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## CLINICAL ARTICLE

### **Risk factors for adverse outcomes among pregnant and postpartum women with acute respiratory distress syndrome due to COVID-19 in Brazil**

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### **Keywords**

COVID-19; Health services accessibility; Health status indicators; Maternal death

### **Synopsis**

Clinical and social risk factors and barriers to access health care are associated with adverse outcomes from COVID-19 disease among Brazilian pregnant and postpartum women.

### **ABSTRACT**

**Objective:** To evaluate whether clinical and social risk factors are associated with negative outcomes for COVID-19 disease among Brazilian pregnant and postpartum women.

**Methods:** A secondary analysis was conducted of the official Acute Respiratory Syndrome Surveillance System database. Pregnant and postpartum women diagnosed with COVID-19 ARDS until July 14, 2020, were included. Adverse outcomes were a

composite endpoint of either death, admission to the intensive care unit (ICU), or mechanical ventilation. Risk factors were examined by multiple logistic regression.

**Results:** There were 2475 cases of COVID-19 ARDS. Among them, 23.8% of women had the composite endpoint and 8.2% died. Of those who died, 5.9% were not hospitalized, 39.7% were not admitted to the ICU, 42.6% did not receive mechanical ventilation, and 25.5% did not have access to respiratory support. Multivariate analysis showed that postpartum period, age over 35 years, obesity, diabetes, black ethnicity, living in a peri-urban area, no access to Family Health Strategy, or living more than 100 km from the notification hospital were associated with an increased risk of adverse outcomes.

**Conclusion:** Clinical and social risk factors and barriers to access health care are associated with adverse outcomes among maternal cases of COVID-19 ARDS in Brazil.

## 1 INTRODUCTION

Despite a continuous decrease in maternal mortality ratio since 2000, 60 maternal deaths per 100 000 live births still occur in Brazil [1]. Most women who die come from vulnerable population groups. The association between maternal mortality with delays in receiving proper care has been vastly documented in Brazil, particularly the difficulties in transferring women to high complexity hospitals, and lack of adequate clinical management within health facilities [2]. The COVID-19 pandemic has stricken the Brazilian healthcare system while chronic and complex obstacles were already in place. Despite initial measures to slow the spread of the virus, the incidence of COVID-19 showed exponential growth, resulting in 3 012 412 cases within 98% of Brazilian cities and 120 000 overall deaths until August 30, 2020 [3]. The first confirmed COVID-19-related maternal death occurred in late March 2020 [4]. The number of fatal cases of COVID-19 among pregnant and postpartum women since then have rapidly increased, resulting in a nationwide tragedy [5].

Several aspects about the effects of SARS-CoV-2 infection on the obstetric population remain to be elucidated. During pregnancy, there seem to be an increased risk of

hospitalization, admission to the intensive care unit (ICU), and mechanical ventilation, although no increment in maternal mortality was observed outside Brazil [6–8]. On attempts to understand the Brazilian context, the Brazilian Group for Studies of COVID-19 and Pregnancy [4, 5, 9–11] hypothesized that social risks and barriers to access to health care could play a role in maternal deaths. The aim of the present study was to analyze risk factors for adverse outcomes in pregnant and postpartum women with COVID-19 in Brazil, analyzing access to health care and social risk factors.

## **2 MATERIALS AND METHODS**

Data from the Brazilian official Acute Respiratory Syndrome Surveillance System (ARDS-SS, SIVEP-Gripe in Portuguese) were abstracted on July 14, 2020. ARDS is of mandatory notification in Brazil, and public and private hospitals report each unique case of ARDS to the national surveillance system [12]. The definition criteria for ARDS is any flu-like symptom in association with either dyspnea or respiratory distress, or oxygen saturation over 95%. Among over 130 variables, specific fields regarding the diagnosis of COVID-19 were analyzed, including COVID-19 final classification, and the availability of a SARS-CoV-2 reverse transcription polymerase chain reaction test result. Pregnant and postpartum women are identified through specific close-ended fields in the database, and additional manual searches were performed for possible missing pregnancies.

