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Are in-hospital COVID-19-related mortality and morbidity in pregnancy associated with gestational age?

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KEYWORDS: COVID-19; gestational age; morbidity; mortality; SARS-CoV-2; trimester

CONTRIBUTION

What are the novel findings of this work?
In pregnant women with confirmed coronavirus disease 2019 (COVID-19), gestational age at infection was not associated with the risk of in-hospital COVID-19-related morbidity and mortality. Admission to a hospital with an obstetric center was associated with lower risk of mortality and private not-for-profit healthcare was associated with lower risk of morbidity in these women.

What are the clinical implications of this work?
Despite the higher percentage of women admitted to hospital in the third trimester, we found no association between gestational age and COVID-19-related mortality and morbidity. The previously reported increase in morbidity and mortality in the third trimester in pregnant women with COVID-19 may be attributable to other gestational-age-affected variables for which adjustment was made in our study.

ABSTRACT

Objective *Pregnancy involves dynamic changes in the maternal immune system, thus potentially affecting women's response to infection. The aim of this study was to investigate whether gestational age at the time of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with mortality and morbidity related to coronavirus disease 2019 (COVID-19) in hospitalized pregnant women.*

Methods *This was a cohort study of pregnant women with confirmed SARS-CoV-2 infection at any gestational age (categorized into trimesters) who were hospitalized in Brazil from February 2020 to November 2021. Sociodemographic and epidemiological characteristics, signs and symptoms, comorbidities, interventions, vaccination status and type of healthcare establishment were obtained from a nationwide database. Multivariate logistic and Cox regression analyses were used to identify independent risk factors for in-hospital COVID-19-related mortality and morbidity (defined as time from hospital admission to recovery).*

Results *A total of 7461 SARS-CoV-2-infected pregnant women were included in the study (9.3%, 28.4% and 62.3% in the first, second and third trimesters, respectively). After adjustment for sociodemographic, epidemiological and clinical characteristics, and intervention-related variables, gestational age at infection was found not to be associated with COVID-19-related mortality and morbidity. Women admitted to establishments with an obstetric center, compared to hospitals without, were 38% less likely to die from SARS-CoV-2 infection (adjusted odds ratio, 0.62; 95% CI, 0.48–0.80), while patients who received private not-for-profit healthcare had a 13% shorter time to recovery (adjusted hazard ratio, 1.13; 95% CI, 1.07–1.20) compared to those who received public healthcare.*

Conclusions *Despite a higher percentage of women being admitted in the third trimester, we found no association between gestational age and COVID-19 mortality and morbidity. The previously reported increase in morbidity and mortality in the third trimester in pregnant women with COVID-19 may be attributable to other gestational-age-affected variables for which adjustment was made in our study.* © *2022 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), one of three coronaviruses that are responsible for acute respiratory disease syndrome in humans, along with Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV)[1]. Symptoms of COVID-19 may include cough, fever and difficulty breathing[2]. Respiratory failure and cytokine release syndrome are common causes of death[3].

Research has been performed to identify COVID-19-related mortality and morbidity risk factors in various population groups, including elderly people[4] and immunocompromised individuals[5]. Because the maternal immune system is suppressed in order to tolerate the fetus[6], a number of studies have investigated the impact of SARS-CoV-2 infection on maternal health. However, the findings remain contradictory. Some studies have found a higher rate of mortality[7–9] and a more severe outcome[9,10] in pregnant women compared with non-pregnant women, whereas other studies found similar clinical characteristics or severity between the two populations[11–14] or even milder symptoms and lower mortality in pregnant women[15–18].

Pregnancy is a complex process characterized by dynamic changes in the maternal immune system[19]. It has been suggested that SARS-CoV-2 infection has different impacts on maternal cytokine profiles according to gestational age[20]. As a result, the stage of pregnancy may be associated with different risks of mortality and morbidity. In this context, this study investigated whether gestational age is associated with in-hospital COVID-19 mortality and morbidity risks in pregnant women.

METHODS

Study cohort

This was a cohort study of pregnant women with confirmed SARS-CoV-2 infection who were hospitalized in Brazil from the index case on 25 February 2020 to 29 November 2021. Data were obtained from SIVEP-Gripe (Sistema de Informação de Vigilância Epidemiológica da Gripe), a Brazilian nationwide database, that has been described in more detail elsewhere[18,21]. Developed by the Federal Government of Brazil during the influenza pandemic in 2009, SIVEP-Gripe aims to strengthen surveillance of severe acute respiratory syndrome-related viral infection. To be registered in SIVEP-Gripe, the patient must be diagnosed with one of the notifiable diseases and be admitted to a public or private hospital. Sociodemographic, epidemiological and clinical measures are registered systematically in a predetermined form. Certified medical practitioners at the point of care verify the content. When SARS-CoV-2 became a notifiable disease[22], SIVEP-Gripe became the primary source of data on hospitalized COVID-19 cases in Brazil.

