Previous dengue infection and mortality in COVID-19

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ABSTRACT -

We studied 2351 participants with COVID-19, 1177 (50%) reported previous dengue infection. Those without previous dengue had a higher risk of death (hazard ratio: 0.44; 95% CI: 0.22 to 0.89; p = 0.023) in 60-day follow-up. These findings raise the possibility that dengue might induce immunological protection against SARS COV-2.

Key words: COVID-19, dengue, mortality

INTRODUCTION

COVID-19 is a pandemic infectious disease notable for high infectivity and potential severity. It can evolve to respiratory distress, the main cause of COVID-19 hospitalization and death [1,2]. The mechanisms for disease severity are likely related to viral load and the host's inflammatory response; common chronic diseases such as diabetes, hypertension and cardiovascular diseases are associated with a poor prognosis [3]. In the absence of an approved effective vaccine, protective factors that increase survival among those infected with SARS COV-2 are of interest to investigators.

Data recently published from an ecological study in Brazil, other Latin American countries, and Asia showed that areas with a higher incidence of dengue fever were less likely to experience COVID-19 cases and deaths [4], raising the possibility of cross-immunity between these two viruses. Indeed, although dengue virus and SARS-COV-2 are from different families, there are reports that antibodies for dengue can be reactive against SARS COV-2, leading to false positive tests for COVID-19 [5,6]. However, it is unknown whether previous dengue episodes can produce some level of immunity against COVID-19. Our aim was to evaluate whether previous contact with endemic infectious diseases such as symptomatic dengue might alter the prognosis of COVID-19.

METHODS

Study design and sample

We prospectively studied 2830 subjects with symptomatic and asymptomatic laboratory-confirmed SARS-CoV-2 infection in Rio Branco, Acre, a municipality in the Brazilian Amazon basin. From the 9,878 cases of COVID-19 registered in the health

department between March 17 and August 26, 2020, we excluded 6391 (65%) individuals as detailed in the supplementary figure 1. Therefore, 2351 were included in the analysis.

Information on all confirmed COVID-19 cases were provided by the State Department of Health of Acre and the Municipal Health Department of Rio Branco. We contacted infected persons during the first days (baseline contact), at the thirtieth day and up to the sixtieth day (end of follow-up) after COVID-19 diagnosis by telephone. During the call, the patient or family member of patients who had died, were hospitalized, or were not at home gave verbal consent to participate in the study and responded to each item on a questionnaire. Researchers were trained to follow a standardized script, and responses were entered in REDCap software. The study was approved by the Research Ethics Committee of the Federal University of Acre, Brazil, according to documentation form no. 4.012.361, of May 6, 2020 – CAAE: 30781620.5.0000.5010.

Studied variables and outcome

Sociodemographic information, clinical data prior to SARS-CoV-2 infection, and COVID-19 specific clinical information were collected. Data provided by telephone from the patient or the patient's family member included: weight, height, skin color, education level, monthly income, active smoking, relevant comorbidities for severe COVID-19 (hypertension, diabetes, heart disease, pulmonary disease and chronic kidney disease), history of symptomatic dengue, and history of other endemic infectious diseases (malaria, zika, chikungunya, leprosy, and visceral leishmaniasis). Symptoms related to COVID-19 infection, self-reported peripheral capillary oxygen saturation values (SpO_2), date of onset of symptoms, and date of resolution of symptoms were recorded. Additionally, data on medications, need for hospitalization, and survival status were ascertained by telephone call to patients or family. The first day of follow-up was defined as onset of COVID-19

symptoms, and the primary outcome was all-cause mortality up to 60 days after symptom onset.

Statistical analysis

Continuous variables with normal and non-normal distribution and categorical variables were expressed as mean ± standard deviation, median [25th - 75th percentile] and percentages, and were compared by student-t, Mann-Whitney, and chi-square tests, respectively. The Kaplan–Meier method estimated the cumulative event rate, and comparisons between curves were made by log-rank test. Multivariable Cox proportional hazards regression models to evaluate the association between symptomatic dengue and mortality were adjusted for selected covariates based on prior literature (age, sex, number of relevant comorbidities [obesity, hypertension, diabetes, heart disease, pulmonary disease and chronic kidney disease], hospitalization, SpO2<95%, and treatment with corticosteroids). Because the main aim of this study was to evaluate the association between dengue and mortality, no adjustment for multiple comparisons was performed. Stata 15.1 was used for statistical analysis. The value of $p < 0.05$ was considered statistically significant.