Female sex, age 10–50 years, pregnancy or postpartum, and final diagnosis of COVID-19 were included for analysis. For the latter, confirmation was the presence of either laboratory, clinical, or epidemiological criteria. Figure 1 displays the selection process and COVID-19 definition criteria. The methods are described elsewhere [13].

The outcome was a composite endpoint expressed as the proportion of maternal cases of ARDS with either death, admission to the ICU, or mechanical ventilation. Risk factors for mortality were previously reported [13] and it was considered that critical cases of COVID-19 are of relevance during pregnancy and postpartum, even if they are non-fatal. The criteria for critical COVID-19 or obstetric near-miss were not available in the database; therefore, admission to the ICU and mechanical ventilation were assumed as proxies. Access to admission to the ICU poses a challenge for obstetric patients during COVID-19 [5, 10], so a secondary analysis was conducted using admission to the ICU as an outcome.



The independent variables examined as potential risk factors for adverse outcome were: (1) demographic (age and ethnicity); (2) clinical (gestational period at notification date [pregnancy or postpartum], gestational trimester at notification date, and co-morbidities); and (3) access to healthcare-related variables (size of city of residence, distance from city of residence to notification hospital, setting of residence [urban, rural, or peri-urban], lack of healthcare infrastructure at city of residence [ICU beds, 24-hour emergency department, Family Health Program]).

Age was dichotomized as 35 years and under or older than 35 years, according to the Brazilian Ministry of Health age-related gestational risk. Missing data on co-morbidities and use of intensive care resources (admission to the ICU and respiratory support) were treated as an absence of the condition. Missingness on ARDS-SS was previously described [5, 14].

Place of residence is recorded as urban, peri-urban or rural in the ARDS-SS. The distance between city of residence and ARDS notification unit was calculated using Google Maps®. Distance was dichotomized as 100 km or less or more than 100 km.

Access to healthcare-related variables were collected using official Brazilian government sources and the code for the city of residence was the common link between databases. The size of the city was obtained from the National Information System of the Unified System of Social Assistance (Rede SUAS) and dichotomized as large (over 100 000 inhabitants) or small to medium (100 000 inhabitants or less). The data source for population was the 2010 Brazilian Census (last available edition). Information on the availability of ICU beds, 24-hour emergency department unit, and Family Health Program was collected using the 2018 Municipalities Basic Information Research (*Pesquisa de Informações Básicas Municipais*).

All eligible records were included in the analysis, regardless of outcome (death or cure). Univariate analyses assessed the association between independent variables and main outcome. Risk ratio (RR) and *P* values were calculated. Backward multiple logistic regression explored the association between independent variables and the risk of adverse outcome, providing the adjusted odds ratio (OR) and corresponding 95% confidence interval. The level of statistical significance was set at 0.05 and all *P* values were two-tailed. Analyses were conducted using STATA 12. STROBE guidelines were followed for observational studies. A secondary analysis of publicly available anonymized

data did not require ethics approval from the Institutional Review Board, in accordance with the Brazilian regulatory requirements for ethics.

### 3 RESULTS

As of July 14, 2020, 2475 cases of COVID-19 ARDS in pregnant and postpartum women in Brazil were identified. The distribution of cases within the Brazilian geographic region and epidemiological week of notification is presented in Figure 2. The number of cases of ARDS steadily increased until epidemiological week 25. Initially, most cases occurred in the north, northeast, and southeast, but since the 23rd epidemiological week, there was a trend of increasing cases in the mid-west and south regions. Data were abstracted at the beginning of the 29th week, and testing for COVID-19 and notifications are usually delayed up to 3 weeks, so data from week 26 may be underestimated.

Among the 2475 maternal cases of ARDS, 590 women had adverse outcomes and 204 deaths were reported. Among the fatal cases, 5.9% of women were not hospitalized, 39.7% were not admitted to an ICU, 42.6% did not receive mechanical ventilation, and 25.5% did not have access to any respiratory support before dying (Table 1).