Data were gathered from the database on 30 November 2021, and cases meeting all of the following criteria were included in the study: (1) SARS-CoV-2 infection confirmed by testing using polymerase chain reaction (PCR), (2) woman aged between 15 and 45 years, inclusive, (3) pregnant at the time of COVID-19 diagnosis, and (4) had reached the clinical endpoint (death or recovery). Patients who died of causes other than SARS-CoV-2 infection were included as a reference but were excluded in subsequent statistical analysis. The included patients were categorized according to trimester (first, second or third trimester).

Outcome measures

The primary aim was to determine whether gestational age was associated with increased risk of in-hospital COVID-19 mortality, defined as death due to COVID-19. The secondary aim was to determine whether gestational age was associated with increased risk of in-hospital COVID-19 morbidity, defined as time from admission to recovery.

Data sources and definitions

The following data were extracted from the database: sociodemographic characteristics (age, ethnicity, location, smoking status), epidemiological characteristics (wave of pandemic, time from symptom onset to admission, time from admission to recovery, nosocomial infection, history of exposure to animals with COVID-19), signs and symptoms (asymptomatic, abdominal pain, abnormal chest X-ray, anosmia, ageusia, coryza, cough, diarrhea, dyspnea, fatigue, fever, headache, myalgia, $SaO_2 < 95\%$, respiratory discomfort, sore throat, vomiting, other), comorbidities (asthma, chronic cardiovascular disease, chronic hematological disease, chronic liver disease, chronic neurological disease, chronic pulmonary disease, chronic renal disease, cancer, diabetes, maternal Down syndrome, immunodeficiency, obesity, respiratory viral infection), intervention (admission to the intensive care unit, ventilation, use of antiviral treatment), history of vaccination (influenza, SARS-CoV-2) and the characteristics of the healthcare establishment (whether the healthcare establishment was in a metropolitan region, whether an obstetric center was present in the healthcare establishment, and the type of healthcare provider).

Age, ethnicity and location were self-identified. Ethnicity was based on the five classifications defined by the Brazilian Institute of Geography and Statistics: white (Branco), black (Preto), mixed (Pardo), Asian (Amarelo) or indigenous (Indígena)[21]. Location refers to the five geopolitical regions in Brazil (North, Northeast, Southeast, Central-West and South). The first wave of the pandemic was defined as cases that were confirmed before 1 November 2020 (before emergence of the P.1 strain)[23]. Signs and symptoms refer to those at symptom onset or at admission. Chest X-ray findings of interstitial infiltrate and consolidation were defined as abnormal. Respiratory viral infections were confirmed using PCR testing for viruses that cause common upper respiratory tract infections, including adenovirus, bocavirus, enterovirus,

human parainfluenza virus, influenza, metapneumovirus, respiratory syncytial virus, rhinovirus, and other coronaviruses that do not generally cause acute respiratory distress syndrome. Antiviral treatment referred to those against influenza, such as oseltamivir and zanamivir. For analysis, the presence of comorbidities was categorized into four groups: none, one, two, and three or more. Metropolitan regions referred to those legally defined as such by the Brazilian government. An obstetric center was defined as an establishment with predelivery, delivery and/or facilities for dilatation and curettage. The type of healthcare provider included private (for profit), private (not for profit) and public.

Complete data were not available for all variables. For deceased patients, the time from admission to recovery was recorded as 'NA' and omitted from the relevant analysis. If data were missing regarding signs, symptoms, history of exposure to animals, nosocomial infection or comorbidities, we assumed that characteristic to be absent[18]. Data on abnormal chest X-ray were missing if imaging was not performed or registered. Cases with missing ethnicity were also excluded from the relevant analysis.

Statistical analysis

Descriptive statistics were computed, and statistical tests between gestational age groups were performed. ANOVA or Kruskal–Wallis tests were used for comparison of continuous variables, depending on data normality, and χ^2 tests were used for comparison of dichotomous variables.

Multivariate logistic regression analysis was used to calculate the relative risk for in-hospital mortality, measured using odds ratio (OR). To further examine the difference in the mortality risk factors according to gestational age, a similar logistic regression procedure was repeated for each gestational-age group. Multivariate Cox regression for survival analysis was used to calculate the relative risk for in-hospital morbidity, measured using hazard ratio (HR), which measures the association with recovery rather than with time to recovery. Both regression models were adjusted for sociodemographic, epidemiological, clinical and intervention variables. For the location variable, Southeast region was chosen as the reference group because it has more advanced healthcare compared with other regions in Brazil. Black/mixed was chosen as the reference group for ethnicity as it represents the largest ethnic group in the Brazilian population. 'First trimester' was chosen as the reference group for gestational age. Public healthcare was chosen as the reference group for the type of healthcare provider. We did not include all covariates in the multivariate analyses because collinearity or confounding may inflate standard errors. Therefore, a forward stepwise procedure was adopted for variable selection, with a P-value < 0.1 as the threshold. The area under the receiver-operating-characteristics curve (AUC) and the concordance index were used to assess the goodness-of-fit of the multivariate logistic regression and multivariate Cox regression models, respectively.

