



# A temporal study of Brazilian pregnant and postpartum women vulnerability for COVID-19: Characteristics, risk factors and outcomes

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## Summary

**Background** During the COVID-19 second wave in Brazil, there has been a significant increase in the number of daily cases and deaths, including pregnant and postpartum women. We assess risk factors and outcomes for this priority group compared to the COVID-19 non-pregnant cohort in two epidemic waves.

**Methods** In this retrospective cohort study we evaluated data of hospitalized pregnant, postpartum, and nonpregnant women aged 15-44 years, between epidemiological weeks 2020-8 and 2021-15, who tested positive for SARS-CoV-2, retrieved from the Influenza Epidemiological Surveillance Information System maintained by Ministry of Health of Brazil. We analysed in-hospital case fatality rate, crude and adjusted risk ratios on different outcomes aiming to compare data in two waves.

**Findings** The study included pregnant women ( $n = 7,132$ ), postpartum women ( $n = 2,405$ ) and nonpregnant women ( $n = 76,278$ ) hospitalized with COVID-19. Case fatality rates of pregnant women were lower in both waves compared to nonpregnant women, but higher among postpartum women. The risk for admission to the intensive care unit and invasive mechanical ventilation requirement in both waves was significantly higher among postpartum women compared to nonpregnant women. Cardiac disease, diabetes, obesity, and asthma were the most frequent underlying medical conditions in all patient groups. These comorbidities were significantly less frequent among pregnant women.

**Interpretation** Pregnant women with COVID-19 are at lower risk of poor outcome compared to nonpregnant women. On the other hand, postpartum women are at higher risk of adverse outcomes compared to pregnant and nonpregnant women, especially during the second wave. There was a significant increase in the in-hospital case fatality rate for all patient groups during the second wave of COVID-19.

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**Keywords:** COVID-19; Pregnancy; Postpartum; In-hospital case fatality rate; Intensive care unit admission; Invasive mechanical ventilation requirement; Risk ratio

## Introduction

Coronavirus disease 2019 (COVID-19) has become a pandemic with sustained transmissibility in several countries, causing multiple infection outbreaks. The etiological agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has given rise to variants with

higher transmissibility, and possibly more lethal.<sup>1</sup> Brazil has been hit hard by the COVID-19 pandemic with a high number of daily reported cases and deaths. As of September, 2021, Brazil registered more than 20 million COVID-19 cases and nearly 586,000 deaths.<sup>2</sup> The reduction in adherence to Non-Pharmaceutical Interventions (NPIs) and the new SARS-CoV-2 variant B.1.1.28.1, named P.1/Gamma variant of concern (VOC), emergence has hampered suppression of transmission. In fact, the outbreak following the first wave

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### Research in context

#### *Evidence before this work*

Preliminary longitudinal evidence has pointed to an increase in the mortality of pregnant and postpartum women with COVID-19 during a second wave in Brazil. However, risks for severe illness and death of Brazilian pregnant and postpartum women with COVID-19 compared to nonpregnant women of reproductive age during the first and second waves of the disease are poorly known.

#### *Added value of this work*

Pregnant women with COVID-19 are at lower risk of adverse outcomes compared to nonpregnant women while postpartum women are at higher risk compared to pregnant and nonpregnant women. During the second wave of COVID-19 in Brazil there was a significant increase in the fatality rate for all patient groups, which coincides with the increased circulation of the SARS-CoV-2 P.1/Gamma variant of concern (VOC).

#### *Implications of all the available evidence*

The very high in-hospital fatality rates for COVID-19 patients aged 15–44 years with cardiac disease, asthma, diabetes and obesity, especially during the second wave, indicate that this population subset deserves special attention. The increased risk of adverse outcomes in hospitalized postpartum women with COVID-19 is evidence for pregnant women to be preventively vaccinated aiming to protect them also in the postpartum period.

has remained at high levels of infection cases and deaths caused by the COVID-19.<sup>2</sup> In Brazil, an oscillating spatio-temporal epidemic dynamic, which we have shown in a previous work<sup>3</sup> has contributed to recurrent COVID-19 outbreaks occurrence.

Studies on risk factors associated with poor outcome for SARS-CoV-2 infected Brazilian pregnant women are still scarce. Preliminary evidence has pointed to an increase in the mortality of pregnant women with COVID-19 during the second wave in Brazil, especially in the second and third trimesters of pregnancy, as well as in the postpartum (up to 45 days after delivery) period.<sup>4</sup> Advanced maternal age, overweight and pre-existing medical conditions (such as hypertension and diabetes) are factors that seem to increase the risk of developing severe COVID-19 for pregnant women or recently pregnant women.<sup>5</sup> Although pregnant women with COVID-19 are less likely than nonpregnant women of reproductive age to have symptoms such as fever and myalgia, they are more vulnerable to severe disease and more likely to be admitted in Intensive Care Units (ICU) or require respiratory support.<sup>6</sup> Data from the US showed that symptomatic pregnant women with

COVID-19 (15–44 years) are more likely to be admitted to ICUs, need Invasive Mechanical Ventilation (IMV), receive extracorporeal membrane oxygenation (ECMO), and dying than nonpregnant women of the same age group. In addition, pregnant women were at increased risk for severe COVID-19.<sup>7</sup>

Like other population groups, most cases of pregnant women with COVID-19 are asymptomatic or moderate.<sup>8</sup> Previous studies have shown that during the first wave of the COVID-19 pandemic, the US pregnant women mortality was low and similar to that of reproductive age nonpregnant women. However, preliminary second wave data from other countries suggest that pregnant and postpartum women are at risk of more severe disease compared to the COVID-19 first wave, which could be related to the emergence of SARS-CoV-2 new variants.<sup>9</sup>

