

CLINICAL ARTICLE

Obstetrics

Is pregnancy a risk factor for in-hospital mortality in reproductive-aged women with SARS-CoV-2 infection? A nationwide retrospective observational cohort study

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Abstract

Objective: To examine the effect of pregnancy on coronavirus disease 2019 (COVID-19) -related in-hospital mortality in women of reproductive age (between 15 and 45 years), with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection confirmed with polymerase chain reaction tests, adjusted for factors such as co-infection and intervention that were not considered in existing literature.

Methods: Data gathered from a nationwide database in Brazil were analyzed using multivariate logistic regression and multivariate Cox regression. Adjusted odds ratios and hazard ratios of independent factors associated with in-hospital death were calculated.

Results: A total of 97 712 women were included in the study. After the adjustment for sociodemographic factors, epidemiologic characteristics, pre-existing medical conditions, and intervention, pregnant women were found to be associated with lower risk for in-hospital mortality as well as longer survival time compared with non-pregnant women. When covariates of intervention were omitted from the analysis, pregnancy did not appear to be a significant factor associated with mortality.

Conclusion: With the adjustment for intervention that was shown to be an independent factor associated with mortality, pregnancy appeared to have a favorable effect on SARS-CoV-2 infection. Given the immunosuppressed state of pregnancy, this finding is in line with the hypothetical protective role of a weaker immune response that inhibits the production of proinflammatory cytokine.

KEYWORDS

Coronavirus disease-2019, gestation, mortality, pregnant, severe acute respiratory syndrome coronavirus 2

1 | INTRODUCTION

The pandemic of the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, formerly known as 2019-nCoV) was declared the sixth public health emergency of international concern by the World Health Organization on January 30,

2020. Causing coronavirus disease 2019 (COVID-19), SARS-CoV-2 is one of the seven members of the Coronaviridae pathogenic to humans. Cohort studies have been performed on different population groups, including women of reproductive age.

Large-scale studies on pregnant and non-pregnant women with SARS-CoV-2 infection have been review studies,^{1,2} including

database reviews,³⁻⁷ that identified independent factors associated with pregnancy. Findings of these studies suggest similar to higher mortality associated with pregnant women compared with non-pregnant women, after adjustment for sociodemographic factors, symptoms, and pre-existing medical conditions.

In Brazil, a number of health information systems have been developed for surveillance including some nationwide ones, such as the Laboratory Environment Manager and the Influenza Epidemiological Surveillance Information System (*Sistema de Informação da Vigilância Epidemiológica da Gripe*, SIVEP-Gripe). The latter contains the data of patients admitted to hospital or who died without admission and was developed for the surveillance of SARS related to influenza and other respiratory viruses and, upon the outbreak, COVID-19 has been incorporated into the surveillance network.

Based on the data gathered from SIVEP-Gripe, the present work identified the independent risk factors associated with COVID-19-related in-hospital mortality in reproductive-aged Brazilian women with the aim to investigate whether pregnancy was a predictor of death.

2 | MATERIALS AND METHODS

The study population was those women registered in SIVEP-Gripe, a publicly available nationwide database managed by the Brazilian Ministry of Health. It has been the primary source of information on COVID-19-related hospital admissions and deaths in Brazil, and has been described elsewhere.⁸

Data were gathered from SIVEP-Gripe on September 1, 2021. All cases registered in the database meeting all the following criteria were included in the study: (1) diagnosed with SARS-CoV-2 infection using polymerase chain reaction tests, (2) female, (3) aged between 15 and 45 years inclusively, and (4) recovered or deceased. This means that cases failing to meet any of these criteria were excluded. Furthermore, patients who had not died from SARS-CoV-2 infection were excluded.

Data are de-identified and publicly available, and therefore ethics approval is not required in the UK and Brazil.

Data of covariates were also gathered from the database, including pregnancy status, sociodemographic factors, clinical characteristics, and intervention, as well as epidemiologic measures. Details of variables collected and treatment for missing data are listed in Table S1.

The statistical analysis consisted of three parts. First, the difference in the summary statistics between pregnant and non-pregnant cohorts was statistically tested. Second, multivariate logistic regression was used to identify independent risk factors for mortality, with the primary aim to see if pregnancy was a predictor of death. The accuracy of the model was assessed by the area under the receiver operating characteristic curve. Furthermore, as a comparison to analyses in the existing literature, the above-mentioned procedure was repeated with covariates on intervention, comorbidities, epidemiologic characteristics, or signs and symptoms omitted. Third,

Kaplan-Meier survival curves and Cox regression were used to model two temporal measures: time from admission to recovery and time from admission to death. Details of statistical analyses can be found in Table S2.