A subgroup analysis restricted to severe cases only (defined as low oxygen saturation $SaO_2 < 95\%$[24]) served as sensitivity analysis. The multivariate logistic and Cox regression models specified in the original analysis were fitted to severe cases.

All statistical analyses were performed using R software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) using the ggm, nnet, survival and ggplot2 packages. A P-value < 0.05 was considered statistically significant.

RESULTS

Descriptive statistics

As of 29 November 2021, a total of 2 825 170 cases of notifiable diseases were identified in the database, of which 1 165 624 (41.3%) were SARS-CoV-2 infections diagnosed by PCR testing (Figure 1). Of the PCR-positive cases, 515 926 (44.3%) were women and 649 551 (55.7%) were men; the gender was missing in 147 cases (< 1%). Of the female patients, 115 098 (22.3%) were aged between 15 and 45 years, of whom 105 395 (91.6%) reached the clinical endpoint (death or recovery); clinical status was missing in 9703 (8.4%). Of these 105 395 women, 97 512 (92.5%) were not pregnant at the time of SARS-CoV-2 diagnosis, and details of obstetric status were missing or were incorrect for 422 (0.4%). The remaining 7461 (7.1%) women were pregnant and were included in the study (Figure 1).

The main findings of the study are shown in Table 1. First-, second- and third-trimester cases accounted for

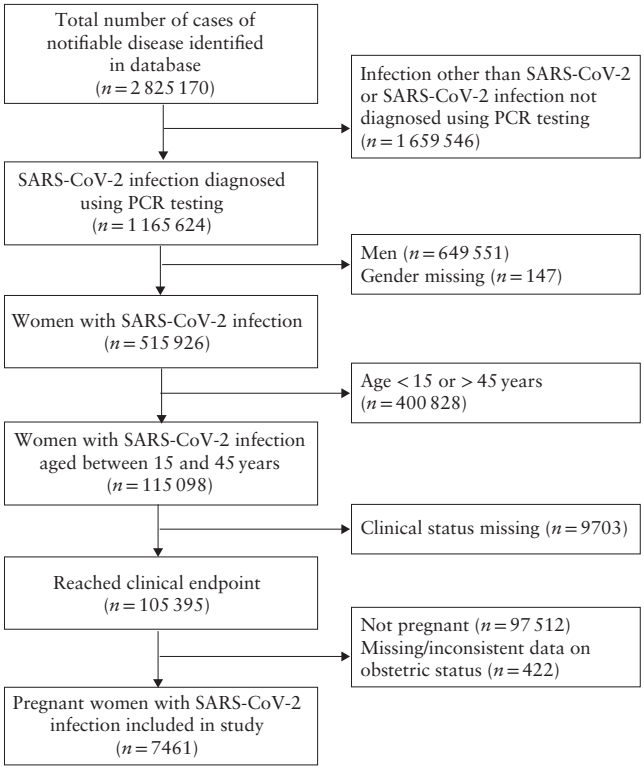

Figure 1 Flowchart showing inclusion in study cohort of pregnant women who were hospitalized with confirmed SARS-CoV-2 infection in Brazil from February 2020 to November 2021. PCR, polymerase chain reaction.