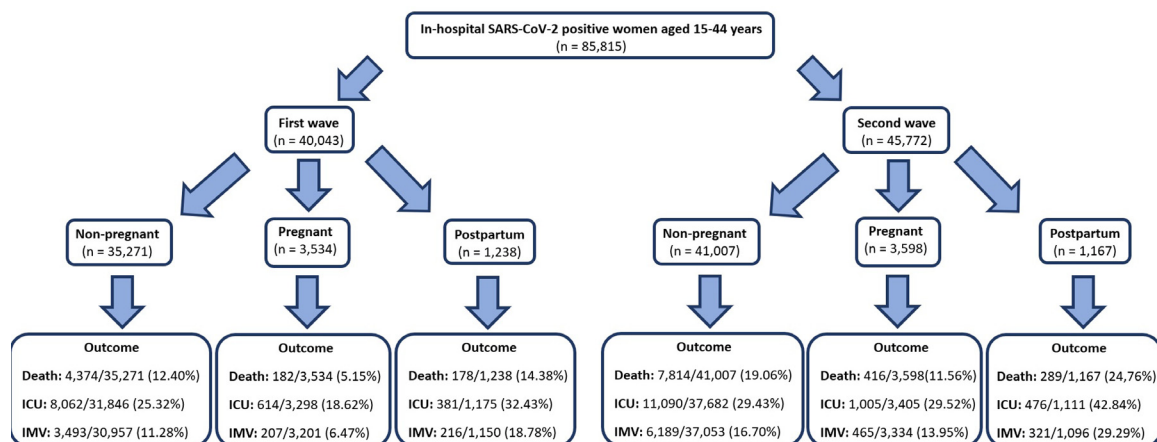
After the P.1 variant emergence, there was a trend towards an increase in ICU admission, IMV need and mortality of patients aged 20–59 years.<sup>3</sup> However, it is unknown if Brazilian pregnant women may be more susceptible than nonpregnant women to severe COVID-19 outcomes during the first and second outbreaks.

Cohort studies of Brazilian pregnant women compared to nonpregnant women of reproductive age infected with SARS-CoV-2 are limited. We consider it is important to compare the two groups in order to verify whether pregnancy and comorbidities are risk factors for developing severe COVID-19. Therefore, we propose to analyze the epidemiological, clinical characteristics, main symptoms, ICU admission, IMV requirement, and outcomes for Brazilian pregnant and postpartum women aged 15–44 years with COVID-19 compared to nonpregnant cohort in the two epidemic waves.

## Methods

### Study design

This is a retrospective cohort study using data collected from the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe)<sup>10</sup> maintained by the Ministry of Health of Brazil. The database concerns nationwide cases of Severe Acute Respiratory Illness (SARI) presenting information of patients hospitalized due to SARI caused by different agents such as SARS-CoV-2, Influenza, Adenovirus, among others (notification is mandatory). We included all cases of hospitalized women aged 15–44 years between epidemiological weeks (EW) 2020–8 and 2021–15 of onset symptoms, who had confirmed SARS-CoV-2 infection. The analyzed period was split in two waves: EW 2020–8 to EW 2020–45, concerning 38 weeks and EW 2020–46 to EW 2021–15, concerning 23 weeks. Data on demographic characteristics, underlying medical conditions, symptoms, maternal status and outcomes was collected. The primary outcome was in-hospital death, and secondary outcomes were ICU admission and IMV requirement



**Figure 1.** Diagram of the study population. Data regarding hospitalized reproductive age women with confirmed SARS-CoV-2 infection, retrieved from SIVEP-Gripe Database and stratified to account for ICU admission, IMV requirement and in-hospital death.

(single incident events) among COVID-19 reproductive age women. [Figure 1](#) presents a diagram of SIVEP-Gripe data used in this study.

### Data analysis

Descriptive statistics are used to provide the features of the data under study. Categorical variables are given in absolute numbers and percentages. In-hospital Case Fatality Rate (hCFR) is given as the number of deaths by the number of hospitalized patients with closed outcome (cure or death) in the given period.

Crude and adjusted Risk Ratios (RR) with 95% Confidence Interval (CI) were calculated using generalized linear regression with a log link and binomial distribution.<sup>11</sup> Risk ratios were adjusted for age, geographical region, and presence of the following symptoms and comorbidities: dyspnoea, respiratory distress,  $SpO_2 < 95\%$ , cardiac disease, diabetes and obesity. Missing information regarding symptoms and comorbidities were assumed as absent in this analysis. Signs/symptoms missing rates correspond to  $\sim 19\%$ ,  $\sim 18\%$  and  $\sim 17\%$  for nonpregnant, postpartum and pregnant women, respectively, while comorbidities missing rates correspond to  $\sim 16\%$ ,  $\sim 35\%$  and  $\sim 17\%$  for nonpregnant, postpartum and pregnant women, respectively. Signs/symptoms and comorbidities are not mutually exclusive. Analysis was conducted separately for each of the two waves of COVID-19 in Brazil.

All analyses were performed using Python (version 3.7.11) and the statistical package scipy (version 1.4.1). P values  $< 0.05$  were considered statistically significant.

### Ethical statement

This retrospective study is based on a publicly available database and did not directly involve patients; it did not require approval by an ethics committee.

### Role of the funding source

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

### Results

We investigated reported cases from the SIVEP-Gripe database of hospitalized reproductive age women (15-44 years) who had positive test results for SARS-CoV-2 throughout 2020 and early 2021 (referred as patients or women along this text). Among all hospitalized patients (85,815 cases), the rates of pregnant and postpartum women were 8.31% (7,132 cases) and 2.80% (2,405 cases), respectively, and the most frequent pregnancy status was the 3rd trimester (4,312 cases; 60.46%) ([Table 1](#)). Disaggregated data of the two waves are reported in [Tables S1](#) and [S2](#).

The highest number of cases for pregnant and postpartum women was in the age group 25-34 years (49.07%; 47.19%, respectively), while for nonpregnant women it was in the age group 35-44 years (62.27%) throughout the analyzed period ([Table 1](#), [Figure 2](#)).

