The Impact of Cardiovascular Risk Factors and Renal Disease on Outcomes in Patients Hospitalized with COVID-19: An Observational Study from Two Public Hospitals in Brazil

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Abstract

Background: Cardiovascular risk factors are prognostic factors in coronavirus disease 2019 (COVID-19) and have been scarcely studied in Brazil.

Objective: The aim of this study was to assess the impact of cardiovascular risk factors on the outcomes of patients admitted for COVID-19.

Methods: From July 2020 to February 2021, 200 patients from two public hospitals were enrolled. Patients were included if they had typical symptoms or signs of COVID-19, a positive real-time polymerase chain reaction test (RT-PCR) for COVID-19, and an age above 18 years. This is a prospective, observational, and longitudinal study. Data were collected within 24 h of admission. The primary endpoint was a combination of hospital lethality, mechanical ventilation, hemodialysis, or length of hospital stay >28 days. Continuous variables were compared with the Student’s t-test for independent samples or the Mann-Whitney test. For comparisons of proportions, the χ² test was applied. ROC curves and survival curves were constructed. Multivariate logistic regression was performed to identify independent predictors of events. The level of significance was 0.05.

Results: There were 98 (49%) events during the hospital course, and 72 (36%) died in the hospital. Patients with a primary endpoint were older and more likely to have a history of hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD). Vital signs at admission associated with events were diastolic blood pressure, respiratory rate, and oxygen saturation in ambient air (O₂Sat). Serum creatinine >1.37 mg/dL at admission had a sensitivity of 51.6 and a specificity of 82% to predict the primary endpoint, with an area under the curve (AUC) of 0.68. In multivariate analysis, age, diabetes, CKD, and COPD were independent predictors of the primary endpoint. Age and CKD were independent predictors of in-hospital lethality.

Conclusion: Cardiovascular risk factors, such as diabetes and CKD, were related to a worse prognosis in patients hospitalized with COVID-19 in this sample from two public hospitals in the state of Rio de Janeiro.

Keywords: COVID-19; Heart Disease Risk Factors; Prognosis.
develop cardiovascular complications either in patients with previous cardiac conditions or in individuals without a history of cardiovascular diseases.\textsuperscript{13-16}

There are some potential mechanisms by which patients with cardiovascular risk factors are at high risk for severe COVID-19. COVID-19 has been viewed as an endothelial and inflammatory disease.\textsuperscript{17} Most of the patients with cardiovascular risk factors are already naturally inflamed and have endothelial dysfunction, which may increase the risk of a bad outcome.\textsuperscript{17-20} Furthermore, cardiac patients are usually elderly people. On contrary, even patients without previous heart disease may have cardiac complications during the course of COVID-19. Likewise, several mechanisms may explain the heart damage, such as virus direct aggression, high expression of angiotensin-converting enzyme (ACE) in the heart, and inflammation.\textsuperscript{18-21}

Some COVID-19 studies with a Brazilian population have been published, mostly with data from private hospitals and no specific focus on cardiovascular diseases.\textsuperscript{22-24} Patients in the public health system have low social and economic status and are vulnerable to coronavirus infection. The prevalence of cardiovascular risk factors in the low-income population is high, and most of them are not under control.\textsuperscript{25,26}

The objectives of this study were to report the clinical characteristics of patients admitted for COVID-19 in two public hospitals in the state of Rio de Janeiro, Brazil, and to assess the impact of cardiovascular risk factors and cardiovascular diseases on hospital outcomes.

**Methods**

The investigation conforms to the principles outlined in the Declaration of Helsinki (Br Med J 1964; ii: 177). The study was approved by the Research Ethics Committee of our hospital and also by the National Ethics Committee (CONEP). All patients or families provided written informed consent. Patients’ families who refused to sign the informed consent or could not be reached were not included in the study. The researchers obeyed the precepts established in Resolution no. 466, dated December 12, 2012, of the National Health Council.

