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**Title:** Clinical characteristics and risk factors for mortality in obstetric patients with severe COVID-19 in Brazil: a surveillance database analysis

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**Running Title:** Risk factors for COVID-19 maternal death in Brazil

### **ABSTRACT**

**Objective:** To describe clinical characteristics of pregnant and postpartum women with severe COVID-19 in Brazil and to examine risk factors for mortality

**Design:** Cross-sectional study based on secondary surveillance database analysis

**Setting:** Nationwide Brazil

**Population or Sample:** 978 Brazilian pregnant and postpartum women notified as COVID-19 Acute Respiratory Distress Syndrome (ARDS) cases with complete outcome (death or cure) until June 18, 2020

**Methods:** Data was abstracted from the Brazilian ARDS Surveillance System (ARDS-SS) database. All eligible cases were included. Data on demographics, clinical characteristics, intensive care resources use and outcomes were collected. Risk factors for mortality were examined by multivariate logistic regression.

**Main Outcome Measures:** Case fatality rate

**Results:** We identified 124 maternal deaths, corresponding to a case fatality rate among COVID-19 ARDS cases in the obstetric population of 12.7%. At least one comorbidity was present in 48.4% of fatal cases compared to 24.9% in survival cases. Among women who died, 58.9% were admitted to ICU, 53.2% had invasive ventilation and 29.0% had no respiratory support. The multivariate logistic regression showed that the main risk factors for maternal death by COVID-19 were postpartum at onset of ARDS, obesity, diabetes, and cardiovascular disease, while white ethnicity had a protective effect.

**Conclusions:** Negative outcomes of COVID-19 in this population are affected by clinical characteristics, but social determinants of health also seem to play a role. It is urgent to reinforce containment measures targeting obstetric population and ensure high quality care throughout pregnancy and postpartum period.

**Funding:** The study received no funding.

**Keywords:** COVID-19, Maternal Death, Health Services Accessibility, Health Status Indicators

#### **Tweetable abstract**

A total of 124 COVID-19 maternal deaths were identified in Brazil. Symptoms onset at postpartum and comorbidities are risk factors.

#### **INTRODUCTION**

COVID-19 is an infection with predominant respiratory features caused by the novel coronavirus SARS-CoV-2. The disease rapidly spread worldwide and was declared a global pandemic on March 11, 2020 by the World Health Organization (WHO). By July 20, 2020, COVID-19 had affected more than 14 million people in 188 territories, with more than 608,000 deaths.<sup>1</sup> Despite the incidence and mortality magnitude, how the infection impacts pregnancy or whether pregnancy and the postpartum period would lead to more vulnerability remain uncertain.<sup>2,3</sup>

Initial case series from China did not identify increased risk of adverse outcomes among obstetric patients when compared to the general population, as well as no maternal deaths were reported.<sup>4,5</sup> However, physiological adaptations in normal pregnancies, mainly cardio-respiratory and immune, are known to increase the susceptibility of pregnant women to several infectious agents and viral pneumonia in particular<sup>6</sup>. Thus, clinicians worldwide remained worried about the impact of COVID-19 in this population. Subsequent data emerging from Europe and North America also concluded that pregnant women were at no increased risk of severe COVID-19 or death<sup>3,7,8</sup>. More recently, further studies reported higher risk of ICU admission and mechanical ventilation during pregnancy<sup>9,10</sup>, as well as the first near miss and maternal deaths cases emerged from Iran, US, UK, France, Mexico and Spain<sup>7-9,11-16</sup>.

In Brazil, approximately two months after the first official COVID-19 case was reported, 1,700 deaths among the general population and five maternal deaths had already been documented, raising concerns that perhaps the pandemic in low- and middle-income countries could pose additional risks for pregnant women.<sup>17</sup> It was hypothesized that higher birth rates, worse population health status, and poor quality of obstetric care, now competing with constraints resulting from the pandemics management, would contribute to an increase in the absolute number of deaths and also in the case fatality rate.<sup>17</sup>

The present analysis continues the initial investigations<sup>17-19</sup> of our group using data from the Brazilian Ministry of Health Acute Respiratory Distress Syndrome (ARDS) Surveillance System (ARDS-SS) to describe clinical characteristic and to examine risk factors for death among COVID-19 cases during pregnancy and the postpartum period in Brazil.

