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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Public Health 213 (2022) 124–126

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Short Communication

Comparing the survival of adult inpatients with COVID-19 during the wild-type, Delta, and Omicron emergence

E. Murillo-Zamora [a, b], J. Guzmán-Esquivel [b, c], J.A. Bricio-Barrios [b], O. Mendoza-Cano [d, *]

[a] Departamento de Epidemiología, Unidad de Medicina Familiar No. 19, Instituto Mexicano Del Seguro Social, Av. Javier Mina 301, Col. Centro, C.P. 28000, Colima, Mexico
[b] Facultad de Medicina, Universidad de Colima, Av. Universidad 333, Col. Las Víboras, C.P. 28040, Colima, Colima, Mexico
[c] Unidad de Investigación en Epidemiología Clínica, Hospital General de Zona No. 1, Villa de Álvarez, Colima, Mexico
[d] Facultad de Ingeniería Civil, Universidad de Colima, Km. 9 Carretera Colima-Coquimatlán, Coquimatlán, C.P. 28400, Colima, Mexico

ARTICLE INFO

Article history:
Received 5 July 2022
Received in revised form
21 September 2022
Accepted 12 October 2022
Available online 20 October 2022

Keywords:
COVID-19
SARS-CoV-2
Inpatients
Survival rate

ABSTRACT

Objective: This study aimed to compare the survival experience of adult inpatients with laboratory-confirmed COVID-19 during the first three waves (wild type, Delta, and Omicron) of the pandemic in Mexico.
Study design: A retrospective and nationwide study was conducted.
Methods: Data from 229,311 participants were analyzed using the Kaplan–Meier method, and estimates per each pandemic wave were obtained. A multivariate Cox proportional hazard regression model was fitted, and hazard ratios (HRs) and 95% confidence intervals (CIs) were computed.
Results: The overall mortality rate was 49.1 per 1000 person-days. Heterogeneous survival rates were observed during the analyzed emergences (log-rank test, $P < 0.001$), and the lowest survival functions were computed during the Omicron variant dominance. In multiple analyses and after adjusting by host characteristics and COVID-19 vaccination status, cases occurring during the Delta (vs wild type: HR = 1.03, 95% CI 1.01–1.05) and Omicron emergence were at increased risk for a fatal in-hospital outcome (HR = 1.17, 95% CI 1.13–1.22).
Conclusions: Our results suggest variant-related differences in the survival rates of hospitalized patients with laboratory-positive COVID-19. When compared with the wild-type virus, lower rates were observed during the Delta and Omicron emergence.
© 2022 The Royal Society for Public Health. Published by Elsevier Ltd. All rights reserved.

Background

The burden of the COVID-19 by the severe acute coronavirus (SARS-CoV-2) in Latin America has been high. In the region and by the end of April 2022, the cumulative mortality rate (per 100 thousand people) observed in Mexico (254) is only lower than the rates in Peru (654), Brazil (314), Chile (302), Argentina (286), Colombia (278), and Paraguay (267).[1]

Worldwide, several SARS-CoV-2 variants have been identified by genomic sequencing. In Mexico, and also by the end of April 2022, three COVID-19 waves had been registered: wild type (March 2020 to February 2021), Delta (B.1.617.2, May 2021 to November 2021), and Omicron (B.1.1.529, December 2021 to February 2022).[2]

Variant-related differences had been documented in terms of transmission risk, impacts on vaccine effectiveness, and illness severity.[3] To the best of our knowledge, no published data are evaluating the survival of hospitalized patients with COVID-19 in the function of the dominant SARS-CoV-2 variant at the time of symptoms onset. This study aimed to compare the survival experience of adult inpatients with laboratory-confirmed COVID-19 during the first three waves (wild type, Delta, and Omicron) of the pandemic in Mexico.

Methods

A nationwide retrospective cohort study was conducted in Mexico. Eligible subjects were adult (aged ≥20 years) inpatients with laboratory-confirmed (reverse transcription polymerase chain reaction) COVID-19 and symptoms onset from March 2020 to February 2022. They were identified from the nominal records of a normative system for the epidemiological surveillance of respiratory viral pathogens (SINOLAVE, the Spanish acronym) that belongs

* Corresponding author. Tel.: +52 (312) 3161167.
E-mail address: oliver@ucol.mx (O. Mendoza-Cano).

https://doi.org/10.1016/j.puhe.2022.10.014
0033-3506/© 2022 The Royal Society for Public Health. Published by Elsevier Ltd. All rights reserved.

to the Mexican Institute of Social Security (IMSS, the Spanish acronym). The IMSS is an employer-based health scheme that provides medical and social services to 64% (≈83 million people) of the total population of the country. Patients with missing clinical or epidemiological data of interest were excluded.