**Patients**

From July 2020 to February 2021, 200 patients were enrolled in two public hospitals in the state of Rio de Janeiro – a university hospital and a municipal hospital in the countryside of the state. In the university hospital, patients were admitted to the specific COVID-19 wards and the intensive care unit (ICU) for patients with COVID-19. The municipal hospital was inaugurated exclusively to care for patients with COVID-19. In this hospital, patients from the ICU and intermediary units were included.

Patients were referred to the hospitals because COVID-19 was suspected based on typical clinical symptoms and/or suggestive computed tomography (CT) scan of the thorax. Patients were included if they had typical symptoms or signs of COVID-19, a positive real-time polymerase chain reaction test (RT-PCR) for COVID-19, and an age above 18 years. No exclusion criteria were applied.

**Study Design**

This is a prospective, observational, and longitudinal study. Data were collected within 24 h of admission. The data collected for this study comprise clinical and demographic variables, routine laboratory tests (hemogram, blood urea, serum creatinine, sodium, and potassium), and the inflammatory and cardiovascular biomarkers such as C-reactive protein (CRP), D-dimer, natriuretic peptides, and cardiac troponin I (TnI). This was an observational study and, as a result, the diagnostic and therapeutic work-up was left to the discretion of the attending physician. Due to this, the specific biomarkers were not available for all patients but rather for those whom the attending physician felt there was an indication for their measurements. For the same reason, not all patients had an echocardiogram. Besides the tests ordered by the attending physician, blood samples were collected and frozen serum samples have been stored at –80°C. Data from these samples are not part of this study and instead will be used in a future biomarker study. These include the patients from this study and additional patients who are not included in the present analysis (1600 samples from 500 patients).

Specific clinical data were collected regarding cardiovascular risk factors and cardiovascular diseases. These included a previous history of hypertension, diabetes mellitus, coronary artery disease (CAD), myocardial infarction, heart failure (HF), chronic kidney disease (CKD), atrial fibrillation/flutter, current smoking, dyslipidemias, and obesity. History of chronic pulmonary obstructive diseases (COPD), cancer, and autoimmune diseases were also collected.
In the university hospital, the measurement of NT-proBNP was performed by the immunofluorescence technique with an automatic analyzer, where the anti-BNP murine monoclonal antibody captures the NT-proBNP that is present in the sample. This complex is then linked by a second fluorescent compound labeled polyclonal antibody. The concentration of NT-proBNP is determined by measuring fluorescence and expressed in pg/mL, starting with the standard curve of the device. Dosing was done within 6 h of collection, using the Elecsys® system (Roche, Basel, Switzerland). TnI was measured using electrochemiluminescence sandwich immunoassay with the I Stat® system (Roche, Basel, Switzerland), with a cutoff value of 0.1 ng/mL. D-dimer was measured using the Cobé assay, with a cutoff value of 500 ng/mL. In the Municipal Hospital, NT-proBNP was measured using the Celer Finecare assay. The assay for TnI was the I-Chroma Troponin I (cutoff value 0.3 ng/mL) and for D-dimer, InnovaCe, Siemens (cutoff value 500 ng/mL).

Transsthoracic echocardiography was performed using the Philips System, model EPIC 7 (Philips, Amsterdam, the Netherlands). The exams were performed according to the recommendations of the European Association of Echocardiography and the American Society of Echocardiography. Left ventricular (LV) systolic and diastolic diameters were recorded, and LV ejection fraction (LVEF) was calculated using the Teicholtz method. According to the CT scans, patients were stratified into one of the following categories according to the degree of lung involvement: <25%, 25–49%, 50–75%, and >75%.

Patients were followed-up during the hospital course to track the outcomes. The primary endpoint was a combination of hospital lethality, mechanical ventilation, hemodialysis, or length of hospital stay >28 days. The secondary endpoint was in-hospital lethality. Cardiovascular risk factors and cardiovascular diseases were compared, along with other variables, in patients with and without events.

