Clinical characteristics and risk factors for maternal deaths due to COVID-19 in Brazil: a nationwide population-based cohort study

Running title: Risk factors for maternal deaths due to COVID-19 in Brazil

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Abstract

Background: Monitoring the characteristics and associated factors for death among pregnant and postpartum women with COVID-19 is necessary. We investigated the clinical characteristics and risk factors associated with maternal deaths in a nationwide cohort of Brazil.

Methods: This was a population-based cohort of all pregnant and postpartum women hospitalised with COVID-19 notified to the *Sistema de Informação de Vigilância Epidemiológica da Gripe* of Brazil (SIVEP-Gripe), from February 2020 to September 2021. The primary outcome was time to in-hospital death, with risks factors analysed with univariable and multivariable Cox proportional hazards regression models.

Results: Cumulative observation time was 248,821 person-days from hospital admission to the end of follow-up for 15,105 individuals. There were 1,858 deaths (12.3%) for a maternal mortality rate of 7.5 (95% CI 7.1-7.8) per 1000 patients-days. The cumulative mortality increased over time. Black/Brown ethnicity had a higher risk of death than women self-identifying as White. Women in the North, Northeast, Central-West and Southeast regions had higher risk of death than women in the South region. The characteristics independently associated with death were a postpartum status on admission (adjusted HR 1.4 [95%CI 1.2-1.6]), pre-existing clinical conditions (adjusted HRs 1.2 [95%CI 1.1-1.3] for one and 1.3 [95%CI 1.1-1.5] for two comorbidities), hypoxemia on admission (adjusted HR 1.2 [95%CI 1.1-1.4]) and requiring non-invasive (adjusted HR 2.6 [95%CI 2.1-3.3]) or invasive ventilatory support (adjusted HR 7.1 [95%CI 5.6-9.2]).

Conclusion: In Brazil, the in-hospital maternal mortality rate due to COVID-19 is high and the risk of death increases with the length of hospitalisation. Socio-demographic and biological factors are associated with an increased risk of maternal death. The presence of respiratory signs and symptoms should be considered as an early markers of disease severity and an adequate management is necessary. Our findings reinforce the need for vaccination of pregnant and postpartum women against COVID-19.

Keywords: COVID-19; Maternal Mortality; Risk factors; Cohort study; Brazil.

Introduction

Coronavirus disease 19 (COVID-19), an emerging infectious disease caused by the Severe Acute Respiratory Coronavirus-2 (SARS-CoV-2), became the largest public health emergency of the 21st century. SARS-CoV-2 clinical spectrum ranges from asymptomatic to acute respiratory distress syndrome (ARDS) and death; and the worst outcomes are associated with older age, pre-existing comorbidities,[1] racial and ethnic minorities, low income, and health disparities.[2,3] Pregnant and postpartum women experience significant physiological, hormonal and immune changes, which predispose to respiratory viral infections and severe pneumonia.[4] Although early small scale studies in high-income countries did not report worse complications from pregnant women with COVID-19,[5–7] as the pandemic progressed, it became established they also experienced adverse outcomes, such as foetal loss, preterm delivery, preeclampsia and emergency caesarean sections [8–11] and intensive care unit (ICU) admission.[10,12–14] Similar to the general population, adverse outcomes are higher among women with pre-existing comorbidities[12] and in areas with marked social inequities.[15,16]

Brazilian studies have reported higher mortality rates among pregnant women with pre-existing diabetes, cardiovascular disease and obesity,[12,13] and the continued monitoring of outcomes and risk factors for death are necessary to further understand the impact of COVID-19 in obstetric populations. In this nationwide population-based cohort in Brazil, we describe the clinical characteristics and factors associated with death in hospitalised pregnant and postpartum women with COVID-19 from February 2020 to September 2021.

Methods

Study design and participants

We conducted a population-based cohort study including all pregnant and postpartum women hospitalised with COVID-19 in Brazil notified to the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe, *Sistema de Informação de Vigilância Epidemiológica da Gripe*). The SIVEP-Gripe is a de-identified national public domain database established by the Brazilian Ministry of Health for the surveillance of severe acute respiratory infections. COVID-19 notifications are compulsory, and the SIVEP-Gripe receives notifications of all COVID-19 public and private hospitalisations and deaths. Notification data includes demographic and clinical features and pregnancy and postpartum status. In SIVEP-Gripe, postpartum is considered to be the period from delivery to the 45th day after delivery. Our analysis included all hospitalised pregnant and postpartum women with laboratory confirmed SARS-CoV-2 and a COVID-19 diagnosis registered in the SIVEP-Gripe from the 27th February 2020 to the 15th September 2021.

