Risk Factors for Death Among 120,804 Hospitalized Patients with Confirmed COVID-19 in São Paulo, Brazil

Patricia Vieira da Silva,† Silvano Barbosa de Oliveira,2,3,4 † Juan José Cortez Ecalante,2,3 Maria Almiron,2,3 Daniel Henrique Tsuha,1 Helena Keico Sato,5 Paulo Rossi Menezes,6 Regiane Cardoso de Paula,6 Tatiana Lang D’Agostini,6 and Julio Croda†1,*†

1Federal University of Mato Grosso do Sul, Campo Grande, Brazil; 2Pan American Health Organization, Brasilia, Brazil; 3World Health Organization, Brasilia, Brazil; 4University of Brasilia, Brasilia, Brazil; 5Epidemiological Surveillance Center “Prof. Alexandre Vranjac” of the São Paulo State Department of Health, São Paulo, Brazil; 6Disease Control Coordination of the São Paulo State Department of Health, São Paulo, Brazil; 7Osvaldo Cruz Foundation, Campo Grande, Brazil

Abstract. São Paulo is a state in Brazil with one of the highest numbers of confirmed and severe cases of coronavirus disease (COVID-19), with an incidence of 294 hospitalizations per 100,000 inhabitants. We report the clinical characteristics and outcomes of 120,804 hospitalized patients with confirmed COVID-19 from February 26 to October 10, 2020, in São Paulo. Characteristics of patients who died and survived were compared using a survival analysis. The median age was 60 years (interquartile range [IQR], 47–72), 67,821 (56.1%) were men, and 61,659 (51.0%) were white. Most hospitalized patients (79,812; 66.1%) reported one or more comorbidities, 41,708 (34.5%) hospitalized patients were admitted to intensive care units, and 33,079 (27.4%) died. Men (hazard ratio [HR], 1.22; 95% confidence interval [CI], 1.18–1.25), elderly individuals (HR, 3.85; 95% CI, 3.68–4.02), and patients with chronic cardiovascular disease including hypertension (HR, 1.05; 95% CI, 1.02–1.08), chronic lung disease (HR, 1.38; 95% CI, 1.31–1.45), diabetes mellitus (HR, 1.14; 95% CI, 1.11–1.18), and chronic neurological disease (HR, 1.48; 95% CI, 1.41–1.55) were at higher risk for death from COVID-19.

BACKGROUND

In December 2019, an outbreak of pneumonia of unknown origin was reported in Wuhan city, Hubei province, China. The etiological agent was subsequently identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the illness was identified as novel coronavirus disease (COVID-19) by the World Health Organization.1 In Brazil, the first COVID-19 case was reported in Sao Paulo City in a 61-year-old man whose onset of symptoms began on February 23, 2020.2 Since the writing of this report, more than 7 million confirmed cases and 180,000 deaths have been reported in Brazil, with the highest number of hospitalized patients and deaths occurring in the state of São Paulo.3

Because COVID-19 is an emerging disease, there is limited knowledge about its clinical characteristics and outcomes among hospitalized patients. Studies have shown that among individuals with confirmed cases of COVID-19, older people and those with underlying clinical conditions are at higher risk for hospitalization and death.4 A systematic review conducted in China found that of 2,087 hospitalized patients with cases considered critical, 49% (1,023) died. Of these 1,023 patients, 81% (829 of 1,023) were 60 years or older. When considering the existence of underlying clinical conditions, mortality among patients without comorbidities was much lower (0.9%; 133 of 15,536) than that of patients with one or more comorbidities.5 A similar pattern was observed in the United States4 and Italy.6

Because Latin-America has a different demographic population than China and many countries in Europe, a notable concern is whether different age groups and severity might be observed as the virus spreads among the Brazilian population.

During this study, we describe the risk factors for death among 120,804 hospitalized patients with confirmed COVID-19 cases in São Paulo, Brazil, from February 26 to October 10, 2020.