Table 2 presents the characteristics of the cases of COVID-19 ARDS and healthcare access-related variables. The median age was 30 years, most cases were notified during pregnancy (78.4%), and 27.5% had at least one co-morbidity. The univariate analysis showed that women with adverse outcomes were older, more likely to be black, notified in the postpartum period, with diabetes, obesity, or any co-morbidity. Living at least 100 km away from the notification hospital, in a peri-urban area, or in a city without Family Health Strategy (FHS) increased the risk of an adverse outcome in the univariate analysis (Table 2).

Symptoms at notification are presented in Figure 3. Cough, fever, dyspnea, respiratory distress, and oxygen saturation over 95% ( $P < 0.0001$  for all comparisons) occurred more frequently among cases with adverse outcomes. A sore throat was more common among cases without adverse outcomes ( $P = 0.018$ ).

A total of 2184 maternal cases of COVID-19 ARDS with complete data for all independent variables in the multiple logistic regression model were included (513 with and 1671 without adverse outcomes). The results for both the adverse outcome and

admission to the ICU regression models are presented in Table 3. Being postpartum at ARDS notification, aged over 35 years, obese, or having diabetes were the clinical variables that remained significant in the multivariate analysis. Black ethnicity increased the chance of an adverse outcome in 1.61 cases. Cases with missing data on ethnicity had 1.45 times more chance of an adverse outcome. Variables regarding access to healthcare infrastructure that remained significantly associated with the outcome were living in a peri-urban area (OR 3.57,  $P=0.0266$ ), without FHS (OR 2.77,  $P=0.0233$ ), or over 100 km away from the notification hospital (OR 1.83,  $P=0.0032$ ). Regarding the risk factors of admission to the ICU, black ethnicity was not retained in the final model, and a lack of ICU beds in the city of residence remained significant (decreasing the chance of admission to the ICU by approximately 31%).

#### 4 DISCUSSION

The present analysis identified clinical, social, and care-related risk factors associated with adverse outcomes among obstetric cases of COVID-19 ARDS. Increased risk of death, admission to the ICU, or mechanical ventilation were associated with age over 35 years, ARDS notification during the postpartum period, obesity, and diabetes. The risk of an adverse outcome was associated with variables related to social vulnerabilities, as well as with access to healthcare barriers: living in peri-urban areas; in a city not covered by FHS; or more than 100 km away from the hospital where ARDS was diagnosed and notified; as well as being black or having missing data for ethnicity. Risk factors for admission to the ICU were only similar, but black ethnicity did not show an association with the outcome, while a lack of ICU beds in the place of residence decreased the risk of adverse outcomes.

As of June 18, 2020, there were 124 COVID-19-related maternal deaths in Brazil [5], and by July 14, 2020, the country had reached 204 deaths. In 5 months, 590 pregnant and postpartum Brazilian women with COVID-19 were admitted to the ICU, required mechanical ventilation, or died. The distribution of severe maternal cases is following the evolution of the pandemic in the country. New cases from all regions are still emerging due to migration to rural and inner areas and to the premature easing of social isolation measures.

A worse prognosis of COVID-19 disease in association with co-morbidities was already established for the general population [15]. The increased risk of death during pregnancy when previous co-morbidities are present was previously described by the study group [13], as well as in Mexico (particularly diabetes) [16]. Obesity and age 35 years and above were also associated with increased admission to hospital for pregnant women with SARS-CoV-2 infection in the UK [17]. Additionally, longstanding barriers to access antenatal and postpartum care in Brazil [18] were aggravated by the COVID-19 pandemic, leading to reduced routine appointments and tests.

The risk of adverse outcomes was 2.4 times higher when the ARDS notification occurred in the postpartum period rather than during pregnancy. Clinical worsening of COVID-19 disease after surgery has already been described [19]. It is likely that most postpartum women in the present study sample had cesarean deliveries, given its high rates in Brazil. A cesarean delivery increases the odds of maternal death regardless of the COVID-19 diagnosis [20], and both COVID-19 [21] and surgery [22] are risk factors for thromboembolic complications, especially for postpartum women.

Pregnant women from ethnic minorities are at increased risk of the severe features of COVID-19 [8, 17, 23]. In the present sample, black women with COVID-19 ARDS had a higher chance of adverse outcomes, without the increased likelihood of admission to the ICU. Black Brazilian women have an increased risk of death and admission to hospital in worse clinical conditions [11], and the findings of the present study show that they seem to face harder barriers to access intensive care.