RESULTS

Of 2351 participants (mean age 40.4±12.7 years, 49% male), 1177 (50%) reported a previous history of dengue. Compared with subjects without a history of dengue, those with a history of dengue had a greater number of relevant comorbidities, were more likely to be hypertensive, and to have a history of malaria, chikungunya or leishmaniasis (Supplementary material - table 1). Subjects with a history of dengue in general had more symptoms and were more likely to have had a CT scan of the chest and received corticosteroids (Supplementary material - table 2). Only 23 patients were asymptomatic, 16 (1.4%) and 7 (0.6%) among those without and with history of dengue, respectively.

After a median follow-up of 60.0 [47.0, 60.0] days, there were 38 deaths (12 in patients with previous dengue and 26 in those without a history of symptomatic dengue). After accounting for key covariables, participants without previous symptomatic dengue had a higher risk of death (adjusted hazard ratio [HR]: 0.44; 95% CI: 0.22 to 0.89; p = 0.023) (Figure).

History of malaria was not associated with mortality in the crude (HR: 1.17; 95% CI 0.57 to 2.41; p=0.67) or adjusted analysis (HR: 0.47; 95% CI 0.22 to 1.00; p=0.050). History of other previous infectious diseases, including, Zika, chikungunya, leprosy and visceral leishmaniasis, were not associated with mortality in patients with COVID-19 (p=NS for all), but the number of individuals with these diseases were very small.

DISCUSSION

The main finding of the present study was a decreased mortality at up to 60 days among COVID-19 patients who had a previous history of symptomatic dengue infection. Participants were included from the community and had a case-fatality rate of 1.6%, similar to previously published data [1]. In a recent ecological study, the spread of COVID-19 was linked to the distribution of dengue cases in Brazil and Asia [4]. Notably, regions with higher incidence of dengue had lower number of COVID-19 cases and lower COVID-19 related mortality. These findings raise the possibility that dengue might induce a degree of immunological protection against SARS COV-2 infection. In agreement with this assumption, false-positive results for COVID-19 tests have been reported in patients with dengue [5,6], and false-positive IgM/IgG serological tests for SARS-CoV-2 have been reported in samples of persons with antibody-positive dengue collected in the pre-pandemic period [5,7]. Furthermore, two patients in Singapore with thrombocytopenia, myalgia and nonspecific symptoms suggestive of dengue had false-positive tests for dengue and were later

diagnosed with COVID-19 [6]. Overall, these reports suggest cross-immunity between the two diseases.

Symptoms of COVID-19 were more prominent among persons who had a history of dengue despite their lower mortality. This might be due to an enhanced inflammatory response, perhaps similar to the severe symptoms associated with a second episode of dengue or severe primary dengue in previously uninfected persons who received the tetravalent dengue vaccine Dengvaxia® [8]. Whether deleterious effects from immune enhancement will occur in COVID-19 reinfection or after COVID-19 vaccination remains to be determined.

This study has limitations. We cannot exclude information bias, since all data were collected directly from patients or in 3.8% of cases, their families. Dengue was self-reported, and participants may have been incorrectly classified as having or not previous history of dengue infection. We performed a sensitivity analysis for nondifferential misclassification of the exposure with probability density functions of sensitivities and specificities ranging from 0.70 to 1. We found that the bias-adjusted incidence rate ratios were further from the null (0.26; 95% CI: 0.08 to 0.63), suggesting that it is unlikely the inverse association between dengue and mortality resulted from misclassification bias. Recall bias is possible since participants who reported previous dengue infection may have been more likely to recall comorbidities than those without dengue infection. Additionally, those without dengue infection may have been less likely to receive treatment for chronic conditions, such as hypertension; however, we did not find differences in antihypertensive medications use between those with or without previous dengue (Supplementary Table 3)." Although we adjusted for covariates known to be associated with mortality from COVID-19, we cannot rule out our results were due to unrecognized or residual confounding. Finally, our findings cannot be generalized to indigenous persons, since none of the participants self-declared as belonging to this population.

Our study suggests that individuals with history of dengue infection have lower mortality from COVID-19. Nevertheless, we cannot assume a causal association between previous dengue and immunity improving prognosis from SARS-COV2 infection. Further studies comparing previous

exposure to dengue virus and the different outcomes of COVID-19 are necessary to elucidate the association between these two viruses. [9,10] This is of particular importance to Brazil, which accounted for 70% of all dengue cases in the Americas during the last three decades. [11,12] Whether other tropical diseases can alter the course of COVID-19 is of relevance to the greater than one billion persons living in areas where these diseases are endemic.