We used the dominant variant at the time of illness onset as an approximation of the etiological variant for each case. This latter was made by using genomic sequencing data from the General Directorate of Epidemiology of Mexico.[3] Enrolled subjects were then classified as follows: wild type, March 2020 to February 2021; Delta (B.1.617.2), May 2021 to November 2021; Omicron (B.1.1.529), December 2021 to February 2022.

Clinical and epidemiological data were retrieved from the audited surveillance system, which primary sources are the medical files and death certificates, when applicable. Vaccinated subjects were those who had received, at 15 or more days before illness onset, at least one shot from any COVID-19 vaccine.[4] Pneumonia patients were those with clinical (fever, cough, and dyspnea) and radiographic findings (ground-glass opacities in computed tomography scanning or X-ray) suggestive of this abnormality.

The main outcome was in-hospital death due to any immediate cause. We used the Kaplan–Meier method to compute survival functions and 95% confidence intervals (CIs). The log-rank test was used to evaluate variant-related differences in survival rates. The association of the dominant SARS-CoV-2 variant at symptoms onset on the risk of death was evaluated through hazard ratios (HRs) and 95% CI, which were calculated by using proportional hazards models. The multiple model was adjusted by patients' age and gender, the COVID-19 vaccination status (unvaccinated/vaccinated), body mass index (≥30 kg/m^2, no/yes), pneumonia diagnosis at admission (no/yes), and days elapsed from symptoms onset to healthcare seeking.

Results

Data from 229,311 adult inpatients were analyzed for a total follow-up of 2,279,854 person-days. A total of 111,893 deaths were registered (49.1 deaths per 1000 person-days). The viral-stratified in-hospital mortality rates were as follows: wild type, 49.8% (n = 91,993/184,860); Delta, 45.3% (n = 17,085/37,740); Omicron, 42.0% (n = 2815/6711). The characteristics of enrolled patients for selected variables are presented in Supplementary data 1.

At any cutoff, the survival functions during the Omicron variant emergence were lower than those from the wild-type and Delta variant, particularly on the fifth day of in-hospital stay and later (Fig. 1). The curves from the wild-type and Delta variants were quite similar.

The computed survival functions, according to the days elapsed since hospital admission, were 1 day (wild type, 95.4% [95% CI 95.3–95.5%]; Delta, 96.5% [95% CI 96.3–96.7%]; Omicron, 95.3% [95% CI = 94.8–95.8%]); 3 days (wild type, 90.9% [95% CI 90.8–91.0%]; Delta, 92.7% [95% CI 92.5–93.0%]; Omicron, 90.1% [95% CI 89.3–90.8%]); 7 days (wild type, 74.2% [95% CI 74.0–74.4%]; Delta, 77.2% [95% CI 76.7–77.6%]; Omicron, 71.1% [95% CI 69.9–72.3%]); 15 days (wild type, 49.4% [95% CI 49.1–49.6%]; Delta, 52.5% [95% CI 51.9–53.1%]; Omicron, 48.4% [95% CI 47.0–49.8]); and 30 days (wild type, 25.5% [95% CI 25.2–25.8%]; Delta, 27.3% [95% CI 26.5–28.0%]; Omicron, 23.8% [95% CI 21.6–26.2%]). The follow-up endpoint was discharged from the hospital.

In the multiple analysis, cases occurring during the Delta and Omicron emergence were at increased risk for a fatal in-hospital outcome (vs wild type: Delta, HR = 1.03 [95% CI 1.01–1.05]; Omicron, HR = 1.17 [95% CI 1.13–1.22]). These estimates were adjusted by the COVID-19 vaccination status, which reduced in about 12% the risk of dying (HR = 0.88 [95% CI 0.86–0.91]). They were also adjusted by other conditions that were associated with reduced survival probabilities, namely, male gender (HR = 1.12 [95% CI 1.10–1.13]), age (per each additional year: HR = 1.02 [95% CI 1.01–1.03]), body mass index of ≥30 kg/m^2 (vs no: 1.13 [95% CI 1.11–1.14]), pneumonia diagnosis at admission (vs no: HR = 1.19 [95% CI 1.17–1.20]), and days elapsed from symptoms onset to healthcare seeking (per each additional day: HR = 1.003 [95% CI 1.002–1.005]).

