*, 2022a). Although several factors in the clinical history of patients with COVID-19 have been associated with a severe or fatal outcome, including comorbidities, age, and smoking history (Zhang *et al.*, 2021), multiple factors must be analyzed to better understand the impact of the Mu variant in the COVID-19 clinical outcome.

Study design

Nasopharyngeal swab samples from 535 cases of SARS-CoV-2 in 27 Colombian departments were included in this study following a probabilistic sampling (Laiton-Donato *et al.*, 2021). Among these cases, 303 correspond to living individuals between June 2020 and August 2021, whereas 232 correspond to fatal cases, mainly during

Abbreviations: SARS-CoV-2, severe acute respiratory syndromecoronavirus 2; COVID-19, coronavirus disease 2019.

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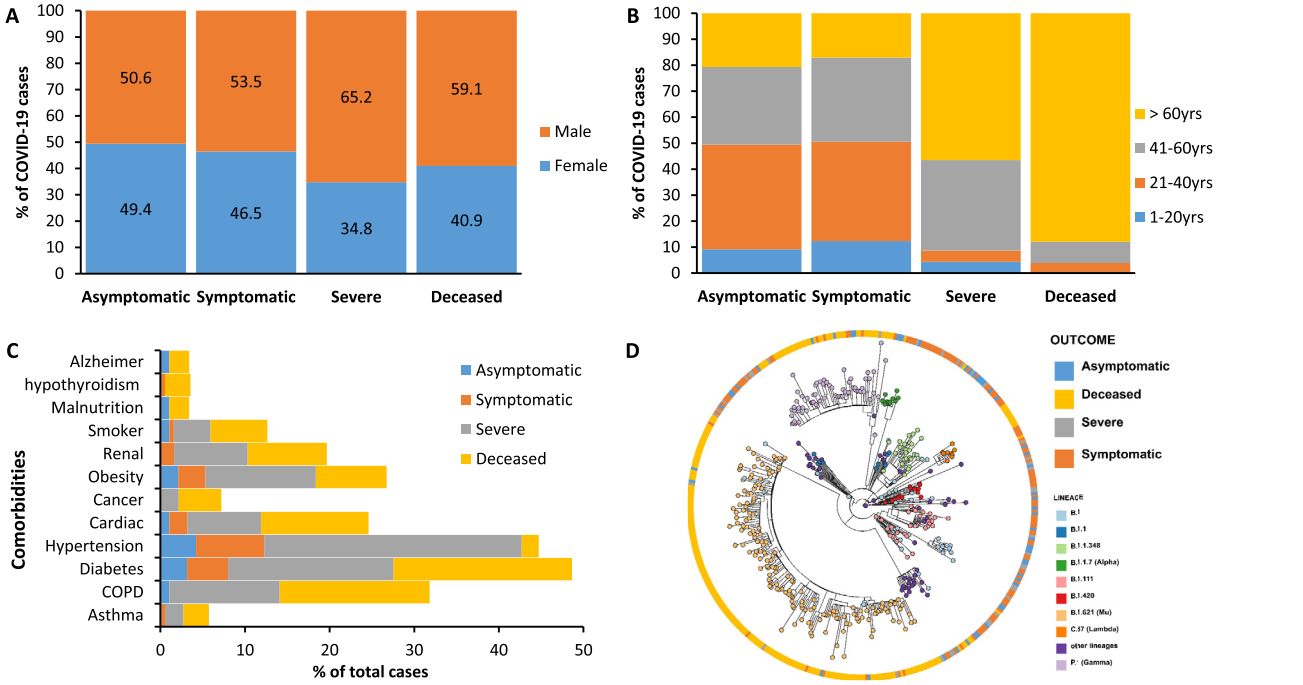

Figure 1. COVID-19 clinical outcome by groups. **(a)** COVID-19 cases by sex, **(b)** age, **(c)** comorbidities, and, **(d)** SARS-CoV-2 lineages representing 88.4% of the cases. A maximum-likelihood phylogeny of the nine-most frequent SARS-CoV-2 lineages was performed IQTREE (v.1.6.12). Modelfinder was used to select GTR+F+I+G4 as the substitution model according to the Bayesian Information Criterion. The process was performed with 2000 ultrafast bootstrap replicates for branch support. The MicroReact visualization of the phylogenetic tree with complete metadata and branch support information is available at https://microreact.org/project/pft6t2eiofQdCXpXyfysZv-clinical-metadata-associated-with-mu-variant-infection-during-the-third-epidemic-peak-of-covid-19-in-colombia. Figure design was based on data by OpenStreetMap, CC BY-SA 2.0; ODbL.

