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ORIGINAL ARTICLE

The impact of chronic cardiovascular disease on COVID-19 clinical course

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Abstract

Background: According to previous univariate analyses, chronic cardiovascular disease (CVD) has been associated with worse prognoses in severe cases of coronavirus disease 2019 (COVID-19). However, in the presence of a complex system, such as a human organism, the use of multivariate analyses is more appropriate and there are still few studies with this approach.
Aim: Using a significant sample of patients hospitalized in a single center, this study aimed to evaluate, whether the presence of CVD was an independent factor in death due to COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We also aimed to identify the clinical and laboratory predictors of death in an isolated group of cardiac patients.
Methods: This case–control study was conducted with patients admitted to a tertiary hospital and affected by COVID-19 in 2020. Variables were collected from the Brazilian surveillance system of hospitalized cases (SIVEP-Gripe) and electronic medical records. Multivariate logistic regressions with backward elimination were performed to analyze, whether CVD was an independent risk factor for death, and variables with $P < 0.05$ remained in the final model.
Results: A total of 2675 patients were analyzed. The median age was 60.4 years, and 55.33% of the patients were male. Odds ratios showed that age (OR 1.059), male sex (OR 1.471), Down syndrome (OR 54.980), diabetes (OR 1.626), asthma (OR 1.995), immunosuppression (OR 2.871), obesity (OR 1.432), chronic lung disease (OR 1.803), kidney disease (OR 1.789), and neurological diseases (OR 2.515) were independently associated with death. Neither the presence of heart disease nor the isolated analysis of each chronic CVD element (systemic arterial hypertension, congenital heart disease, previous acute myocardial infarction and cardiac surgery, obstructive coronary artery disease, valvular heart disease, and pacemaker use) showed as independent risk factors for death. However, an analysis restricted to 489 patients with chronic CVD showed troponin T (TnT) as an independent predictor of death (OR 4.073).
Conclusions: Neither chronic CVD nor its subcomponents proved to be independent risk factors for death due to SARS-CoV-2 infection. A TnT level of 14 pg/mL was associated with a higher occurrence of death in the isolated group of patients with chronic heart disease.
Relevance for Patients: Patients with chronic CVD may require more attention in the context of COVID-19 due to higher proportions of these individuals having a more severe progression of disease. However, regarding mortality in these patients, further studies should be conducted concerning comorbidities and acute myocardial injury.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has persisted since March 2020 and created dramatic statistics – as of February 2022, there have been more than 400 million people infected and approximately 5.9 million deaths worldwide [1]. Consistent with the

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disease's capacity for reach and devastation, COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may also be associated with multisystem injury [2].

One of the possible explanations for organ damage outside of the respiratory system, particularly in severe cases, is the circulatory derangement that occurs due to pro-thrombotic and pro-inflammatory states during infection [3]. As cardiovascular disorders often indicate an interaction between infection and illness severity [4], we sought to understand, whether the preexistence of cardiovascular disease (CVD) was an independent risk factor for death using multivariate analysis.

Univariate analyses have found that having chronic CVD before COVID-19 infection is associated to worse prognoses, with factors such as elevation of cell injury markers [5-7], inflammation [7] and thrombosis [6,7], lymphopenia [7], desaturation [6], and ultimately death [6-19]. However, with multivariate analyses, there is still no consensus that prior CVD is an independent risk factor for death from SARS-CoV-2 infection.

According to San Román *et al*. (n = 522) [6], Wang *et al*. (n = 399) [11], and Tessitore *et al*. (n = 839) [20], chronic CVD was independently associated with higher mortality in COVID-19. This was particularly evident with arterial hypertension in Guan *et al*. [21] and coronary artery disease in Gu *et al*. [10] and Ciceri *et al*. [13]

On the other hand, Di Castelnuovo *et al*. (n = 3894 in 30 centers) [22], Grasselli *et al*. (n = 3988) [14], Huang *et al*. (n = 310) [8], Iaccarino *et al*. (n = 1591 in 26 centers) [15], and Zhou *et al*. (n = 191) [17] reported that, using multivariate analyses, the pre-existence of CVD was not an independent risk factor for death in COVID-19.

Therefore, given the present uncertainty and urgency of recognizing patients with higher probabilities of worse prognoses and death, it is important to assess the impact of chronic CVD on the clinical outcomes (i.e., hospital discharge or death) of COVID-19. In addition, in our study, clinical and laboratory predictors of death were examined to further explain mortality in patients with heart disease, particularly those with prior CVD.