Missing data on ethnicity were observed in one-quarter of the study sample, and women with adverse outcomes had slightly higher missing data on ethnicity. They also had 1.4 times higher risk of having an adverse outcome or being admitted to the ICU.

Underreporting of proper ethnicity data is, per se, an obstacle in opposing racial disparities in health care, specifically during the COVID-19 pandemic [24]. Black movement activists state that most people with missing ethnicity data are probably non-white, due to the cultural barriers of asking non-white people about their skin color.

Living in peri-urban areas increased the risk of a COVID-19 adverse outcome by more than three times in the present study sample. Peri-urban areas in Brazil are defined as transitional regions between urban and rural settings, with high population density, precarious housing, and irregular settlements. They are usually located in the

surroundings of large cities, with a lack of sewage treatment, drinkable water supply, and waste disposal [25]. People living in vulnerable areas in terms of socioeconomic level, population group, housing, and commute are at higher risk of being diagnosed or dying due to COVID-19 [26].

Not having access to FHS, a primary care policy endorsed by the Brazilian Ministry of Health, was also associated with adverse outcomes. FHS is a powerful primary care policy that allows the integration of socially vulnerable people within the healthcare system, improving health promotion and early diagnosis of several conditions [27]. It is understood that the poor outcomes that occurred when FHS was not available originated at a primary level, since the women showed worse clinical features on arrival at the hospital [11].

Women living more than 100 km away from the ARDS notification unit have an increased risk of adverse outcomes. The “pilgrimage” of Brazilian pregnant women to access in-hospital care during pregnancy and birth, including emergency care, is associated with increasing maternal near-miss [28]. Small Brazilian municipalities are not equipped with ICUs and no hospitals are available in several settings. While field hospitals were built around major cities during the pandemic, the lack of specialized care continued all over rural Brazil. This might explain why not having a local ICU reduced the risk of admission to the ICU in the study model.

The findings of the present study relate to the three-delays model adopted to identify factors that prevent women from accessing the care they need to survive pregnancy and birth [29]. Women living in settings without FHS, together with the “stay at home” recommendation, and restrictions on public transportation may have lengthened the time to seek care (first delay). Black ethnicity and living more than 100 km away from a specialized ARDS hospital are both markers of social vulnerability, leading to delays on reaching an appropriate facility, especially the ICU (second delay). Postpartum women and high-risk pregnant women may not receive proper care for their co-morbidities and risk factors, such as thromboprophylaxis after cesarean delivery (third delay). The high proportion of deaths during the postpartum period suggests that some of these women may have acquired the infection during their stay in hospital, reinforcing the need for improving patient safety and surveillance after discharge.

### **Strengths and limitations**

The present study is based on official ARDS surveillance system data, ensuring nationwide coverage. Bias introduced by missing variables cannot be ruled out. For instance, there are dichotomous variables, such as the presence of co-morbidities and use of intensive care resources, that were treated as “absent” when missing, which may have led to an underestimation in prevalence. However, the present study examined a large sample size compared to previously published series of severe, critical, and fatal cases of COVID-19 during pregnancy, as well as a comprehensive set of variables, including access barriers to proper care. It is believed that this is the first study addressing risk factors for adverse outcomes of COVID-19 among the obstetric population that also included social risks.

Future retrospective studies including hospital records may identify additional factors that contribute to adverse outcomes. Studies enrolling women who survived maternal near-miss may help understand the delays specifically related to SARS-CoV-2 infection.

### **Author contributions**

All authors contributed equally for study conception and study design. MLST and MOM were responsible for data collection. MLST, MOM, CBA, RK, and MNP were responsible for data analysis and interpretation. MLST, MOM, CBA, and RK wrote the first draft of the paper. All authors reviewed and provided comments on the first draft and approved the final manuscript. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

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### **Conflicts of interest**

The authors have no conflicts of interest.

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## FIGURE LEGENDS

**Figure 1.** Flow chart of case selection. Abbreviations: ARDS-SS, Acute Respiratory Syndrome Surveillance System; RT-PCR, reverse transcription polymerase chain reaction.