Statistical analysis

This was a convenience sample of 200 patients. The normality of data distribution was assessed using the D’Agostino-Pearson test. Data are presented as mean and standard deviation for variables with normal distribution or median and interquartile range for non-normal distributions. Categorical data are presented as absolute values and percentages. To compare numerical data, the Student’s t-test for independent samples or the Mann-Whitney test was used. The homogeneity of the variance was tested using the Levene test. For comparisons of proportions (categorical data), the $\chi^2$ test or the Fisher’s exact test was applied, when applicable. Receiver operating characteristic (ROC) curves were constructed to determine the best cutoff point for continuous variables to predict the primary outcome. Survival-free Kaplan-Meier curves were also constructed and compared using the log-rank test. Multivariate logistic regression analysis was performed to determine the independent relationship of variables with the primary outcome and with hospital death. The variables included in the multivariate model were those with a p-value <0.05 in the univariate analysis (the Student’s t-test or Mann-Whitney test, the $\chi^2$ test or Fisher’s exact test). Three models were constructed. The first one included only the previous history data and the primary outcome as a dependent variable. The second one included vital signs at the presentation as well. In the third one, hospital death was used as the dependent variable. The criterion for determining significance was the 5% level. The analysis was performed using MedCalc for Windows, version 19.5 (MedCalc Software, Ostend, Belgium).

Results

In the university hospital, 230 patients were screened for COVID-19, with 139 (60.4%) having a confirmed diagnosis with a positive RT-PCR. In the municipal hospital, the screening was performed before admission to other health care units. Therefore, all 61 patients included in the study had a confirmed diagnosis of COVID-19. A total of 200 patients from the two hospitals were included in the analysis. The study flowchart is depicted in Figure 1. Table 1 shows the baseline characteristics stratified by the degree of lung involvement: <25%, 25–49%, 50–75%, and >75%.

Patients were followed-up during the hospital course to track the outcomes. The primary endpoint was a combination of hospital lethality, mechanical ventilation, hemodialysis, or length of hospital stay >28 days. The secondary endpoint was in-hospital lethality. Cardiovascular risk factors and cardiovascular diseases were compared, along with other variables, in patients with and without events.
Table 2 shows the laboratory tests at presentation stratified according to the primary endpoint. Variables related to renal function – serum creatinine and blood urea – were higher in patients with events. Conversely, hemoglobin levels were lower in patients with the primary endpoint. Figure 2 shows the ROC curve for serum creatinine. Serum creatinine >1.37 mg/dL at admission had a sensitivity of 51.6 and a specificity of 82% to predict the primary endpoint, with an area under the curve (AUC) of 0.68. Event-free survival time was shorter for patients with hypertension (hazard ratio 1.59, 95%CI 1.05–2.4, p=0.027) and for patients with CKD (hazard ratio 3.22, 95%CI 1.6–6.2, p=0.006), as demonstrated in Figure 3.

In the multivariate analysis, using only pathological history, age, diabetes, COPD, and CKD were independent predictors of the primary endpoint (Table 3, Model 1). When vital signs were added to the model, diabetes persisted as an independent predictor, along with the diastolic blood pressure and respiratory rate at admission (Table 4, Model 2). When hospital death was used as the endpoint, age (odds ratio 1.03, 95%CI 1.01–1.06, p=0.0016) and CKD (OR 3.01, 95%CI 1.09–8.33, p=0.033) were independent predictors.

**Discussion**

In this study, we demonstrated that diabetes mellitus and CKD, very well-known cardiovascular risk factors, were independent predictors of worse outcomes in patients hospitalized for COVID-19 in Rio de Janeiro state in the years 2020 and 2021. Additionally, we found that age and COPD were independent predictors as well. Hospital lethality was high (36%), and almost half of the population had at least one of the combined endpoints. Age and CKD were independent predictors of in-hospital lethality.