MATERIALS AND METHODS

This case series included all hospitalized patients with confirmed COVID-19 in the state of São Paulo registered in the Influenza Epidemiological Surveillance System (SIVEP-GRIPE) from February 26, 2020 to October 10, 2020.7 The SIVEP-GRIPE is a system used by health professionals and institutions from the public or private sector throughout the national territory to report hospitalized patients with severe acute respiratory illness (SARI) and deaths attributable to SARI regardless of hospitalization. For this analysis, epidemiological, clinical, and outcome data of the hospitalized patients with COVID-19 (confirmed by real-time RT-PCR)8 from SIVEP-GRIPE were used.

The criteria for hospitalization and case management according to the guidelines of the World Health Organization (WHO)8 and Brazilian Ministry of Health9 were followed during the observation period. According to these guidelines, cases of COVID-19 that progressed to SARI were observed in patients who presented with clinical criteria for flu and at least one of the following symptoms: shortness of breath (dyspnea/respiratory distress); sensation of persistent pressure in the chest; O2 saturation less than 95% in ambient air; or bluish coloring of the lips or face.

Critical cases were defined as hospitalization with SARI, the need to be admitted to the intensive care unit (ICU) because of the presence of organic disorders or hemodynamic instability, and requiring mechanical ventilation or other intensive care procedures. To qualify for admission to the ICU, it was necessary to present at least one of the following criteria: acute respiratory failure requiring invasive mechanical ventilation; acute respiratory failure with the need for noninvasive ventilation (especially when
there is a need for FiO₂ > 50%, or inspiratory positive airway pressure > 10 cm H₂O or expiratory positive airway pressure > 10 cm H₂O to maintain SpO₂ > 94% and/or respiratory frequency ≤ 24 rpm; PaCO₂ ≥ 50 mm Hg, and pH ≤ 7.35; or hemodynamic instability or shock defined as arterial hypotension (systolic blood pressure < 90 mmHg or mean arterial pressure < 65 mmHg). The care of these patients with SARI followed the protocols nationally standardized by the Ministry of Health.

The χ² test was used to compare the differences among fatal cases. The Kaplan-Meier survival analysis was performed to analyze the probability of death during the hospitalization of severely ill patients with COVID-19. For the occurrence of death, the observation period was considered from the date of symptom onset until the occurrence of the fatal outcome. When the outcome of death did not occur, October 10 was selected as the final date of observation. Furthermore, the four more prevalent comorbidities among the patients included in the study were analyzed (chronic cardiovascular disease including hypertension, chronic lung disease, diabetes mellitus, and chronic neurological disease). The outcome was adjusted for age, sex, and all comorbidities, as well as their interactions using Cox regression. The survival analysis was performed using three age categories; younger 60 years, 60 to 79 years, and older than 80 years. Statistical analyses were conducted using R software with Survival package.

Although the research did not require approval, the researchers express their ethical commitment to the management, analysis, and publication of data in accordance with Resolution 466/12 and 510/16 of the National Health Council.

**RESULTS**

In São Paulo state, from February 26 to October 10, 2020, a total of 120,804 hospitalized patients with laboratory-confirmed COVID-19 were reported in 623 of 645 municipalities, comprising an incidence of 294 hospitalizations per 100,000 inhabitants. The characteristics of patients with COVID-19 during hospitalization and outcomes are summarized in Table 1. The median age of hospitalized patients was 60 years (interquartile range [IQR], 47–72 years), 67,821 (56.1%) were men, and 61,659 (51.0%) were white. Most hospitalized patients (79,812; 66.1%) reported one or more comorbidities; among them, 27,000 (33.8%) died. More than 41,000 hospitalized patients (34.5%) were admitted to ICUs and 33,079 (27.4%) died.

Associations among sex, age group, four other prevalent comorbidities (chronic cardiovascular disease plus hypertension, chronic lung disease, diabetes mellitus, and chronic neurological disease) and the risk of COVID-19-related death are shown in Table 2. The corresponding Kaplan-Meier graph is presented in Figure 1. Men were at higher risk for death than women (HR, 1.22; 95% CI, 1.18–1.25), and the number of deaths was slightly higher for men than for women (28.1% versus 26.4%).