The number of pregnant patients was higher in the Southeast (38.03%) and Northeast (22.91%) regions, with a predominance of brown (51.96%) and white (39.80%) race/color. A similar result was observed for postpartum women. As for education, the highest frequency ( $\sim 54\%$ ) was for women from high school ([Table 1](#)).

The hospitalization records in the first wave (38 epidemiological weeks) account for 40,043 cases with 3,534 (8.82%) pregnant and 1,238 (3.09%) postpartum women, and in the second wave (23 epidemiological weeks) there were 45,772 cases with 3,598 (7.89%) pregnant and 1,167 (2.55%) postpartum women. Therefore, in the second wave there was a significant increase in the hospitalizations in a short period of time, but the

Characteristic	nonpregnant n (%)	postpartum n (%)	pregnant n (%)	total n (%)
<b>wave</b>	76,278 (100.00)	2,405 (100.00)	7,132 (100.00)	85,815 (100.00)
1st wave	35,271 (46.24)	1,238 (51.48)	3,534 (49.55)	40,043 (46.66)
2nd wave	41,007 (53.76)	1,167 (48.52)	3,598 (50.45)	45,772 (53.34)
<b>age group</b>	76,278 (100.00)	2,405 (100.00)	7,132 (100.00)	85,815 (100.00)
15-24	6,533 (8.56)	595 (24.74)	1,793 (25.14)	8,921 (10.40)
25-34	22,246 (29.16)	1,135 (47.19)	3,500 (49.07)	26,881 (31.32)
35-44	47,499 (62.27)	675 (28.07)	1,839 (25.79)	50,013 (58.28)
<b>status</b>			7,132 (100.00)	85,815 (100.00)
1st tri			648 (9.09)	648 (0.76)
2nd tri			1,830 (25.66)	1,830 (2.13)
3rd tri			4,312 (60.46)	4,312 (5.02)
unknown time			342 (4.80)	342 (0.40)
<b>region</b>	76,278 (100.00)	2,405 (100.00)	7,132 (100.00)	85,815 (100.00)
southeast	36,876 (48.34)	876 (36.42)	2,712 (38.03)	40,464 (47.15)
south	12,668 (16.61)	287 (11.93)	961 (13.47)	13,916 (16.22)
northeast	11,476 (15.04)	626 (26.03)	1,634 (22.91)	13,736 (16.01)
midwest	7,791 (10.21)	290 (12.06)	916 (12.84)	8,997 (10.48)
north	7,467 (9.79)	326 (13.56)	909 (12.75)	8,702 (10.14)
<b>race<sup>b</sup></b>	61,097 (100.00)	2,011 (100.00)	5,980 (100.00)	69,088 (100.00)
white	30,843 (50.48)	719 (35.75)	2,380 (39.80)	33,942 (49.13)
brown <sup>c</sup>	26,137 (42.78)	1,130 (56.19)	3,107 (51.96)	30,374 (43.96)
black	3,204 (5.24)	126 (6.27)	367 (6.14)	3,697 (5.35)
asian	681 (1.11)	15 (0.75)	53 (0.89)	749 (1.08)
indigenous <sup>c</sup>	232 (0.38)	21 (1.04)	73 (1.22)	326 (0.47)
<b>education<sup>b,d</sup></b>	29,763 (100.00)	1,054 (100.00)	3,090 (100.00)	33,907 (100.00)
HS	14,987 (50.35)	564 (53.51)	1,673 (54.14)	17,224 (50.80)
HE	7,623 (25.61)	197 (18.69)	565 (18.28)	8,385 (24.73)
ES2	4,184 (14.06)	186 (17.65)	610 (19.74)	4,980 (14.69)
ES1	2,502 (8.41)	96 (9.11)	228 (7.38)	2,826 (8.33)
illiterate	467 (1.57)	11 (1.04)	14 (0.45)	492 (1.45)

**Table 1: Demographic characteristics of reproductive age women with confirmed SARS-CoV-2 infection, by maternal status - Brazil, EW<sup>a</sup> 2020-8 to EW 2021-15.**

<sup>a</sup> EW = epidemiological week.  
<sup>b</sup> Race and education information is partially available. Missing rates correspond to 20% and 60% for race and education, respectively.  
<sup>c</sup> brown = miscegenated race/color, indigenous = Brazilian indigenous.  
<sup>d</sup> ES-1= Elementary School 1; ES-2= Elementary School 2; HS= High School; HE= Higher Education.