the third epidemic peak between April and July 2021. SARS-CoV-2 genome sequencing and lineage determination was performed as previously described (Laiton-Donato *et al.*, 2020). A total of 427 genomic sequences were resolved and submitted to the GISAID repository (Table S1, see online supplementary material). Clinical data from patients with COVID-19 were obtained from the SIVIGLIA database at the Instituto Nacional de Salud - Colombia. COVID-19 clinical outcomes were classified into asymptomatic, symptomatic, severe (when the patient was hospitalized), and deceased. A binary logistic regression model was applied to determine the weight of variables for the COVID-19 fatal outcome defined as a dependent variable (yes = 1, no = 0). Variables included in the model were the most frequent ones that met the Hosmer and Lesmeshow criteria, including age, sex, Mu, C.37 (Lambda), P.1 (Gamma), cough, fever, odynophagia, headache, chronic obstructive pulmonary disease (COPD), diabetes, cardiac, obesity, and renal. The associations between clinical outcomes with health conditions and SARS-CoV-2 lineages were analyzed using the multidimensional unfolding approach where symptoms, comorbidities, sex, age, smoking history, and SARS-CoV-2 lineage were scored as attributes of COVID-19 clinical outcomes.

Results

Although the distribution of fatal cases by sex suggested that males tended to develop severe and deceased outcomes (Figure 1a), the COVID-19 severity between males and females was not significantly different (Tables S2 and S3). The clinical outcomes by age showed higher percentages of severe and deceased in the variable >60 years (Figure 1b). Furthermore, COPD, diabetes, and cardiac diseases were the three most common comorbidities observed in deceased and severe outcomes, whereas hypertension was most associated with severe outcomes but not with mortality (Figure 1c). A total of 39 SARS-CoV-2 lineages were identified; however, nine lineages accounted for 88.5% of the cases (Figure 1d, Table S1). Mu and Gamma were the most observed lineages among the deceased and accounted for 69% and 18% of the deceased, respectively.

Figure 2.

The binary logistic regression model shows that the most significant variables explaining the COVID-19 fatal outcome were age and lineages Mu, Lambda, and Gamma. The variables Mu and Gamma showed the highest odds ratio (OR), indicating that the risk of a fatal COVID-19 outcome with lineage Mu or Gamma is 135.8 and 18.6 times the risk of a fatal outcome without these lineages. Furthermore, OR values supported that the risk of having a fatal outcome is higher as age increases (Table S4).

The multidimensional unfolding plot grouped the deceased and closely associated variables including age >60 years, followed by smoking history and diabetes, COPD, asthma, cancer, heart, and renal diseases. The lineages Mu, Gamma were also included in this cluster, followed by C37 (Figure 2).

Furthermore, symptomatic and severe outcomes were grouped with the age group 41-60 years, hypertension, and common COVID-19 symptoms. The lineages B.1 and B.1.1 were plotted close to these outcomes. The variables male sex and obesity were plotted together at approximately equal distances from the deceased-severe-symptomatic axis. Finally, the asymptomatic outcome was grouped with the younger age groups (0-20 and 21-40 years) were grouped with the SARS-CoV-2 lineages B.1.420, B.1.1.348, B.1.111, B.1.1.7, and female sex (Figure 2).

Discussion

The analysis of COVID-19 cases suggests an association between the older age, sex, comorbidities, and a worse COVID-19 clinical outcome. Several studies have reported similar findings with older age and comorbidities, such as cancer, hypertension, COPD, dia-