The rates of death among races (white, black, yellow, mixed, and indigenous) were similar, ranging from 21.8% to 33.5%. When the groups were separated into white and non-white (blacks and other minority ethnicities), the death rates were similar (white: 29.0% [17,902 of 61,659]; non-white: 29.0% [9,102 of 31,355]).

Increasing age was strongly associated with the risk of death, with patients 80 years or older having a more than three-fold increased risk compared with patients younger than 60 years (hazard ratio [HR], 3.85; 95% confidence interval [CI], 3.68–4.02). The death rates among the younger than 30 years (6.1%; 358 of 5,879) and 30 to 59 years (13.6%; 7,278 of 53,368) age groups were considerably lower than that of the 60 years or older (41.3%; 25,415 of 61,475) age group, again highlighting the possible relationship of old age and death (Table 1).

The four most prevalent comorbidities, chronic cardiovascular disease plus hypertension (HR, 1.05; 95% CI, 1.02–1.08), chronic lung disease (HR, 1.38; 95% CI, 1.31–1.45), diabetes mellitus (HR, 1.14; 95% CI, 1.11–1.18), and chronic neurological disease (HR, 1.48; 95% CI, 1.41–1.55), were associated with an increased risk of death. As can be observed in Table 1, almost half of the patients who had chronic lung disease and chronic neurological disease died. Approximately half of the patients who needed care in the ICU died (48.5%; 20,220).

**DISCUSSION**

The state of São Paulo is the most populous state in Brazil, with approximately 46 million inhabitants, and it is one of the main protagonists of the COVID-19 pandemic in Brazil. This study showed that a large number of laboratories confirmed that COVID-19 cases led to hospitalization in the state (120,804; incidence of 294 hospitalizations per 100,000 inhabitants), and that approximately one-third of those hospitalized evolved into serious illness with the need for ICU care (34.5%) and death (27.4%). These results serve as an alert to the government and the population to recognize the need for urgent measures to control the pandemic.

Our findings revealed that men are at higher risk for death than women. These data are similar to those of recent studies that reported that SARS-CoV-2 infection was more likely to affect males. Therefore, male sex is a well-established risk factor for serious COVID-19 outcomes.

The results also showed that the majority of hospitalized patients were white, consistent with the first report of cases among people who had traveled internationally; however, the numbers of deaths among races were similar when analyzed individually and equal when compared between whites and non-whites (blacks and other minority ethnicities). Non-white race was previously found to be associated with a higher risk of COVID-19 infection, risk of ICU admission, and death. This topic needs to be studied further because it is related to other characteristics, such as cultural and socioeconomic factors. Although there was no difference in the number of deaths among the non-white population in this study, there is an information gap for the race variable because this information only started to be collected more than 1 month after the beginning of the pandemic in Brazil, thus showing the disregard for racial vulnerability in the country during the pandemic.

Increasing risks of death were observed with increasing age, and advanced age is also a well-established risk factor for serious COVID-19 outcomes; these results were widely observed during other studies performed in several countries worldwide. Although the death rates among young people are considerably lower than those among elderly
individuals, it is very important to discuss the roles of these people in maintaining the disease. In general, young people are more resistant to maintaining social isolation and safety measures to contain the spread of the virus, and they can also be a vital source of transmission for individuals at increased risk for serious outcomes of COVID-19.

Several studies have shown that individuals with chronic diseases are at higher risk for serious outcomes of COVID-19. Several studies have shown that individuals with chronic diseases are at higher risk for serious outcomes of COVID-19. Studies have shown that individuals with chronic diseases are at higher risk for serious outcomes of COVID-19.

