Analysis of Survival of Patients Hospitalized with COVID-19 in Espírito Santo, Brazil

Juliana Rodrigues Tovar Garbin 1,*, Franciêle Marabotti Costa Leite 2, Luís Carlos Lopes-Júnior 2,*,†, Cristiano Soares da Silva Dell’Antonio 3, Larissa Soares Dell’Antonio 4 and Ana Paula Brioschi dos Santos 1

1 Secretaria de Estado da Saúde do Espírito Santo, Special Epidemiological Surveillance Nucleus, Vitoria 29050-625, ES, Brazil; lissadellantonio@gmail.com (L.S.D.); anapaulabsantos86@gmail.com (A.P.B.d.S.)
2 Graduate Program in Public Health, Federal University of Espírito Santo (UFES), Vitoria 29047-105, ES, Brazil; francielenmarabotti@gmail.com
3 Hospital Sírio-Libanês, Instituto de Ensino e Pesquisa, São Paulo 01308-901, SP, Brazil; cristianoss@outlook.com
* Correspondence: julianatovar.sesa@gmail.com (J.R.T.G.); lopesjr.lc@gmail.com (L.C.L.-J.)

Abstract: Objective: To analyze the survival of patients hospitalized with COVID-19 and its associated factors. Methods: Retrospective study of survival analysis in individuals notified and hospitalized with COVID-19 in the state of Espírito Santo, Brazil. As data source, the reports of hospitalized patients in the period from 1 March 2020, to 31 July 2021 were used. The Cox regression analysis plus the proportional risk assessment (assumption) were used to compare hospitalization time until the occurrence of the event (death from COVID-19) associated with possible risk factors. Results: The sample comprised 9806 notifications of cases, with the occurrence of 1885 deaths from the disease (19.22%). The mean age of the group was 58 years (SD ± 18.3) and the mean hospital length of stay was 10.5 days (SD ± 11.8). The factors that presented a higher risk of death from COVID-19, associated with a lower survival rate, were non-work-related infection (HR = 4.33; p < 0.001), age group 60–79 years (HR: 1.62; p = 0.028), chronic cardiovascular disease (HR = 1.18; p = 0.028), chronic kidney disease (HR = 1.5; p = 0.004), smoking (HR = 1.41; p < 0.001), obesity (HR = 2.28; p < 0.001), neoplasms (HR = 1.81; p < 0.001) and chronic neurological disease (HR = 1.68; p < 0.001). Conclusion: It was concluded that non-work-related infection, age group above or equal to 60 years, presence of chronic cardiovascular disease, chronic kidney disease, chronic neurological disease, smoking, obesity and neoplasms were associated with a higher risk of death, and, therefore, a lower survival in Brazilian patients hospitalized with COVID-19. The identification of priority groups is crucial for Health Surveillance and can guide prevention, control, monitoring, and intervention strategies against the new coronavirus.

Keywords: hospitalization; COVID-19; SARS-CoV-2; survival; risk factors

1. Introduction

COVID-19 (Coronavirus Disease 2019) has gained prominence as it has become the most widespread acute respiratory infection with global distribution and is characterized as a disease caused by the novel coronavirus SARS-CoV-2. The incubation period varies from 1 to 14 days, with a median of 5 to 6 days [1] and is responsible for variable symptomatology ranging from mild signs to severe conditions requiring hospitalization [2]. The most common symptoms in hospitalized patients are fever, dyspnea, and ground-glass opacity demonstrated by imaging tests [3].

The risk for a more severe form of the disease was associated with comorbidities such as diabetes mellitus, hypertension and smoking [4]. Similarly, sociodemographic aspects such as advanced age (80 years or older), male sex, race/non-white color and being a public hospital user have been shown to contribute to a higher risk of death [5–7]. In addition, it...
should be noted that a more critical course of the disease may promote increased hospital admissions and hospital length of stay [8], generating demands for health systems.

In this sense, by identifying characteristics that favor a more severe outcome, the studies of survival analysis have been useful since they report the time elapsed between the onset and the event of interest [9]. After electing hospital admission and/or the onset of the symptoms of COVID-19 as the initial event and death as the final event, researchers pointed out that patients with a worse survival from COVID-19 were those with dyspnea, pneumonia, ground-glass opacity, admitted to the Intensive Care Unit (ICU) with the support of mechanical ventilation, with chronic kidney disease, in addition to being of advanced age and belonging to the male sex [7,10–12].

In Brazil, from 26 February 2020, to 4 December 2021, a total of 22,138,247 cases and 615,570 deaths from COVID-19 were confirmed, with an incidence rate of 10,454.6 cases per 100,000 population and mortality of 290.7 deaths per 100,000 population [13].

When monitoring cases of Severe Acute Respiratory Syndrome (SARS) in the country, the Influenza Epidemiological Surveillance System (SIVEP-Gripe) recorded 2,812,789 hospitalizations in the same period. During the year 2021, from the total of 1,635,448 hospitalized SARS cases, 71.9% (1,176,355) were COVID-19 infections, and the most affected region was the Southeast, with 48.5% of the confirmed cases (571,034) [13].

The state of Espírito Santo, also located in the aforementioned region, reported 622,498 confirmed cases for COVID-19 and 13,208 deaths [14] in the same period. In the year 2021 alone, there were 7126 cases of SARS requiring hospitalization [15]. However, the understanding of these data through survival studies has not yet been elucidated. Thus, the evidence resulting from survival studies is important to establish the epidemiological and clinical profile of COVID-19 in the hospital setting. Therefore, the objective of the present study is to analyze the survival of patients hospitalized due to COVID-19 and its associated factors.