All computations were performed using the software R Version 4.1.1. A P value <0.05 was considered significant.

A sensitivity analysis was performed following VanderWeele and Ding.⁹ E-values, defined as the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates, were reported.

3 | RESULTS

Data were gathered from SIVEP-Gripe on September 1, 2021. As of August 30, 2021, a total of 2 633 133 cases of flu-like syndrome were identified in the database (Figure 1). After the removal of non-SARS-CoV-2 cases and SARS-CoV-2 cases not diagnosed with polymerase chain reaction tests, 1 102 777 cases (42%) were left. Of these, 615 049 were men (56%) and 142 had details of sex missing ($<1\%$) and so were excluded. Of the remaining 487 586 cases (44%), 109 175 patients (22%) were aged between 15 and 45 years. After the removal of 11 299 cases (10%) with final clinical status missing and 164 patients ($<1\%$) who died of non-COVID-19-related causes, 97 712 cases (89%) met all the inclusion criteria and were included in the study. Of the included cases, 7235 patients were pregnant (7%). Incidence of cases over time is shown in Figure 2. Two major waves of cases occurred around epidemiologic weeks 10–30 then weeks 50–75. The cases of pregnant and non-pregnant patients generally followed a similar pattern, suggesting that both cohorts were affected equally over time.

Pregnant and non-pregnant women were characterized by different measures (Table 1). The death rates were 10% and 17% for the pregnant and non-pregnant groups, respectively, and the difference was significant ($P < 0.001$). However, such a difference might be explained by the difference in other measures. First, the non-pregnant group was generally older, as indicated by the median of age (38 years versus 31 years, $P < 0.001$). The proportion of Caucasian women by ethnic composition was higher in the non-pregnant cohort (55% versus 47%, $P < 0.001$) and a higher proportion of Latino (52% versus 44%, $P < 0.001$) and indigenous (0.3% versus 0.2%, $P < 0.001$) women was found in the pregnant cohort. With respect to temporal measures, the time from symptom onset to death was 14 and 10 days for the pregnant and non-pregnant cohorts, respectively ($P < 0.001$). However, the times from symptom onset to admission were 6 and 7 days ($P < 0.001$) for the two cohorts, respectively; indicative of earlier hospitalization in the pregnant group. Of note, there was no significant difference for time from admission to recovery ($P = 0.388$).

The need for intensive care might be associated with death. Despite the higher rate of intensive care unit (ICU) admission in the