### Table 1: Characteristics of patients with COVID-19 during hospitalization and outcomes

| Characteristics                                      | Total   | Dead    | Alive   | P-value |
|------------------------------------------------------|---------|---------|---------|---------|
| Total                                                | 120,804 | 33,079  | 87,725  |         |
| Sex                                                  |         |         |         |         |
| Male                                                 | 67,821  | 19,087  | 48,734  | < 0.001 |
| Female                                               | 52,974  | 13,992  | 38,982  |         |
| Missing                                              | 9 (100) | 0 (0.0) | 9 (100) |         |
| Age group, y                                         |         |         |         |         |
| < 30                                                  | 5879 (100.0) | 358 (6.1) | 5,521 (93.9) | < 0.001 |
| 30–59                                                | 53,368 (100.0) | 7,278 (13.6) | 46,090 (86.4) |         |
| ≥ 60                                                 | 61,475 (100.0) | 25,415 (41.3) | 36,060 (58.7) |         |
| Missing                                              | 82 (100.0) | 28 (34.1) | 54 (65.9) |         |
| Race*                                                |         |         |         |         |
| White                                                | 61,659 (100.0) | 17,902 (29.0) | 43,757 (71.0) | < 0.001 |
| Black                                                | 6,382 (100.0) | 2,013 (31.5) | 4,369 (68.5) |         |
| Yellow                                               | 1,500 (100.0) | 503 (33.5) | 997 (66.5) |         |
| Mixed                                                | 23,386 (100.0) | 6,567 (28.1) | 16,819 (71.9) |         |
| Indigenous                                           | 87 (100.0) | 19 (21.8) | 68 (78.2) |         |
| Missing                                              | 27,790 (100.0) | 6,075 (21.9) | 21,715 (78.1) |         |
| Comorbidity (none, 1, or > 1†)                       |         |         |         |         |
| Yes                                                  | 79,812 (100.0) | 27,000 (33.8) | 52,812 (66.2) | < 0.001 |
| No                                                   | 224 (100.0) | 46 (20.5) | 178 (79.5) |         |
| Missing                                              | 40,768 (100.0) | 6,033 (14.8) | 34,735 (85.2) |         |
| Chronic cardiovascular disease + hypertension         |         |         |         |         |
| Yes                                                  | 44,041 (100.0) | 16,213 (36.8) | 27,828 (63.2) | < 0.001 |
| No                                                   | 22,187 (100.0) | 6,832 (30.8) | 15,355 (69.2) |         |
| Missing                                              | 54,576 (100.0) | 10,034 (18.4) | 44,542 (81.6) |         |
| Chronic lung disease                                  |         |         |         |         |
| Yes                                                  | 4,723 (100.0) | 2,252 (47.7) | 2,471 (52.3) | < 0.001 |
| No                                                   | 47,025 (100.0) | 15,693 (33.4) | 31,332 (66.6) |         |
| Missing                                              | 69,056 (100.0) | 15,134 (21.9) | 53,922 (78.1) |         |
| Diabetes mellitus                                     |         |         |         |         |
| Yes                                                  | 31,903 (100.0) | 11,702 (36.7) | 20,201 (63.3) | < 0.001 |
| No                                                   | 29,847 (100.0) | 9,806 (32.9) | 20,041 (67.1) |         |
| Missing                                              | 59,054 (100.0) | 11,571 (19.6) | 47,483 (80.4) |         |
| Chronic neurological disease                          |         |         |         |         |
| Yes                                                  | 5,580 (100.0) | 2,954 (52.9) | 2,626 (47.1) | < 0.001 |
| No                                                   | 46,515 (100.0) | 15,261 (32.8) | 31,254 (67.2) |         |
| Missing                                              | 68,709 (100.0) | 14,864 (21.6) | 53,845 (78.4) |         |
| ICU                                                  |         |         |         |         |
| Yes                                                  | 41,708 (100.0) | 20,220 (48.5) | 21,488 (51.5) | < 0.001 |
| No                                                   | 79,096 (100.0) | 12,859 (16.3) | 66,237 (83.7) |         |

* Severe cases: patients had been hospitalized in the general ward only. Critical cases: patients have been hospitalized in the ICU. Source: RECAP and Influenza Epidemiological Surveillance System (SIVEP-GRIPES) Epidemiological Surveillance Center of the State Health Secretary of São Paulo (CVE/SES-SP).