**Figure 2.** Cases of COVID-19-related ARDS among pregnant and postpartum women by region and epidemiological week and total confirmed cases in Brazil. Abbreviation: ARDS, acute respiratory distress syndrome.

**Figure 3.** Maternal symptoms at diagnosis of COVID-19 ARDS. \*Statistically significant at  $P<0.05$ .

**Table 1.** Frequency of individual outcomes among cases with the composite outcome and fatal cases.<sup>a</sup>

	Composite outcome	Death
<b>Total</b>	590 (100.0)	204 (100.0)
<b>Death</b>	204 (34.6)	-
<b>In-hospital admission</b>	574 (97.3)	192 (94.1)
Admission to ICU	494 (83.7)	123 (60.3)
<b>Invasive ventilation</b>	242 (41.0)	117 (57.4)
<b>Non-invasive ventilation</b>	178 (30.2)	35 (17.1)
<b>No ventilation</b>	170 (28.8)	52 (25.5)

Abbreviation: ICU, intensive care unit.

<sup>a</sup> Values are given as number (percentage).

**Table 2.** Characteristics of cases of COVID-19 ARDS among pregnant and postpartum women.<sup>a</sup>

	Total (n=2475)	Adverse outcome (n=590)	No adverse outcome (n=1885)	P value	RR (95% CI)
<b>Demographic and clinical characteristics</b>					
Age (years)	30 (24–34)	31 (26–36)	29 (23–34)	<0.0001 <sup>b</sup>	-
Age > 35 years	488 (19.7)	148 (25.1)	340 (18.0)	<0.0001	1.36 (1.16–1.60)
<i>Skin color/ethnicity</i>					
White	535 (21.6)	120 (20.3)	415 (22.0)	-	Reference
Black	134 (5.4)	45 (7.6)	165 (8.8)	0.0056	1.49 (1.12–1.99)
Yellow	16 (0.6)	2 (0.3)	14 (0.7)	0.3802	0.55 (0.15–2.05)
Brown	1161 (46.9)	257 (43.6)	904 (48.0)	0.8924	0.99 (0.81–1.19)
Indigenous	14 (0.6)	1 (0.2)	13 (0.7)	0.2367	0.32 (0.05–2.12)
Missing	610 (24.6)	164 (27.8)	446 (23.7)	0.0830	1.20 (0.97–1.47)
<i>Gestational status at notification</i>					

Pregnancy	1940 (78.4)	389 (65.9)	1551 (82.3)	<.0001	Reference
Postpartum	535 (21.6)	201 (34.1)	334 (17.7)		1.87 (1.63–2.15)
<i>Co-morbidities</i>					
Asthma	87 (3.5)	22 (3.7)	65 (3.4)	0.7445	1.06 (0.73–1.53)
Cardiovascular	271 (10.9)	84 (14.2)	187 (9.9)	0.0023	1.35 (1.11–1.64)
Diabetes	198 (8.0)	74 (12.5)	124 (6.6)	<0.0001	1.65 (1.35–2.00)
Obesity	116 (4.7)	48 (8.1)	68 (3.6)	<0.0001	1.80 (1.43–2.26)
Any co-morbidity	680 (27.5)	219 (37.1)	461 (24.5)	<0.0001	1.56 (1.35–1.79)
<b>Healthcare access-related variables</b>					
Distance from city of residence to notification hospital >100 km (n=2284) <sup>c</sup>	138/2284 (6.0)	53/574 (9.2)	85/1710 (5.0)	<0.0001	1.58 (1.26–1.98)
<i>Size of city of residence</i>					
Large/Metropolis	1911 (77.2)	469 (79.5)	1442 (76.5)	0.1351	Reference
Small/Medium	564 (22.8)	121 (20.5)	443 (23.5)		0.87 (0.73–1.04)
<i>Setting of residence</i>					
Urban	2044 (82.6)	482 (81.7)	1562 (82.9)	-	Reference
Peri-urban	13 (0.5)	7 (1.2)	6 (0.3)	0.0015	2.28 (1.37–3.80)
Rural	132 (5.3)	25 (4.2)	107 (5.7)	0.2346	0.80 (0.56–1.15)
<i>Lack of healthcare infrastructure at city of residence</i>					
No ICU beds	543 (21.9)	118 (20.0)	425 (22.5)	0.1969	0.89 (0.74–1.06)
No 24-hour ED	32 (1.3)	7 (1.2)	25 (1.3)	0.7956	0.92 (0.47–1.77)
No FHS	28 (1.1)	11 (1.9)	17 (0.9)	0.0329	1.66 (1.04–2.64)