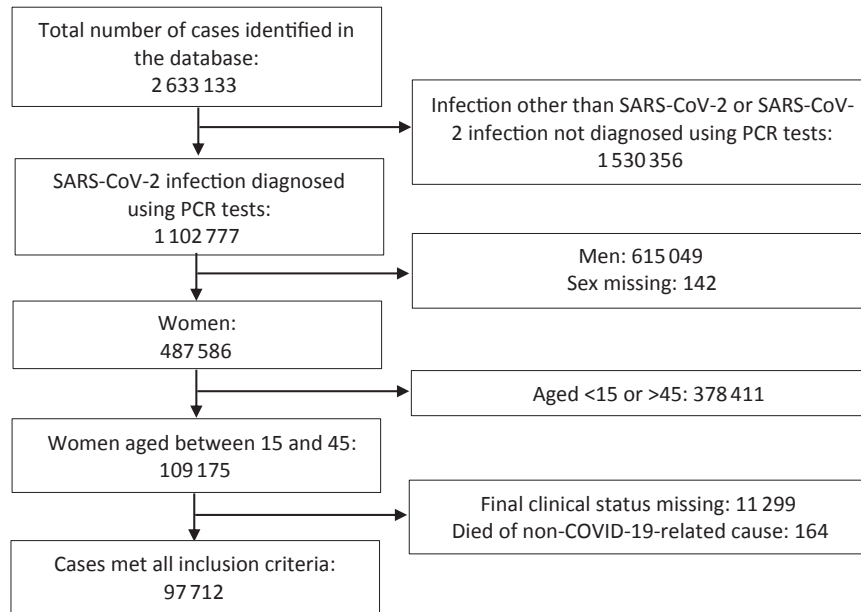


FIGURE 1 Flow diagram of case selection

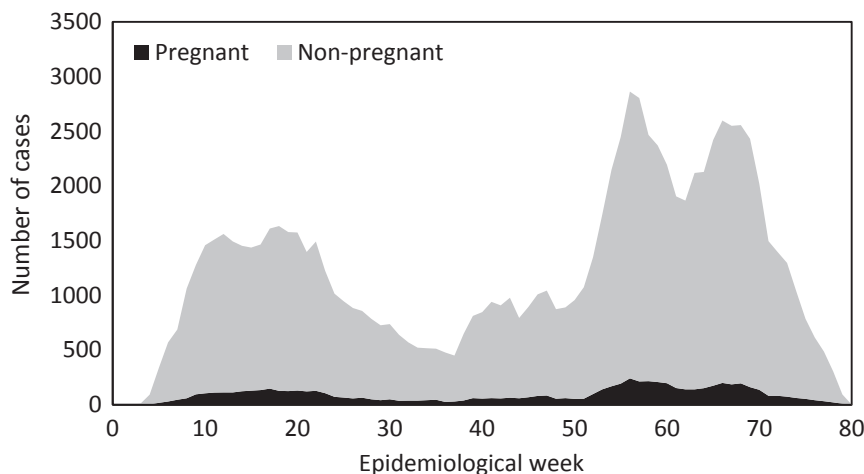


FIGURE 2 Incident cases of SARS-CoV-2 infection in hospitalized female patients aged between 18 and 40 years through 80 epidemiologic weeks in Brazil

pregnant cohort (29% versus 27%, $P < 0.001$), the median days in ICU was eight in both cohorts and the difference was not significant ($P = 0.836$, excluding those not admitted to the ICU). About 48% of the patients in the pregnant cohort required the use of ventilation, significantly lower than the other cohort (60%, $P < 0.001$). Similarly, the pregnant cohort saw a lower proportion of abnormal chest X-rays (87% versus 92%, $P < 0.001$). Nevertheless, it is not clear if vaccination and therapeutics play a role in disease severity. The pregnant cohort saw a lower rate of vaccination against SARS-CoV-2 (3% for non-pregnant versus 2% for pregnant, $P < 0.001$) but higher rates of vaccination against influenza (16% versus 8%, $P < 0.001$) and the use of antiviral agents (12% versus 8%, $P < 0.001$).

For clinical manifestations, asymptomatic cases were 2.8-fold higher in the pregnant cohort than in the non-pregnant cohort

(0.44% versus 0.16%, $P < 0.001$). Moreover, the pregnant cohort saw fewer lower respiratory tract symptoms including dyspnea (60% versus 70%, $P < 0.001$) and respiratory discomfort (45% versus 54%, $P < 0.001$). In line with this, 38% of the pregnant patients had oxygen saturation below 95%, compared with 54% of the non-pregnant patients ($P < 0.001$). Although this tends to suggest that pregnant patients fared better, the pregnant cohort showed similar upper respiratory tract symptoms. There was no significant difference in the prevalence rate of cough between the two groups ($P = 0.989$). Pregnant patients had fewer sore throats (22% versus 23%, $P < 0.001$), but had two-fold higher prevalence of coryza (9% versus 4%, $P < 0.001$).

The death rate between the two groups might also be affected by the underlying medical conditions. About 79% of the pregnant