9.3%, 28.4% and 62.3% of the included cases, respectively. The COVID-19 case-fatality rates for the first-, second- and third-trimester groups were 7.5%, 11.0% and 8.7%, respectively, and the difference was significant ($P = 0.002$). The median time to recovery was also significantly different between groups ($P < 0.001$), with the second-trimester group having the longest median time to recovery (7 days), followed by the third-trimester group (6 days) and the first-trimester group (5 days), similar to the pattern seen for case-fatality rate. However, this may be attributed to a variety of factors, such as the significant differences in maternal age and Northeast and Southeast locations between the trimester groups. The prevalence of many pre-existing conditions also differed between groups, including maternal Down syndrome ($P = 0.018$), asthma ($P = 0.008$), diabetes ($P = 0.017$), obesity ($P = 0.034$) and chronic renal disease ($P = 0.013$). Not surprisingly, gestational diabetes had significantly higher prevalence in the third trimester ($P < 0.001$) than in the second and first trimesters (first trimester, 0.3%; second trimester, 1.2%; third trimester, 2.1%). Signs and symptoms such as $SaO_2 < 95\%$ (33.5%, 47.0% and 35.3% in the first-, second- and third-trimester groups, respectively; $P < 0.001$) and dyspnea (54.0%, 68.8% and 56.6% in the first-, second- and third-trimester groups, respectively; $P < 0.001$), which usually indicate a more severe clinical course, were also found to be significantly different according to the trimester of pregnancy. Interestingly, the pattern of prevalence of these variables also matched the pattern of the case-fatality rate. Finally, patients with advanced gestational age were more likely to be admitted to healthcare establishments with better facilities, as indicated by the location of the establishment (i.e. in the metropolitan region) (53.4%, 59.1% and 62.8% in the first-, second- and third-trimester groups, respectively; $P < 0.001$) and the presence of an obstetric center (80.0%, 82.5% and 89.0% in the first-, second- and third-trimester groups, respectively; $P < 0.001$).

Association between mortality and gestational age

The results of the multivariate logistic regression analysis are shown in Figure 2. Using first-trimester exposure as the reference group, the adjusted ORs (aORs) for second- and third-trimester exposure were not significant. Therefore, gestational age at SARS-CoV-2 infection was not associated with increased risk for mortality. Moreover, confounding effects among these measures were apparent, as shown by the difference in the 95% CIs between the crude ORs and aORs. With respect to location, patients in the North region of Brazil (aOR, 1.87; 95% CI, 1.30–2.66) were 87% more likely to die compared with those in the Southeast region. Compared to women of black/mixed ethnicity, women of Caucasian ethnicity were 36% less likely to die from SARS-CoV-2 infection (aOR, 0.64; 95% CI, 0.52–0.79). Patients admitted to establishments with an obstetric center, compared to those without, were 38% less likely to

Table 1 Sociodemographic factors, epidemiological characteristics, signs and symptoms, comorbidities and healthcare-related factors in 7461 pregnant women who were hospitalized with confirmed SARS-CoV-2 infection in Brazil

Variable	*First trimester (n = 696)*	*Second trimester (n = 2117)*	*Third trimester (n = 4648)*	P
Died of COVID-19	52/695 (7.5)	233/2111 (11.0)	402/4640 (8.7)	0.002
Died of causes other than COVID-19	1 (0.1)	6 (0.3)	8 (0.2)	0.599
Sociodemographic				
Age (years)	31 (26–35)	31 (26–36)	30 (25–35)	< 0.001
Region in Brazil				
North	42 (6.0)	133 (6.3)	287 (6.2)	0.969
Northeast	113 (16.2)	294 (13.9)	771 (16.6)	0.017
Southeast	336 (48.3)	1032 (48.7)	2082 (44.8)	0.005
Central-West	91 (13.1)	317 (15.0)	685 (14.7)	0.452
South	114 (16.4)	341 (16.1)	823 (17.7)	0.232
Ethnicity				
White	271/583 (46.5)	886/1792 (49.4)	1822/3917 (46.5)	0.110
Asian	7/583 (1.2)	21/1792 (1.2)	29/3917 (0.7)	0.205
Black/mixed	303/583 (52.0)	880/1792 (49.1)	2051/3917 (52.4)	0.071
Indigenous	2/583 (0.3)	5/1792 (0.3)	15/3917 (0.4)	0.826
Smoker	1 (0.1)	15 (0.7)	20 (0.4)	0.124
Epidemiological				
Nosocomial infection	7 (1.0)	16 (0.8)	44 (1.0)	0.706
Exposure to animal with COVID-19	4 (0.6)	16 (0.8)	37 (0.8)	0.821
First-wave infection	248 (35.6)	674 (31.8)	1562 (33.6)	0.140
Time from symptom onset to admission (days)*	6 (3–9)	7 (4–9)	6 (3–9)	< 0.001
Time from admission to recovery (days)†	5 (3–8.5)	7 (4–12)	6 (3–10)	< 0.001
Time from admission to death from COVID-19 (days)‡	13 (7.5–21)	14.5 (7–22)	14 (7–21)	0.661
Signs and symptoms				
Asymptomatic	1 (0.1)	1 (0.05)	31 (0.7)	0.001
Abdominal pain	62 (8.9)	143 (6.8)	267 (5.7)	0.004

Continued over.