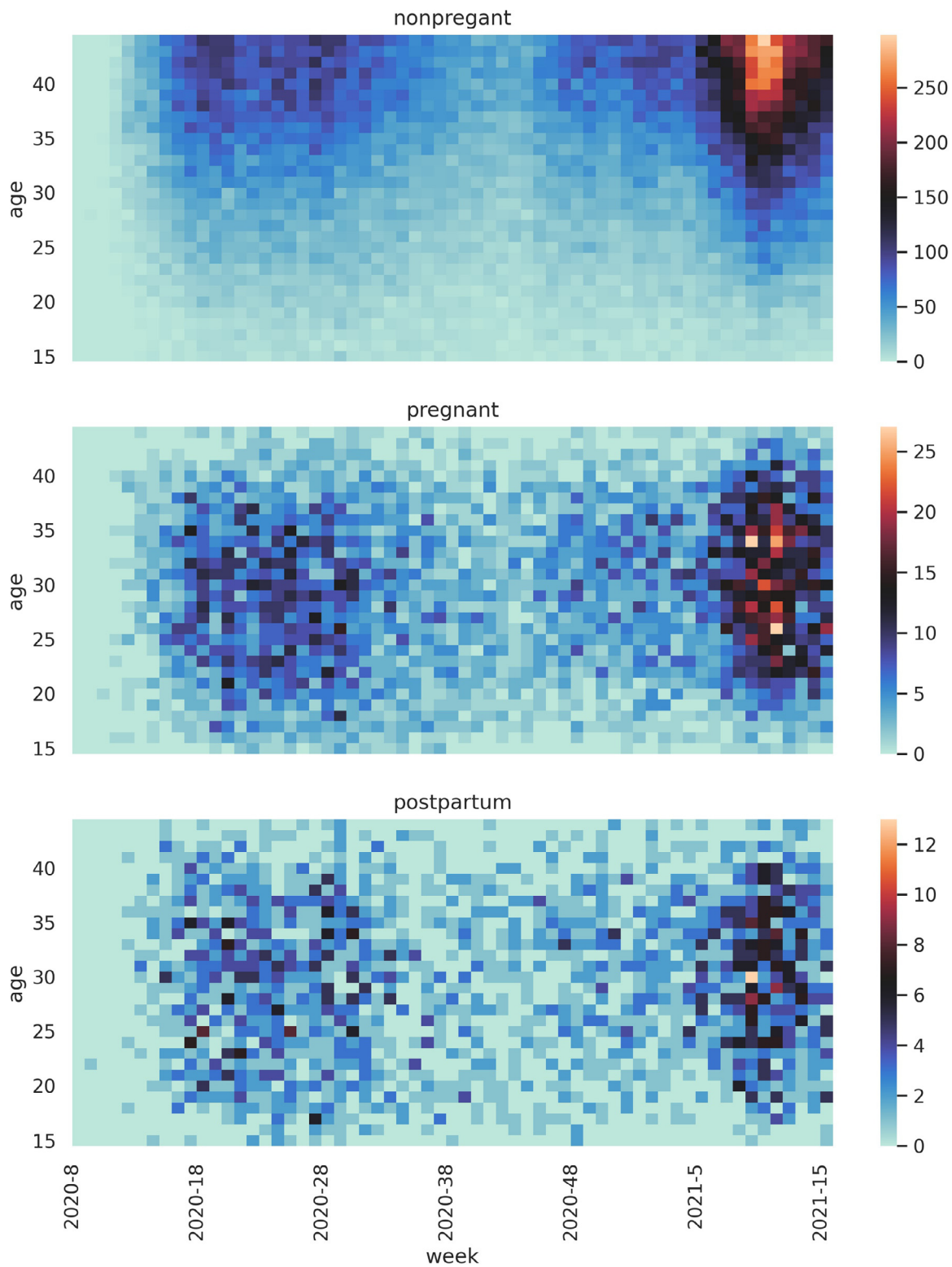
proportion of pregnant, postpartum and nonpregnant cases did not change significantly (Table 1).

The most frequent underlying medical conditions were cardiac disease, diabetes, obesity, and asthma in all groups in both waves. Among pregnant women, cardiac disease, diabetes and obesity were significantly less frequent when compared to nonpregnant women in both waves (Figure 3, Table S3). There was a significant increase in the hospitalization rates of obese patients in the second wave: pregnant (from 4.77% to 7.84%,  $p < 0.001$ ), postpartum (from 7.48% to 11.17%,  $p=0.012$ ) and nonpregnant (from 10.69% to 17.82%,  $p < 0.001$ ) (Figure 3, Table S3).

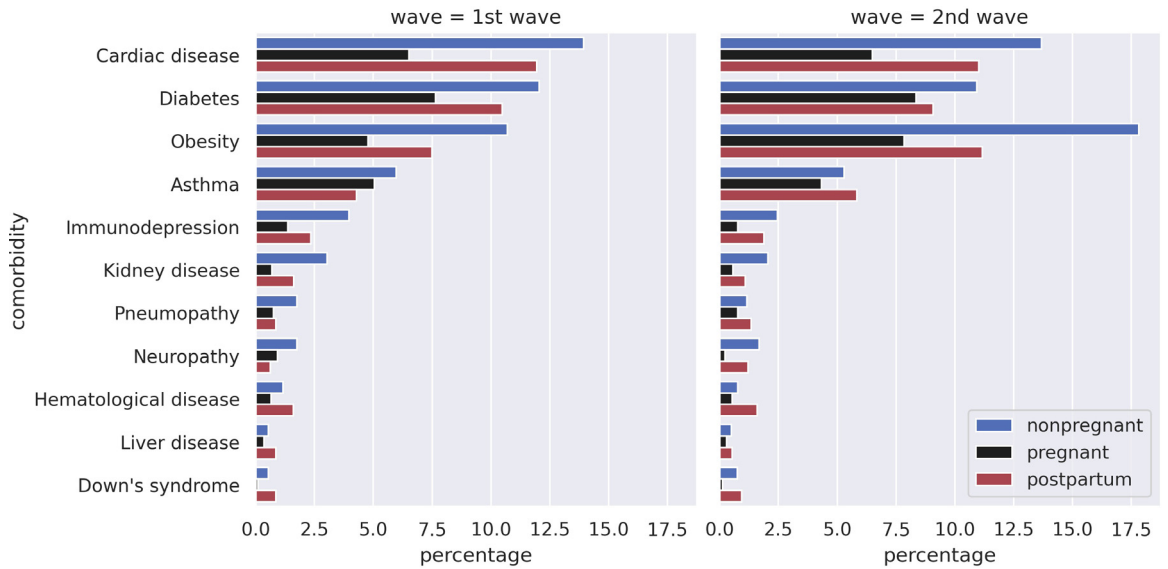
Cough, fever, dyspnoea, respiratory distress and low oxygen saturation were the most frequently reported signs/symptoms, while gastrointestinal symptoms such as diarrhea and vomit were less frequent in all groups.

The frequencies of all signs/symptoms presented by pregnant and postpartum women were lower when compared to nonpregnant women (Figure 4, Table S4). The comparison of signs/symptoms from the first to the second wave shows that there is a significant increase in the frequency of dyspnoea, respiratory distress, and low oxygen saturation for all groups. It is worth mentioning the increase of 77%, 34% and 33% among pregnant, postpartum and nonpregnant women, respectively, in the frequency of low oxygen saturation cases (Figure 4, Table S4).