The lethality rate observed in our study was similar to that observed in a large Brazilian Registry of COVID-19. Ranzani et al., after studying 250000 hospital admissions for COVID-19 in Brazil, found an overall in-hospital lethality of 38%. The mean age in their study and our study was practically the same, i.e., 60 years. These lethality rates are similar to the ones observed in Chinese, European, and American series. However, if we take into account that our population was on average 10 years younger than patients in such studies, in-hospital lethality in Brazil was remarkably high. Unfortunately, Ranzani et al. did not report independent predictors of outcomes.

Another Brazilian registry, published recently, found an overall in-hospital lethality slightly lower than our study. Among 238000 hospitalizations, 32% of the patients died. Again, the predictors of outcome were not established, and data on comorbidities were not collected.

Several systematic reviews found the predictors of severity and lethality in COVID-19 non-Brazilian patients. Our findings in a Brazilian population are in accordance with such studies. In a systematic review by Harrison et al., CKD was the strongest predictor of higher lethality and severe disease (OR 3.07, 95%CI 2.43–3.88), followed by diabetes mellitus (OR 2.09, 95%CI 1.8–2.42) and hypertension (OR 2.5, 95%CI 2.02–3.11). One could speculate that CKD in our study was a strong predictor of the combined endpoint because it was more likely to undergo renal replacement therapy, which was one of the combined endpoints. Indeed, this may be the case. However, it does not diminish the prognostic value of CKD since it is also an independent predictor of death.
Table 1 – Previous pathological history and vital signs at presentation stratified according to the presence of the primary endpoint

| Characteristics                             | All patients | Events (n=98) | No events (n=102) | p-value |
|---------------------------------------------|--------------|---------------|-------------------|---------|
| Age (years)                                 | 59.9±16      | 64.1±13.3     | 56±17.6           | 0.0004  |
| Male gender                                 | 118 (59%)    | 61 (62.2%)    | 57 (55.8%)        | 0.36    |
| Hypertension                                | 124 (62%)    | 70 (71.4%)    | 54 (52.9%)        | 0.021   |
| Diabetes                                    | 62 (31%)     | 41 (41.8%)    | 21 (20.6%)        | 0.001   |
| Coronary artery disease                     | 23 (11.5%)   | 13 (13.2%)    | 10 (9.8%)         | 0.47    |
| Atrial fibrillation                         | 8 (4%)       | 5 (5.1%)      | 3 (2.9%)          | 0.44    |
| Heart failure                               | 14 (7%)      | 9 (9.2%)      | 5 (4.9%)          | 0.26    |
| Obesity                                     | 47 (23.5%)   | 24 (24.5%)    | 23 (22.5%)        | 0.77    |
| COPD                                        | 18 (9%)      | 13 (13.2%)    | 5 (4.9%)          | 0.04    |
| Chronic kidney disease                      | 22 (11%)     | 20 (20.4%)    | 2 (1.9%)          | <0.0001 |
| Autoimmune disease                          | 10 (5%)      | 6 (6.1%)      | 4 (3.9%)          | 0.49    |
| Cancer                                      | 35 (17%)     | 19 (19.4%)    | 16 (15.7%)        | 0.37    |
| Stroke                                      | 8 (4%)       | 5 (5.1%)      | 3 (2.9%)          | 0.44    |
| Use of ACEi/ARB                              | 59 (29.5%)   | 37 (37.7%)    | 22 (21.5%)        | 0.012   |
| Use of statin                                | 32 (16%)     | 19 (19.4%)    | 13 (12.7%)        | 0.13    |
| Use of immunosuppressor                     | 21 (10.5%)   | 10 (10.2%)    | 11 (10.8%)        | 0.87    |
| Systolic blood pressure (mmHg)              | 127.2±22.5   | 124±23.5      | 130±21            | 0.10    |
| Diastolic blood pressure (mmHg)             | 74.8±13.2    | 72.9±14       | 76.9±12           | 0.04    |
| Heart rate (bpm)                            | 90±19.8      | 92±19.5       | 87.8±20           | 0.16    |
| Respiratory rate (ipm)*                     | 20 (18–25)   | 21 (18–28)    | 20 (18–22)        | 0.0012  |
| Temperature (°C)                            | 36.8±0.97    | 36.7±0.96     | 36.9±0.97         | 0.21    |
| O2Sat in ambient air (%)*                   | 95 (90–98)   | 94 (88–97)    | 96 (93–98)        | 0.0017  |

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; COPD: chronic obstructive pulmonary disease; O2Sat: oxygen saturation. *Median and interquartile range. Bold indicates statistically significant values.