2. Materials and methods

This observational and retrospective case–control study was conducted at the Epidemiology Center of the Hospital de Base of the São José do Rio Preto Medical School Regional Foundation, a tertiary-level referral center for 102 municipalities in the state of São Paulo. We studied all positive COVID-19 cases (confirmed by RT-PCR or serological testing) that were admitted to the hospital between March 1 and December 31, 2020. These cases were documented in the Influenza Epidemiological Surveillance and Information System (Sistema de Informação e Vigilância Epidemiológica da Gripe – SIVEP-Gripe), a form used for hospitalized individuals in Brazil. The study was submitted to the Local Research Ethics Committee, approved under opinion number 4.586.77, and was exempted from the Free and Informed Consent Form.

With the aim of evaluating the impact of chronic CVD on the course of COVID-19 disease, the following diagnoses were considered before a SARS-CoV-2 infection diagnosis: ischemic heart disease with exercise tests and myocardial scintigraphy positive for ST segment alteration; obstructive coronary artery disease, demonstrated on cardiac catheterization; congenital heart disease; valvopathy characterized by significant stenosis or insufficiency; myocardial hypertrophy, demonstrated on echocardiography; enlargement of the cardiac area (on chest X-ray), continuous use of anticoagulants, and/or antiplatelet agents accompanied by other chronic CVD; Chagas disease; use of pacemakers; previous cardiac surgery and/or angioplasty; continuous use of anti-arrhythmics; and arterial hypertension, associated with the use of anti-hypertensives or diuretics; and/or other heart diseases recorded in electronic medical records.

In addition, age; sex; Down syndrome (DS) diagnosis; chronic renal, neurological, lung, hepatic, and hematological diseases; asthma; obesity; diabetes mellitus; and immunosuppression were listed as comorbidities by the Brazilian Ministry of Health (MH) on the COVID-19 notification form (SIVEP-Gripe) as well as covariates in this study. Therefore, based on a diagnosis before COVID-19, the following criteria were considered for covariates: chronic kidney disease in stages 3, 4, and 5, as well as patients on dialysis; stroke; cerebral palsy; multiple sclerosis; hereditary and degenerative diseases of the nervous or muscular system; severe neurological impairment; cirrhosis; chronic hepatitis; biliary atresia; severe hemoglobinopathies (i.e., sickle cell anemia and thalassemia major); asthma with exacerbations requiring the use of inhaled or systemic corticosteroids; body mass index ≥30 kg/m²; type I and II diabetes using medication; congenital or acquired immunodeficiency and immunosuppression due to diseases or medication use; chronic obstructive pulmonary disease; bronchiectasis; cystic fibrosis; interstitial lung disease; bronchopulmonary dysplasia; pulmonary arterial hypertension; and children with lung disease of prematurity.

The electronic medical records of 2706 patients were consecutively evaluated and those with severe COVID-19 were defined by the Brazilian MH as having a flu-like syndrome accompanied by dyspnea/respiratory discomfort, persistent pressure/pain in the chest, oxygen saturation lower than 95% on room air, or lip/face cyanosis. To meet the proposed objective of studying the independent predictive potential of chronic CVD on COVID-19, the total number of participants were divided into two clinical outcome groups: deaths and hospital discharges. In addition, to characterize patients with prior CVD, a descriptive analysis was performed to compare patients with chronic CVD and those without.

2.1. Global statistics analysis

Chi-square and Fisher's exact tests were used for the comparative inferential analysis of categorical variables and were presented in absolute numbers and percentages. Continuous variable analyses were performed using the nonparametric Mann–Whitney test and presented as medians and interquartile ranges (IR).

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2.1.1. Model development

To assess whether preexisting heart disease was an independent predictor of death, two models were developed using the multivariate logistic regression backward elimination technique. Morbidities $P < 0.20$ in the univariate analysis were used in the multivariate regression models.

In the first model, heart disease was considered globally. Clinical outcome (i.e., hospital discharge or death) was the dependent variable, while the independent variables were age, sex, and presence of the comorbidities (in addition to CVD, age, and male sex: chronic renal, neurological, and lung diseases, asthma, obesity, diabetes mellitus, immunosuppression, and DS).

