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Short Communication

Predictors of severe symptomatic laboratory-confirmed SARS-CoV-2 reinfection

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ABSTRACT

Objective: The aim of the study was to evaluate factors predicting severe symptomatic laboratory-confirmed (via Reverse transcription polymerase chain reaction, RT-PCR polymerase chain reaction) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection.
Study design: This is a nationwide retrospective cohort study that was conducted in Mexico.
Methods: Data from 258 reinfection cases (at least 28 days between both episodes onset) were analyzed. We used risk ratios (RRs) and 95% confidence intervals (CIs) to evaluate predictors of severe (dyspnea requiring hospital admission) secondary SARS-CoV-2 infection.
Results: The risk of severe disease was 14.7%, and the observed overall fatality rate was 4.3%. Patients with more serious primary disease were more likely to develop severe symptoms (39.5% vs. 5.5%, $P < 0.001$) during reinfection. In multiple analysis, factors associated with an increased risk of severe symptomatic SARS-CoV-2 reinfection were increasing age ($RR_{per\ year} = 1.007$, 95% CI = 1.003–1.010), comorbidities (namely, obesity [RR = 1.12, 95% CI = 1.01–1.24], asthma [RR = 1.26, 95% CI = 1.06–1.50], type 2 diabetes mellitus [RR = 1.22, 95% CI = 1.07–1.38]), and previous severe laboratory-confirmed coronavirus disease 2019 (RR = 1.20, 95% CI = 1.03–1.39).
Conclusions: To the best of our knowledge, this is the first study evaluating disease outcomes in a large set of laboratory-positive cases of symptomatic SARS-CoV-2 reinfection, and factors associated with illness severity were characterized. Our results may contribute to the current knowledge of SARS-CoV-2 pathogenicity and to identify populations at increased risk of a poorer outcome after reinfection.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a major impact in healthcare systems. In Mexico, by middle of January 2021, more than 1.6 million confirmed cases and nearly 142 thousand deaths had been registered.[1]

Even when there is no consensus regarding its definition, reinfection risk is a major debate related to the COVID-19 pandemic.[2] Given the high observed mortality in Mexico, there is concern regarding the impact of subsequent COVID-19 in recovered patients. The aim of this study was to evaluate factors predicting severe SARS-CoV-2 symptomatic reinfection in a large cohort of laboratory-confirmed COVID-19 survivors.

Methods

We conducted a nationwide retrospective cohort study including adults (aged 20 years or older) with laboratory-

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confirmed symptomatic (via quantitative reverse transcription polymerase chain reaction [RT-qPCR], wherein nasopharyngeal or deep nasal swabs were used) SARS-CoV-2 reinfection. The research group previously published a broader description of the used methods.[3]

Subjects with primary COVID-19 onset from March to July 2020 who recovered from severe (dyspnea requiring hospital admission) or non-severe illness were eligible. Recovery was defined as resolution of fever without the use of antipyretic drugs and self-reported improvement in respiratory symptoms (i.e., cough, shortness of breath) at 7–10 days from symptom appearance. The main binary outcome was severe symptomatic laboratory-confirmed (via RT-PCR) reinfection, and it was defined by the reappearance of COVID-19 symptoms at 28 days or more from a primary laboratory-positive COVID-19.[4]

Clinical and epidemiological data of interest were obtained from medical files and death certificates, if applicable. We used linear regression models to calculate risk ratios (RRs) and 95% confidence intervals (CIs) to evaluate factors associated with the risk of severe symptomatic SARS-CoV-2 reinfection. The next models were built: one for each evaluated predictor and a multiple model. The Health Research Committee 601 of the Mexican Institute of Social Security provided approval (R-2020-601-015).

Results

Data from 100,432 first-time and recovered patients with COVID-19 were analyzed, and 258 laboratory-confirmed cases of reinfection were identified (0.26%). The study profile is presented as Supplementary Fig. 1.

The median elapsed days between first- and second-time COVID-19 were 56 days (interquartile range [IQR] = 40–81), and no significant differences were observed between patients with non-severe and severe primary disease ($P = 0.431$). Most of the participants who tested positive for SARS-CoV-2 reinfection were women (53.9%) and were aged 49 years or younger (81.8%). The overall risk of severe subsequent illness was 14.7% (n = 38). The observed fatality rate was 4.3% (11/258), and it was higher among patients with severe symptoms (23.3% vs. 4.5%, $P < 0.001$).

When severe and non-severe second-time infections were compared, patients with more serious primary disease (39.5% vs. 5.5%, respectively, $P < 0.001$), as well as those aged 50 years or older (52.6% vs. 12.3%, $P < 0.001$), were more likely to develop subsequent severe symptoms. In general, the prevalence of chronic non-communicable diseases (namely, type 2 diabetes mellitus, arterial hypertension, and kidney disease) was higher among severe subsequent cases. Other characteristics of interest are presented in Supplementary Table 1.

In multiple analysis (Table 1), factors associated with a more severe symptomatic SARS-CoV-2 reinfection were increasing age ($RR_{per\ year} = 1.007$, 95% CI = 1.003–1.010) and personal history of obesity (RR = 1.12, 95% CI = 1.01–1.24), asthma (RR = 1.26, 95% CI = 1.06–1.50), type 2 diabetes mellitus (RR = 1.22, 95% CI = 1.07–1.38), and chronic kidney disease (RR = 1.47, 95% CI = 1.21–1.80). Subjects with previous severe COVID-19 had a 20% increased risk (RR = 1.20, 95% CI = 1.03–1.39) of also presenting severe symptoms during secondary disease.

Discussion

The results from our analysis characterized factors determining the risk of severe symptomatic SARS-CoV-2 infection. However, because currently, there is no consensus regarding the definition of SARS-CoV-2 reinfection, our findings must be carefully considered.