Covariables and definitions

Demographic data included age, ethnicity and geopolitical region. Brazil is divided into five geopolitical regions (North, Northeast, Central-West, Southeast and South) which have different social and economic indicators, health system capacity and coverage. Ethnicity was self-identified and based on the five classifications defined by the Brazilian Institute of Geography and Statistics: *Branco* (White), *Preto* (Black), *Pardo* (Brown), *Amarelo* (East Asian), or *Indígena* (Indigenous). Clinical data included pregnancy and postpartum status, trimester of gestation at the time of reporting; signs and symptoms at presentation (fever, cough, sore throat, shortness of breath, respiratory distress, gastrointestinal symptoms, and oxygen saturation), and the presence or absence of pre-existing comorbidities (cardiovascular, renal,

neurological, haematological, or hepatic comorbidities, diabetes, chronic respiratory disorder, obesity, or immunosuppression). Data on comorbidities was dichotomised (yes/no) and categorised according to the number of pre-existing conditions (none, one, two, and ≥ three). Clinical course was reported in terms of the need for respiratory support (none, non- invasive oxygen support and invasive ventilation), admission to an intensive care unit (ICU), recovery (discharge) or death situations. The dates of hospital admission, death or discharge were also registered.

Outcomes

The primary outcome was the time to in-hospital death. Survival time was estimated from the day of hospital admission to the day of in-hospital death.

Data analysis

The data analysed comprised all pregnant and postpartum women aged 13 to 48 years with COVID-19 admitted to the hospital and registered in the database between epidemiological weeks 9, 2020 and 37, 2021. Complete data were not available for all variables. We did not impute missing data for ethnicity and trimester of gestation. However, missing values were interpreted as the absence of pre-existing symptoms and co-morbidities. We also interpreted missing data as non-admission to ICU.

Categorical variables are reported as frequencies (with percentages and 95% confidence intervals [CIs]) and continuous variables as means (with Standard Deviations [SD]) or medians (with interquartile ranges [IQRs] and 95% CIs) according to their distribution. We used the Wilcoxon rank sum test to compare the length of hospital stay between survivors and non-survivors. We calculated Kaplan-Meier survival estimates and used the log-rank test to compare

groups in terms of survival. The association of risk factors with time to in-hospital death was assessed using univariable and multivariable Cox proportional hazards regression models. The proportional hazard assumption was tested by plotting the Nelson-Aalen cumulative hazard function and the Schoenfeld residuals test.[17]

Ethical considerations

As data in SIVEP-Gripe are deidentified and publicly available, an institutional review board approval and informed consent were not required.

Role of the role funding source

The funder of the study had no role in study design, data collection, management, analysis, interpretation or writing of the report.

Results

A total of 2,670,106 cases of severe acute respiratory syndrome were reported to SIVEP-Gripe between February 2020 and September 2021, of which 1,770,404 had Reverse Transcription Polymerase Chain Reaction (RT-PCR)-confirmed SARS-CoV-2 infection. Of these, 15,105 were reported in pregnant and postpartum women aged 13 to 48 years admitted to hospital and had information on the times of admission and outcome, and they were included in the analysis (Supplementary Figure 1).

Table 1 describes the demographic and clinical characteristics of the patients included. Median age at the time of hospital admission was 30 (IQR 25-34) years. Black/Brown patients accounted for slightly more than half of the participants (7,361 [57.1%] of 15,105) and 43.8% (6,615 out of 15,105) resided in the Southeast region. Among the 15,105 women reported, 1,061 (7.0%) were

in the 1st trimester, 3,074 (20.4%) in the 2nd trimester, 7,460 (49.4%) in the 3rd trimester and 2,960 (19.6%) postpartum at the time of hospital admission.

The median time from symptoms onset to hospital admission was three (IQR 6–9) days. The most frequent signs and symptoms on admission were cough (67.1%), shortness of breath (56.4%), fever (53.0%) and respiratory distress (44.4%). Hypoxaemia (SpO_2 <95%) was present in 5,715 (37.8%) patients. Overall, 8,936 (59.2%) patients had no comorbidities, 4,117 (30.6%) had one, 1,164 (7.7%) had two and 388 (2.6%) had three or more comorbidities. Diabetes (6.7%), obesity (6.4%) and cardiovascular disease (6.1%) were the most common pre-existing comorbidities (Table 1).

A total of 4,339 (28.7%) patients were admitted to ICU, with a median time from symptom onset to ICU admission of eight (IQR 4-12) days. Data on respiratory support was available for 13,563 patients. Of these, 6,431 (47.4%) did not require respiratory support during hospitalization, 4,982 (36.7%) required non-invasive support and 2,150 (15.8%) needed invasive ventilation. The distribution of ICU admission and type of ventilatory support according to the Brazilian region is shown in Supplementary Table 1.

Cumulative observation time for 15,105 individuals was 248,821 person-days from hospital admission to the end of follow-up. There were 1,858 deaths (overall mortality, 12.3%) for a maternal mortality rate of 7.5 (95% CI 7.1-7.8) per 1000 patients-days, with the cumulative incidence increasing over time. The probability of death per 1000 patient-days was 1.9 (95% CI 1.7 to 2.3) during the initial five days of hospitalisation, 3.5 (95% CI 3.1 to 4.1) during the first 10 days, and 12.8 (95% CI 12.1 to 13.4) at the end of the follow-up (Figure 1). The length of hospital stay was higher among non-survivors than survivors (Median [IIQ] 19 [12-28] *vs.* 13 [8-

18]; P < 0.001). A higher maternal mortality rate was found in the North region and lower rate in the South region (Supplementary Figure 2).