In the second model, we aimed to study the predictive capacity of different types of chronic CVD that we considered subcomponents, such as systemic arterial hypertension, Chagas disease, congenital heart disease, obstructive coronary disease, pacemaker implantation, previous acute myocardial infarction, and cardiac surgery. The covariates explored in the first model as well as the arrangement of dependent and independent variables were maintained.

In the third, the objective was to evaluate the predictive potential of chronic CVDs excluding arterial hypertension as their only diagnosis. With this, we intend to study CVD in a less broad sense, at the level of heart disease. The other components of the multivariate logistic regression design used in the previous models were kept.

Applying the backward technique in both analyses, only the variables with $P < 0.05$ remained in the final versions of the models.

2.2. Cardiac patients group analysis

As a complement to the study of mortality in patients with heart disease, this analysis was restricted to patients with chronic CVD based on laboratory variables (within 24 h of hospital admission) of troponin T (TnT), creatinine, lactate dehydrogenase, lymphocytes, hemoglobin, D-dimer, and C-reactive protein (CRP). In addition to these, signs and symptoms recorded in electronic medical records were analyzed, including fever, cough, sore throat, dyspnea, oxygen saturation below 95%, diarrhea, vomiting, abdominal pain, and loss of smell and taste.

The cutoff values adopted for the laboratory variables were: for TnT, the 99% percentile of the ultrasensitive TnT of 14 pg/mL, using the electrochemiluminescence technique; for CRP, values above 0.5 mg/dL, applying the immunoturbidimetric assay technique; for creatinine, values above 1.2 mg/dL, using the colorimetric technique by modified Jaffé reaction, for lactate dehydrogenase, values above 250 U/L, using the colorimetric enzymatic technique; for D-dimer, values above 0.5 ug/mL, using immunoturbidimetric technique; for hemoglobin, values below and above the 12–17 g/dL range; and for absolute lymphocytes, values below and above the 600–3960 cells/mm^3 range. Both hemoglobin and lymphocytes were analyzed using the automated flow cytometry technique.

Statistical analysis, to search for independent clinical and laboratory predictors of mortality specifically in patients with heart disease, was performed by multivariate logistic regression using the backward elimination technique. The dependent variable was clinical outcome (i.e., death or hospital discharge), and the independent variables (included in the exploratory model) were the clinical signs and symptoms and the laboratory variables (TnT, creatinine, lactate dehydrogenase, D-dimer, CRP, lymphocytes, and hemoglobin) with $P < 0.20$ in the univariate analysis specific to cardiac patients group.

In the final multivariate model, only variables with $P < 0.05$ remained.

The regression models and their analyses may be found in their entirety in the Supplementary File. All statistical analyses were performed using StatsDirect program version 3.3.5 (2022).

3. Results

3.1. Global analysis

Of the total 2706 patients, 31 were excluded from the study. Of those excluded, 21 did not present with diagnostic confirmation of chronic CVD after reviewing the electronic medical records, seven were excluded due to duplication, and three lacked documentation of covariates (Figure 1). Therefore, the data of 2675 participants, including age, sex, presence of comorbidities (chronic cardiovascular, renal, neurological, hepatic, lung, and hematological diseases; asthma; obesity; diabetes mellitus; DS; and immunosuppression), and clinical outcomes (i.e., hospital discharge or death) were collected and analyzed.

Population characteristics are presented in Table 1. The median age was 60.40 years (IR 47.73–72.38), with 55.33% of participants being male. In our univariate analysis, chronic heart disease was associated with death ($P < 0.0001$); similarly, advanced age (median of 72.3 years [IR 61.4–81]), male sex, and other explored

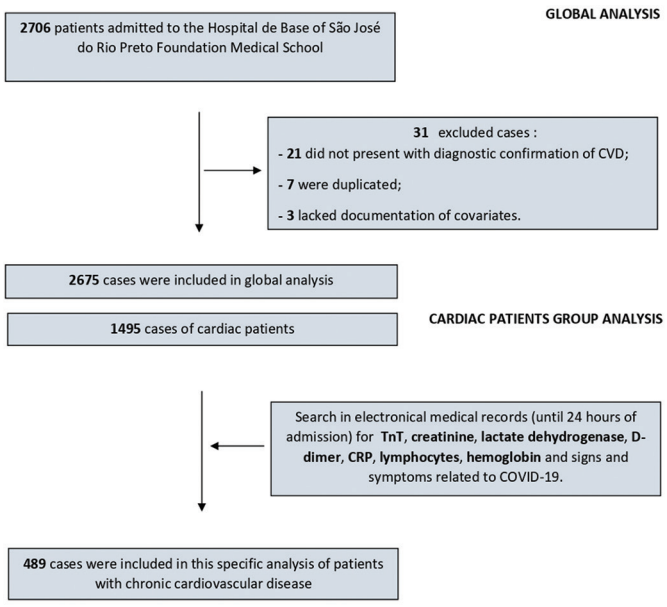

Figure 1. Participants recruitment flowchart.