Table 1
Predictors of severe symptomatic laboratory-confirmed SARS-CoV-2 reinfection in Mexico in 2020.

Characteristic	RR (95% CI), *P*					
	Bivariate analysis			Multiple analysis		
Gender						
Female	1.00			1.00		
Male	1.06	(0.97–1.15)	0.221	1.02	(0.95–1.10)	0.589
Age-group (years)						
20–49	1.00			1.00		
50–59	1.36	(1.21–1.54)	<0.001	1.22	(1.09–1.37)	0.001
60–69	1.41	(1.10–1.81)	0.007	1.18	(0.93–1.49)	0.176
70+	1.63	(1.27–2.09)	<0.001	1.17	(0.89–1.51)	0.262
Disease severity (at primary infection)[a]						
Mild to moderate	1.00			1.00		
Severe	1.58	(1.38–1.80)	<0.001	1.20	(1.03–1.39)	0.019
Personal history of:						
Obesity (BMI = 30 or higher)						
No	1.00			1.00		
Yes	1.10	(0.97–1.24)	0.131	1.12	(1.01–1.24)	0.025
Asthma						
No	1.00			1.00		
Yes	1.22	(0.99–1.49)	0.062	1.26	(1.06–1.50)	0.009
Type 2 diabetes mellitus						
No	1.00			1.00		
Yes	1.52	(1.34–1.72)	<0.001	1.22	(1.07–1.38)	0.003
Immunosuppression[b]						
No	1.00			1.00		
Yes	1.02	(0.76–1.36)	0.893	0.91	(0.72–1.16)	0.467
Chronic kidney disease						
No	1.00			1.00		
Yes	1.88	(1.55–2.28)	<0.001	1.47	(1.21–1.80)	<0.001

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RR, risk ratio; CI, confidence interval; BMI, body mass index.
Generalized linear regression models were used to obtain RR and 95% CI. Multiple regression coefficients were adjusted by variables listed in the table.
[a] Severe illness included the register of dyspnea requiring hospital admission.
[b] Immunosuppression referred to any cause of the related deficiency except for type 2 diabetes mellitus or renal impairment.

The cutout points that we used, which correspond to one of the criteria proposed by Tomassini et al.,[2] seem highly plausible because they are based on the observed viral decay in laboratory-positive cases of COVID-19.[5] All the enrolled subjects from our study became asymptomatic between both episodes.

We would like to highlight that enrolled patients who recovered from severe primary illness had a 20% increase in the risk of severe subsequent disease (RR = 1.20, 95% CI = 1.03–1.39). Besides, a shorter interval between both disease episodes was documented in patients with severe primary illness (median days [IQR] = 48 [33–62] vs. 57 [41–84]; $P = 0.040$).

If later replicated in other populations, this finding may be highly relevant for public health policymakers because it would imply the following: (i) even when higher antibody titers have been documented among patients with severe COVID-19,[5] these would not protect them from a secondary severe illness about 4–8 weeks later, and (ii) these initially recovered patients would benefit from particularly strict measures in preventing the spread of respiratory viral pathogens. However, in our study sample, the risk of second-time disease seemed to be low (0.26%).

The rest of the factors predicting severe symptomatic SARS-CoV-2 reinfection (namely, increasing age, obesity, asthma, type 2 diabetes mellitus, and chronic kidney disease) did not seem to differ from those determining a severe primary disease.[6] These findings support that medical and control interventions used in subsequent COVID-19 cases, in general terms, do not seem to differ from those used in primary infection cases.[7]

Interestingly, most of the laboratory-positive second-time cases were young (younger than 50 years). A reduced COVID-19 awareness among younger subjects may be implied,[8] particularly owing to a high prevalence (87.0%) of non-severe primary illness in this age-group.

The potential limitations of this study must be cited. First, the used definition of severe COVID-19 in our study represents a limitation that must be cited, given that no laboratory-related data (e.g., PaO_2) were collected. However, a meta-analysis including 15 studies evidenced that dyspnea is a stand-alone prognostic factor of COVID-19–related mortality.[9] Besides, and as per normative standards that have been followed since the beginning of the pandemic in Mexico, hospitalization criteria include the use of validated scales such as the Pneumonia Severity Index and CURB-65 (Confusion, Urea level, Respiratory rate, Blood pressure, and age $\geq$ 65).[10] Therefore, this severity indicator seems to be plausible in the study population.

Second, because no mass screening has been performed in Mexico, we were unable to identify second-time asymptomatic cases of SARS-CoV-2 infection. Moreover, an undetermined fraction of patients that are currently being identified as primary COVID-19 may correspond to subsequent infections, and the related public health implications are unknown.

And third, and as presented in Supplementary Fig. 1, we observed a high mortality rate (8.4%) among patients classified as non-severe first-time COVID-19. However, this rate was significantly lower than the one observed among patients with severe illness (51.3%; $P < 0.001$). Mortality rate from second-time disease was also higher among severe cases (23.7% vs. 0.5%, $P < 0.001$). Because we relied on data from medical records, we consider plausible that illness severity from an undetermined fraction of enrolled subjects may be misclassified.

Conclusions

We identified factors predicting severe symptomatic SARS-CoV-2 reinfection, which seemed to be a rare event. To the best of our knowledge, this is the first study aiming to characterize clinical outcomes in patients with second-time COVID-19. If later replicated, our results may be highly useful for implementing interventions focusing on the reduction of disease burden in populations at risk, including vaccination efforts.

Author statements

Ethical approval

The Health Research Committee 601 of the Mexican Institute of Social Security provided approval (R-2020-601-015).

Funding

This study was self-funded by the researchers.

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.2021.01.021.

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