The univariate risk factor analysis for deaths is shown in Table 2. The risk of death was higher in women aged ≥ 35 years (HR 1.4 [95%CI 1.1-1.7]) compared to women under 20 years, in women from Black/Brown ethnicity (HR 1.2 [95%CI 1.1-1.3]) compared to women self-identifying as White ethnicity, and those living in the Southeast (HR 1.2 [95%CI 1.1-1.4]), Northeast (HR 1.3 [95%CI 1.1-1.5]) and North (HR 1.5 [95%CI 1.3-1.8]) regions compared to the South region. Shortness of breath (HR 2.0 [95%CI 1.7-2.2]), respiratory distress (HR 1.7 [95%CI 1.5-1.8]) and hypoxemia (HR 2.2 [95%CI 1.9-2.4]), but not fever, cough or gastrointestinal symptoms, were associated with death. Pre-existing diabetes (HR 1.4 [95%CI 1.1-1.7]), cardiovascular disease (HR 1.6 [95%CI 1.3-2.0]) and obesity (HR 2.1 [95%CI 1.7-2.5]) and the number of comorbidities (1, 2 or ≥3 *vs* none) increased the risk of death in the univariate analysis. Pregnant and postpartum women who required non-invasive respiratory support (HR 2.8 [95%CI 2.3-3.4]), invasive ventilation (HR 9.0 [95%CI 7.5-11.0]) and those admitted to ICU (HR 3.1 [95%CI 2.7-3.4]) were more likely to die.

The multivariable cox proportional hazards regression analysis of factors associated with maternal mortality is shown in Table 3. Women of Black/Brown ethnicity had a higher risk of death than White women. Women hospitalised in the North, Northeast, Central-West and Southeast regions had higher risk of death than women hospitalised in the South region. Other characteristics independently associated with death were being on postpartum at admission (adjusted HR 1.4 [95% CI 1.2-1.6]), pre-existent clinical conditions (adjusted HRs 1.2 [95%CI 1.1-1.3] for one comorbidity and 1.3 [95%CI 1.1-1.5] for two comorbidities), hypoxemia

on admission (adjusted HR 1.2 [95%CI 1.1-1.4]) and requiring non-invasive (adjusted HR 2.6 [95%CI 2.1-3.3]) or invasive ventilatory support (adjusted HR 7.1 [95%CI 5.6-9.2]). ICU admission was not associated with an increased risk of death in the multivariate analysis. Figure 2 shows the survival probability curves in the presence of these risk factors.

Discussion

In this nationwide population-based cohort study of hospitalised pregnant and postpartum women with laboratory-confirmed SARS-CoV-2 infection, the estimated in-hospital maternal mortality rate was 12.3% (7.5 per 1000 patient-days), with the probability of death increasing with the length of hospitalisation. The mortality rate among pregnant and postpartum women in this cohort was higher than reported from France (0.2%),[18] the United States (0.7%)[19] and the United Kingdom (1%).[20,21] Our rate is also higher than a previous study using SIVEP-Gripe data between February and December 2020, the first year of the pandemic,[22] which reported a mortality rate of 7.8%. However, the death rate reported in this cohort study was similar to that found in an earlier Brazilian study based on SIVEP-Gripe, which was carried out from February to June 2020. In that study, Takemoto et al.[23] showed that 124 out of 978 pregnant and postpartum women hospitalised in Brazil died due to complications of COVID-19, resulting in a rate of 12.7%. COVID-19 mortality rates in obstetric populations are known to vary according to the pandemic period and across countries. High-income settings with well-structured obstetric care services and sufficient supplies for maternal ICU, tend to report the lowest death rates. The distribution within countries is also heterogeneous.[24] A recent study in Brazil demonstrated that COVID-19 cases and deaths in obstetric population have heterogeneous geographical distributions, with spatial clusters with high mortality rates located in countryside and areas

with high socioeconomic deprivation.[24] In this cohort, the highest mortality rates were found among women hospitalised in the North (15%), the region with the lowest socioeconomic and infrastructure indicators. This North region also experienced a rapid and greater overload of cases, especially during the 2nd wave of the pandemic, exacerbating pre-existing socioeconomic and health structure differences across the regions.[25,26]

Our findings demonstrate an increased risk of death among Black/Brown ethnicity. Racial and ethnic groups have been disproportionately affected by COVID-19,[27–29] which is a pattern previously reported by others.[12,30] Black/Brown pregnant women are also likely to have pre-existing comorbidities and adverse outcomes, including preeclampsia, foetal loss and death.[31,32] Further, Black/Brown women receive lower quality and intensity of healthcare for preventive, diagnostic and therapeutic services.[33–35] It is thus likely the pandemic synergises the deficiencies of a pre-existing obstetric healthcare and limited access to specialised health services.