Table 1 *Continued*

Variable	*First trimester (n = 696)*	*Second trimester (n = 2117)*	*Third trimester (n = 4648)*	P
Abnormal chest X-ray	85/102 (83.3)	388/452 (85.8)	659/754 (87.4)	0.456
Anosmia	102 (14.7)	330 (15.6)	664 (14.3)	0.374
Ageusia	91 (13.1)	295 (13.9)	593 (12.8)	0.413
Coryza	61 (8.8)	165 (7.8)	484 (10.4)	0.002
Cough	491 (70.5)	1632 (77.1)	3297 (70.9)	< 0.001
Diarrhea	89 (12.8)	261 (12.3)	406 (8.7)	< 0.001
Dyspnea	376 (54.0)	1457 (68.8)	2633 (56.6)	< 0.001
Fatigue	139 (20.0)	512 (24.2)	869 (18.7)	< 0.001
Fever	423 (60.8)	1339 (63.2)	2571 (55.3)	< 0.001
Headache	136 (19.5)	380 (17.9)	775 (16.7)	0.114
Myalgia	98 (14.1)	331 (15.6)	685 (14.7)	0.507
$SaO_2 < 95\%$	233 (33.5)	996 (47.0)	1639 (35.3)	< 0.001
Respiratory discomfort	288 (41.4)	1121 (53.0)	1942 (41.8)	< 0.001
Sore throat	160 (23.0)	444 (21.0)	978 (21.0)	0.480
Vomiting	105 (15.1)	255 (12.0)	464 (10.0)	< 0.001
Other	324 (46.6)	945 (44.6)	2171 (46.7)	0.277
Comorbidity				
None	522 (75.0)	1559 (73.6)	3432 (73.8)	0.772
One	124 (17.8)	377 (17.8)	842 (18.1)	0.946
Two	35 (5.0)	141 (6.7)	289 (6.2)	0.303
Three or more	15 (2.2)	40 (1.9)	85 (1.8)	0.838
Chronic cardiovascular disease	37 (5.3)	116 (5.5)	279 (6.0)	0.593
Chronic hematological disease	5 (0.7)	17 (0.8)	37 (0.8)	0.974
Chronic liver disease	1 (0.1)	2 (0.1)	12 (0.3)	0.355
Chronic neurological disease	5 (0.7)	17 (0.8)	24 (0.5)	0.353
Chronic pulmonary disease	5 (0.7)	16 (0.8)	30 (0.6)	0.872
Chronic renal disease	8 (1.1)	12 (0.6)	16 (0.3)	0.013
Asthma	28 (4.0)	102 (4.8)	152 (3.3)	0.008
Cancer	3 (0.4)	3 (0.1)	11 (0.2)	0.373
Diabetes	36 (5.2)	148 (7.0)	373 (8.0)	0.017
Down syndrome (maternal)	2 (0.3)	1 (0.05)	1 (0.02)	0.018
Endocrine disease	6 (0.9)	39 (1.8)	81 (1.7)	0.197
Gestational diabetes	2 (0.3)	25 (1.2)	96 (2.1)	< 0.001
Human immunodeficiency virus	1 (0.1)	3 (0.1)	5 (0.1)	0.916
Immunocompromised	8 (1.1)	22 (1.0)	42 (0.9)	0.758
Maternal hypertensive disorder	31 (4.5)	79 (3.7)	201 (4.3)	0.488
Mental disorder	4 (0.6)	7 (0.3)	15 (0.3)	0.567
Obesity§	60 (8.6)	179 (8.5)	319 (6.9)	0.034
Respiratory viral infection	3 (0.4)	1 (0.05)	10 (0.2)	0.099
Intervention				
Antiviral treatment	68 (9.8)	258 (12.2)	512 (11.0)	0.161
ICU admission	147 (21.1)	737 (34.8)	1257 (27.0)	< 0.001
Ventilation	304 (43.7)	1196 (56.5)	2104 (45.3)	< 0.001
Vaccination				
Against influenza	78 (11.2)	302 (14.3)	796 (17.1)	< 0.001
Against SARS-CoV-2	38 (5.5)	108 (5.1)	238 (5.1)	0.925
CoronaVac	15 (2.2)	49 (2.3)	99 (2.1)	0.889
BNT162b2	15 (2.2)	37 (1.7)	104 (2.2)	0.423
AZD1222	4 (0.6)	13 (0.6)	13 (0.3)	0.099
Ad26.COV2.S	3 (0.4)	1 (0.05)	1 (0.02)	< 0.001
Not known	1 (0.1)	8 (0.38)	21 (0.5)	0.478
Type of healthcare establishment				
In metropolitan region	372 (53.4)	1251 (59.1)	2921 (62.8)	< 0.001
Obstetric center in establishment	557 (80.0)	1747 (82.5)	4136 (89.0)	< 0.001
Type of healthcare provider				
Private (for profit)	219/692 (31.6)	631/2099 (30.1)	1496/4619 (32.4)	0.165
Private (not for profit)	141/692 (20.4)	422/2099 (20.1)	805/4619 (17.4)	0.013
Public	332/692 (48.0)	1046/2099 (49.8)	2318/4619 (50.2)	0.556

Data are given as *n*/*N* (%), *n* (%) or median (interquartile range). Data available in: *648 women in first-trimester, 2026 in second-trimester and 4492 in third-trimester group; †575 women in first-trimester, 1745 in second-trimester and 4002 in third-trimester group; ‡51 women in first-trimester, 224 in second-trimester and 397 in third-trimester group. §Obesity was defined as body mass index > 30 kg/m^2. ICU, intensive care unit; SaO_2, oxygen saturation measured by blood analysis.

die from SARS-CoV-2 infection (aOR, 0.62; 95% CI, 0.48–0.80).