## **MATERIALS AND METHODS**

This is a secondary database, cross-sectional analysis of the ARDS-SS. Data were extracted from the ARDS-SS, which comprises mandatory notifications of all ARDS cases in the country, from both public and private units in all states. ARDS-SS was established in 2009, as a response to the H1N1 pandemic and specific fields to track pregnant and postpartum women has been available since then<sup>20</sup>. New specific fields were incorporated to the ARDS Notification Form to gather information on COVID-19 cases and are included in the database as well. Anonymized data is made publicly available by the Ministry of Health. Data was abstracted in June 18, 2020 and inclusion criteria were: i) pregnant or postpartum women; ii) confirmed (nasopharyngeal RT-PCR) SARS-CoV2 infection or confirmed COVID-19 case based on Brazilian Ministry of Health case



definition; iii) final outcome (death or cure) recorded in the database; iv) registered from February 26 (date of the first COVID-19 case in the country) to June 18, 2020. We have been monitoring maternal deaths due to COVID-19 in Brazil since the beginning of the pandemic. We have published so far preliminary data on subsets of the present sample as they were available in each publication date<sup>17–19,21</sup>, the last one including all 124 fatal cases notified until June 18, 2020, as well as 854 cases who evolved to cure<sup>18</sup>.

Besides ARDS-SS specific fields indicating whether a case is pregnant or in the postpartum period, we also hand-searched for mentions to pregnancy or postpartum in an open-ended field related to other comorbidities or risk factors. Information on gestational age or pregnancy outcome are not routinely collected by the ARDS-SS (only gestational trimester information is available). A COVID-19 diagnosis was defined as the final classification of each case in the database according to the epidemiological investigation performed by the notifying unit. Figure 1 presents the case selection process, as well as the proportion of cases to whom a SARS-CoV-2 RT-PCR result was available. Among fatal cases, 95.2% had COVID-19 laboratory confirmation and 80.6% had SARS-CoV-2 RT-PCR results available (serological antibodies and rapid test were recorded for the other cases). These proportions were 97.4% and 78.7%, respectively, among survivors.

The main outcome was COVID-19 case fatality rate among ARDS-cases in pregnant and postpartum women and the following variables were analyzed for each case: age, ethnicity, pregnancy or postpartum status at notification date, gestational trimester at notification date (for pregnant cases), comorbidities (diabetes, cardiovascular disease, asthma, obesity), ICU admission and respiratory support requirement. Pregnancy or postpartum status and gestational trimester at notification date were assumed to be a proxy of symptoms onset timing, once the Notification Form collecting this information is usually filled in upon hospital admission due to ARDS. Comorbidity-related ARDS-SS fields do not allow identification of gestational or pre-gestational diabetes and hypertension and did not separate heart diseases from hypertensive disorders; thus, these conditions are grouped under “diabetes” and “cardiovascular disease” variables. For the present analysis, we interpreted missing data as absence of the specific condition or characteristic. This assumption was applicable to comorbidities, ICU admission and respiratory support. Overall missingness for comorbidities on ARDS-SS was previously described by Baqui et al for the general population<sup>22</sup> and by Takemoto et al<sup>18</sup> for the obstetric population.

Core outcome sets and patient involvement requirements are not applicable to this analysis due to its retrospective, secondary database nature. Brazilian ethical regulations do not require Institutional Review Board approval for secondary anonymized data analysis.

Sample size calculation was not performed once we included all eligible cases from the nationwide ARDS-SS database. STATA 12 was used for statistical analyses. Continuous variables were described using measures of central tendency and dispersion and compared using the Mann-Whitney test. Categorical variables were described using measures of frequency and compared by exact Fisher's and Chi-squared test. Multiple logistic regression with a simultaneous entry method was used to explore association of demographic and clinical characteristics with risk of death. Variables with statistically significant differences in hypothesis tests were selected to enter the model (age data was dichotomized as  $\leq$  or  $>$  35 years). Statistical significance level was set at 0.05 and all p-values were two-tailed.