Discussion

Our study characterized the survival experience of a large set of adult inpatients with COVID-19 during the first 2 years of the pandemic in Mexico. We documented that after adjusting by host characteristics and vaccination status, adults who were hospitalized during the Omicron variant emergence had lower survival rates than those from the previous waves.

A smaller involvement of the lower respiratory tract has been documented in cases of the Omicron variant infection and therefore to a reduced risk of hospital admission.[5,6] This latter results from the specific entry pathway of the Omicron variant, which is endocytic rather than through the transmembrane serine protease 2 (TMPRSS2).[7] The TMPRS22 is highly expressed in alveolar cells.[8] In our study and as presented in Supplementary data 1, cases occurring during the Omicron emergence were less likely to develop pneumonia (28.2%) than those from the previous waves (wild type, 39.0%; Delta, 34.7%). In addition, recently published data found that the viral load of Omicron infections is not higher than that of previous variants; therefore, its increased infectivity is more likely to be related to increased affinity to cell receptors or immune escape.[8]

We observed high in-hospital mortality rates during the dominance of the analyzed SARS-CoV-2 variants (wild type, 49.8%; Delta, 45.3%; Omicron, 42.0%). One factor that might be determining this scenario is that 4 of 10 analyzed hospitalized patients had pneumonia at admission. We also observed a decreasing trend in the frequency of severe pulmonary manifestations of COVID-19 and when from 39.0%, 34.7%, and 28.2% during the dominance of the wild-type, Delta, and Omicron variants, respectively.

The heterogeneous survival rates that were documented in our study could not be explained by host characteristics that had been consistently associated with a poorer in-hospital prognosis (i.e. high body index or increasing age).[9] It is important to emphasize that we evaluated the factors associated with the survival of hospitalized patients and not the determinants of hospitalization. The risk of hospitalization during the dominance of the Omicron variant was lower than the risk of its predecessors.[10] As presented in Supplementary data 1, enrolled patients during the Omicron dominance and when compared with previous waves were older, were less likely to be COVID-19 vaccinated or obese (body mass index of 30 or above), and had a higher prevalence of pneumonia at hospital admission. These factors may be determining, at least partially, the observed scenario. If replicated in other populations, further research is needed to elucidate the factors determining these heterogeneous survival rates.

The potential limitations of our study must be cited. First, low hospitalization rates were registered all over Mexico during the Omicron emergence. Therefore, the case fatality rate would be low when compared with the wild-type or Delta emergence. Second, no genomic sequencing was performed on all the enrolled subjects, and we are unable to ensure the pathogenic strain for each case. However, and as observed in other regions of the world, a high dominance of each variant was observed in Mexico during the study periods. By August 22, 2022, nearly 73 thousand genomic sequences have been processed (about 1% of the cumulative number of laboratory-positive cases in Mexico).[2]