The AUC for the multivariate logistic regression model was 0.844 (95% CI, 0.832–0.856), indicating excellent accuracy. The results of the sensitivity analysis of severe cases are shown in Figure S1. As shown by the overlapping 95% CIs, the aORs for severe cases were similar to their counterparts in the original analysis, indicating robust results.

The results of a similar logistic regression analysis by gestational-age group are shown in Figure S2. The impact of risk factors was similar between gestational-age groups, as shown by the overlapping 95% CIs.

Association between morbidity and gestational age

The results of the multivariate Cox regression analysis are shown in Figure 3. Using first-trimester exposure as reference, the adjusted HRs (aHRs) for second- and third-trimester exposure were not significant. Therefore, gestational age at SARS-CoV-2 infection was not associated with increased risk of morbidity. Patients from the North (aHR, 0.80; 95% CI, 0.70–0.90) and Northeast (aHR, 0.90; 95% CI, 0.83–0.98) regions of Brazil had 20% and 10% longer times to recovery, compared with those from the Southeast region. Time to recovery was reduced by 7% in Caucasian women (aHR, 1.07; 95% CI, 1.00–1.14) compared with women of black/mixed ethnicity. Vaccination against SARS-CoV-2 reduced the time to recovery by 14% (aHR, 1.14; 95% CI, 1.01–1.28). Compared to public healthcare, patients who received private (not for profit) healthcare had a 13% shorter time to recovery (aHR, 1.13; 95% CI, 1.07–1.20).

The concordance index was 0.708 (95% CI, 0.701–0.716), indicating good accuracy. The 95% CIs from the sensitivity analysis overlapped with the corresponding 95% CIs from the original analysis, demonstrating robustness of the results (Figure S3).