### ***Funding***

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## **RESULTS**

We identified 978 COVID-19 cases in pregnant or postpartum women in the ARDS-SS with recorded outcome. The case fatality rate among women with COVID-19 ARDS during pregnancy and postpartum was 12.7% (124 deaths). Figure 2 illustrates the distribution of cases within the country with most cases occurring in São Paulo (SP, n=359), Rio de Janeiro (RJ, n=107), Ceará (CE, n=106), and Amazonas (AM, n=92). Mortality rate among COVID-19 maternal ARDS cases in these states were: 14.1%, 9.4%, 29.0%, and 5.8% (data not shown).

Demographic and clinical characteristics of fatal and non-fatal cases are shown in Table 1. Non-survivors were older and symptoms onset occurred more frequently in postpartum. At least one comorbidity was present in 48.4% of fatal cases compared to 24.9% in survival cases, and the most common was cardiovascular disease, followed by diabetes. Among women who died, 58.9% were admitted to ICU, 53.2% had invasive ventilation and 29.0% had no respiratory support.

The multivariate logistic regression showed that the main risk factors for maternal death by COVID-19 were postpartum at onset of ARDS (OR=2.48; 1.65-3.72), obesity (OR=2.31; 1.10-

4.84), diabetes (OR=1.82; 1.01-3.28) and cardiovascular disease (OR=1.74; 1.02-2.94), while white ethnicity had a protective effect (OR=0.58; 0.35-0.99) (Table 2).

## **DISCUSSION**

### ***Main findings***

We identified 978 maternal cases of ARDS and 124 maternal deaths due to COVID-19 in Brazil. Women in our sample were generally young, and the age difference between survivors and non-survivors was only 2 years although statistically significant. Besides, a significant proportion (51.6%) of women who died from COVID-19 had no comorbidities or risk factors recorded in the ARDS-SS database. This seems to indicate that apparently young and healthy women have died due to COVID-19 complications during pregnancy or just after birth. Among those who had comorbidities, the most common condition was cardiovascular disease followed by diabetes. Similar findings have been documented in a systematic review with non-pregnant subjects.<sup>23</sup>

In our sample, 41.1% of women were not admitted to the ICU and 29.0% did not have records of any type of respiratory support. These findings may indicate that barriers to access intensive care may be playing a role in the overwhelming number of COVID-19 maternal deaths in Brazil. A US Center for Disease Control report examining more than 8,000 pregnant women with COVID-19 and 16 cases of maternal deaths identified an increased risk of hospital admission, admission to the ICU and mechanical ventilation in pregnant women, although there was no higher risk of death<sup>9</sup>. Similar findings were also described in Sweden<sup>10</sup>, demonstrating that pregnant women may be more susceptible to COVID-19 complications, but with adequate and timely intensive care the survival rate could be similar to non-pregnant women.

Obstetric cases of ARDS due to COVID-19 in Brazil are at an increased risk of death if symptoms onset occurs during the postpartum period, they had obesity, diabetes, or cardiovascular disease. Similarly, an analysis from Mexico<sup>24</sup> identified that having a comorbidity, particularly diabetes, increases the risk of death among pregnant women with COVID-19. In our sample, being White was protective against death. Previous finds from UK and US have indicated that pregnant women from ethnic minority groups are at increased risk of adverse outcomes<sup>8,9</sup>. Similar findings were expected in Brazil, where racial disparities in the access to health care are well documented.<sup>25</sup>

### ***Strengths and limitations***

Our study is secondary data analysis of an official nationwide database. In Brazil, ARDS cases due to any cause have been considered of mandatory notification to the Ministry of Health since 2009 and the specific aetiology is recorded, as well as the diagnostic method. Both aspects contribute to the robustness of our analysis in terms of nationwide representativeness and to the higher rate of laboratory-confirmed SARS-CoV-2. Additionally, our findings about risk factors for death are consistent with a previous report from Mexico<sup>24</sup> and also with analysis for the general population<sup>23,26</sup>. It is important to highlight that the available data refer to COVID-19 ARDS cases only and that we do not have information on non-ARDS COVID-19 cases in the obstetric population systematically collected in the country. Also, underreporting of maternal deaths is a recognized issue in the country.<sup>27</sup>