The mortality rate among postpartum women with COVID-19 was around 21% (12.8 per 1000 person-days), with 1.5 times higher risk of death than pregnant women. This increased risk resembles the pre-COVID-19 era, when about two-thirds of maternal deaths occurred in the postpartum period.[36] Postpartum women have a greater risk of haemodynamic complications than pregnant women; and SARS-CoV-2 infections are associated with immune system dysregulation, resulting in cytokine storms as well as haemodynamic abnormalities.[1]

Pregnant and postpartum women with pre-existing comorbidities were at higher risk of death, with the prevalence of comorbidities being about 40% among all women, but around 52% in individuals who died. The clinical features increasing the risk of death were similar to reports

for the general[37] and obstetric populations,[12,13] and included pre-existing diabetes, cardiovascular disease and obesity. Pregnant and postpartum women with hypoxaemia and those requiring non-invasive or invasive ventilatory support were also more likely to die than those not requiring oxygen support. Although SIVEP-Gripe does not distinguish the types of cardiovascular disease, it is likely most women had hypertension, since it is the most common clinical condition in the Brazilian obstetric populations,[38] and historically hypertension has been the leading cause of maternal *near miss* and death (~35% of maternal deaths).[36,39,40]

SARS-CoV-2 use the angiotensin-converting enzyme 2 (ACE2) receptor to invade host cells especially in kidney, heart and lungs leads to the enhanced release of cytokines and a hyperinflammatory state implicated in multi-organ damage.[41] In the lungs, inflammatory responses increase alveolar-capillary permeability resulting in alveolar oedema, hypoxemia and progressive respiratory distress.[1,41] Pregnant and postpartum women with hypoxaemia had a 20% higher risk of dying than women admitted with oxygen saturation >95%. Hypoxemia is thus an important marker of COVID-19 severity commonly associated with ARDS, requiring ICU management.[1,42–45]

A high proportion of people affected by COVID-19 requires non-invasive or invasive ventilatory support an ICU care.[42–45] In this cohort, *circa* 30% of pregnant and postpartum women were admitted to ICU and over 60% required respiratory support. Counterintuitively however, *circa* 25% and 7% of deaths occurred among women without ventilatory support and who were not admitted to the ICU, respectively. These findings expose the lack of access to intensive care, as only 15% of maternity wards have ICU and their distribution is heterogeneous across the regions, with a higher concentration in the South and Southeast regions.[46]

This cohort study assessed a large sample size of pregnant and postpartum women with laboratory-confirmed COVID-19, allowing a comprehensive analysis of the clinical characteristics and risk factors associated with in-hospital deaths in all Brazilian states and regions. Nevertheless, our findings should be interpreted with caution. The analyses were based solely on hospitalised pregnant and postpartum women, who may represent the most severe end of the disease spectrum. The data were obtained from a surveillance information system and therefore only represent women who accessed the health system and may underrepresent women from areas with limited access to obstetric hospital services. Moreover, until August 2020, Brazil did not have a universal SARS-CoV-2 testing strategy for obstetric populations, and RT-PCR tests were offered only to women who presented with suggestive symptoms of COVID-19 who had access to health services with laboratory facilities. Consequently, cases in poor communities could be missing and undetected, which would bias the detection rates from these areas.

In Brazil, the estimated mortality rate is higher than reported from other countries and the probability of death increases with length of hospitalisation. The risk of death increased among Black/Brown, postpartum, and with the presence of comorbidities, especially diabetes, cardiovascular disease, and obesity. Additionally, pregnant and postpartum women with hypoxaemia and requiring ventilatory support were more likely to die. Hypoxaemia and the need for ventilatory support is a marker of disease severity requiring standardised service protocols for obstetric populations. The high mortality of obstetric populations reinforces the need to vaccinate this at-risk group against COVID-19, as the safety and efficacy of mRNA-based COVID-19 vaccines during pregnancy is well established.[47] Continued monitoring of cases and

deaths from COVID-19 in the obstetric population is necessary, even after the adoption of widespread vaccination for this population.

Authors' contributions

TSS and EKGS: conceptualisation, methodology, data collection and writing original draft. JRSS: data collection, interpretation, and supervision. PMF, RQG and LEC: literature search, data interpretation, and writing. VSS: conceptualisation, methodology, project administration, data curation, formal data analysis and writing. All authors discussed the results and contributed to the final manuscript.

Declaration of interests

The authors declare that there is no conflict of interest.

Data sharing

SIVEP-Gripe dataset and all other databases used in this study are publicly available. Our analysis code is available upon request to the corresponding author.

Funding

This study did not receive funding.

References

1 Martins-Filho PR, Tavares CSS, Santos VS. Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data. *Eur J Intern Med* 2020; **76**:97-9.

2 Martins-Filho PR, Araújo AAS, Quintans-Júnior LJ, Santos VS. COVID-19 fatality rates related to social inequality in Northeast Brazil: a neighborhood-level analysis. *J Travel Med* 2020; **27**:taaa128.

3 Martins-Filho PR, Quintans-Júnior LJ, Araújo AAS, *et al.* Socio-economic inequalities and COVID-19 incidence and mortality in Brazilian children: a nationwide register-based study. *Public Health* 2021; **190**:4–6.

4 Somerville LK, Basile K, Dwyer DE, Kok J. The impact of influenza virus infection in pregnancy. *Future Microbiol* 2018; **13**:263–74.

5 Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. *Acta Obstet Gynecol Scand* 2020; **99**:823–9.

6 Di Toro F, Gjoka M, Di Lorenzo G, *et al.* Impact of COVID-19 on maternal and neonatal outcomes: a systematic review and meta-analysis. *Clin Microbiol Infect* 2021; **27**:36–46.

7 Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: A systematic review and meta-analysis. *Cmaj* 2021; **193**: E540–8.

8 Villar J, Ariff S, Gunier RB, *et al.* Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: The INTERCOVID multinational cohort study. *JAMA Pediatr* 2021; **175**:817-26.