2. Materials and Methods

This is a retrospective study of survival analysis in notified and hospitalized individuals with COVID-19 in the state of Espírito Santo, the smallest and least populous state in the southeastern region of Brazil, with a population of 4,108,508 inhabitants distributed in 78 municipalities [15]. According to a ranking by the nongovernmental organization Open Knowledge Brazil (OKBR), it was considered the most transparent state in the disclosure of data on COVID-19 in Brazil, [16].

The data used were from the State Secretariat of Public Health of Espírito Santo (SESA-ES) through the e-SUS Health Surveillance information system (e-SUS-VS) [17]. The notifications of inpatients in the period from 1 March 2020 to 31 July 2021, were used as data source. The adopted inclusion criterion was confirmation of the diagnosis for COVID-19 and hospitalization in Espírito Santo resulting from this diagnosis. Exclusion criteria were hospitalizations before the onset of symptoms, absence of the date of discharge/outcome, and hospitalization interval shorter than 24 h.

For survival time, the start date was considered the date of admission, and the end date was the date of death (for failures), the date of discharge, and the date of death from other causes (censoring data).

Sociodemographic variables were used, including information to know whether the patients were health professionals and whether they had a work-related infection. The state of Espírito Santo is the only one in Brazil that has this last variable in its notification form. Information on clinical variables and comorbidities was also used. The programs used in the analyses were IBM SPSS Statistics version 24 and STATA version 14. Multiple logistic regression with the forward variable selection method associated the outcome (death from COVID-19) with possible influencing factors. We only included in the model confounding variables that could be independently associated with death. Therefore, signs and symptoms were not included. The factors that remained in the final model were used for further analyses. The permanence in the model was given by a p value of < 0.05.
The Kaplan-Meier estimator was used to observe the failure event (death) in addition to estimating the mean of hospital length of stay of patients in each factor. The Log-rank test was used to compare the equality of the survival curves. Cox regression in conjunction with proportional hazards assessment (assumption) was used to compare the hospital length of stay until the occurrence of the event (death from COVID-19) associated with possible risk factors. When the proportionality assumption was not met, the extended Cox model, commonly called the model with time-dependent covariates, was used. The alpha level of significance used in all analyses was 5%.

Ethical approval was obtained by the Research Ethics Committee under number 5.180.941 on 20 December 2021.

3. Results

The sample totaled 9806 notifications of confirmed cases of hospitalized COVID-19 patients in the period from 1 March 2020 to 31 July 2021, with the occurrence of 1885 deaths from the disease (19.22%). The mean age of the group was 58 years (SD ± 18.3) and the mean of the hospital length of stay was 10.5 days (SD ± 11.8).

Characterization of the inpatients was based on the following information: individuals aged 0–59 years (52.4%) were the most prevalent age group, 4 out of 10 patients had not finished elementary school, were not pregnant, and belonged to a non-white race/color. Regarding sex, about 54% were men. Regarding the place of origin of the notification of the case, the tertiary care level was responsible for 62.5% of the sample, and almost all the notifications were from people without disabilities (PWD) (96.5%) and non-homeless people (97.8%). As for data on residence and hospitalization, the Metropolitan Health Region (Regional de Saúde Metropolitana), a division of the national health system, accounted for the majority of the notifications of the cases, with 64.4% and 63.9%, respectively, with 86.7% of the inpatients living in the urban area. Regarding work, 89.3% were not health professionals and 75.8% had no work-related infection. Regarding clinical aspects, they did not meet the criteria for ICU admission (50.2%) and the most observed confirmation criterion was the one provided by confirmatory laboratory tests (97%). Regarding symptoms, cough (66.5%) and fever (58.5%) were predominant, and, as comorbidity, diabetes mellitus stood out (20.5%) (Table 1).

| Sociodemographic variables | Categories | Death due to COVID-19 |  | Total |
|----------------------------|------------|-----------------------|---|-------|
| Age range                  | 0–59 years | 4681                  | 59.1 | 453 | 24 | 5134 | 52.4 |
| Education                  | Elementary school | 1599 | 38.9 | 594 | 48.9 | 2193 | 41.2 |
| Pregnant women             | No         | 3550                  | 44.8 | 847 | 44.9 | 4397 | 44.8 |
| Race/Color                 | Nonwhite   | 3577                  | 45.2 | 894 | 47.4 | 4471 | 45.6 |
| Sex                        | Male       | 4278                  | 54 | 1034 | 54.9 | 5312 | 54.2 |
| Place of Notification      | Tertiary   | 4861                  | 61.4 | 1265 | 67.1 | 6126 | 62.5 |
| PCD                        | No         | 7628                  | 96.3 | 1838 | 97.5 | 9466 | 96.5 |
| Homeless                   | Yes        | 7715                  | 97.4 | 1876 | 99.5 | 9591 | 97.8 |
| Household Health Region    | Metropolitan | 4792 | 60.5 | 1527 | 81 | 6319 | 64.4 |
| Household Health Region    | Metropolitan | 4726 | 59.7 | 1537 | 81.5 | 6263 | 63.9 |
| Zone                       | Urban      | 6778                  | 85.6 | 1727 | 91.6 | 8505 | 86.7 |
| Health Professional        | No         | 7013                  | 88.5 | 1742 | 92.4 | 8755 | 89.3 |
| Work-related Infection     | No         | 5822                  | 73.5 | 1609 | 85.4 | 7431 | 75.8 |
Table 1. Cont.