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Figure:

A: Kaplan-Meier estimates of the probability of death in patients with COVID-19 according to the history of dengue.

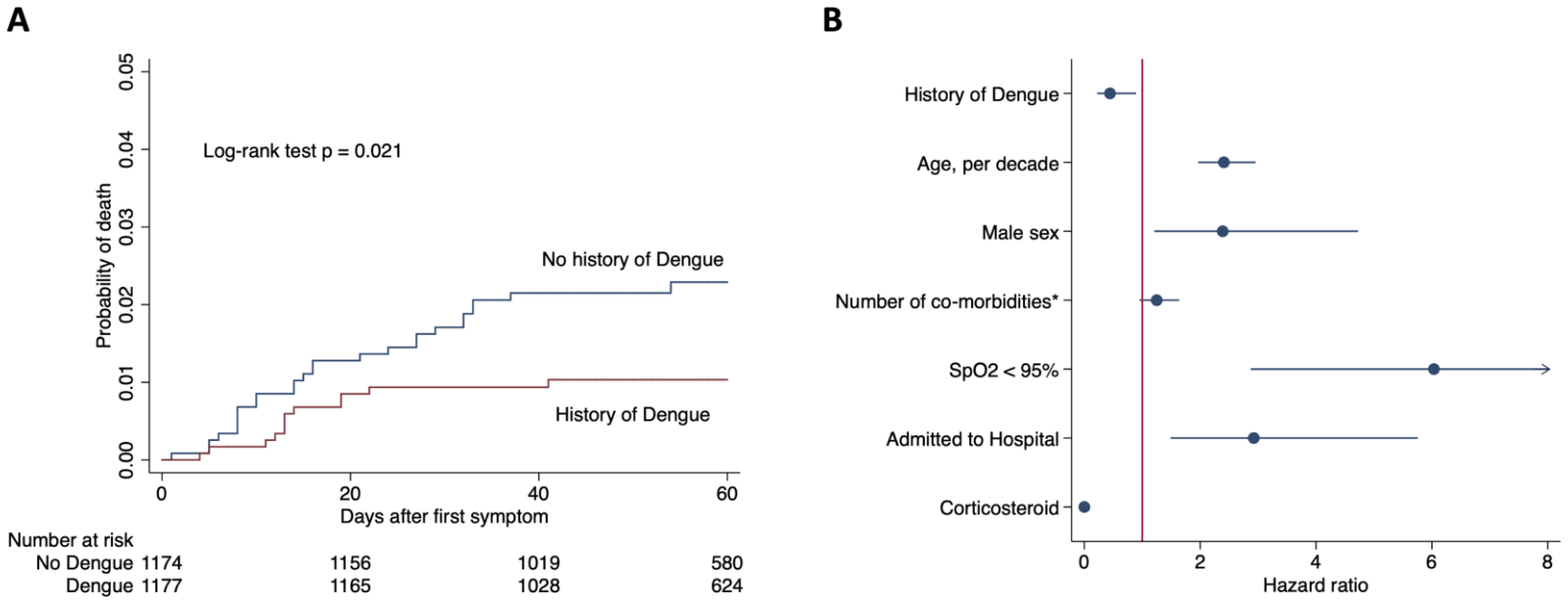
B: Association of history of Dengue, clinical characteristics and treatment with mortality in patients with COVID-19.

Forest plot displays the respective hazard ratios (HR) and 95% confidence intervals (95%CI) in the multivariate Cox regression analysis.

SpO2 – peripheral capillary oxygen saturation; “no hypoxemia” includes persons who did not have SpO2 measured.

*Represents the HR (95%CI) for each additional comorbidity (obesity, hypertension, diabetes, heart disease, pulmonary disease or chronic kidney disease). Participants with missing body mass index (n=37) were considered non obese.

Figure 1


A
Log-rank test p = 0.021
No history of Dengue
History of Dengue
Probability of death
0.00
0.01
0.02
0.03
0.04
0.05
0
20
40
60
Days after first symptom
Number at risk
No Dengue 1174 1156 1019 580
Dengue 1177 1165 1028 624
B
History of Dengue
Age, per decade
Male sex
Number of co-morbidities*
SpO2 < 95%
Admitted to Hospital
Corticosteroid
0
2
4
6
8
Hazard ratio