### ***Interpretation***

According to our findings, the number of COVID-19-related maternal deaths is up to now surpassing the published available combined figures from other countries<sup>28</sup>. To our knowledge, available data on maternal deaths with COVID-19 worldwide officially consisted of 36 deaths when our data was abstract on June 18, 2020. It is not possible to rule out globally underreported maternal deaths due to COVID-19. Although maternal mortality is an important health indicator and is usually strictly monitored worldwide, the data might be incomplete within the pandemic context. Comparatively, during the H1N1 epidemic in 2009, Brazil had 83 maternal deaths due to any influenza pneumonia in a 12-month period.<sup>29</sup> The number of COVID-19 maternal deaths in the country in a 3-months period is 49% higher than the figures for H1N1 in the entire 2009 year. COVID-19 pandemic hit Brazil while the country was still struggling with unacceptably high maternal death ratio<sup>29</sup>. Despite possible greater susceptibility to severe acute respiratory syndromes in pregnant women in general, it is worth mentioning the significant variation in the number of deaths between different Brazilian States. These findings suggest that negative outcomes in pregnancy during the COVID-19 pandemic might also be associated with poor quality obstetric care, social risks and barriers to access health care, once physiological adaptations and clinical factors are not anticipated to be markedly different across different geographic regions. Notably, Brazilian's federal government actions to contain COVID-19 pandemic are being recognized as not only ineffective but also endangering. Against universal recommendations, the government failed to reinforce the need for social isolation or to provide universal screening, as well proper investments in health units and supplies.<sup>30</sup>

Currently, the first cause of maternal death and near miss in Brazil is hypertension<sup>29,31</sup>, and inflammatory states have been described as relevant etiological hypothesis for both hypertension and preeclampsia.<sup>32</sup> Thus, when hypertension and COVID-19 simultaneously occur, it is possible to conjecture that inflammatory response may play a role in worsening prognosis, especially during pregnancy. Another possible explanation may be a combination of the country's high prevalence of overweight and obesity with metabolic syndrome,<sup>33</sup> considering the same inflammatory aspect of immune system response to coronavirus. Obesity was associated with antepartum severe maternal morbidity and may contribute to maternal deaths due its association with preeclampsia<sup>34,35</sup>.

The prioritization of COVID-19 cases through the health care systems have been described as impacting maternal and neonatal outcomes worldwide.<sup>36</sup> In Brazil, even before the COVID-19 global pandemic, access to antenatal care faced chronic and complex barriers.<sup>25,37</sup> Therefore, barriers to access routine assessment and testing may lead to delays in receiving proper care, potentially contributing to maternal deaths. Additionally, Brazilian caesarean rates are historically high and local data evidenced a three times higher risk of maternal death associated with caesarean sections.<sup>38</sup> In the pandemic context, at least one study already raised awareness of increased risk of adverse and/or severe features of COVID-19 disease for patients undergoing surgeries.<sup>39</sup>

The disquieting findings about maternal deaths due to COVID-19 in Brazil are worrisome, since the country was not able to control the pandemic and the number of new cases and deaths are still rising. Our data highlights the urgent need for containment measures aimed to the obstetric population, particularly women with high-risk pregnancies and postpartum women. These measures should include timely and detailed analysis of each COVID-19-related maternal death along with COVID-19-related maternal near misses (the latter not even auditable through Brazilian health information system). . This might allow producing guidelines and local strategies to improve patients' journey specifically designed for COVID-19 during pregnancy and postpartum, to enhance maternal and perinatal outcomes.

A call for action in April 2020 already anticipated that women during pregnancy and postpartum might be a vulnerable population for COVID-19 not only due to biological or clinical factors, but also due to social risks.<sup>40</sup> We believe that Brazil is currently facing the tragedy of the aforementioned prediction, and that estimating its real dimension can contribute to reverse the present disaster.

## **CONCLUSION**

COVID-19-related maternal deaths in Brazil surpassed worldwide combined published figures. Negative outcomes of COVID-19 in this population are affected by clinical characteristics, but social determinants of health and barriers to access proper care seem to play a role. It is urgent to reinforce containment measures targeting the obstetric population and ensure high quality care throughout pregnancy and the postpartum period.