TABLE 1 Summary statistics of the studied cohort^a

	Non-pregnant	Pregnant	P value
Age, years	38 [32–42] (90 477)	31 [26–35] (7235)	<0.001
Deceased	16.5 (14 898/90 477)	10.4 (755/7235)	<0.001
Location			
North	4.4 (3948/90 477)	6.7 (487/7235)	<0.001
Northeast	13.7 (12 417/90 477)	17.0 (1231/7235)	<0.001
Southeast	53.0 (47 912/90 477)	45.3 (3277/7235)	<0.001
Center West	11.8 (10 628/90 477)	14.4 (1041/7235)	<0.001
South	17.2 (15 572/90 477)	16.6 (1199/7235)	0.168
Ethnicity			
Caucasian	54.6 (39 038/71 554)	46.5 (2837/6102)	<0.001
Asian	1.2 (878/71 554)	1.0 (58/6102)	0.058
Latino	44.0 (31 498/71 554)	52.2 (3187/6102)	<0.001
Indigenous	0.2 (140/71 554)	0.3 (20/6102)	0.038
Epidemiologic characteristics			
First wave	36.3 (21 814/60 080)	35.4 (2378/6719)	0.141
Hospital-acquired	1.6 (1453/90 477)	1.0 (70/7235)	<0.001
Animal contact	0.7 (635/90 477)	0.8 (57/7235)	0.382
Time from symptom onset to admission, d	7 [4–10] (84 238)	6 [3–9] (6925)	<0.001
Time from admission to recovery, days	6 [4–10] (66 727)	6 [3–10] (6016)	0.388
Time from admission to death, days	10 [5–18] (13 861)	14 [7–22] (739)	<0.001
Intervention			
ICU admission	26.6 (24 038/90 477)	29.2 (2113/7235)	<0.001
Days in ICU	8 [4–15] (15 267)	8 [3–15] (1460)	0.836
Ventilation	60.1 (54 379/90 477)	48.4 (3500/7235)	<0.001
Use of antiviral	7.9 (7179/90 477)	11.9 (862/7235)	<0.001
Vaccination against influenza	8.3 (7512/90 477)	15.8 (1143/7235)	<0.001
Vaccination against SARS-CoV-2	3.0 (2735/90 477)	2.3 (164/7235)	<0.001
Signs and symptoms			
Asymptomatic	0.2 (141/90 477)	0.4 (32/7235)	<0.001
Abdominal pain	5.5 (5015/90 477)	6.3 (456/7235)	0.008
Abnormal chest X-ray	92.1 (19 386/21 042)	86.8 (1134/1307)	<0.001
Anosmia	12.0 (10 824/90 477)	14.5 (1052/7235)	<0.001
Ageusia	11.7 (10 578/90 477)	13.0 (941/7235)	0.001
Coryza	4.4 (3937/90 477)	9.3 (674/7235)	<0.001
Cough	72.5 (65 617/90 477)	72.5 (5248/7235)	0.989
Diarrhea	16.2 (14 654/90 477)	10.2 (734/7235)	<0.001
Dyspnea	69.8 (63 114/90 477)	59.7 (4322/7235)	<0.001
Fatigue	21.3 (19 256/90 477)	20.4 (1475/7235)	0.073
Fever	61.2 (55 389/90 477)	58.0 (4195/7235)	<0.001
Headache	15.9 (14 344/90 477)	16.8 (1216/7235)	0.034
Myalgia	13.6 (12 268/90 477)	14.6 (1058/7235)	0.012
Sao ₂ <95%	54.2 (48 998/90 477)	38.3 (2774/7235)	<0.001
Respiratory discomfort	53.6 (48 521/90 477)	45.2 (3272/7235)	<0.001
Sore throat	23.4 (21 123/90 477)	21.5 (1558/7235)	<0.001
Vomit	10.8 (9757/90 477)	10.9 (788/7235)	0.768
Others	39.7 (35 896/90 477)	45.5 (3295/7235)	<0.001

TABLE 1 (Continued)

	Non-pregnant	Pregnant	P value
Comorbidities			
No comorbidities	65.0 (58 831/90 477)	79.0 (5715/7235)	<0.001
One comorbidity	24.3 (22 005/90 477)	16.2 (1173/7235)	<0.001
Two comorbidities	8.2 (7385/90 477)	3.9 (285/7235)	<0.001
Three or more comorbidities	2.5 (2256/90 477)	0.9 (62/7235)	<0.001
Chronic cardiovascular disease	12.2 (11 078/90 477)	5.8 (422/7235)	<0.001
Chronic hematologic disease	0.7 (645/90 477)	0.4 (27/7235)	<0.001
Down syndrome	0.5 (461/90 477)	0.1 (4/7235)	<0.001
Chronic liver disease	0.4 (390/90 477)	0.2 (16/7235)	0.006
Asthma	4.5 (4093/90 477)	3.6 (260/7235)	<0.001
Diabetes	9.6 (8662/90 477)	7.4 (537/7235)	<0.001
Chronic neurologic disease	1.3 (1194/90 477)	0.6 (45/7235)	<0.001
Chronic pneumopathy	1.0 (944/90 477)	0.5 (39/7235)	<0.001
Immunocompromised	2.4 (2166/90 477)	1.0 (70/7235)	<0.001
Chronic renal disease	1.9 (1731/90 477)	0.5 (36/7235)	<0.001
Obesity	13.9 (12 575/90 477)	6.7 (484/7235)	<0.001
Respiratory viral infection	0.1 (53/90 477)	0.2 (12/7235)	0.003

Abbreviations: ICU, intensive care unit; Sao₂, arterial oxygen saturation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

^a Values are presented as percentage (number/total number) or as median [interquartile range] (total number).

patients had no pre-existing medical conditions, compared with 65% of non-pregnant patients. Non-pregnant patients had about 1.5-fold, 2.0-fold, and 2.9-fold higher prevalence of one, two, and three or more comorbidities, respectively. Moreover, they had significantly higher prevalence rates of all types of comorbidities, except for respiratory viral infection other than SARS-CoV-2 where a higher prevalence rate was observed in pregnant patients (0.17% versus 0.06%, $P = 0.003$).