Some laboratory tests were associated with the severity of the disease. Patients with events were more likely to have higher values of serum creatinine and blood urea. On the contrary, hemoglobin levels were lower in such patients. These laboratory findings were probably related to the presence of previous CKD. A creatinine value at admission >1.37 was associated with worse outcomes. Cardiac biomarkers such as cardiac troponins and natriuretic peptides have been shown to predict outcomes.23,28 In a Brazilian study, cardiac troponin T at admission was an independent predictor of death or mechanical ventilation.23 Unfortunately, in this study, cardiac biomarkers were measured in a few patients, which made an adequate analysis impossible. However, we have stored serum from these patients, and the biomarker analysis will be part of a future study.

We found an elevated rate of CV comorbidities in patients hospitalized for COVID-19. In general, public health policies must increase their actions to improve the diagnosis and treatment of these comorbidities. Regarding COVID-19, this high-risk population needs
Table 2 – Laboratory tests and image findings stratified according to the presence of the primary endpoint

| Results                  | All patients | Events (n=98) | No events (n=102) | p-value |
|--------------------------|--------------|---------------|-------------------|---------|
| Hemoglobin (g/dL)        | 11.3±2.5     | 10.9±2.6      | 11.7±2.2          | 0.023   |
| WBC counts               | 8800 (6170–12490) | 9200 (6505–13375) | 8600 (5875–12057) | 0.22    |
| Lymphocytes              | 740 (21–1372) | 740 (26–1442) | 690 (18–1250)     | 0.39    |
| Platelet counts          | 209769±121780 | 19832±118952  | 220884±124166     | 0.21    |
| Creatinine (mg/dL)       | 1.09 (0.81–1.68) | 1.42 (0.93–2.45) | 0.98 (0.73–1.24) | <0.0001 |
| Blood urea (mg/dL)       | 40 (29–68)   | 49 (34–83.7)  | 34 (28–48)        | 0.0002  |
| Ferritin (µg/L)          | 972 (552–2057) | 1313 (744–2039) | 684 (406–2229)    | 0.21    |
| D-dimer (ng/mL)          | 1112 (549–2785) | 1122 (809–2847) | 718 (423–2593)    | 0.30    |
| LDH (UI/L)               | 400 (276–655) | 453 (283–656) | 380 (260–642)     | 0.46    |
| CRP (mg/dL)              | 9.6 (3.45–17.5) | 9.6 (4.49–18.6) | 9.5 (2.52–16.6)   | 0.33    |
| Troponin I (ng/mL)       | 0.42±0.82    | 0.35±0.51     | 0.52±1.15         | 0.75    |
| NT-proBNP (pg/mL)        | 285 (107–3759) | NA            | NA                | NA      |
| Sodium (mEq/L)           | 137±5.8      | 136±6.4       | 138±5             | 0.07    |
| Potassium (mEq/L)        | 4.2±0.9      | 4.4±1.04      | 4.1±0.76          | 0.051   |
| CT scan ≥50%             | 45 (21.5%)   | 24 (24.5%)    | 19 (18.6%)        | 0.31    |
| LVEF (%)                 | 67.3±12.6    | 64.8±15.4     | 70.2±8.5          | 0.36    |

CRP: C-reactive protein; CT scan >50%: lung involvement on CT scan >50%; LDH: lactate dehydrogenase; LVEF: left ventricle ejection fraction; WBC: white blood cell; NA: not applicable. Results are available only for 5 patients, and no comparison was done. Bold indicates statistically significant values.