* Brazilian Institute of Geography and Statistics (IBGE) classification

† Chronic cardiovascular disease plus hypertension, diabetes mellitus, chronic lung disease, chronic liver disease, chronic hematological disease, Down syndrome, chronic neurological disease, immunodeficiency or immunodeficiency/HIV, chronic kidney disease, obesity, neoplasm (solid or hematological tumor).

There is a need for immediate measures to prevent and control the pandemic, especially for groups at higher risk for serious outcomes, so there will be fewer hospitalizations and deaths. Decreased mobility, social distancing, and the implementation of biosafety measures, such as wearing a mask, are essential for reducing the spread of the virus until vaccination coverage is sufficient to prevent high transmission. Another important factor is the government’s attention to the socioeconomically vulnerable population, which is predominantly black. This population has greater difficulty maintaining social isolation and has less access to the health system.

Our investigation of risk factors for deaths in São Paulo state had several limitations. Data extraction from hospitalized SARS-CoV-2-positive patients in São Paulo occurred on
October 10, 2020. The frequency and distribution of underlying conditions after that period may have changed as additional data became available. Many patients were still hospitalized at the time of data extraction. The notifications in the SIVEP-GRIPE system are detailed and longitudinal, but a considerably large amount of data were missing data, which may have impacted these results and introduced important information bias. Furthermore, some deaths related to COVID-19 may have been mistakenly classified as non-COVID-19, particularly during the beginning of the pandemic. However, it is possible that this inaccuracy has decreased rapidly as the number of deaths has increased.

CONCLUSIONS

In São Paulo state, men, elderly individuals, and patients with chronic cardiovascular disease, including hypertension, chronic lung disease, diabetes mellitus, and chronic neurological disease, are at higher risk for death from COVID-19.

Received December 17, 2020. Accepted for publication April 17, 2021. Published online May 31, 2021.

Acknowledgment: The American Society of Tropical Medicine and Hygiene has waived the Open Access fee for this article due to the ongoing COVID-19 pandemic.

| Variable     | Univariate analysis | Multivariate analysis |
|--------------|---------------------|-----------------------|
|              | HR                  | 95% CI                | HR                  | 95% CI                |
| Sex          |                     |                       |                     |                       |
| Female       | 1.00                | 1.00                  | 1.00                | 1.00                  |
| Male         | 1.07                | 1.04–1.09             | 1.22                | 1.18–1.25             |
| Age group, y |                     |                       |                     |                       |
| < 60         | 1.00                |                       | 1.00                |                       |
| 60–79        | 3.22                | 3.13–3.31             | 2.20                | 2.11–2.28             |
| ≥ 80         | 6.04                | 5.86–6.22             | 3.85                | 3.68–4.02             |
| CCD + H      |                     |                       |                     |                       |
| No           | 1.00                |                       | 1.00                |                       |
| Yes          | 1.23                | 1.20–1.23             | 1.05                | 1.02–1.08             |
| CLD          |                     |                       |                     |                       |
| No           | 1.00                |                       | 1.00                |                       |
| Yes          | 1.58                | 1.51–1.65             | 1.38                | 1.31–1.45             |
| DM           |                     |                       |                     |                       |
| No           | 1.00                |                       | 1.00                |                       |
| Yes          | 1.14                | 1.11–1.17             | 1.14                | 1.11–1.18             |
| CND          |                     |                       |                     |                       |
| No           | 1.00                |                       | 1.00                |                       |
| Yes          | 1.94                | 1.86–2.02             | 1.48                | 1.41–1.55             |

CCD + H = chronic cardiovascular disease plus hypertension; CLD = chronic lung disease; DM = diabetes mellitus; CND = chronic neurological disease. Source: Influenza Epidemiological Surveillance System (SIVEP-GRIPE) Epidemiological Surveillance Center of the State Health Secretary of São Paulo (CVE/SES-SP).