Pregnancy was identified as an independent factor associated with COVID-19-related mortality, as shown in Figure 3. However, pregnancy appeared to have a favorable effect on SARS-CoV-2 infection (odds ratio [OR] 0.7, 95% confidence interval [CI] 0.57–0.84), after the adjustment for sociodemographic factors, epidemiologic characteristics, comorbidities, and intervention. For instance, advanced age was independently associated with mortality (OR 1.02, 95% CI 1.01–1.03). There is also evidence ethnicity played a role in mortality, as demonstrated by Latino (OR 1.17, 95% CI 1.07–1.29).

The area under the receiver operating characteristic curve was 0.82 (95% CI 0.82–0.83), indicative of excellent accuracy. E-values for association between pregnancy and covariates are included in Table S1. Based on the rule of thumb that an E-value of 2 when the outcome is all-cause mortality is considered to provide evidence for robustness to confounding,¹⁰ these E-values, which ranged from 1 to 5.4, suggest that relatively strong confounding assumptions would be needed to eliminate the association between these factors and pregnancy.

Results of covariate omission analysis are shown in Figure S1. For most covariates, the 95% CI of the OR overlapped with the exception of pregnancy. With covariates on intervention omitted,

pregnancy remained independently associated with mortality but the OR was insignificant.

As graphically illustrated in the left panel, the pregnant cohort enjoyed a longer survival time only until the 37th day, as suggested by the log rank test ($P < 0.001$; Figure 4). For time from admission to recovery, no significant difference in prognosis was observed ($P = 0.080$). For temporal measures, the results of the Cox regression suggested that pregnancy was a predictor of time to recovery and death (Table 2). However, the effect of pregnancy remains unclear. While pregnant patients had 1.19 times lower rate of death than non-pregnant patients (hazard ratio [HR] 0.84, 95% CI 0.72–0.99), they had a 1.15 times lower rate of recovery than non-pregnant patients (HR 0.87, 95% CI 0.82–0.94). The concordance indices for the models on survival and recovery time were 0.671 and 0.668, respectively.

4 | DISCUSSION

The present work identified independent risk factors for mortality in women of reproductive age in Brazil based on the data of nearly 100 000 COVID-19 patients registered in the nationwide database. It was found that pregnant women had a lower risk for in-hospital mortality (OR 0.7) after the adjustment for sociodemographic factors, epidemiologic characteristics, symptoms, pre-existing medical conditions, and intervention. The covariate omission analysis showed that intervention played an important role in the finding of lower mortality risk associated with pregnancy. In line with this, Kaplan-Meier curves and the corresponding log-rank tests showed