| Clinical Variables            | No       | %      | Yes      | %      | Total | %      |
|------------------------------|----------|--------|----------|--------|-------|--------|
| Death due to COVID-19        |          |        |          |        |       |        |
|                              | N        |        | N        |        | N     |        |
| Fever Yes                     | 4542     | 57.3   | 1197     | 63.5   | 5739  | 58.5   |
| Difficulty Breathing Yes      | 2824     | 35.7   | 1188     | 63     | 4012  | 40.9   |
| Flapping Wing Nose Yes        | 69       | 0.9    | 36       | 1.9    | 105   | 1.1    |
| Intercostal Tachycardia Yes   | 141      | 1.8    | 46       | 2.4    | 187   | 1.9    |
| Cyanosis Yes                  | 51       | 0.6    | 41       | 2.2    | 92    | 0.9    |
| O₂ Saturation < 95% Yes       | 1745     | 22     | 1020     | 54.1   | 2765  | 28.2   |
| Coma Yes                      | 20       | 0.3    | 22       | 1.2    | 42    | 0.4    |
| Coughing Yes                  | 5208     | 65.7   | 1287     | 68.3   | 6495  | 66.2   |
| Sputum Production Yes         | 437      | 5.5    | 108      | 5.7    | 545   | 5.6    |
| Nasal or Conjunctival         |          |        |          |        |       |        |
| Congestion Yes                | 946      | 11.9   | 201      | 10.7   | 1147  | 11.7   |
| Runny Nose Yes                | 2034     | 25.7   | 429      | 22.8   | 2463  | 25.1   |
| Sore Throat Yes               | 1474     | 18.6   | 297      | 15.8   | 1771  | 18.1   |
| Difficulty Swallowing Yes     | 254      | 3.2    | 62       | 3.3    | 316   | 3.2    |
| Diarrhea Yes                  | 1171     | 14.8   | 252      | 13.4   | 1423  | 14.5   |
| Nausea/Vomiting Yes           | 1057     | 13.3   | 218      | 11.6   | 1275  | 13     |
| Cephalgia Yes                 | 3079     | 38.9   | 555      | 29.4   | 3634  | 37.1   |
| Irritability/Confusion Yes    | 106      | 1.3    | 37       | 2      | 143   | 1.5    |
| Adynamia/Weakness Yes         | 2403     | 30.3   | 805      | 42.7   | 3208  | 32.7   |
| Pharyngeal Exudate Yes        | 64       | 0.8    | 17       | 0.9    | 81    | 0.8    |
| Conjunctivitis Yes            | 40       | 0.5    | 7        | 0.4    | 47    | 0.5    |
| Convulsion Yes                | 22       | 0.3    | 9        | 0.5    | 31    | 0.3    |
| Loss of Sense of Smell Yes    | 712      | 9      | 148      | 7.9    | 860   | 8.8    |
| Loss of Taste Yes             | 804      | 10.2   | 156      | 8.3    | 960   | 9.8    |
| Comorbidities                 |          |        |          |        |       |        |
| Chronic Pulmonary Disease Yes | 336      | 4.2    | 197      | 10.5   | 533   | 5.4    |
| Chronic Cardiovascular Disease | Yes    | 2816   | 35.6   | 1208    | 64.1  | 4024  | 41     |
| Chronic Kidney Disease Yes    | 140      | 1.8    | 100      | 5.3    | 240   | 2.4    |
| Chronic Liver Disease Yes     | 20       | 0.3    | 31       | 1.6    | 51    | 0.5    |
| Diabetes Mellitus Yes         | 1368     | 17.3   | 643      | 34.1   | 2011  | 20.5   |
| Immunodeficiency Yes          | 41       | 0.5    | 27       | 1.4    | 68    | 0.7    |
| HIV Infection Yes             | 30       | 0.4    | 9        | 0.5    | 39    | 0.4    |
| Neoplasm (Solid or Hematological Tumor) Yes | 58 | 0.7 | 40 | 2.1 | 98 | 1 |
| Smoking Yes                   | 177      | 2.2    | 155      | 8.2    | 332   | 3.4    |
| Bariatric Surgery Yes         | 17       | 0.2    | 1        | 0.1    | 18    | 0.2    |
| Obesity Yes                   | 505      | 6.4    | 442      | 23.4   | 947   | 9.7    |
| Tuberculosis Yes              | 4        | 0.1    | 7        | 0.4    | 11    | 0.1    |
| Neoplasms Yes                 | 92       | 1.2    | 101      | 5.4    | 193   | 2      |
| Chronic Neurological Disease  | Yes      | 191    | 2.4     | 217     | 11.5  | 408   | 4.2    |

Note: * Ischemic heart disease, heart failure, ischemic stroke and high blood pressure.