Mortality from COVID-19 markedly increased in absolute numbers in the second wave in Brazil, including hospitalized pregnant and postpartum women. Thus, the hCFR analysis showed a significant increase in the second wave in pregnant (11.56% vs. 5.15%,  $p < 0.001$ ), postpartum (24.76% vs. 14.38%,



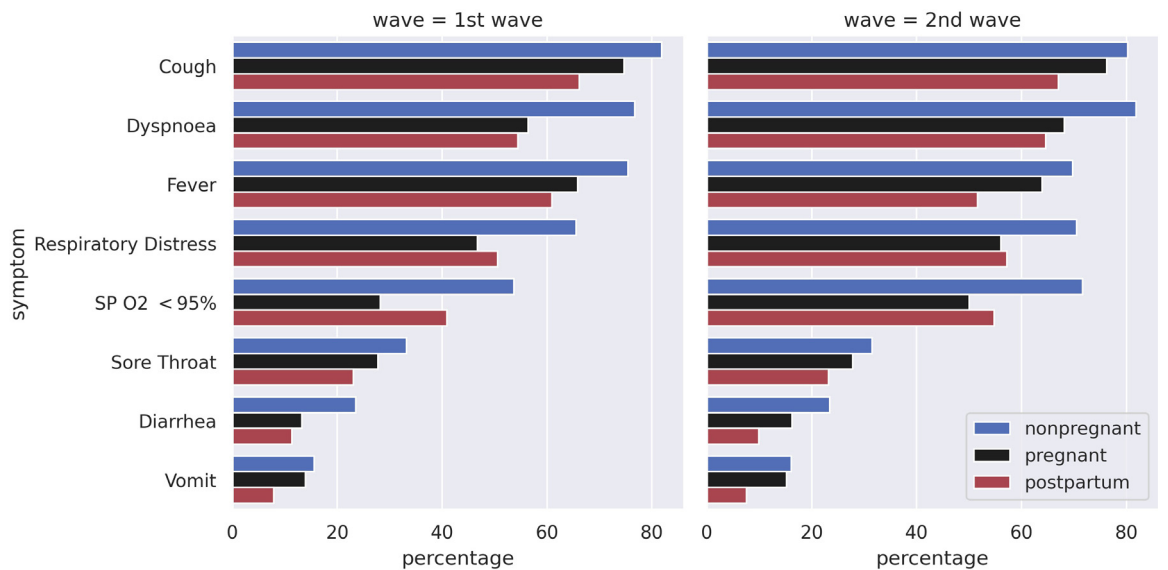
**Figure 2.** Heatmap of hospitalization cases among reproductive age women with confirmed SARS-CoV-2 infection, by maternal status. Colors show the confirmed number of COVID-19 cases from epidemiological week 2020-8 to epidemiological week 2021-15.



**Figure 3.** Most frequent comorbidities among reproductive age women with confirmed SARS-CoV-2 infection, by maternal status - Brazil, 1st wave (EW 2020-8 to EW 2020-45) and 2nd wave (EW 2020-46 to EW 2021-15).

$p < 0.001$ ) and nonpregnant women (19.06% vs. 12.40%,  $p < 0.001$ ) (Table 2). However, fatality rates among pregnant women were much lower than the corresponding cohort of nonpregnant women. In contrast, the highest fatality rates were among postpartum women in both COVID-19 outbreaks (Table 2). The highest hCFR were observed in the 35–44 years age group regardless of the maternal status, and among non-white race/color in both waves. Compared to nonpregnant women, very high hCFR was found among postpartum women in the North (38.30% vs. 23.58,

$p < 0.001$ ) and Northeast (35.16% vs. 23.89,  $p < 0.001$ ) regions during the second wave, while for other regions (Midwest, South and Southeast) it was similar to that of nonpregnant women. In addition, hCFR were higher among women presenting clinical respiratory events, especially low oxygen saturation, and mainly among postpartum women during the second wave. Other relevant findings were high hCFR among patients carrying comorbidities such as cardiac disease, diabetes and obesity, regardless of maternal status (Table 2).



**Figure 4.** Most frequent signs and symptoms among reproductive age women with confirmed SARS-CoV-2 infection, by maternal status - Brazil, 1st wave (EW 2020-8 to EW 2020-45) and 2nd wave (EW 2020-46 to EW 2021-15).

hCFR (%) Characteristic	1st wave			2nd wave		
	nonpregnant	postpartum	pregnant	nonpregnant	postpartum	pregnant
<b>all</b>	12.40	14.38	5.15	19.06	24.76	11.56
<b>age group</b>						
15-24	10.97	11.53	3.81	14.97	16.53	6.88
25-34	10.00	14.39	5.12	17.00	26.08	10.60
35-44	13.83	17.31	6.89	20.45	28.53	16.76
<b>status</b>						
1st tri			4.10			9.67
2nd tri			7.16			13.00
3rd tri			4.75			10.83
unknown time			2.63			16.45
<b>region</b>						
midwest	11.18	6.58	5.38	18.59	18.12	11.44
north	13.22	14.05	5.96	23.58	38.30	13.55
northeast	18.55	15.97	4.98	23.89	35.16	10.19
south	8.49	10.53	2.73	16.94	20.83	8.56
southeast	11.25	16.79	5.53	17.86	19.50	12.90
<b>race</b>						
asian	13.29	16.67	12.12	13.73	22.22	5.00
black	16.47	22.39	8.95	25.54	27.12	14.69
brown <sup>b</sup>	15.94	16.61	5.27	22.08	25.79	13.59
indigenous <sup>b</sup>	15.62	7.14	5.00	23.08	42.86	0.00
white	9.88	13.98	4.49	17.48	23.64	10.14
<b>education<sup>c</sup></b>						
ES1	22.33	7.41	6.92	27.76	21.43	15.31
ES2	18.06	18.28	2.79	24.83	25.81	12.89
HE	07.05	18.48	1.95	14.61	29.52	13.27
HS	11.39	14.92	5.73	19.78	28.25	13.94
<b>symptom</b>						
Dyspnoea	14.34	23.66	8.20	21.23	37.17	15.64
Respiratory Distress	15.19	24.20	09.01	22.54	35.45	16.19
SP O2 <95%	19.17	29.98	13.62	23.53	40.83	19.75
<b>comorbidity</b>						
Cardiac disease	21.12	19.80	14.51	28.59	30.12	19.90
Asthma	12.58	14.29	06.04	20.34	22.73	17.69
Diabetes	24.64	25.29	9.65	30.82	23.19	18.90
Obesity	21.82	29.51	15.71	32.05	38.10	27.31