Abbreviations: CI, confidence interval; ED, Emergency Department; FHS, Family Health Strategy; ICU, intensive care unit; IQR, interquartile range; RR, relative risk.

<sup>a</sup> Values are given as n (%) or median (IQR) unless otherwise specified.

<sup>b</sup> Mann–Whitney test.

<sup>c</sup> 179 cases were recorded as non-hospitalized and were not included in this analysis.

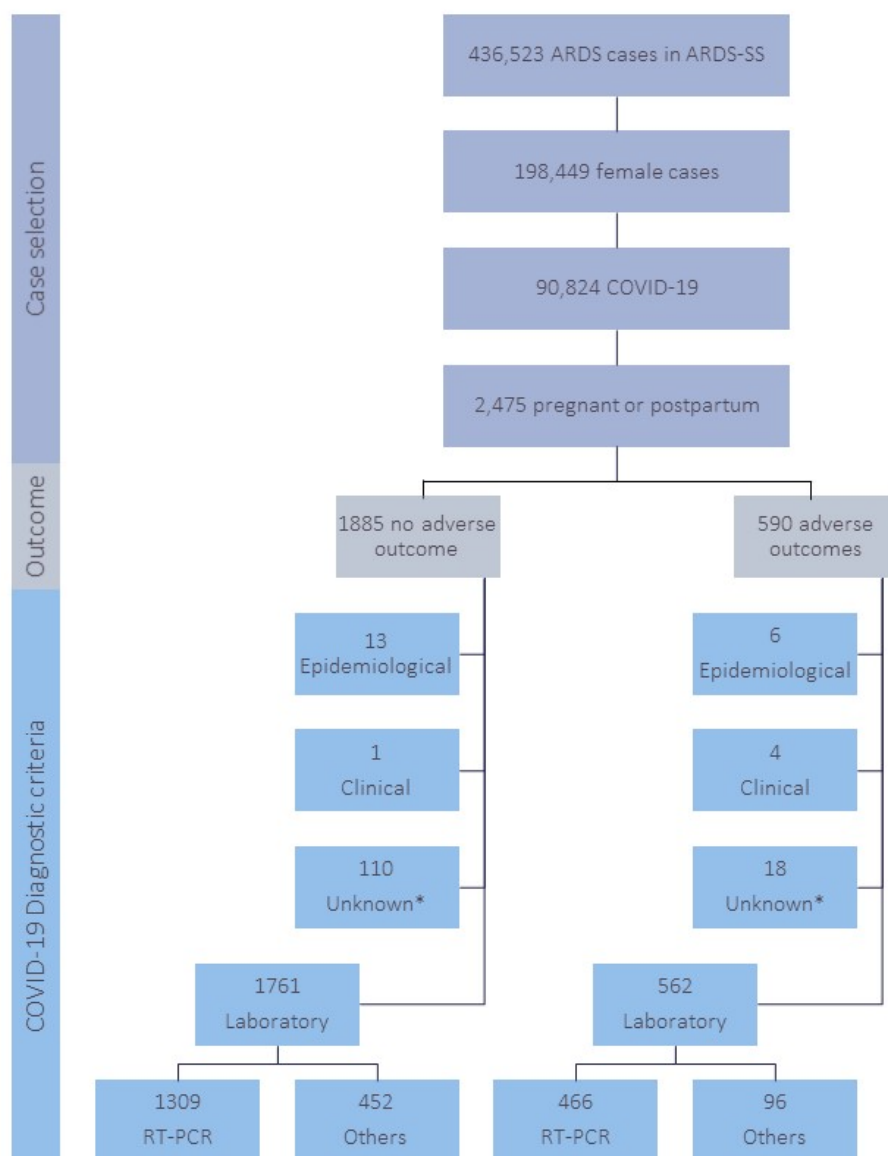
**Table 3.** Risk factors for adverse outcomes among maternal cases of COVID-19 ARDS: multiple logistic regression.