In the crude and adjusted multiple logistic regression after the odds ratios were calculated, the clinical and sociodemographic factors associated with death from COVID-19 were the following: absence of a work-related infection (OR = 3.8; 95%CI = 1.89–7.65) when compared to its presence; age groups 60–79 (OR = 3.59; 95%CI = 2.94–4.39) and 80 years or older (OR = 8.3; 95%CI = 6.40–10.77) when compared to age group up to 59 years; education in the categories illiterate (OR = 1.42; 95%CI = 1.06–1.89), high school (OR = 1.68; 95%CI = 1.21–2.32) when compared to higher education, and of comorbidities such as chronic cardiovascular disease (OR = 1.73; 95%CI = 1.45–2.07), chronic kidney disease (OR = 2.66; 95%CI = 1.68–4.19), immunodeficiency (OR = 4.54; 95%CI = 1.78–11.55), smoking (OR = 2.73; 95%CI = 1.90–3.91), obesity (OR = 8.33; 95%CI = 6.68–10.38), neoplasms...
(OR = 5.40; 95%CI = 3.27–8.93) and chronic neurological disease (OR = 5.83; 95%CI = 4.0–8.5) when compared to their absence (Table 2).

Table 2. Univariable survival for the outcome of death from COVID-19 (Kaplan Meier and Log-Rank test) in hospitalized patients in Espirito Santo, Brazil, in the period from 1 March 2020 to 31 July 2021.

| Dependent Variable (Death from COVID-19) | p-Value * | OR  | 95% CI Lower Limit | 95% CI Upper Limit |
|-----------------------------------------|-----------|-----|--------------------|--------------------|
| Work-related Infection                  | No <0.001 | 3.80| 1.89               | 7.65               |
|                                         | Yes -     | 1.00| -                  | -                  |
| Age group                               |           |     |                    |                    |
|                                         | 0–59 years| <0.001| 3.59       | 2.94               | 4.39               |
|                                         | 60–79 years| <0.001| 8.30        | 6.40               | 10.77              |
|                                         | 80 years or older| <0.001| 8.30       | 6.40               | 10.77              |
| Education                               | Illiterate| 0.018| 1.42       | 1.06               | 1.89               |
|                                         | Elementary School| 0.061| 1.34        | 0.99               | 1.81               |
|                                         | High School | 0.002| 1.68        | 1.21               | 2.32               |
|                                         | Higher Education| -   | 1.00       | -                  | -                  |
| Chronic Cardiovascular Disease          | No -      | 1.73| 1.45               | 2.07               |
|                                         | Yes <0.001| 2.66| 1.68               | 4.19               |
| Chronic Kidney Disease                  | No -      | 1.00| -                  | -                  |
|                                         | Yes 0.001 | 1.00| -                  | -                  |
| Immunodeficiency                        | No -      | 1.00| -                  | -                  |
|                                         | Yes <0.001| 1.00| -                  | -                  |
| Smoking                                 | No -      | 1.00| -                  | -                  |
|                                         | Yes <0.001| 1.00| -                  | -                  |
| Obesity                                 | No -      | 1.00| -                  | -                  |
|                                         | Yes <0.001| 1.00| -                  | -                  |
| Neoplasms                               | No -      | 1.00| -                  | -                  |
|                                         | Yes <0.001| 1.00| -                  | -                  |
| Chronic Neurological Disease            | No -      | 1.00| -                  | -                  |
|                                         | Yes <0.001| 1.00| -                  | -                  |

* Significant if p < 0.05.

Based on this rationale, these were the variables chosen for the survival analysis. The proportionality assumption for the Cox model was tested using the Pearson’s chi-square test (Table 3).

Table 3. Assessment of the risk proportionality assumption by the Cox model.

| Variables                      | Qui-Square | p-Value * |
|--------------------------------|------------|-----------|
| Work-related Infection         | 0.16       | 0.694     |
| Age Group                      | 7.86       | 0.020     |
| Education                      | 16.46      | 0.001     |
| Chronic Cardiovascular Disease | 7.44       | 0.006     |
| Chronic Kidney Disease         | 5.81       | 0.016     |
| Immunodeficiency               | 0.29       | 0.590     |
| Smoking                        | 19.4       | <0.001    |
| Obesity                        | 22.9       | <0.001    |
| Neoplasms                      | 0.94       | 0.333     |
| Chronic Neurological Disease   | 16.9       | <0.001    |

* Significant if p < 0.05 based on Pearson’s chi-square test. ** Ischemic heart disease, heart failure, ischemic stroke, and high blood pressure.

Table 4 presents the results of the univariable survival analysis using the Kaplan-Meier method. The result of the log-rank test for comparison of the categories of the study variables showed that the probability of survival of individuals hospitalized with
the disease with a work-related infection at the end of the observation period was 94.3%, while the result was 78.4% for individuals who did not have the infection.

Table 4. Univariable survival for the outcome of death from COVID-19 (Kaplan Meier and Log-Rank test) in hospitalized patients in Espírito Santo, Brazil, in the period from 1 March 2020 to 31 July 2021.