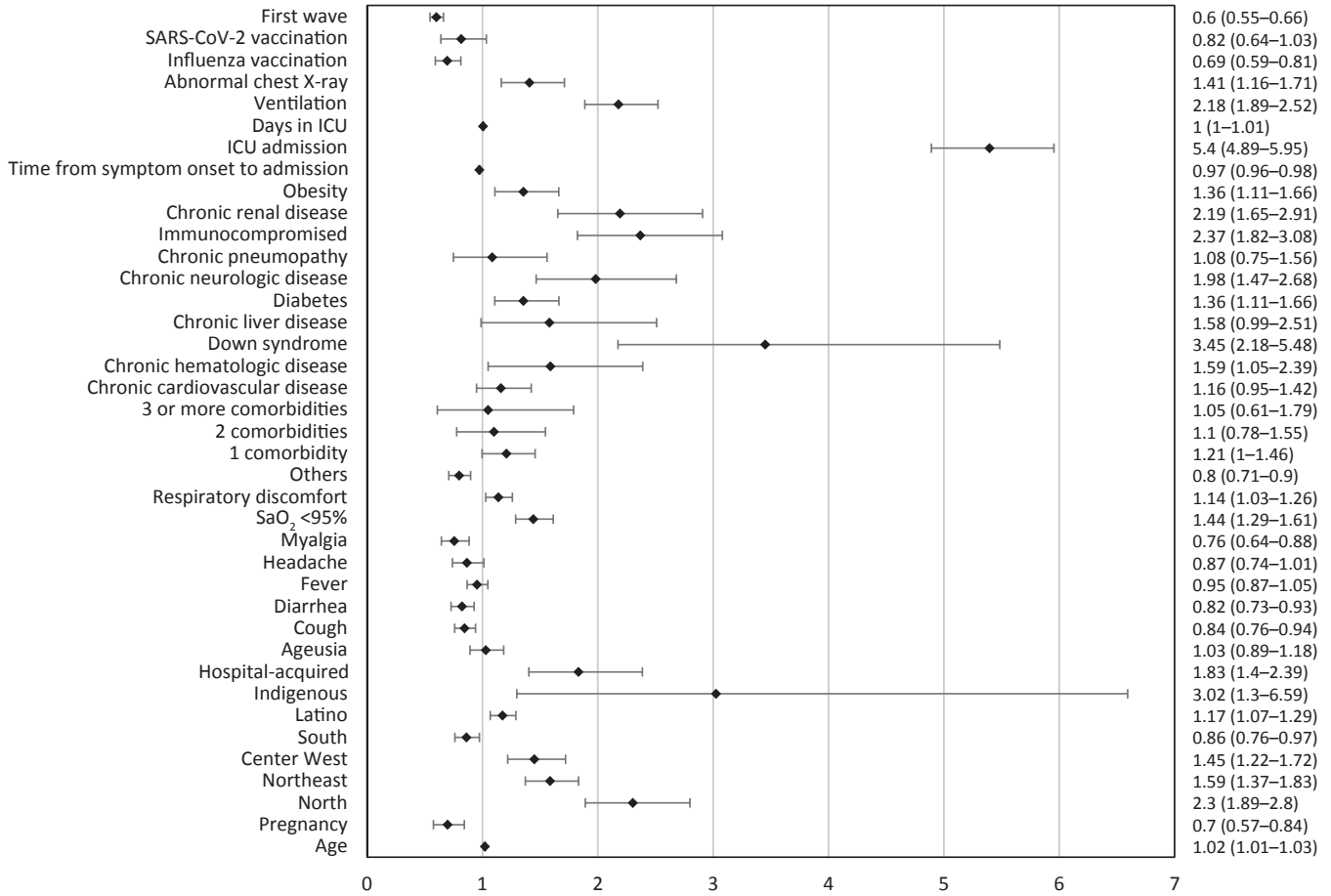


FIGURE 3 Adjusted odds ratios of independent factors associated with death

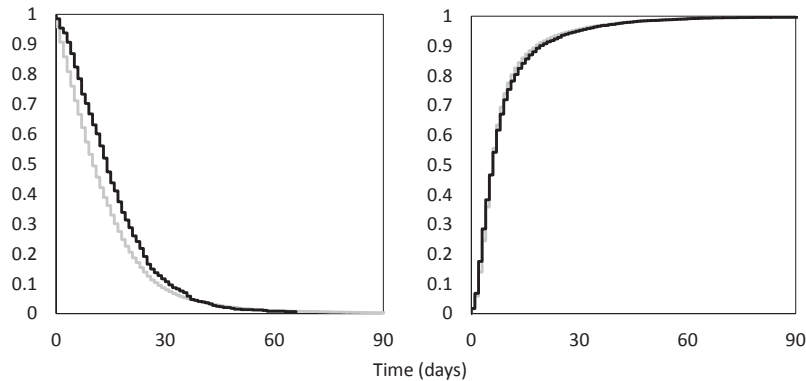


FIGURE 4 Kaplan-Meier survival curves for time from admission to death (left) and time from admission to recovery (right) (black line: pregnant cohort)

longer survival times in the pregnant cohort. Similar findings were supported by the multivariate Cox regression showing longer survival time in pregnant patients (HR 0.84). It is important to note that the inconclusive result of the survival analysis on time to recovery does not necessarily contradict other findings in the present work because the analysis considered recovered patients only.

Strengths of the study include the broad geographical coverage of the database as well as variations in ethnicities in Brazil. Another strength is the inclusion of covariates on epidemiologic

characteristics and interventions that were not considered in existing literature. The use of covariate omission analysis allows us to make comparisons with existing literature. Moreover, our findings were reinforced by the results of survival analysis on temporal measures that were not considered in existing literature.