Variables	OR (95% CI)	P value
<b>Composite outcome (death or admission to the ICU or invasive ventilation)<sup>a</sup></b>		
Living in a peri-urban area	3.577 (1.159–11.039)	0.0266
Living in a city without FHS	2.772 (1.148–6.694)	0.0233
Postpartum at the time of ARDS notification	2.427 (1.935–3.046)	<0.0001
Obesity	2.124 (1.381–3.268)	0.0006
Living >100 km away from the notification hospital	1.829 (1.225–2.731)	0.0032
Diabetes	1.664 (1.178–2.349)	0.0038
Black ethnicity	1.610 (1.062–2.442)	0.0250
Missing data on ethnicity	1.446 (1.131–1.851)	0.0033
Age >35 years	1.385 (1.078–1.779)	0.0109
<b>Admission to ICU<sup>b</sup></b>		
Living in a peri-urban area	3.257 (1.063–9.972)	0.0386
Living in a city without FHS	2.747 (1.121–6.730)	0.0271
Living >100 km away from the notification hospital	2.539 (1.612–3.999)	0.0001
Postpartum at the time of ARDS notification	2.115 (1.668–2.681)	<0.0001
Obesity	1.910 (1.227–2.974)	0.0041
Diabetes	1.626 (1.065–2.185)	0.0211
Missing data on ethnicity	1.426 (1.103–1.845)	0.0068
Age >35 years	1.345 (1.0349–1.747)	0.0266
Absence of ICU beds in the city of residence	0.694 (0.508–0.947)	0.0211

Abbreviations: ARDS, acute respiratory distress syndrome; AUC, area under the receiver operating characteristic curve; CI, confidence interval; FHS, Family Health Strategy; ICU, intensive care unit; OR, odds ratio.

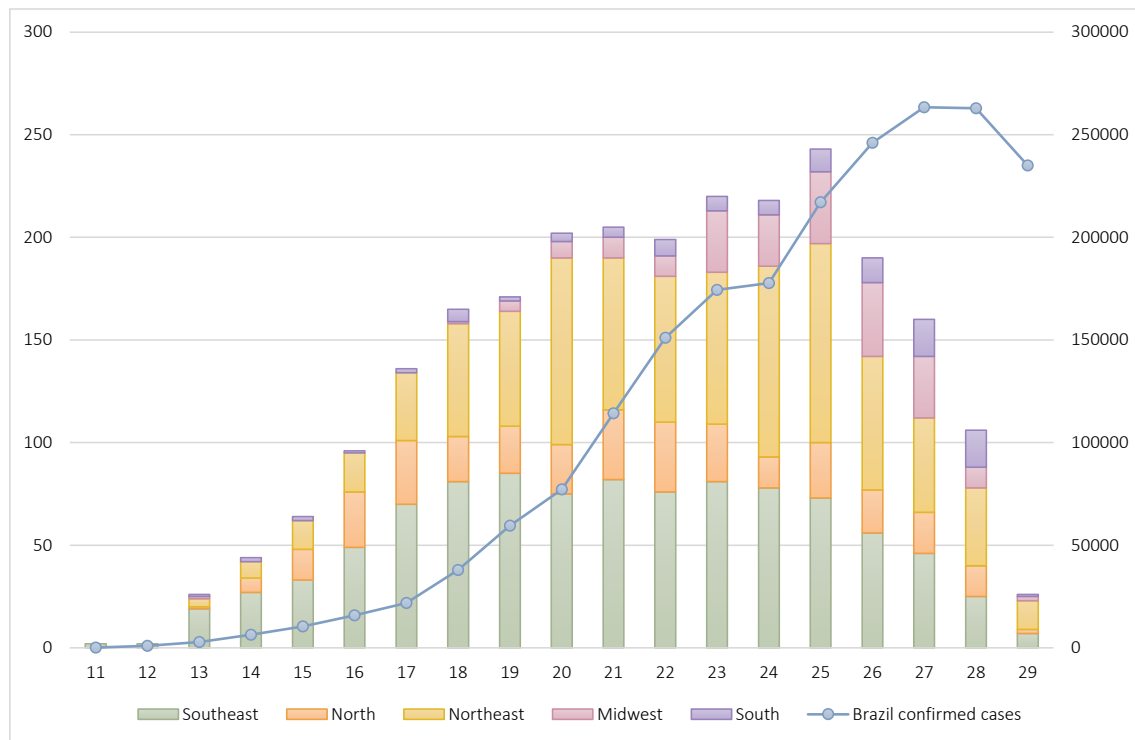
<sup>a</sup> Composite outcome: Classification table 75.5% correctly classified using backward multiple logistic regression method, Constant = −1.692. AUC 0.653, 95% CI 0.632–0.674.