## **DISCLOSURE OF INTERESTS**

We declare no competing interests. Completed disclosure of interest forms are available to view online as supporting information.

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## **CONTRIBUTION TO AUTHORSHIP**

MLST contributed for study conception and study design, conducted literature search and data extraction, conducted data analysis and interpretation, wrote the first draft of the paper, reviewed and approved the final manuscript.

MOM contributed for study conception and study design, conducted literature search and data extraction, conducted data analysis and interpretation, wrote the first draft of the paper, reviewed and approved the final manuscript.

CAB contributed for study conception and study design, conducted data analysis and interpretation, reviewed and provided comments on the first draft, reviewed and approved the final manuscript.

RK contributed for study conception and study design, conducted data analysis and interpretation, reviewed and provided comments on the first draft, reviewed and approved the final manuscript.

LARS contributed for study conception and study design

LK contributed for study conception and study design, reviewed and approved the final manuscript.

EBF contributed for study conception and study design, reviewed and approved the final manuscript.

MNP contributed for study conception and study design, conducted data analysis and interpretation, reviewed and provided comments on the first draft, reviewed and approved the final manuscript.

CGM contributed for study conception and study design, reviewed and approved the final manuscript.

CSGD contributed for study conception and study design, reviewed and approved the final manuscript.

ASOM contributed for study conception and study design, conducted literature search and data collection, conducted data analysis and interpretation, wrote the first draft of the paper, reviewed and approved the final manuscript.

MMRA contributed for study conception and study design, wrote the first draft of the paper, reviewed and approved the final manuscript.

#### **DETAILS OF ETHICS APPROVAL**

According to Brazilian ethics regulatory requirements, secondary analysis of publicly available anonymized data does not require Institutional Review Board ethics approval.

#### **FUNDING**

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## Figure Legends

**Figure 1. Case selection flowchart**

**Figure 2. Geographic distribution of pregnant and postpartum cases with COVID-19 on ARDS-SS and complete outcome by June 18, 2020**

**Table 1. Characteristics of COVID-19 maternal ARDS cases in Brazil (n=978)**

	Death (n=124)		Cure (n=854)		p-value
	n	%	n	%	
Age – median (IQR)	32 (25-37)		30 (24-35)		0.0039*
Postpartum	50	40.3	174	20.4	<0.0001**
Pregnancy	74	59.7	680	79.6	
1 <sup>st</sup> trimester	2	2.7	55	8.1	0.1662***
2 <sup>nd</sup> trimester	21	28.4	148	21.8	
3 <sup>rd</sup> trimester	46	62.2	449	66.0	
Unknown	5	6.7	28	4.1	
Skin color/ethnicity					
White	23	18.5	212	24.8	0.5013***
Black	5	4.0	46	5.4	
Yellow	1	0.8	2	0.2	
Brown	64	51.6	387	45.3	
Indigenous	1	0.8	5	0.6	
Missing	30	24.2	202	23.7	
Comorbidities or risk factors					
Asthma	5	4.0	17	2.0	0.1839**
Cardiovascular disease	26	21.0	91	10.7	<0.0001**
Diabetes	21	16.9	65	7.6	<0.0001**
Obesity	12	9.7	31	3.6	<0.0001**
Any comorbidity or risk factor	60	48.4	213	24.9	<0.0001**
Use of Intensive care					
ICU admission	73	58.9	134	15.7	<0.0001**
Invasive ventilation	66	53.2	32	3.7	<0.0001***
Non-invasive ventilation	22	17.7	197	23.1	
No respiratory support	36	29.0	625	73.2	

\* Mann-Whitney test; \*\*Exact Fisher's test; \*\*\*Chi-squared test; SD, standard deviation; ICU, intensive care unit