| Variables                  | Categories               | Survival Rate (Days) |  |  | Lower Limit | Upper Limit | Log-Rank p-Value |
|----------------------------|--------------------------|----------------------|---|---|-------------|-------------|------------------|
| Work-related Infection     | Yes                      | 183                  | 94.3 | 121.2 | 75.7        | 166.7       | <0.001           |
|                            | No                       | 5582                 | 78.4 | 39.5 | 37.0        | 42.0        |                  |
|                            | General                  | 5765                 | 78.8 | 44.9 | 39.2        | 50.6        |                  |
| Age Group                  | 0–59 years               | 4494                 | 91.2 | 71.0 | 64.5        | 77.5        | <0.001           |
|                            | 60–79 years              | 2409                 | 73.7 | 45.9 | 38.4        | 53.4        |                  |
|                            | 80 years or older        | 672                  | 57.0 | 26.6 | 23.4        | 29.8        |                  |
|                            | General                  | 7575                 | 80.8 | 48.9 | 42.7        | 55.1        |                  |
| Education                  | Illiterate               | 77                   | 72.5 | 28.8 | 23.2        | 34.3        |                  |
|                            | Elementary School        | 565                  | 72.8 | 38.9 | 34.7        | 43.1        | 0.001            |
|                            | High School              | 323                  | 82.0 | 37.7 | 33.9        | 41.5        |                  |
|                            | Higher Education         | 200                  | 78.7 | 40.8 | 32.2        | 49.4        |                  |
|                            | General                  | 1165                 | 77.1 | 44.5 | 38.7        | 50.4        |                  |
| Obesity                    | Yes                      | 483                  | 53.3 | 35.7 | 28.7        | 42.7        | 0.001            |
|                            | No                       | 7068                 | 83.7 | 47.6 | 44.3        | 50.9        |                  |
|                            | General                  | 7551                 | 80.7 | 48.2 | 42.3        | 54.1        |                  |
| Neoplasms                  | Yes                      | 83                   | 47.4 | 24.5 | 19.9        | 29.2        | <0.001           |
|                            | No                       | 7478                 | 81.4 | 49.3 | 43.1        | 55.4        |                  |
|                            | General                  | 7561                 | 80.8 | 48.2 | 42.4        | 54.1        |                  |
| Chronic Neurological Disease| Yes                     | 180                  | 46.3 | 28.8 | 23.2        | 34.4        | <0.001           |
|                            | No                       | 7380                 | 82.3 | 52.8 | 46.1        | 59.5        |                  |
|                            | General                  | 7560                 | 80.8 | 48.2 | 42.4        | 54.1        |                  |
| Chronic Cardiovascular Disease*| Yes                   | 2675                 | 69.9 | 37.2 | 34.4        | 40.0        | <0.001           |
|                            | No                       | 4883                 | 88.3 | 61.6 | 50.4        | 72.8        |                  |
|                            | General                  | 7558                 | 80.8 | 48.2 | 42.4        | 54.1        |                  |
| Chronic Kidney Disease     | Yes                      | 135                  | 59.2 | 34.1 | 25.4        | 42.8        | <0.001           |
|                            | No                       | 7425                 | 81.3 | 48.5 | 42.6        | 54.4        |                  |
|                            | General                  | 7560                 | 80.8 | 48.2 | 42.3        | 54.1        |                  |
| Immunodeficiency           | Yes                      | 40                   | 59.7 | 25.7 | 21.0        | 30.4        | 0.127            |
|                            | No                       | 7520                 | 80.9 | 48.5 | 42.6        | 54.4        |                  |
|                            | General                  | 7560                 | 80.8 | 48.2 | 42.4        | 54.1        |                  |
| Smoking                    | Yes                      | 171                  | 53.4 | 35.5 | 28.4        | 42.5        | <0.001           |
|                            | No                       | 7389                 | 81.7 | 49.1 | 42.5        | 55.8        |                  |
|                            | General                  | 7560                 | 80.8 | 48.2 | 42.4        | 54.1        |                  |

Note: * Ischemic heart disease, heart failure, ischemic stroke and high blood pressure.

When considering the age group, a lower probability of cumulative survival is observed with advancing age groups (up to 59 years—91.2%; 60–79 years—73.7%; and 80 years or older—57%). As for schooling, people who had a high school education had an 82% probability of cumulative survival, while illiterate people had 72.5%.

Regarding comorbidities, in individuals without comorbidities, the cumulative survival was 88.3% for chronic cardiovascular disease, 81.3% for chronic kidney disease, and 81.7% for smoking, 83.7% for obesity, 81.4% for neoplasms and 82.3% for chronic neurological disease, while in individuals with comorbidities, the cumulative survival was 69.9%, 59.2%, 53.4%, 53.3%, 47.4%, and 46.3%, respectively. For the overall variables mentioned,
there were statistically significant differences in the survival curves between the groups ($p < 0.05$).

In the multivariable analysis (Table 5), after adjustment, the factors with a higher risk of occurrence of deaths from COVID-19 (associated with a lower survival) were non-work-related infection (HR = 4.33; $p < 0.001$), age groups 60–79 (HR = 1.62; $p < 0.001$) and 80 years or older (HR = 2.56; $p < 0.001$), presence of chronic cardiovascular disease (HR = 1.18; $p = 0.028$), chronic kidney disease (HR = 1.5; $p = 0.004$), smoking (HR = 1.41; $p < 0.001$), obesity (HR = 2.28; $p < 0.001$), neoplasms (HR = 1.81; $p < 0.001$ and chronic neurological disease (HR = 1.68; $p < 0.001$).