<sup>b</sup> Admission to ICU outcome: Classification table 78.7% correctly classified using backward multiple logistic regression method, Constant = −1.781. AUC 0.653, 95% CI 0.632–0.674.



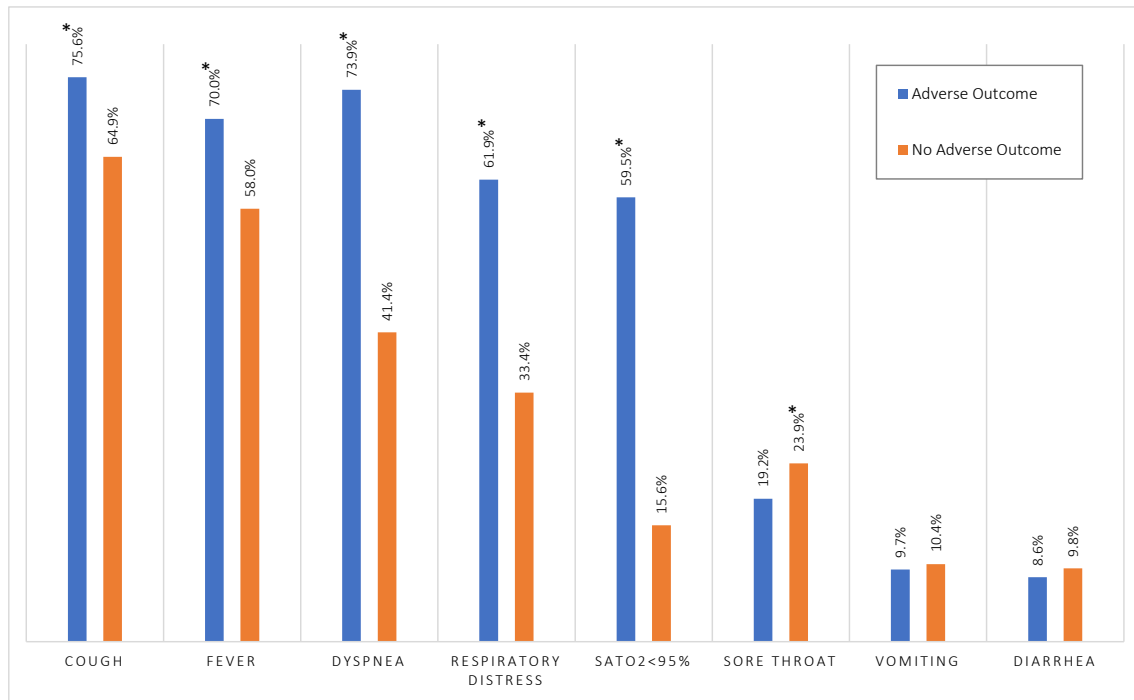
**Figure 1. Case selection flowchart**

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**Figure 2.** COVID-19-related ARDS cases among pregnant and postpartum women by region and epidemiological week and total confirmed cases in Brazil





**Figure 3.** Maternal symptoms at diagnosis of COVID-19 ARDS.

\*statistically significant at  $P < 0.05$