**Table 2. Multivariate Logistic Regression Analysis of Risk Factors for Maternal Death with ARDS due to COVID-19**

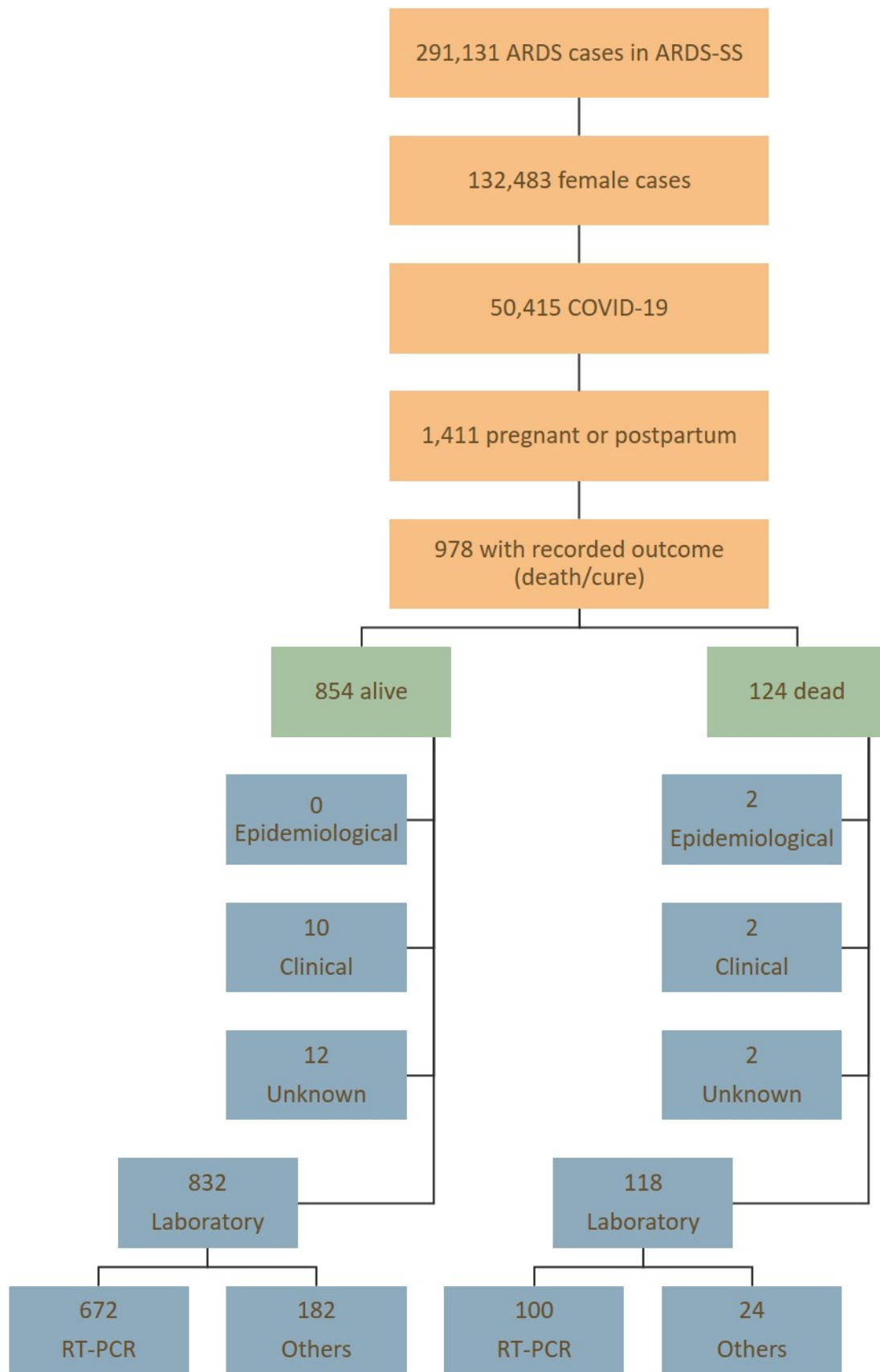
Variables	OR (95% CI)	p-value
Postpartum at the time of ARDS notification	2.481 (1.654-3.720)	<0.0001
Obesity	2.307 (1.101-4.837)	0.0268
White ethnicity	0.585 (0.346-0.991)	0.0463
Diabetes	1.817 (1.007-3.278)	0.0472
Cardiovascular disease	1.736 (1.024-2.945)	0.0407