9 Zambrano LD, Ellington S, Strid P, *et al.* Update: Characteristics of symptomatic women

of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22-October 3, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**:1641–7.

10 Ko JY, DeSisto CL, Simeone RM, *et al.* Adverse pregnancy outcomes, maternal complications, and severe illness among US delivery hospitalizations with and without a Coronavirus Disease 2019 (COVID-19) diagnosis. *Clin Infect Dis* 2021; **73**:S24–31.

11 Gurol-Urganci I, Jardine JE, Carroll F, *et al.* Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: national cohort study. *Am J Obstet Gynecol* 2021; **225**:522.e1–11.

12 Menezes MO, Takemoto MLS, Nakamura-Pereira M, *et al.* Risk factors for adverse outcomes among pregnant and postpartum women with acute respiratory distress syndrome due to COVID-19 in Brazil. *Int J Gynecol Obstet* 2020; **151**:415–23.

13 Takemoto M, Menezes MO, Andreucci CB, *et al.* Clinical characteristics and risk factors for mortality in obstetric patients with severe COVID-19 in Brazil: a surveillance database analysis. *BJOG* 2020; **127**:1618–26.

14 Pirjani R, Hosseini R, Soori T, *et al.* Maternal and neonatal outcomes in COVID-19 infected pregnancies: A prospective cohort study. *J Travel Med* 2020; **27**:taaa158.

15 Prasannan L, Rochelson B, Shan W, *et al.* Social determinants of health and coronavirus disease 2019 in pregnancy. *Am J Obstet Gynecol MFM* 2021; **3**:100349.

16 Siqueira TS, Silva JRS, Souza M do R, *et al.* Spatial clusters, social determinants of health and risk of maternal mortality by COVID-19 in Brazil: a national population-based ecological study. *Lancet Reg Heal - Am* 2021; **3**:100076.

17 Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. Hoboken, NJ, USA: John Wiley & Sons, Inc., 2002.

18 Kayem G, Lecarpentier E, Deruelle P, *et al.* A snapshot of the COVID-19 pandemic among pregnant women in France. *J Gynecol Obstet Hum Reprod* 2020; **49**:101826.

19 Delahoy MJ, Whitaker M, O'Halloran A, *et al.* Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed COVID-19 – COVID-NET, 13 States, March 1-August 22, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**:1347–54.

20 Vousden N, Bunch K, Morris E, *et al.* The incidence, characteristics and outcomes of pregnant women hospitalized with symptomatic and asymptomatic SARS-CoV-2 infection in the UK from March to September 2020: A national cohort study using the UK Obstetric Surveillance System (UKOSS). *PLoS One* 2021; **16**:e0251123.

21 Knight M, Bunch K, Vousden N, *et al.* Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. *BMJ* 2020; **369**:m2107.

22 Scheler CA, Discacciati MG, Vale DB, *et al*. Mortality in pregnancy and the postpartum period in women with severe acute respiratory distress syndrome related to COVID-19 in Brazil, 2020. *Int J Gynecol Obstet* 2021; **155**:475–82.

23 Takemoto MLS, Menezes M de O, Andreucci CB, *et al.* The tragedy of COVID-19 in Brazil: 124 maternal deaths and counting. *Int J Gynecol Obstet* 2020; **151**:154–6.

24 Lopes A de SA, Vieira SCF, Porto RLS, *et al.* Coronavirus disease-19 deaths among children and adolescents in an area of Northeast, Brazil: why so many? *Trop Med Int Heal* 2021;

26:115–9.

25 Naveca FG, Nascimento V, de Souza VC, *et al.* COVID-19 in Amazonas, Brazil, was driven by the persistence of endemic lineages and P.1 emergence. *Nat Med* 2021; **27**:1230–8.

26 Castro MC, Kim S, Barberia L, *et al.* Spatiotemporal pattern of COVID-19 spread in Brazil. *Science* 2021; **372**:821–6.

27 Martins-Filho PR, Araújo BCL, Sposato KB, *et al*. Racial disparities in COVID-19-related deaths in brazil: Black lives matter? *J Epidemiol* 2021; **31**:239–40.

28 Santos VS, Araújo AAS, de Oliveira JR, *et al*. COVID-19 mortality among Indigenous people in Brazil: a nationwide register-based study. *J Public Health (Oxf)* 2020; **43**:e250–1.

29 Baqui P, Bica I, Marra V, *et al*. Ethnic and regional variations in hospital mortality from COVID-19 in Brazil: a cross-sectional observational study. *Lancet Glob Heal* 2020; **8**:e1018–26.

30 Santos D de S, Menezes M de O, Andreucci CB, *et al.* Disproportionate impact of Coronavirus disease 2019 (COVID-19) among pregnant and postpartum Black women in Brazil through structural racism lens. *Clin Infect Dis* 2021; **72**:2068–9.

31 Martins AL. Mortalidade materna de mulheres negras no Brasil. *Cad Saude Publica* 2006; **22**: 2473–9.

32 Leal M do C, Gama SGN da, Pereira APE, *et al*. A cor da dor: iniquidades raciais na atenção pré-natal e ao parto no Brasil. *Cad Saude Publica* 2017; **33(Suppl 1)**:e00078816.