**Table 2: In-hospital Case Fatality Rate of reproductive age women with confirmed SARS-CoV-2 infection, by maternal status - Brazil, 1st wave (EW<sup>a</sup> 2020-8 to EW 2020-45) and 2nd wave (EW 2020-46 to EW 2021-15).**

<sup>a</sup> EW = epidemiological week.

<sup>b</sup> brown = miscegenated race/color, indigenous = Brazilian indigenous.

<sup>c</sup> ES-1= Elementary School 1; ES-2= Elementary School 2; HS= High School; HE= Higher Education.

A total of 9,057 patients were admitted to ICU (614 pregnant, 381 postpartum and 8,062 nonpregnant women) in the first wave. In the second wave, the number of admissions reached 12,571 (1,005 pregnant, 476 postpartum and 11,090 nonpregnant), showing a significant increase in the number of ICU admissions in a brief period of time. A total of 3,916 patients (216 pregnant, 207 postpartum and 3,493 nonpregnant women) required IMV in the first wave; while, in the second wave, other 6,975 patients (465 pregnant, 321

postpartum and 6,189 nonpregnant women) needed IMV (Table 3).

The hCFRs were significantly high among postpartum and nonpregnant women admitted to the ICU in both waves. Likewise, high fatality rates were observed among postpartum and nonpregnant women requiring IMV. As shown in Table 3, fatality rates increased significantly in the second wave, even among pregnant women admitted to the ICU (from 18.89% to 29.65%) and requiring IMV (from 46.38% to 50.11%).

outcome	1st wave			2nd wave		
	n	total n (%)	deaths, hCFR (%)	n	total n (%)	deaths, hCFR (%)
<b>ICU<sup>b</sup></b>	36,319	9,057 (24.94)	2,817 (31.10)	42,198	12,571 (29.79)	5,451 (43.36)
nonpregnant	31,846	8,062 (25.32)	2,568 (31.85)	37,682	11,090 (29.43)	4,922 (44.38)
postpartum	1,175	381 (32.43)	133 (34.91)	1,111	476 (42.84)	231 (48.53)
pregnant	3,298	614 (18.62)	116 (18.89)	3,405	1,005 (29.52)	298 (29.65)
<b>IMV<sup>b</sup></b>	35,308	3,916 (11.09)	2,308 (58.94)	41,483	6,975 (16.81)	4,526 (64.89)
nonpregnant	30,957	3,493 (11.28)	2,093 (59.92)	37,053	6,189 (16.70)	4,086 (66.02)
postpartum	1,150	216 (18.78)	119 (55.09)	1,096	321 (29.29)	207 (64.49)
pregnant	3,201	207 (6.47)	96 (46.38)	3,334	465 (13.95)	233 (50.11)

**Table 3: Intensive care unit admissions and invasive mechanical ventilation need among reproductive age women with confirmed SARS-CoV-2 infection, by maternal status - Brazil, 1st wave (EW 2020-8 to EW 2020-45) and 2nd wave (EW 2020-46 to EW 2021-15).**

<sup>a</sup> EW = epidemiological week.

<sup>b</sup> ICU and IMV information is partially available. N values according to data availability.

According to our analysis, pregnancy was not a risk factor for IMV requirement in the first wave (aRR = 0.80; 95% CI = 0.70-0.92), but an increased risk was found during the second wave (aRR = 1.12; 95% CI = 1.03 - 1.22) when compared to nonpregnant women. However, pregnant women were significantly less likely to die than nonpregnant women in both the first (aRR = 0.57; 95% CI = 0.49 - 0.66) and the second waves (aRR = 0.80; 95% CI = 0.73-0.87) (Table 4). Compared to nonpregnant women, the risk for ICU admission in the first (aRR = 1.44; 95% CI = 1.36 - 1.52) and in the second wave (aRR = 1.41; 95% CI = 1.35 - 1.48) were significantly higher among postpartum women. Similarly, postpartum women were more likely to require IMV in both the first (aRR = 1.76; 95% CI = 1.61 - 1.92) and second wave (aRR = 1.84; 95% CI = 1.73 - 1.97). However, the risk for death was lower in the first wave (aRR = 0.77; 95% CI = 0.72 - 0.82) and only slightly higher in the second wave (aRR = 1.09; 95% CI = 1.04 -

1.15) among postpartum women compared to nonpregnant women (Table 4). Of note, although crude risk ratios point to an increased risk among postpartum women both in the first and second waves, adjusted risk ratios demonstrate the existence of confounding and how several explanatory variables affect the patient prognosis.

### Discussion

Our study has shown that over the analyzed period there was a significant number of cases of hospitalized pregnant and postpartum women with COVID-19, and a relevant increase in the frequency of cases during the second wave. The fatality rates also increased significantly during the second wave, a period with the Gamma/P.1 variant of concern predominance.