**FIGURE 1.** Kaplan-Meir plots for risk factors associated with death for coronavirus disease (COVID-19) patients. This figure appears in color at www.ajtmh.org.
Authors’ addresses: Patricia Vieira da Silva, Daniel Henrique Tsuha, and Julio Croda, Federal University of Mato Grosso do Sul, Campo Grande, MS, Brazil, E-mails: patriciavieira.s@hotmail.com, daniel.tsuha@saude.ms.gov.br, and juliocroda@gmail.com. Silvana Barbosa de Oliveira, Juan José Cortez Escalante, and Maria Almiron, Pan American Health Organization, World Health Organization, University of Brasilia, Brasilia, DF, Brazil, E-mails: silbaroli@gmail.com, cortezj@paho.org, and almironm@paho.org. Helena Keico Sato, Epidemiological Surveillance Center “Prof. Alexandre Vranjac” of the São Paulo State Department of Health, São Paulo, SP, Brazil, E-mail: helenakeicosato@gmail.com. Paulo Rossi Menezes, Regiane Cardoso de Paula, and Tatiana Lang D’Agostini, Disease Control Coordination of the São Paulo State Department of Health, São Paulo, SP, Brazil, E-mails: paulo.menezes@saude.sp.gov.br, depaula.regiane7@gmail.com, and tlang@saude.sp.gov.br.

This is an open-access article distributed under the terms of the Creative Commons Attribution (CC-BY) License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

REFERENCES

1. WHO, 2020. Novel Coronavirus – China. Geneva, Switzerland: World Health Organization. Available at: http://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/. Accessed November 5, 2020.

2. WHO, 2020. Coronavirus Disease (COVID-19) Situation Reports. Geneva, Switzerland: World Health Organization. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed November 5, 2020.

3. Coronavirus Brasil, 2020. Brazilian Ministry of Health. Available at: https://covid.saude.gov.br/. Accessed November 5, 2020.

4. CDC, 2020. COVID-19 response team. severe outcomes among patients with coronavirus disease 2019 (COVID-19) — United States, February 12–March 16, 2020. MMWR Morb Mortal Wkly Rep 69: 343–346.

5. Epidemiology Working Group for NCIP Epidemiic Response, Chinese Center for Disease Control and Prevention, 2020. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi Zhonghua Liuxingbingxue Zazhi 41: 145–151 (in Chinese).

6. EpiCentro, 2020. Sorveglianza Integrata COVID-19: i Principali dati Nazionali. Available at: https://www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati. Accessed November 5, 2020.

7. Dados Abertos, 2020. Governo do Estado de São Paulo. Available at: https://www.saopaulo.sp.gov.br/planosp/sim/dados-abertos/. Accessed November 17, 2020.

8. World Health Organization, 2020. Clinical Management of Severe Acute Respiratory Infection when Novel Coronavirus 2019 Infection is Suspected: Interim Guidance, 28 January 2020. Geneva, Switzerland: WHO. Available at: https://apps.who.int/iris/handle/10665/330893. Accessed April 2, 2021.

9. Correia de Medeiros A, Elio Franco Filho A. Orientações para manejo de Pacientes com COVID-19.

10. Wang D et al., 2020. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 323: 1061–1069.

11. Candido DDS et al., 2020. Routes for COVID-19 importation in Brazil. J Travel Med 27. doi: 10.1093/jtm/taaa042.

12. Thebault R, Tran AB, Williams V, 2020. The coronavirus is infecting and killing black Americans at an alarmingly high rate. Washington Post. Available at: https://www.washingtonpost.com/nation/2020/04/07/coronavirus-is-infecting-killing-black-americans-an-alarmingly-high-rate-post-analysis-shows/. Published April 7, 2020. Accessed April 1, 2021.

13. Sze S et al., 2020. Ethnicity and clinical outcomes in COVID-19: a systematic review and meta-analysis. EClinicalMedicine 29–30: 100630.

14. Chen N et al., 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395: 507–513.

15. CDC, 2020. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-confirmed Coronavirus Disease 2019 — COVID-NET, 14 States, March 1–30, 2020 | MMWR. Available at: https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e3.htm. Accessed November 5, 2020.

16. Yang J et al., 2020. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis IJID Off Publ Int Soc Infect Dis 94: 91–95.