Table 5. Multivariable survival (crude and adjusted Hazard Ratio by Cox regression model) for the outcome of death from COVID-19 in hospitalized patients in the state of Espírito Santo, Brazil, from 1 March 2020 to 31 July 2021.

| Variables                  | $p$-Value | HR $^1$ | 95%CI to HR Lower | 95%CI to HR Upper | $p$-Value | HR $^1$ | 95%CI to HR Lower | 95%CI to HR Upper |
|----------------------------|-----------|---------|-------------------|-------------------|-----------|---------|-------------------|-------------------|
| Work-related Infection     | No        | <0.001  | 5.60              | 2.90              | 10.81     | <0.001  | 4.33              | 2.21              | 8.46               |
|                            | Yes       |         |                   |                   |           |         |                   |                   |                    |
| Age Group **               | 0–59 years| -       | 1                 | -                 | -         | -       | 1                 | -                 |
|                            | 60–79 years| <0.001  | 2.16              | 1.89              | 2.48     | <0.001  | 1.62              | 1.38              | 1.89               |
|                            | 80 years or older| <0.001  | 4.33              | 3.59              | 5.23     | <0.001  | 2.56              | 2.13              | 3.08               |
| Education **               | Illiterate| 0.025   | 1.35              | 1.04              | 1.76     | 0.105   | 1.23              | 0.96              | 1.58               |
|                            | Elementary School| 0.016  | 1.22              | 1.04              | 1.43     | 0.142   | 1.22              | 0.94              | 1.59               |
|                            | High School| 0.667   | 0.96              | 0.80              | 1.15     | 0.128   | 1.24              | 0.94              | 1.64               |
|                            | Higher Education| -     | 1                 | -                 | -         | -       | 1                 | -                 |
| Obesity **                 | No        | -       | 1                 | -                 | -         | 1       | -                 | -                 |
|                            | Yes       | <0.001  | 2.72              | 2.31              | 3.20     | <0.001  | 2.28              | 1.99              | 2.60               |
| Neoplasms *                | No        | -       | 1                 | -                 | -         | 1       | -                 | -                 |
|                            | Yes       | <0.001  | 1.99              | 1.62              | 2.43     | <0.001  | 1.81              | 1.40              | 2.35               |
| Chronic Neurological Disease **| No    | -       | 1                 | -                 | -         | 1       | -                 | -                 |
|                            | Yes       | <0.001  | 3.05              | 2.44              | 3.80     | <0.001  | 1.68              | 1.39              | 2.02               |
| Chronic Cardiovascular Disease **| No  | -       | 1                 | -                 | -         | 1       | -                 | -                 |
|                            | Yes       | <0.001  | 2.20              | 1.90              | 2.50     | 0.028   | 118               | 1.02              | 1.37               |
| Chronic Kidney Disease **  | No        | -       | 1                 | -                 | -         | 1       | -                 | -                 |
|                            | Yes       | <0.001  | 1.73              | 1.41              | 2.11     | 0.004   | 1.50              | 1.14              | 1.99               |
| Immunodeficiency *         | No        | -       | 1                 | -                 | -         | 1       | -                 | -                 |
|                            | Yes       | 0.134   | 1.34              | 0.91              | 1.96     | 0.379   | 1.24              | 0.78              | 1.99               |
| Smoking **                 | No        | -       | 1                 | -                 | -         | 1       | -                 | -                 |
|                            | Yes       | <0.001  | 2.52              | 1.95              | 3.26     | 0.001   | 1.41              | 1.15              | 1.75               |

* Cox model; HR—Hazard Ratio; $^1$ reference category; significant if $p < 0.05$. ** Cox model with time-dependent covariate.

Figures 1 and 3 show the difference in survival between the variables with statistical significance in the Cox Regression Model. It can be seen that the group with no work-related infection had a shorter survival time. The same occurred with the group belonging to the age group 80 or older and chronic cardiovascular disease, chronic kidney disease, smoking, obesity, neoplasms and chronic neurological disease ($p < 0.05$).
Figure 1. Survival curves of patients hospitalized with COVID-19 in Espírito Santo, Brazil. Log-rank test was used for comparison of equality of survival curves of sociodemographic variables in the period from 1 March 2020 to 31 July 2021. (A) Survival function according to the hospital length of stay of patients hospitalized with COVID-19 in Espírito Santo, Brazil, according to the independent variable work-related infection. (B) Survival function according to the hospital length of stay of patients hospitalized with COVID-19 in Espírito Santo, Brazil, according to the independent variable age group.

Figure 2. Cont.
Figure 3. Cont.
Figure 2. Survival curves of patients hospitalized with COVID-19 in Espírito Santo, Brazil. Log-rank test was used for comparison of equality of survival curves of clinical variables in the period from 1 March 2020 to 31 July 2021. (A) Survival function according to the hospital length of stay of patients hospitalized with COVID-19 in Espírito Santo, Brazil, according to the independent variable chronic cardiovascular disease. (B) Survival function according to the hospital length of stay of patients hospitalized with COVID-19 in Espírito Santo, Brazil, according to the independent variable chronic kidney disease. (C) Survival function according to the hospital length of stay of patients hospitalized with COVID-19 in Espírito Santo, Brazil, according to the independent variable smoking. (D) Survival function according to the hospital length of stay of patients hospitalized with COVID-19 in Espírito Santo, Brazil, according to the independent variable obesity. (E) Survival function according to the hospital length of stay of patients hospitalized with COVID-19 in Espírito Santo, Brazil, according to the independent variable neoplasms. (F) Survival function according to the hospital length of stay of patients hospitalized with COVID-19 in Espírito Santo, Brazil, according to the independent variable chronic neurological disease.