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morbidities, with the exception of chronic liver and hematological diseases, were too associated with death.

However, notably, chronic CVD considered as a unique group (OR 1.203; 95% Confidence Interval [CI] 0.959–1.509; *P*= 0.1097), using multivariate regression analyses, did not appear to explain the deaths in the cases studied. The statistically significant variables are listed in Table 2.

The distribution of chronic CVD by subcomponent is shown in Figure 2. In the second regression model, results were consistent with the global analysis model in that none of them alone was able to independently predict death (Table 3). Other statistically significant variables are shown in Table 2.

These same results were confirmed in the third multivariate logistic regression (**Supplementary Table 3**): the pre-existence of chronic CVD (excluding arterial hypertension as a sole CVD diagnosis) was not independently associated with death (OR 1.317; 95% Confidence Interval [CI] 0.959 – 1.810; *P* = 0.0891), as well as isolated arterial hypertension itself (OR 1.046; 95% Confidence Interval [CI] 0.829 – 1.321; *P* = 0.7028).

The age of participants with chronic CVD (55.89% of the participants) was in line with the expectation that more chronic CVD patients would be elderly. The average median age of patients with heart disease (median age of 66.61 years [IR 55.95–76.52]) exceeded that of the overall population and that of non-cardiac patients by 6.23 and 15.77 years. The presence of morbidities in the group with chronic heart disease was also notable. Of those with chronic heart disease, 66.89% had 2–3 morbidities and 6.29% had 4 or more. In contrast, 10.34% had 2–3 morbidities and 0.17% had 4 or more, in those without chronic heart disease. Further results are presented in Table 4.

3.2. Cardiac patients group analysis

In the exclusive study of patients with chronic CVD (those with clinical and laboratory variables explored as predictive factors), 489 patients were included in the study. Of these, 282 (57.67%) were male, and the median age was 66.0 (1R 56–74).

Except oxygen saturation <95%, none of the other clinical variables considered were associated with death in this analysis, including fever, cough, sore throat, diarrhea, vomiting, abdominal pain, and loss of smell and taste. Even dyspnea (OR 1.366; CI 0.771–2.422); *P* = 0.2854), studied as a potential predictor of death

Table 1. Univariate analysis. Comparison of deaths with hospital discharges in patients with COVID-19.

Variables	Total (*n*=2675)	Death (*n*=683)	Hospital discharge (*n*=1992)	*P*
Age in years (median; [Q1–Q3])	60.38 (47.73–72.38)	72.3 (61.4–81)	56.45 (43.7–67.6)	<0.0001
Male sex (*n* [%])	1480 (55.33)	410 (60.03)	1070 (53.71)	0.0048
Asthma (*n* [%])	75 (2.80)	25 (3.66)	50 (2.5)	0.1507
Diabetes (*n* [%])	767 (28.67)	283 (41.43)	484 (24.29)	<0.0001
Chronic cardiovascular disease (*n* [%])	1495 (55.89)	496 (72.62)	999 (50.15)	<0.0001
Chronic hematological disease (*n* [%])	27 (1)	10 (1.46)	17 (0.85)	0.2476
Chronic liver disease (*n* [%])	37 (1.38)	12 (1.76)	25 (1.26)	0.4357
Chronic neurological disease (*n* [%])	220 (8.22)	121 (17.72)	99 (4.97)	<0.0001
Chronic kidney disease (*n* [%])	108 (4.04)	54 (7.91)	96 (4.82)	<0.0001
Chronic lung disease (*n* [%])	156 (5.83)	80 (11.71)	76 (3.82)	<0.0001
Immunosuppression (*n* [%])	129 (4.82)	56 (8.20)	73 (3.66)	<0.0001
Down syndrome (*n* [%])	7 (0.26)	4 (0.58)	3 (0.15)	0.0753
Obesity (*n* [%])	854 (31.93)	191 (27.96)	663 (33.28)	0.0116

Q1-25th percentile; Q3-75th percentile

Table 2. Multivariate analysis. Variables that were independently associated with death in the model that considered heart disease as a single group (*n*=2675).