Classification table 86.9% correctly classified using enter logistic regression method, Constant = -2.316. Area under the receiver operating characteristic (ROC) curve [95% CI] = 0.674 [0.643-0.703]; OR, Odds Ratio; CI, Confidence Interval; ARDS, Acute Respiratory Distress Syndrome

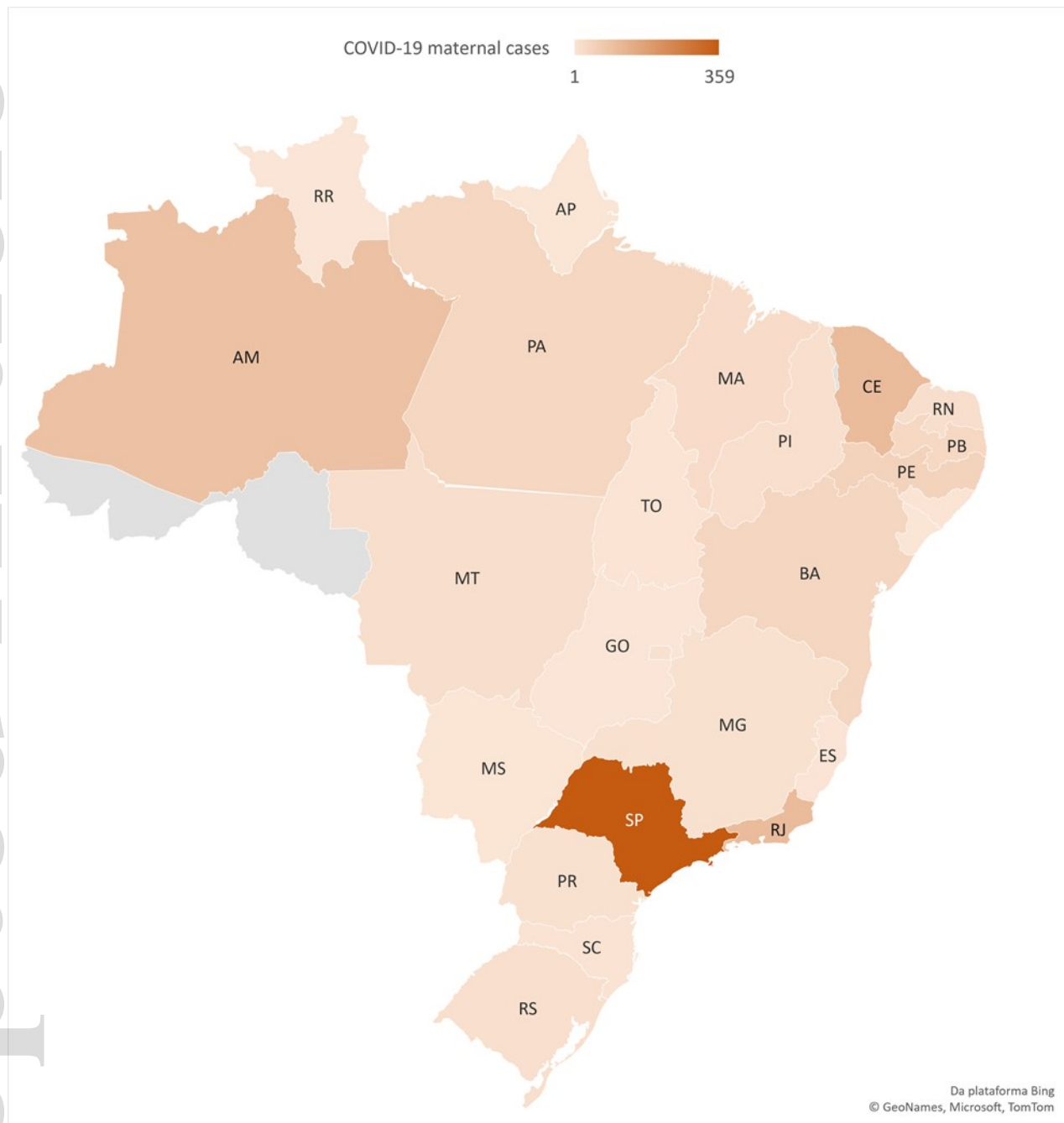
Case selection

Outcome

COVID-19 Diagnostic criteria



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