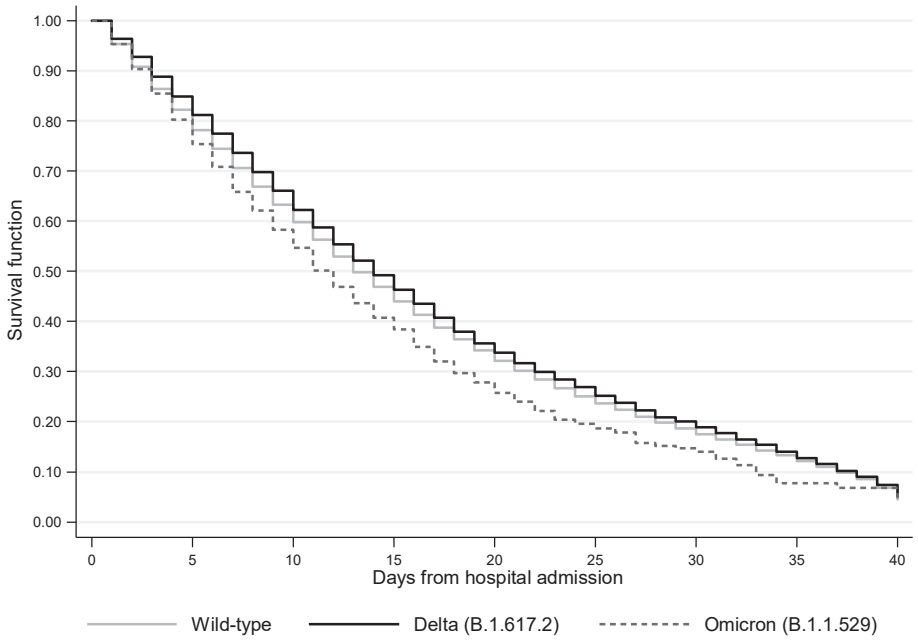

Fig. 1. Survival in adult inpatients with laboratory-confirmed COVID-19 ($n = 229{,}311$) according to the dominant SARS-COV-2 variant at symptoms onset, Mexico 2020–2022. Log-rank test: $P < 0.001$.

Conclusions

We compared the survival experience of 229 thousand adult inpatients with laboratory-positive COVID-19 according to the dominant variant at illness onset. We found variant-related differences in the risk of a fatal in-hospital outcome and the lowest rates were documented during the Omicron emergence. If later replicated, the results from our study would contribute to the knowledge of the development of the pandemic.

Author statements

Acknowledgments

The authors thank the Mexican Institute of Social Security for promoting the scientific research and for supporting and facilitating researchers with resources and pertinent information.

Ethical approval

This study was reviewed and approved by the Committee of Ethics in Health Research (601) of the IMSS (approval R-2020-601-022).

Funding

None to declare.

Competing interests

None to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.10.014.

References

1. Johns Hopkins, University of Medicine. Coronavirus resource center: mortality analyses (updated on April 21, 2022). Available at: https://coronavirus.jhu.edu/data/mortality (Accessed on April 21, 2022).
2. General Directorate of Epidemiology of Mexico. reportGenomic surveillance report of the SARS-CoV-2 virus in Mexico. National and state distribution of variants as of April 04, 2022. Available at: https://coronavirus.gob.mx/wp-content/uploads/2022/08/2022.08.22-Variantes-COVID-MX.pdf (Accessed on August 27, 2022) [Online document in Spanish].
3. Lin L, Liu Y, Tang X, He D. The disease severity and clinical outcomes of the SARS-CoV-2 variants of concern. *Front Public Health* 2021;**9**:775224. https://doi.org/10.3389/fpubh.2021.775224.
4. Murillo-Zamora E, Sánchez-Piña RA, Trujillo X, Huerta M, Ríos-Silva M, Mendoza-Cano O. Independent risk factors of COVID-19 pneumonia in vaccinated Mexican adults. *Int J Infect Dis* 2022;**118**:244–6. https://doi.org/10.1016/j.ijid.2022.02.003.
5. Menni C, Valdes AM, Polidori L, Antonelli M, Penamakuri S, Nogal A, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. *Lancet* 2022;**399**(10335):1618–24. https://doi.org/10.1016/S0140-6736(22)00327-0.
6. Hussey H, Davies MA, Heekes A, Williamson C, Valley-Omar Z, Hardie D, et al. Assessing the clinical severity of the Omicron variant in the Western Cape Province, South Africa, using the diagnostic PCR proxy marker of RdRp target delay to distinguish between Omicron and Delta infections - a survival analysis. *Int J Infect Dis* 2022;**118**:150–4. https://doi.org/10.1016/j.ijid.2022.02.051.
7. Zhao H, Lu L, Peng Z, Chen LL, Meng X, Zhang C, et al. SARS-CoV-2 Omicron variant shows less efficient replication and fusion activity when compared with Delta variant in TMPRSS2-expressed cells. *Emerg Microb Infect* 2022;**11**(1):277–83. https://doi.org/10.1080/22221751.2021.2023329.
8. Yuasa S, Nakajima J, Takatsuki Y, Takahashi Y, Tani-Sassa C, Iwasaki Y, et al. Viral load of SARS-CoV-2 Omicron is not high despite its high infectivity. *J Med Virol* 2022. 10.1002. https://doi.org/10.1002/jmv.27974.
9. Fang X, Li S, Yu H, Wang P, Zhang Y, Chen Z, et al. Epidemiological, comorbidity factors with severity and prognosis of COVID-19: a systematic review and meta-analysis. *Aging (Albany NY)* 2020;**12**(13):12493–503. https://doi.org/10.18632/aging.103579.
10. Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet (London, England)* 2022;**399**(10332):1303–12. 2022 https://doi.org/10.1016/S0140-6736(22)00462-7.