33 Small MJ, Allen TK, Brown HL. Global disparities in maternal morbidity and mortality. *Semin Perinatol* 2017; **41**:318–22.

34 Alves LGR, Guimarães RM. Race inequalities in maternal mortality in the city of Rio de

Janeiro, Brazil: 2010-2019. *Rev Assoc Med Bras* 2021; **67**:120–4.

35 Leal M do C, da Gama SGN, da Cunha CB. Desigualdades raciais, sociodemográficas e na assistência ao pré-natal e ao parto, 1999-2001. *Rev Saude Publica* 2005; **39**:100–7.

36 Brasil. Ministério da Saúde. Departamento de Informática do Sistema Único de Saúde (DATASUS). Sistema de Informações sobre Mortalidade (SIM). 2019. Available in: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sim/cnv/obt10uf.def. Accessed in August 20, 2021.

37 de Lima THB, Amorim MM, Buainain Kassar S, Katz L. Maternal near miss determinants at a maternity hospital for high-risk pregnancy in northeastern Brazil: a prospective study. *BMC Pregnancy Childbirth* 2019; **19**:271.

38 Nakamura-Pereira M, Esteves-Pereira AP, Dias MAB, *et al.* 62 Maternal and neonatal outcomes associated with hypertensive disorders during pregnancy: Data from "Birth in Brazil" study. *Pregnancy Hypertens An Int J Women's Cardiovasc Heal* 2016; **6**:167.

39 Zanette E, Parpinelli MA, Surita FG, *et al.* Maternal near miss and death among women with severe hypertensive disorders: A Brazilian multicenter surveillance study. *Reprod Health* 2014; **11**:1–11.

40 Giordano JC, Parpinelli MA, Cecatti JG, *et al.* The burden of eclampsia: Results from a multicenter study on surveillance of severe maternal morbidity in Brazil. *PLoS One* 2014; **9**:e97401.

41 Shi Y, Wang Y, Shao C, *et al.* COVID-19 infection: the perspectives on immune responses. *Cell Death Differ* 2020; **27**:1451–4.

42 Grasselli G, Greco M, Zanella A, *et al.* Risk factors associated with mortality among

patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med* 2020; **180**:1345-55.

43 Grasselli G, Zangrillo A, Zanella A, *et al.* Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA* 2020; **323**:1574-81.

44 Gupta S, Hayek SS, Wang W, *et al.* Factors associated with death in critically ill patients with Coronavirus disease 2019 in the US. *JAMA Intern Med* 2020; **180**:1436-47.

45 Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**:497–506.

46 Roberton T, Carter ED, Chou VB, *et al.* Early estimates of the indirect effects of the COVID-19 pandemic on maternal and child mortality in low-income and middle-income countries: a modelling study. *Lancet Glob Health* 2020; **8**:e901–8.

47 Shimabukuro TT, Kim SY, Myers TR, *et al.* Preliminary findings of mRNA Covid-19 vaccine safety in pregnant persons. *N Engl J Med* 2021; **384**: 2273–82.

List of tables

Table 1. Demographic and clinical characteristics of the pregnant and postpartum women with COVID-19 included in the study.

Variables	**N = 15,105**
Age, median (IQR)	30 (25-35)
Age group (years)	
<20	1,104 (7.3%)
20 to 34	9,836 (65.1%)
≥35	4,165 (27.6%)
Ethnicity [a]	
White	5,303 (41.1%)
Black/Brown	7,361 (57.1%)
East Asian	116 (0.9%)
Indigenous	121 (0.9%)
Brazilian region	
North	1,699 (11.3%)
Northeast	3,246 (21.4%)
Central-West	1,294 (8.6%)
Southeast	6,615 (43.8%)
South	2,251 (14.9%)
Pregnancy trimester	
First	1,061 (7.0%)
Second	3,074 (20.4%)
Third	7,460 (49.4%)

Unknown	550 (4.5%)
Postpartum at hospital admission	2,960 (19.6%)
Signs and symptoms	
Cough	10,129 (67.1%)
Shortness of breath	8,511 (56.4%)
Fever	8,002 (53.0%)
Respiratory distress	6,701 (44.4%)
Hypoxaemia	5,715 (37.8%)
Sore throat	3,079 (20.4%)
Fatigue	2,935 (19.4%)
Anosmia	2,079 (13.8%)
Ageusia	1,872 (12.4%)
Diarrhoea	1,484 (9.8%)
Vomiting	1,451 (9.6%)
Abdominal pain	950 (6.3%)
Comorbidities	
0	8,936 (59.2%)
1	4,617 (30.6%)
2	1,164 (7.7%)
≥3	388 (2.6%)
Type of comorbidity	
Diabetes	1,008 (6.7%)
Obesity	969 (6.4%)
Cardiovascular disease	915 (6.1%)
Asthma	497 (3.3%)
Immunosuppression	143 (1.0%)
Renal disease	89 (0.6%)
Pulmonary disease	88 (0.6%)
Neurological disease	87 (0.6%)
Haematological disease	80 (0.5%)
Liver disease	39 (0.3%)

[a] Missing value = 2,204

Table 2. Demographic, clinical characteristics, comorbidities, and outcome of 15,105 pregnant and postpartum women with covid-19 admitted to hospital in Brazil from February 2020 to September 2021.