Figure 3. Survival curves of patients hospitalized with COVID-19 in Espírito Santo, Brazil. Log-rank test was used for comparison of equality of survival curves of clinical variables in the period from 1 March 2020 to 31 July 2021. (A) Survival function according to the hospital length of stay of patients hospitalized with COVID-19 in Espírito Santo, Brazil, according to the independent variable chronic cardiovascular disease. (B) Survival function according to the hospital length of stay of patients hospitalized with COVID-19 in Espírito Santo, Brazil, according to the independent variable chronic kidney disease. (C) Survival function according to the hospital length of stay of patients hospitalized with COVID-19 in Espírito Santo, Brazil, according to the independent variable smoking. (D) Survival function according to the hospital length of stay of patients hospitalized with COVID-19 in Espírito Santo, Brazil, according to the independent variable obesity. (E) Survival function according to the hospital length of stay of patients hospitalized with COVID-19 in Espírito Santo, Brazil, according to the independent variable neoplasms. (F) Survival function according to the hospital length of stay of patients hospitalized with COVID-19 in Espírito Santo, Brazil, according to the independent variable chronic neurological disease.
4. Discussion

The present study aimed at analyzing the survival of patients hospitalized with COVID-19 and identifying its associated factors. In general, we found that the group of patients who did not have a work-related infection had a shorter survival time. Similarly, the group of patients belonging to the age group 80 and older with presence of chronic cardiovascular disease, chronic kidney disease, chronic neurological disease, smoking, obesity and neoplasms were associated with a shorter survival time.

To the best of our knowledge, after extensive review of the scientific literature to date, it was noted that this is the first study conducted with the objective of analyzing the survival of patients hospitalized due to COVID-19 in the state of Espírito Santo, Brazil having as data source the state’s official Health Surveillance Information System, the e-SUS-VS.

We found that 1885 patients hospitalized due to COVID-19 progressed to death from the disease, which corresponds to about 19% of the total notifications of patients confirmed and hospitalized for COVID-19 (N = 9806) in the period from March 2020 to July 2021. This finding is similar to that found in a historical cohort from Brazil, in which approximately 17% of patients hospitalized due to COVID-19 progressed to death [18]. Regarding the average of hospital length of stay, the results show a mean of 10.5 days (SD ± 11.8). A survey conducted in São Paulo, Brazil, showed an average of hospital length of stay of nine days. Considering only critically ill patients, the average of hospital length of stay in the ICU was 15 days and the average total of hospital length of stay was 22 days, while for patients who did not require ICU, the average of hospital length of stay was seven days [19]. Another similar study reported a case of hospital length of stay of 10 days in men and 15 days in women with mechanical ventilation time similar to the hospital length of stay in both sexes [20].

As regards the risk factors for death from COVID-19, the following factors were associated with shorter survival: age group 60–79 years and 80 years or older, non-work-related infection, patients with comorbidities, especially the cardiovascular ones, chronic kidney disease, chronic neurological disease, smoking, obesity and neoplasms.

It is important to consider that the pandemic caused by COVID-19 that intensely ravaged the world impacted individuals in their different life cycles. In terms of mortality, the elderly population was the most affected. In several countries, it was found that persons aged 60 years or older are more vulnerable to the disease [3,12,20]. Individuals aged 60–79 years presented a relative risk of lower survival of 1.62 (p < 0.0001) compared to individuals aged 0–59 years, while a risk of 2.56 (p < 0.001) was observed in the age group 80 years or older. This finding corroborates other studies [3,11,12,18]. Elderly patients with COVID-19 are subject to progress to a severe disease, as they are more susceptible to a multisystem organ dysfunction and even organ failure. Furthermore, it was observed that the presence of lung lesions on imaging examinations and the number of white blood cells and neutrophils in laboratory examinations were significantly higher in the older patients group compared to the young and middle-aged group, thus suggesting that the former is also more prone to acquire a bacterial coinfection [11,21–23].

A large number of patients have cardiovascular disease as a comorbidity or develop cardiovascular dysfunction during the pathological process after SARS-CoV-2 infection [24]. The findings of the current study showed that chronic cardiovascular disease, including hypertension, is a factor associated with a higher risk for death and a shorter survival among hospitalized patients, thus corroborating the literature [25]. The impact of COVID-19 on the cardiovascular system is worth noting, as individuals with pre-existing disease are among the most affected by the disease and have a more severe clinical course [24–30].

To understand the dynamics of transmission and analyze the presence of a possible relationship between illness and work, the state of Espírito Santo, Brazil, created a variable called “Work-Related Infection” for e-SUS-VS. The results pointed out that although most of the sample (75.8%) had not shown the relationship between illness and work, when associating it with the outcome death from COVID-19, it was observed that non-work-related infections had a relative risk of 4.33 (p < 0.0001) of a worse survival when compared
to professionals who had a work-related infection. Since the state of Espírito Santo is the only one that has this field to fill out, it is a challenge to compare it to other states in this regard.

In spite of the fact that the Occupational Safety and Health Administration of the United States of America stated that professional categories other than health care have a lower risk of becoming ill [31], a document published in the state of Bahia, Brazil [32], raised the problem of the official notification systems which are not very sensitive to identifying work-related deaths, and estimated a high number of underreporting [32–34]. The work-related infections are based on the assumption that the determinants of this illness are related to the physical and social environment of work. Thus, a variety of diseases can be related to work, as long as they find favorable conditions for their occurrence in the environments. However, there is a major limitation in official notification systems, which are insensitive to identifying work-related infections and deaths. Thus, it is important to highlight the need of a complementary epidemiological investigation to identify situations of exposure to SARS-Cov-2 at work, which was not possible to accomplish in the current study. Indeed, we consider this to be a limitation of our study.