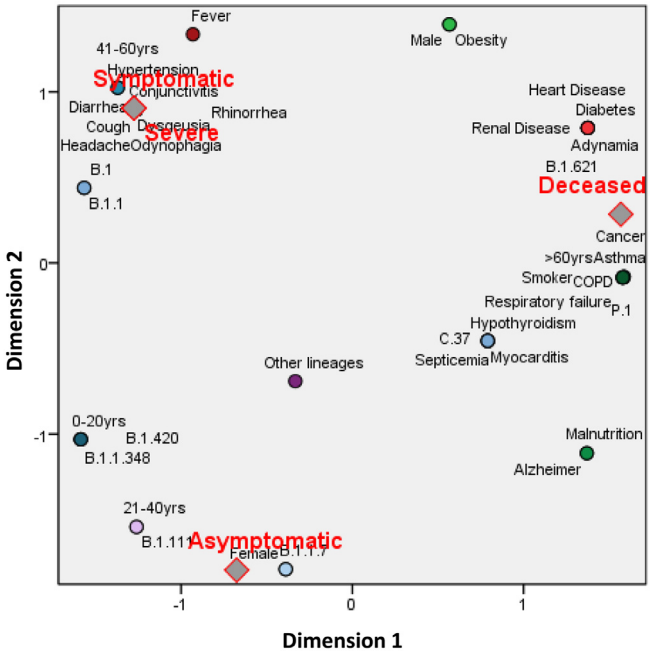

Figure 2. Joint multidimensional unfolding plot for COVID-19 outcomes and health conditions and SARS-CoV-2 lineages. The variables closer to each other suggest a greater association. Gray diamonds delineated in red represent clinical outcomes (asymptomatic, symptomatic, severe and deceased), circles represent, SARS-CoV-2 lineages, symptoms, sex, age groups, and comorbidities.

betes, cardiovascular, and kidney diseases, as the factors most associated with mortality in patients with COVID-19 (Ng *et al.*, 2021). In this study, hypertension was one of the most frequent comorbidities among patients with COVID-19; however, this condition was observed in patients with the severe outcome, a scenario that changed since 2020, when hypertension was the main comorbidity associated with mortality in patients with COVID-19 (De la Hoz-Restrepo *et al.*, 2020). Public health measures, such as prioritization of patients with hypertension to health services and the national vaccination plan, are maybe the main causes of this improvement (Minsalud, 2021).

The Mu and Gamma variants showed higher OR values for fatal outcomes and were responsible for 69% and 18% of the deceased, respectively. This was comparable with the proportion of circulating lineages during the third epidemic peak in Colombia (Álvarez-Díaz *et al.*, 2022b). Hence, it is possible that the concentration of deceased patients around these variants is a direct consequence of their higher representativeness because these cases were sampled mainly during the third epidemic peak.

The predominance of local variants and its association with a high burden of morbidity and mortality was described in Peru with the Lambda lineage, which reached 70% of the cases during the second epidemic peak, despite co-circulation of the Alpha and Gamma variants of concern (Padilla-Rojas *et al.*, 2021).

This study shows the effectiveness of the public health measures based on the observation of comorbidities and COVID-19 severity in the control of the associated mortality; however, more efforts must be applied to control the dispersion of variants with local predominance because the examples given by the Lambda and Mu variants clearly prove that dominant SARS-CoV-2 lineages drive morbimortality despite the variant classification.

CRediT authorship contribution statement

Diego A. Álvarez-Díaz: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Funding acquisition. **Hector A. Ruiz-Moreno:** Software, Formal analysis, Investigation, Data curation. **Silvana Zapata-Bedoya:** Formal analysis, Writing – review & editing. **Carlos Franco-Muñoz:** Methodology, Writing – review & editing. **Katherine Laiton-Donato:** Methodology, Writing – review & editing. **Carolina Ferro:** Data curation, Writing – review & editing. **Maria T. Herrera Sepulveda:** Investigation. **Mauricio Pacheco-Montealegre:** Formal analysis. **Diana M. Walteros:** Investigation, Data curation, Funding acquisition. **Laura C. Carrero-Galindo:** Formal analysis. **Marcela Mercado-Reyes:** Supervision, Funding acquisition.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval

According to the national law 9/1979, decrees 786/1990 and 2323/2006, the Instituto Nacional de Salud is the reference laboratory and health authority of the national network of laboratories and in cases of a public health emergency or those in which scientific research for public health purposes are required, the Instituto Nacional de Salud may use the biological material for research purposes, without written informed consent, which includes the anonymous disclosure of results. The information used for this study comes from the National Public Health Surveillance System - SIVIGILA that was previously anonymized and does not represent a risk to the community in accordance with the Declaration of Helsinki.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.10.028.

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