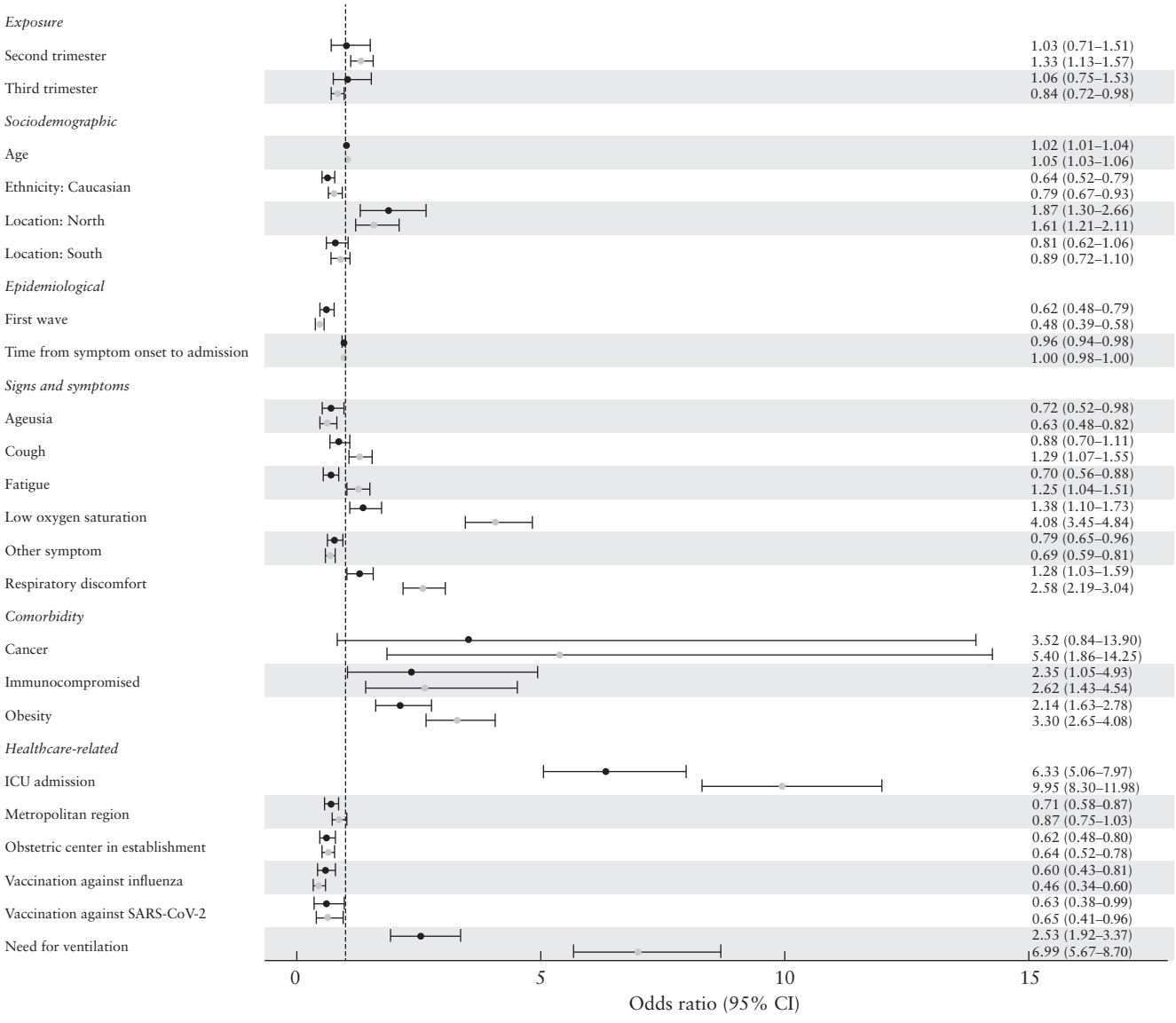

Figure 2 Multivariate logistic regression analysis of predictors of in-hospital mortality in pregnant women who were hospitalized with confirmed SARS-CoV-2 infection in Brazil. ICU, intensive care unit. ●, crude odds ratio; ●, adjusted odds ratio.