Our findings pointed out that obesity, when present, is 2.3 times more likely to have a worse survival among people affected by COVID-19. The correlation between obesity as a risk factor for COVID-19 was not initially described in some countries such as China, Italy and the United States [35], despite the fact that obesity is closely associated with some diseases that indicate a high morbidity and mortality from this new infection, such as heart disease, diabetes and respiratory conditions [36]. Studies began to emerge linking obesity as a risk factor for worse outcomes of COVID-19 [37,38]. Furthermore, a study [38] has reported a risk of death due to COVID-19 up to four times higher in people with obesity, in addition to those 85% of patients with a BMI $\geq 40$ kg/m$^2$ who require invasive mechanical ventilation. Obesity is associated with a chronic state of meta-inflammation with systemic implications for immunity in which antiviral responses are delayed and insensitive, with a weakened immune response that may trigger the worsening of the disease [39].

It was also evidenced that the habit of smoking increases by 1.4 times the chance of a worse survival when affected by SARS-CoV-2. It is known that smoking predisposes to the development of several diseases that increase the severity of COVID-19 and therefore can be considered a risk factor [40]. Studies indicate that besides increasing the chances of hospitalization, smoking worsens the clinical picture, influences the progression of pneumonia and worsens the prognosis of the disease [41,42], in addition to increasing the risk of death from SARS-CoV-2 infection [43].

Smokers are 2.4 times more likely to be admitted to the Intensive Care Unit, need invasive mechanical ventilation or die compared to non-smokers [44]. It is known that tobacco can cause chronic obstructive pulmonary disease that promotes increased expression of the Angiotensin-2 Converting Enzyme that facilitates the entry of SARS-CoV-2 into cells. Thus, the lung damage caused by tobacco use increases the risk of COVID-19 and progression to severe disease [45].

The concern with patients with chronic kidney disease (CKD) and hospitalized due to SARS-CoV-2 infection has also been described in the literature, as this association leads to increased hospital mortality and a worse clinical outcome [46], which corroborates our findings in which a risk of 1.50 ($p < 0.001; 95\% CI = 1.14–1.99$) was demonstrated. Similarly, a study conducted with a sample of 3391 patients with COVID-19 in New York showed that patients with chronic kidney disease had a higher risk of mortality (RR = 2.51 [95\% CI: 1.82–3.47], $p < 0.001$) and intubation (RR = 2.05 [95\% CI: 1.40–3.01], $p < 0.001$) [47]. Therefore, it is suggested that a history of CKD should be taken into account during risk stratification of patients with COVID-19 [46].

Patients with neoplasms are more susceptible to infections in general, due to the systemic immunosuppressive state caused by the treatments and are likely to have an increased risk of a worse prognosis. In China, patients with various types of cancer, particularly hematologic and lung cancers, were more likely to develop serious complications from
COVID-19 [48] with the advanced stage of the disease being an even greater aggravating factor [49].

It is also known that people with pre-existing neurological diseases were also unequally affected by COVID-19, as they suffered from the exacerbation of their underlying disease. Previous studies have shown that chronic neurological disorders are independently associated with increased mortality in hospitalized COVID-19 patients (HR = 2.13; 95%CI: 1.38–3.28) [50,51].

Some limitations should be considered. Although it is the most common data source for studies with survival analysis, a secondary bank is subject to information bias. It is believed that, due to the high turnover during the pandemic, untrained professionals may have failed to understand the variables on the notification form when filling it out, and thus promoted inconsistencies in the information, especially those related to work-related infection. Another relevant limiting factor was the incompleteness of the variables, especially those related to the patient’s hospitalization, such as hospital bed and dates of hospitalization and discharge, which were responsible for the exclusion of most of the sample. However, even with the limitations pointed out, most of the findings are consistent with the world literature and can contribute to epidemiological and survival analyses of COVID-19, extrapolating the state of Espírito Santo, Brazil. We suggest the conduction of other studies on the subject that can direct efforts to the understanding of a possible relationship between illness and work. Moreover, the in-service training of professionals, in a systematic and continuous way, is essential for reducing failures in filling out the notification and improving data collection.

As a strength and implications of this study, our results provide further evidence that there is an increased risk of death for elderly patients with chronic cardiovascular disease, chronic kidney disease, smoking, obesity, neoplasms and chronic neurological disease, as it results in a worsening of the patient’s condition. Undoubtedly, the identification of factors associated with the severity of the disease can effectively facilitate the management and provide assistance in order to improve the patients’ survival.

5. Conclusions

This study represents the first survival analysis on COVID-19 in the state of Espírito Santo, Brazil. Through it, it was possible to trace the factors associated with death and better understand the disease, especially the death of hospitalized patients. In summary, given the heterogeneity of the population, special attention shall be given to the elderly population, the patients with comorbidities, especially the cardiovascular ones, chronic kidney disease, chronic neurological disease, smoking, obesity and neoplasms. Thus, the identification of priority groups can direct the implementation of more specific prevention and control strategies, such as those that protect the elderly, people with comorbidities and prioritize testing for early detection of positive cases. Similarly, it is also important to disseminate the information on the most susceptible groups to the media, care networks, community, and other sectors beyond the health area.

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Institutional Review Board Statement: This study involves human participants and was approved by an Ethics Committee or Institutional Board—Centro de Ciências da Saúde da Universidade Federal do Espírito Santo—CEP/CCS/UFES) and approved under opinion number 5.180.941 on 20 December 2021), in accordance with the relevant guidelines from the Declaration of Helsinki and the ethical principles in the National Health Council of Brazil.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.
Data Availability Statement: Not applicable.

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