The identification of risk factors for COVID-19 poor outcomes is essential for the establishment of priority

outcome	1st wave				2nd wave			
	Crude		Adjusted <sup>b</sup>		Crude		Adjusted <sup>b</sup>	
	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
<b>ICU</b>								
postpartum vs. nonpregnant	1.28 (1.18-1.39)	<0.001	1.44 (1.36-1.52)	<0.001	1.46 (1.36-1.56)	<0.001	1.41 (1.35-1.48)	<0.001
pregnant vs. nonpregnant	0.74 (0.68-0.79)	<0.001	0.94 (0.87-1.01)	0.079	1.00 (0.95-1.06)	0.917	1.23 (1.17-1.30)	<0.001
<b>IMV</b>								
postpartum vs. nonpregnant	1.66 (1.47-1.89)	<0.001	1.76 (1.61-1.92)	<0.001	1.75 (1.60-1.93)	<0.001	1.84 (1.73-1.97)	<0.001
pregnant vs. nonpregnant	0.57 (0.50-0.66)	<0.001	0.80 (0.70-0.92)	<0.005	0.84 (0.76-0.91)	<0.001	1.12 (1.03-1.22)	0.010
<b>Death</b>								
postpartum vs. nonpregnant	1.16 (1.01-1.33)	0.037	0.77 (0.72-0.82)	<0.001	1.30 (1.17-1.44)	<0.001	1.09 (1.04-1.15)	<0.005
pregnant vs. nonpregnant	0.42 (0.36-0.48)	<0.001	0.57 (0.49-0.66)	<0.001	0.61 (0.55-0.67)	<0.001	0.80 (0.73-0.87)	<0.001

**Table 4: Crude and Adjusted risk ratios of pregnant vs. nonpregnant and postpartum vs. nonpregnant reproductive age women with confirmed SARS-CoV-2 infection - Brazil, 1st wave (EW 2020-8 to EW 2020-45) and 2nd wave (EW 2020-46 to EW 2021-15).**

<sup>a</sup> EW = epidemiological week.

<sup>b</sup> Adjusted for age, region, and presence of the following symptoms and comorbidities: dyspnoea, respiratory distress, SP O<sub>2</sub> <95%, cardiac disease, diabetes and obesity. Missing information regarding symptoms and comorbidities were assumed as absence.



groups during the pandemic, aiming at prevention, protection and appropriate healthcare. During pregnancy, in addition to increased susceptibility to respiratory infection due to physiological cardiorespiratory changes, the maternal immune system undergoes adaptations according to the different gestational stages. Considering that severe COVID-19 is characterized by a cytokine storm, pregnancy women infected by SARS-CoV-2 are at potential risk of developing a more pro-inflammatory severe state, notably in the first and third trimesters of pregnancy, as well as inducing preterm birth.<sup>12</sup> Therefore, a more comprehensive analysis with the objective of delineating the risk factors for this particular group would be fundamental at a time of new variants emergence.

Here, we have demonstrated that pregnant women with COVID-19 aged 15-44 years are not at increased risk of poor outcome compared to nonpregnant cohort, despite the increase in case numbers during the second wave in a brief period of time. On the contrary, in both waves the risk for death was lower among pregnant women compared to postpartum and nonpregnant women with COVID-19. A previous study covering the COVID-19 first wave in Brazil showed a fatality rate of 7.8% among obstetric patients (pregnant/postpartum women) and 13.9% for nonpregnant women.<sup>13</sup> However, our disaggregated data showed that the fatality rate is significantly higher among postpartum women (14.38%) than for pregnant women (5.15%). A recent preliminary study showed a ~2-fold increase in the maternal fatality rate of Brazilian pregnancy or postpartum women in the three first months of 2021 in comparison to 2020, suggesting that it could be due to the circulation of the more infectious and perhaps more lethal SARS-CoV-2 P.1 variant.<sup>14</sup> However, our comparative study showed that the hCFR and risk ratios for pregnant women with COVID-19 were significantly lower in both waves. Our data showed that the main risk group for adverse outcomes are postpartum women, especially in the second wave. In agreement with a recent review showing that among maternal patients the majority of the admission to hospital occurred during pregnancy and death occurred in the postpartum period,<sup>15</sup> we also found the same in both waves of COVID-19. Comparing in-hospital death among US pregnant women with COVID-19,<sup>16</sup> fatality for Brazilian pregnant aged 15-44 years is extremely high (5.15% vs 0.8% in first wave and 11.56% in second wave). On the other hand, our study demonstrated a lower fatality rate among pregnant patients compared to nonpregnant patients, in agreement with Pineles et al. study.<sup>16</sup>

Among Brazilian pregnant women with COVID-19, the fatality rates were higher for second trimester pregnant women in both waves (7.16%; 13.00%). Considering that second trimester pregnant women have a predominance of the Th2 (anti-inflammatory)

immunological response as a protective mechanism for the fetus,<sup>12</sup> it is possible to speculate that they would be more vulnerable to viral infection and complications. It is important to highlight that the highest number of hospitalizations were for postpartum and third trimester pregnant women among maternal patients, but hCFR was higher for second trimester of pregnancy and postpartum women in both COVID-19 waves.

A previous review has shown that COVID-19 severity in pregnancy seems to be similar to nonpregnant women.<sup>17</sup> Despite the small cohort size, a study comparing the clinical characteristics and outcomes of severe and critical cases of COVID-19 for pregnant and nonpregnant women showed higher risk of morbidity, ICU admission, IMV requirement, and disease severity among hospitalized pregnant women.<sup>18</sup> We have not seen such results, as we have shown that COVID-19 severity in pregnant women is lower. Hospitalized pregnant woman group had lower rates of comorbidities, signs/symptoms compared to nonpregnant women. Fatality rates among pregnant women admitted to the ICU and requiring IMV were lower compared to nonpregnant and postpartum women. In contrast, the group of pregnant American patients admitted to the ICU and those who died had more comorbidities compared to the non-pregnant women group. Possibly, these differences in the comorbidities frequencies could explain the results.