Limitations include the lack of data on laboratory results, such as interleukin-6, that can help to describe the pathophysiology of SARS-CoV-2 infection in pregnant women. Moreover, the nature of the database limited the study to hospitalized cases only,

TABLE 2 Results of Cox regression

	Time from admission to death		Time from admission to recovery	
	HR (95% CI)	P value	HR (95% CI)	P value
Age			1 (0.99–1)	<0.001
Pregnancy	0.84 (0.72–0.99)	0.037	0.87 (0.82–0.94)	<0.001
North	1.19 (1.03–1.37)	0.018	0.78 (0.71–0.86)	<0.001
Northeast			0.86 (0.8–0.91)	<0.001
Center West			0.88 (0.82–0.94)	<0.001
South	1.11 (1.01–1.23)	0.033	1.04 (0.99–1.09)	0.094
Latino	1.04 (0.96–1.12)	0.319	0.92 (0.89–0.96)	<0.001
Hospital-acquired	0.76 (0.63–0.91)	0.003	0.65 (0.57–0.74)	<0.001
Asymptomatic	9.59 (1.33–69.16)	0.025	0.47 (0.21–1.04)	0.063
Abdominal pain			0.93 (0.86–1)	0.045
Anosmia			1.15 (1.05–1.25)	0.002
Ageusia			1.03 (0.94–1.12)	0.583
Coryza	0.84 (0.69–1.03)	0.094	1.12 (1.03–1.22)	0.009
Diarrhea	0.99 (0.9–1.1)	0.906		
Dyspnea	1.06 (0.96–1.17)	0.255	1.03 (0.99–1.08)	0.129
Fatigue	1.1 (1.01–1.19)	0.026		
Fever	0.94 (0.87–1.01)	0.089	0.92 (0.89–0.95)	<0.001
Headache			0.97 (0.92–1.03)	0.316
SaO ₂ <95%			0.9 (0.86–0.94)	<0.001
Respiratory discomfort			0.93 (0.9–0.97)	<0.001
Others	0.99 (0.92–1.07)	0.872	1.08 (1.04–1.13)	<0.001
One comorbidity	1.06 (0.98–1.14)	0.14	0.89 (0.84–0.93)	<0.001
Two comorbidities			0.85 (0.78–0.93)	<0.001
Three or more comorbidities			0.83 (0.72–0.96)	0.012
Down syndrome	1.3 (0.99–1.69)	0.056	0.73 (0.56–0.96)	0.024
Diabetes	1.13 (1.04–1.24)	0.005	0.98 (0.91–1.05)	0.565
Chronic neurologic disease			0.83 (0.71–0.96)	0.014
Immunocompromised	0.83 (0.72–0.96)	0.011	0.77 (0.68–0.86)	<0.001
Chronic renal disease	0.93 (0.8–1.09)	0.376	0.78 (0.68–0.9)	<0.001
Obesity	1.06 (0.98–1.15)	0.144	1.01 (0.95–1.08)	0.689
Time from symptom onset to admission	1.01 (1–1.01)	0.002	1.01 (1.01–1.01)	<0.001
ICU admission	1.02 (0.94–1.11)	0.657	0.62 (0.59–0.65)	<0.001
Days in ICU	0.97 (0.96–0.97)	<0.001	0.97 (0.96–0.97)	<0.001
Ventilation	1.12 (0.98–1.28)	0.093	0.87 (0.84–0.91)	<0.001
Abnormal chest X-ray	0.84 (0.71–0.99)	0.034	0.95 (0.9–1.01)	0.093
Influenza vaccination	0.84 (0.73–0.96)	0.011	1.09 (1.04–1.15)	0.001
SARS-CoV-2 vaccination			1.15 (1.04–1.27)	0.007

Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; SaO₂, arterial oxygen saturation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

translating to a death rate that was higher than the usual case-fatality rates because mild COVID-19 cases that are less likely to die are not included in the study. Given the case-fatality rate of COVID-19 of 12.7% in pregnant women¹¹ due to the lack of access and availability of healthcare services in Brazil, the death rate

reported here is not unreasonable. The pandemic aggravated old and persistent problems in Brazil, such as insufficient resources to manage emergency care and racial disparities in access maternity services¹². In addition, there may be selection bias that pregnant patients with relatively mild cases of COVID-19 were hospitalized

as a precaution while non-pregnant patients with disease of similar severity were not admitted. To evaluate the effect of the bias, a multivariate logistic regression was performed on data of severe cases only, defined as patients with low arterial oxygen saturation (SaO_2)¹³ (<95%), an objective biomarker, and the results were compared with the original analysis. By restricting the analysis to severe cases, the pregnant and non-pregnant groups are on an equal footing, eliminating the effect of disparity in admission. The results are shown in Table S5—the adjusted ORs were similar in both analyses, indicating small effect of bias. Selection bias may also arise from socio-economic disparity where health care is more accessible in some regions. To assess the effect of this bias, a stratified analysis was performed. Based on the socio-economic vulnerability index,¹⁴ multivariate logistic regression was performed on cases in North, Northeast and Center West, and in Southeast and South. As demonstrated by the overlapped 95% CI (Table S6), the adjusted ORs for mortality with pregnancy do not differ significantly among the two strata.

The most striking finding was the favorable effect of pregnancy, as demonstrated by the multivariate logistic and Cox regressions. Existing studies have found higher or similar mortality in pregnant women compared with non-pregnant women,^{3–7} demonstrating mixed results. In most studies,^{3–5,7} pregnancy was treated as the outcome rather than the exposure. From a statistical perspective, the exponential of the coefficient represents the adjusted ORs of pregnancy associated with death. In contrast, the present work examined whether pregnancy was an independent predictor of in-hospital death and estimated the effect of pregnancy on COVID-19-related in-hospital mortality. The methodology used in the present work makes sense because mortality is the outcome whereas pregnancy is the exposure, resulting in adjusted ORs of death associated with pregnancy. In a study conducted in Mexico,⁶ death was treated as the outcome variable.

Although varying mortality risk factors between communities can attribute to this finding, the results of the covariate omission analysis showed that findings of pregnancy associated with higher risk for mortality reported in existing literature may be the result of the omission of intervention covariates. Although further investigation is needed to examine this finding, the hypothetical protective role of a weaker immune response where favorable disease course was observed in immunosuppressed hosts may serve as a possible explanation.¹⁵ Although the maternal immune system protects the mother from infection, it is suppressed for successful pregnancy, so as to tolerate the fetus, which is considered as “foreign”.¹⁶ In immunosuppression, on the one hand, inhibition of viral replication by the immune system is restricted. On the other hand, immunosuppression can inhibit the production of proinflammatory cytokines, for example interleukin-6, which has been found to be an adequate predictor of severe COVID-19¹⁷ because of its role in cytokine release syndrome and acute respiratory distress syndrome.¹⁸ In fact, some studies have suggested that immunosuppression during pregnancy could protect the mother from the cytokine release syndrome.^{19–22} Nevertheless, this is not to say that immunosuppression is beneficial

to SARS-CoV-2 infection. In fact, the present work found immunocompromise associated with increased risk for mortality (Figure 3). Taken together, how immunosuppression is related to COVID-19-related mortality is dependent on the type of immunosuppression, as pointed out in some systematic reviews.^{23–25}

Looking beyond pregnancy, the present work also demonstrated measures that can influence the risk of mortality. As addressed, intervention played a key role in mortality risk. Vaccination against SARS-CoV-2, for instance, reduced the risk of mortality although the insignificant OR might be attributed to the small sample size, which accounted for only 3% (2899 out of 97 712) of the study cohort. For influenza-related intervention, it was shown that vaccination appeared to offer some beneficial effects but the use of antivirals did not. A recent study in the USA on individuals aged 65 years or older have found similar results—that influenza vaccination prevented the development of severe COVID-19²⁶ with the adjusted OR of 0.76 between those infected with SARS-CoV-2 with and without vaccination.

In conclusion, the data of 97 712 reproductive-aged women in Brazil infected with SARS-CoV-2 showed that pregnancy has a favorable effect on preventing SARS-CoV-2-related in-hospital mortality, as supported by the results of the multivariate logistics and Cox regression that took into account the confounding effects of sociodemographic factors, epidemiologic characteristics, signs and symptoms, pre-existing medical conditions, and intervention. The covariate omission analysis showed that intervention played an important role in the finding of lower mortality risk pregnant women.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Char Leung was responsible for study design, data collection, data analysis, data interpretation, and drafting the manuscript. Karina Mary de Paiva was responsible for literature review and data interpretation.

CODE AVAILABILITY

Code available upon reasonable request.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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