Figure 2 – Use of ROC curve to determine the performance of creatinine in the prediction of events. The best cutoff value was 1.37 mg/dL.

intensive preventive care, such as a complete vaccination schedule and the use of masks, even if the law allows relaxation of social distancing measures.

An important limitation of our study was that cardiac biomarkers were not included in the multivariate analysis due to insufficient data. However, the main objective of the study was to assess the impact of previous cardiovascular conditions on prognosis, independently of laboratory findings. Nevertheless, a complete analysis of biomarkers, such as natriuretic peptides, cardiac troponins, GDF-15, and others, will be done in a future study, using frozen samples.

Conclusion

We found that cardiovascular risk factors were associated with the severity of the disease and hospital death. Older age, diabetes, and CKD were strong predictors of the disease severity. Additionally, age and CKD were independent predictors of in-hospital lethality.
Figure 3 – Kaplan-Meier event-free survival curves stratified by the presence of hypertension (p=0.027) and chronic kidney disease (p=0.0006).

Table 3 – Multivariate logistic regression (Model 1 – previous pathological history)

| Variable                  | ß-Coefficient | Odds Ratio | 95%CI        | p-value |
|---------------------------|---------------|------------|--------------|---------|
| Age                       | 0.0304        | 1.03       | 1.009–1.052  | 0.0044  |
| Hypertension              | -0.2658       | 0.76       | 0.34–1.69    | 0.51    |
| Diabetes                  | 1.1213        | 3.06       | 1.41–6.63    | 0.0044  |
| COPD                      | 1.2630        | 3.53       | 1.09–11.38   | 0.034   |
| Chronic kidney disease    | 2.5827        | 13.2       | 2.7–63.1     | 0.0012  |
| ACEi/ARB                  | 0.0175        | 1.01       | 0.45–2.27    | 0.96    |

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; COPD: chronic obstructive pulmonary disease; CI: confidence interval. Bold indicates statistically significant values.

Table 4 – Multivariate logistic regression (Model 2 – previous pathological history plus vital signs at presentation)

| Variable                        | ß-Coefficient | Odds Ratio | 95%CI        | p-value |
|---------------------------------|---------------|------------|--------------|---------|
| Age                             | 0.0208        | 1.02       | 0.99–1.05    | 0.18    |
| Hypertension                    | -0.0826       | 0.92       | 0.26–3.23    | 0.89    |
| Diabetes                        | 1.4289        | 4.17       | 1.15–15.06   | 0.029   |
| COPD                            | 0.5317        | 1.7        | 0.36–8.01    | 0.50    |
| Chronic kidney disease          | 2.0313        | 7.62       | 0.96–60.45   | 0.054   |
| ACEi/ARB                        | -0.4781       | 0.61       | 0.16–2.37    | 0.48    |
| Diastolic blood pressure        | -0.0478       | 0.95       | 0.91–0.99    | 0.033   |
| Respiratory rate                | 0.1645        | 1.17       | 1.05–1.32    | 0.005   |
| O₂Sat in ambient air            | -0.0606       | 0.94       | 0.85–1.03    | 0.22    |

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; COPD: chronic obstructive pulmonary disease; CI: confidence interval; O₂Sat: oxygen saturation. Bold indicates statistically significant values.
Author contributions

Conception and design of the research, statistical analysis and writing of the manuscript: Villacorta H; acquisition of data: de Ávila DX, de Souza TP, de Souza ALC, Meyas GA, Santos MCV, Mendonça JC, da Costa LMM, Sousa BP, de Oliveira MVB, Guimarães JCC; analysis and interpretation of the data: Villacorta H, de Ávila DX, de Melo UO; critical revision of the manuscript for intellectual content: de Ávila DX, de Souza TP, de Oliveira MVB, Guimarães JCC; conception and design of the research, statistical analysis and writing of the manuscript: Villacorta H; for institutional review: de Souza ALC, Meyas GA, Santos MCV, Mendonça JC, da Costa LMM, Sousa BP, de Oliveira MVB, Guimarães JCC; for institutional review: de Souza ALC, Meyas GA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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