An update data from the USA showed that symptomatic pregnant women with COVID-19 (15-44 years) are more likely to be admitted to the ICU, to need IMV, to receive extracorporeal membrane oxygenation (ECMO), and dying than nonpregnant women of the same age group.<sup>7</sup> Among Brazilian pregnant women with COVID-19, only in the second wave the risk for ICU admission and IMV requirement was higher than among nonpregnant women, and on the contrary, pregnant women were significantly less likely to die than nonpregnant women in both waves. Also, the data indicates that postpartum women are at highest risk for ICU admission and IMV requirement when compared to pregnant and nonpregnant cohorts.

Preliminary second wave data in some countries suggest that pregnant and peripartum women are at risk for more severe disease compared to the COVID-19 first-wave, which could be related to the emergence of SARS-CoV-2 new variants.<sup>9</sup> A study performed with Spanish obstetric COVID-19 patients showed worsening respiratory symptoms during the second wave.<sup>19</sup> A major data analysis carried out in the UK covering the waves March 2020-November 2020 and December 2020-February 2021 showed that among hospitalized COVID-19 pregnant women aged 20-39 years, 10% received critical care, 1% died, and 18% had a preterm birth. In addition, since the B.1.1.7 variant became predominant (second wave), the number of pregnant women with COVID-19 admitted to the hospital were more than twice higher

and more likely to require respiratory support, and obesity was significantly associated with adverse outcome.<sup>20</sup> We also found a similar picture among Brazilian pregnant women with COVID-19 during the second wave, when the P.1 variant circulation increased, and likewise, obesity has become a relevant risk factor in this group of patients. Notably, several studies have suggested that maternal obesity is a risk factor for more severe COVID-19, possibly due to changes in the immune response induced by obesity.<sup>21</sup>

It is known that underlying health conditions may worsen the COVID-19 severity. Among US women, symptomatic pregnant and nonpregnant women with COVID-19 had underlying medical conditions such as chronic lung disease, diabetes mellitus, and cardiovascular disease more frequent among pregnant women than among nonpregnant women.<sup>7,22</sup> Contrary to the aforementioned studies, comorbidities such as cardiac disease, diabetes and obesity were more frequent among nonpregnant women with COVID-19 aged 15-44 years in our study.

A systematic review showed that maternal mortality rate was 1.3% among pregnant/postpartum women aged 15-48 years with COVID-19. However, this rate was quite variable, with lower rates in high-income countries compared to low-income countries, suggesting the influence of socioeconomic factors and access to healthcare.<sup>23</sup> In fact, in addition to the possible risk due to pregnancy, maternal mortality can be influenced by access to the healthcare for prenatal care, childbirth and postpartum, which is quite varied in Brazil. The higher mortality among pregnant and postpartum women with COVID-19 in Brazil compared to other countries is possibly also due to the lower access and availability of healthcare. Overall, we have found higher hCFR among women aged 15-44 years with COVID-19 from the North and Northeast regions, economically less-developed, demonstrating that there are regional differences. Brazil has a Unified Health System (SUS), which guarantees full, universal and free access for the Brazilian population, however, due to regional socioeconomic differences, hospital infrastructure and healthcare in all 27 federative units varies. Indeed, a recent study showed a heterogeneous distribution of cases and deaths in different Brazilian regions with higher maternal death by COVID-19 associated to poor urban infrastructure and high social inequality.<sup>24</sup> Importantly, during the second wave, Brazil had an explosion of cases and, in some regions, there was a lack of ICU beds and medicinal oxygen, which may also have compromised the care of COVID-19 patients aged 15-44 years.

A previous review has shown that COVID-19 severity in pregnancy seems to be similar to nonpregnant women.<sup>17</sup> Another comprehensive review involving pregnant women with COVID-19 from fifteen different countries demonstrated that maternal characteristics, clinical symptoms, maternal and neonatal outcomes are not worse or different from the general population.<sup>25</sup>

Therefore, our study suggests that special attention should be given to hospitalized women with COVID-19 aged 15-44 years, regardless of gestational status, and especially for second trimester pregnant women and postpartum, at this time of SARS-CoV-2 new variants emergence. In addition, the very high in-hospital fatality rates for COVID-19 patients aged 15-44 years with cardiac disease, asthma, diabetes and obesity, especially during the second wave, indicate that this population subset deserves special attention. Brazil included pregnant, postpartum and breastfeeding women as priority groups for vaccination in July, 2021.<sup>26</sup> However, our study shows that nonpregnant women with comorbidities should be considered a priority as well.

In summary, our study demonstrated that clinical respiratory events, comorbidities such as cardiac disease, diabetes and obesity, and certain demographic characteristics are risk factors for poor outcome during pregnancy and postpartum period. The identification of risk factors can assist in prevention, protection and establishment of priority groups for vaccination. Thus, preventive vaccination of pregnant women, especially those with comorbidities, could protect them in the postpartum period.

The main strengths of our study were the extensive data analysis of hospitalized reproductive age patients (15-44 years) with COVID-19 and the comparison of outcomes between pregnant, postpartum and nonpregnant women during the two COVID-19 waves that have hit Brazil. Considering that the largest and main database in Brazil that we use is fed with information only from hospitalized COVID-19 patients, the main limitation of our study was the impossibility of comparison with data from asymptomatic/mild/moderate pregnant women or even from non-infected pregnant by the SARS-CoV-2.

#### Contributors

FSHS, NSH-S and DLG conceived and designed the study. FSHS, NSH-S, CMS and DLG analysed and interpreted the data. NSH-S, FSHS and DLG wrote the manuscript. All authors reviewed earlier drafts and approved its final version.

#### Data sharing

The data used in this work is publicly available.<sup>10</sup>

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**Declaration of interests**

The authors declare no competing interests.

**Supplementary materials**

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2022.100197.

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