Variables	No. of patients (n=15,105)	No. of deaths (n = 1,858)	Maternal Mortality rate per 1000 patient-days	Hazard Ratio (95% CI)	P value
Age group					
<20	1,104	79 (7.2%)	5.6 (4.5-7.0)	1	NA
20 to 34 years	9,836	1,131 (11.5%)	7.1 (6.6-7.5)	1.2 (0.9-1.5)	0.310
≥35 years	4,165	648 (15.6%)	8.7 (8.1-9.4)	1.4 (1.1-1.7)	0.021
Ethnicity [a]					
White	5,303	619 (11.7%)	7.0 (6.5-7.6)	1	NA
Black/Brown	7,361	1,015 (13.8%)	8.4 (7.9-8.9)	1.2 (1.1-1.3)	0.001
East Asian	116	16 (13.8%)	8.5 (5.2-13.9)	1.2 (0.7-1.9)	0.483
Indigenous	121	12 (9.9%)	6.1 (3.5-10.7)	0.9 (0.5-1.5)	0.627
Brazilian region					
North	1,699	256 (15.1%)	9.3 (8.2-10.5)	1.5 (1.3-1.8)	<0.001
Northeast	3,246	427 (13.2%)	8.0 (7.3-8.8)	1.3 (1.1-1.5)	0.002
Central-West	1,294	170 (13.2%)	7.6 (6.6-8.9)	1.2 (0.9-1.5)	0.067
Southeast	6,615	774 (11.7%)	7.1 (6.7-7.6)	1.2 (1.1-1.4)	0.037
South	2,251	231 (10.3%)	6.2 (5.4-7.1)	1	NA
Pregnancy trimester					
First	1,061	85 (8.0%)	5.4 (4.3-6.6)	1	NA
Second	3,074	384 (12.5%)	6.9 (6.2-7.6)	1.1 (0.9-1.4)	0.559
Third	7,460	702 (9.4%)	5.8 (5.4-6.3)	1.0 (0.8-1.2)	0.694
Unknown	550	67 (12.2%)	7.7 (6.1-9.8)	1.2 (0.9-1.7)	0.185
Postpartum	2,960	620 (20.9%)	12.9 (11.9-13.9)	2.0 (1.8-2.2)	<0.001
Signs and symptoms					
Cough	10,129	1,309 (12.9%)	7.4 (7.0-7.9)	1.0 (0.9-1.1)	0.235
Shortness of breath	8,511	1,491	9.4 (9.0-10.0)	2.0 (1.7-	<0.001

		(17.5%)		2.2)	
Fever	8,002	1,044 (13.1%)	7.4 (7.0-7.9)	1.0 (0.9-1.1)	0.127
Respiratory distress	6,701	1,229 (18.3%)	9.8 (9.2-10.4)	1.7 (1.5-1.8)	<0.001
Hypoxaemia	5,715	1,285 (22.4%)	11.2 (10.6-11.8)	2.2 (1.9-2.4)	<0.001
Sore throat	3,079	342 (11.1%)	6.6 (5.9-7.3)	0.9 (0.8-0.9)	0.024
Fatigue	2,935	430 (14.7%)	8.2 (7.4-9.0)	1.1 (1.0-1.2)	0.137
Anosmia	2,079	177 (8.5%)	5.1 (4.4-5.9)	0.7 (0.6-0.8)	<0.001
Ageusia	1,872	153 (8.2%)	4.9 (4.1-5.7)	0.6 (0.5-0.8)	<0.001
Diarrhoea	1,484	151 (10.2%)	6.1 (5.2-7.1)	0.8 (0.7-0.9)	0.025
Vomiting	1,451	148 (10.2%)	5.9 (5.1-7.0)	0.8 (0.7-0.9)	0.022
Abdominal pain	950	108 (11.4%)	6.8 (5.6-8.2)	0.9 (0.8-1.1)	0.506
Comorbidities					
0	8,936	890 (9.8%)	6.3 (5.9-6.7)	1	NA
1	4,617	631 (13.5%)	7.8 (7.2-8.4)	1.2 (1.1-1.3)	0.005
2	1,164	245 (20.9%)	11.2 (9.8-12.6)	1.5 (1.3-1.8)	<0.001
≥3	388	92 (23.4%)	11.5 (9.4-14.1)	1.6 (1.2-1.8)	<0.001
Type of comorbidity					
Diabetes	1,008	187 (18.5%)	8.6 (7.1-10.6)	1.4 (1.1-1.7)	0.005
Obesity	969	278 (28.7%)	13.4 (11.1-16.2)	2.1 (1.7-2.5)	<0.001
Cardiovascular disease	915	187 (20.4%)	10.7 (8.8-13.0)	1.6 (1.3-2.0)	<0.001
Asthma	497	71 (14.2%)	6.0 (4.1-8.5)	0.9 (0.7-1.2)	0.595
Immunosuppression	143	28 (19.6%)	9.7 (5.5-17.1)	1.3 (0.9-1.9)	0.125
Renal disease	89	19 (21.4%)	7.9 (3.2-18.9)	1.6 (1.0-2.5)	0.052
Pulmonary disease	88	19 (21.6%)	9.0 (4.5-18.1)	1.5 (1.0-	0.067