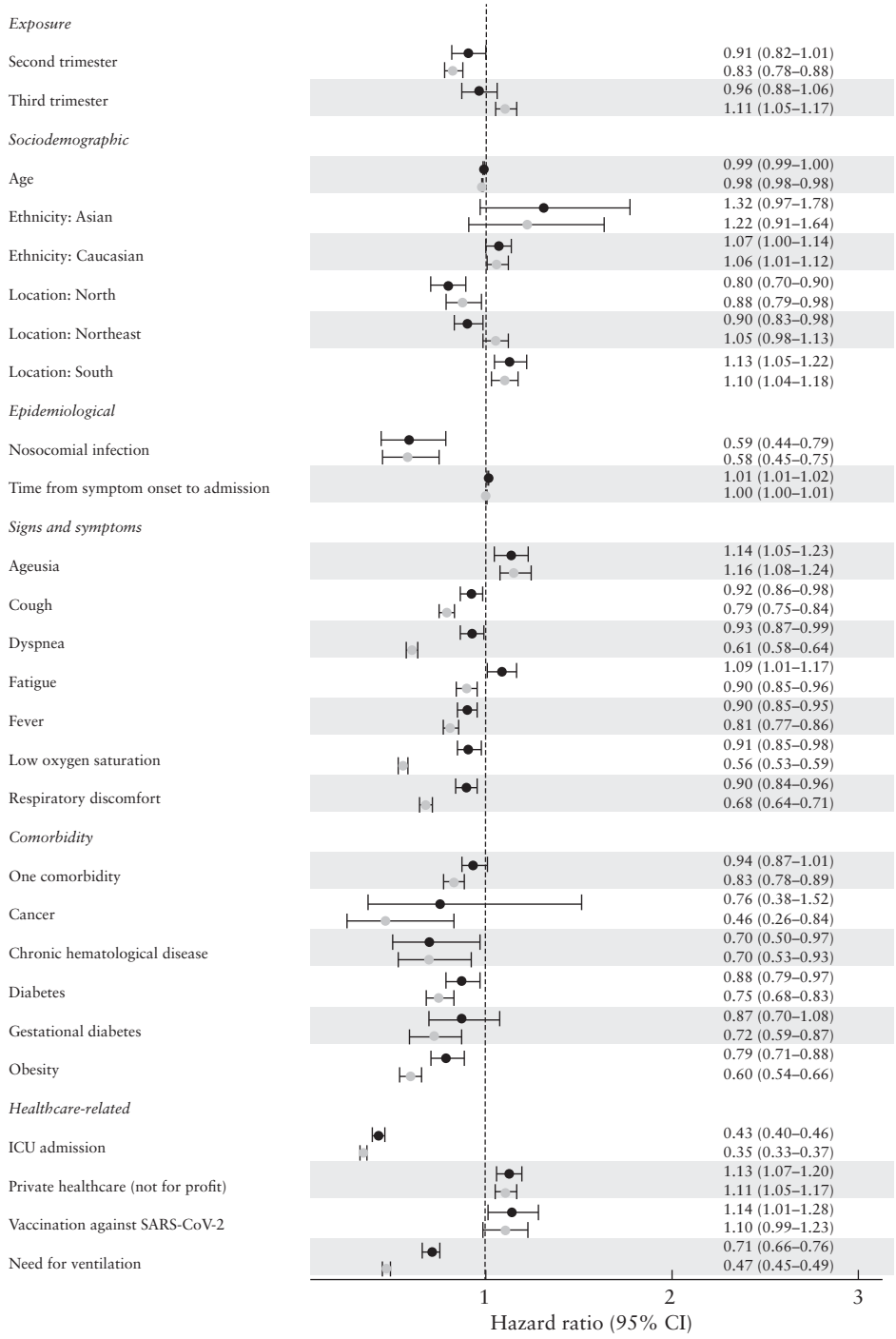

Figure 3 Multivariate Cox regression analysis of predictors of time from hospital admission to recovery in pregnant women with confirmed SARS-CoV-2 infection in Brazil. ICU, intensive care unit. ●, crude hazard ratio; ●, adjusted hazard ratio.

DISCUSSION

Based on data obtained from a nationwide database in Brazil, the present study found that hospitalized SARS-CoV-2-infected pregnant women at different gestational ages had similar risk of mortality and morbidity.

Previous studies have suggested that patients in their third trimester of pregnancy have a higher mortality risk[25–27] and greater severity of symptoms[7,17,28], although opposing findings exist[30,31]. These findings are not in line with those of the present study, and the discrepancy may be attributed to the fact that our analysis considers a number of variables that were not considered elsewhere. These include intervention[26,32–34] and type of healthcare provider[25,26,32,33,35]. These variables were found to be significantly different between trimester groups in our study, suggesting that studies omitting these variables may be prone to confounding. Although intervention variables such as ventilation and admission to the intensive care unit are severity markers, they also have an impact on the clinical course of the patient, and hence should be included in the analysis. The higher fatality rate in the

third trimester reported in previous studies may be due to the fact that patients in the third trimester are more likely to be admitted to hospital for precautionary reasons[36]. In fact, as shown in Table 1, the prevalence of symptoms that usually indicate a more severe clinical course, such as dyspnea and oxygen saturation, were not higher in the third trimester compared with the other gestational-age groups.

Our results also suggest that obstetric centers and not-for-profit healthcare play a role in reducing the risk of COVID-19 mortality and morbidity. Not-for-profit healthcare is provided under legislation that allows private organizations to use public resources to provide such healthcare. Therefore, the reduced risk of mortality and morbidity may be attributed to the management of the resources by private healthcare providers rather than the resources per se. Previous research suggested that not-for-profit healthcare contributed to the reduced hospitalization rate for health conditions that required primary healthcare[37]. Similarly, the present study showed a reduced COVID-19 recovery time in pregnant women who received not-for-profit healthcare compared with treatment by other types of healthcare provider.

The present study has a number of strengths. First, the overall sample size was large because of the nationwide coverage, with broad coverage of ethnicities, including indigenous peoples. Second, a wide range of variables was included, such as epidemiological characteristics and interventions, which were not considered elsewhere. Third, collection of data using a standardized form reduced the likehood of errors and may have been more cost- and time-efficient, even though some detailed information, such as mode of delivery and severity of comorbidities, was not recorded.

A major limitation of this study is the difficulty of generalizing our findings due to differences in public health systems between different countries and the fact that we considered only hospitalized cases that were confirmed by PCR testing. PCR tests remain the gold standard for SARS-CoV-2 diagnosis and have higher accuracy than other diagnostic tests, such as antigen and antibody tests, and their use to confirm infection in hospitalized cases avoids the possible bias due to local factors that results from use of diagnostic tests in the community[38]. In addition, under-reporting may be an issue, especially in rural regions due to accessibility.

In conclusion, women in the third trimester do not appear to have an increased risk of in-hospital COVID-19 morbidity and mortality. The discrepancy in findings between our work and previous studies is probably due to the mitigation of selection bias through the use of a nationwide database and the inclusion of confounders that were not considered elsewhere. SARS-CoV-2-infected pregnant women who were admitted to an establishment with an obstetric center and those who received private not-for-profit healthcare in Brazil had lower risks of mortality and morbidity, respectively.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Sensitivity analysis of predictors of in-hospital mortality.

Figure S2 Subgroup analysis of predictors of in-hospital mortality in the first, second and third trimesters.

Figure S3 Sensitivity analysis of predictors of time from hospital admission to recovery.