				2.4)	
Neurological disease	87	15 (17.2%)	7.3 (2.3-22.9)	1.3 (0.7-2.1)	0.361
Haematological disease	80	18 (22.5%)		1.6 (1.0-2.5)	0.052
Liver disease	39	9 (23.1%)	9.1 (5.7-28.4)	1.9 (1.0-3.6)	0.066
Intensive Care Unit admission					
No	10,766	486 (4.5%)	3.2 (2.9-3.5)	1	NA
Yes	4,339	1,372 (31.6%)	13.7 (13.0-14.4)	3.1 (2.7-3.4)	<0.001
Ventilatory support [b]					
None	6,431	121 (1.9%)	1.4 (1.2-1.7)	1	NA
Non-invasive	4,982	414 (8.3%)	4.8 (4.3-5.3)	2.8 (2.3-3.4)	<0.001
Invasive	2,150	1,138 (52.9%)	20.2 (19.1-21.4)	9.0 (7.5-11.0)	<0.001

[a] Missing = 2,204; [b] Missing = 1,542

Table 3. Multivariable cox proportional hazards regression analysis of factors independently associated with maternal mortality.

Variables	Multivariable Hazard Ratio (95% CI)	P value
Age group		
<20	1	NA
20 to 34 years	1.0 (0.8-1.2)	0.547
≥35 years	1.0 (0.7-1.3)	0.841
Ethnicity		
White	1	NA
Black/Brown	1.2 (1.1-1.3)	0.025
East Asian	1.4 (0.8-2.4)	0.191
Indigenous	1.4 (0.7-2.6)	0.382
Region		
North	1.6 (1.3-2.0)	<0.001
Northeast	1.6 (1.3-1.9)	<0.001
Central-West	1.3 (1.1-1.7)	0.017
Southeast	1.3 (1.1-1.5)	0.007
South	1	NA
Postpartum	1.4 (1.2-1.6)	<0.001
Comorbidities		
None	1	NA
1	1.2 (1.1-1.3)	0.007
2	1.3 (1.1-1.5)	0.004
≥3	1.2 (0.9-1.5)	0.237
Symptoms		
Shortness of breath	1.1 (0.9-1.3)	0.392
Respiratory distress	1.1 (0.9-1.3)	0.147
Hypoxaemia	1.2 (1.1-1.4)	0.008
Ventilatory support		
None	1	NA
Non-invasive	2.6 (2.1-3.3)	<0.001
Invasive	7.1 (5.6-9.2)	<0.001
Intensive Care Unit admission		
No	1	NA
Yes	1.1 (0.9-1.3)	0.692

List of figures

Figure 1. Cumulative incidence function for in-hospital death.

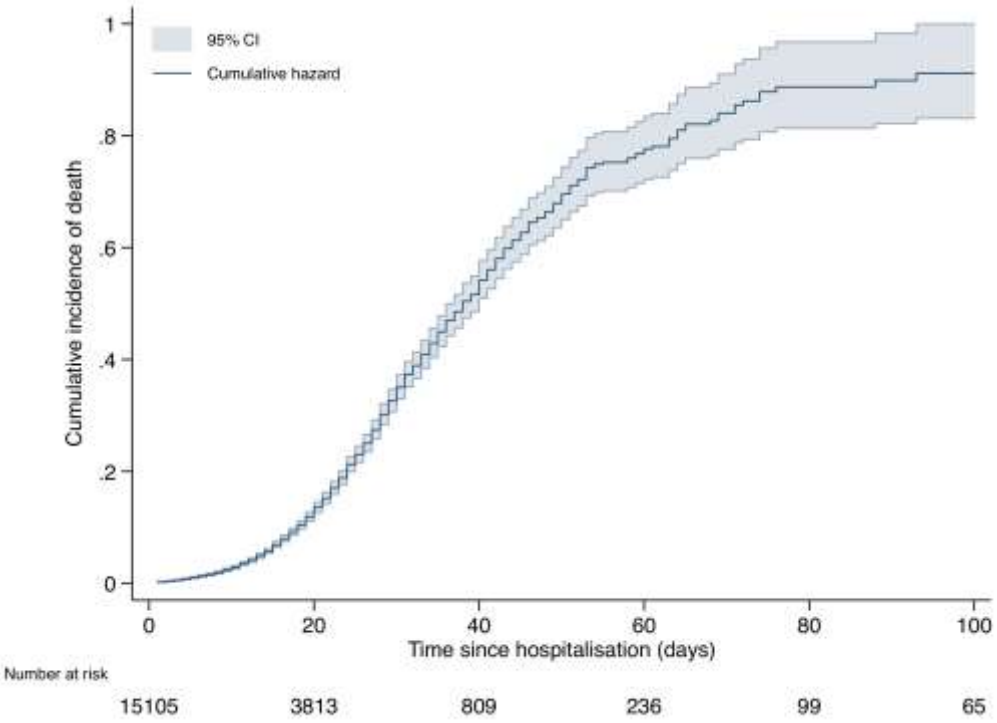

Figure 2. Kaplan-Meier analysis of survival of pregnant and postpartum women with COVID-19 according to postpartum, number of comorbidities, hypoxaemia and ventilatory support.