Variables	Coefficient	Odds ratio (95% CI)	Standard error	Z Value	*P*
Age	0.058	1.059 (1.051–1.067)	0004	14.993	<0.0001
Male sex	0.386	1.471 (1.205–1.797)	0.102	3.783	0.0002
Diabetes	0.484	1.626 (1.325–1.994)	0.104	4.661	<0.0001
Chronic neurological disease	0.922	2.515 (1.833–3.540)	0.161	5.719	<0.0001
Chronic kidney disease	0.582	1.789 (1.162–2.753)	0.220	2.645	0.0082
Chronic lung disease	0.590	1.803 (1.259–2.583)	0.183	3.216	0.0013
Obesity	0.359	1.432 (1.141–1.798)	0.116	3.099	0.0019
Immunosuppresion	1.055	2.871 (1.925–4.282)	0.204	5.169	<0.0001
Asthma	0.690	1.995 (1.158–3.437)	0.278	2.487	0.0129
Down syndrome	4.007	54.980 (9.703–311.528)	0.885	4.528	<0.0001

CI: confidence interval; Multivariate logistic equation: logit Death = −5.488214+0.386201 Male Sex +0.057663 Age +4.006971 Down syndrome +0.690494 asthma +0.485909 diabetes +0.922279 Chronic neurological disease +0.589728 chronic lung disease +1.054624 Immunossuppresion +0.581579 chronic kidney disease +0.35937 obesity

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Table 3. Multivariate analysis. Performance of heart disease subtypes in the model that considered them by subcomponents (*n*=2675).

Variables	Coefficient	Odds ratio (95% CI)	Standard error	Z Value	*P*
Systemic arterial hypertension	−0.004	0.996 (0.795–1.247)	0.115	−0.038	0.9698
Obstructive coronary artery disease	0.114	1.120 (0.742–1.691)	0.210	0.539	0.590
Previous cardiac surgery	0.232	1.261 (0.665–2.391)	0.711	0.711	0.4769
Previous acute myocardial infarction	-0.186	0.827 (0.494–1.387)	0.263	−0.720	0.4718
Chagas disease	0.334	1.398 (0.598–3.269)	0.433	0.773	0.4396
Use of pacemaker	0.475	1.607 (0.664–3.890)	0.451	1.052	0.293
Congenital heart disease	1.647	5.187 (0.636–42.324)	1.710	1.537	0.1243
Valvopathy	0.408	1.499 (0.770–2.916)	0.340	1.191	0.2334

CI: confidence interval, Multivariate logistic equation: logit Death = -5.455232-0.004345 systemic arterial hypertension−0.18606 PREVIOUS acute myocardial infarction +0.334197 Chagas disease +0.474955 use of pacemaker +1.646996 congenital heart disease +0.232434 previous cardiac surgery +0.11425 obstructive coronary artery disease +0.407899 valvopathy +0.384001 male sex +0.057082 age +3.397061 Down syndrome +0.676799 asthma +0.4938 diabetes +0.921108 chronic neurological disease +0.577038 chronic lung disease +1.048036 immunodeppresion +0.528661 chronic kidney disease +0.377886 obesity

Table 4. Comparison between non-cardiac and cardiac patients with COVID-19.

Variables	Total (*n*=2675)	Non-cardiac patients (*n*=1180)	Cardiac patients (*n*=1495)
Age in years (median; [Q1–Q3])	60.38 (47.73–72.38)	50.84 (39.63–62.90)	66.61 (55.95–76.52)
Male sex (*n* [%])	1480 (55.33)	687 (58.22)	793 (53.04)
Asthma (*n* [%])	75 (2.80)	35 (2.97)	40 (2.68)
Diabetes (*n* [%])	767 (28.67)	146 (12.37)	621 (41.54)
Chronic hematological disease (*n* [%])	27 (1)	14 (1.19)	13 (0.87)
Chronic liver disease (*n* [%])	37 (1.38)	12 (1.02)	25 (1.67)
Chronic neurological disease (*n* [%])	220 (8.22)	66 (5.59)	154 (10.30)
Chronic kidney disease (*n* [%])	108 (4.04)	12 (1.02)	96 (6.42)
Chronic lung disease (*n* [%])	156 (5.83)	41 (3.47)	115 (7.69)
Immunosuppresion (*n* [%])	129 (4.82)	51 (4.32)	78 (5.22)
Down syndrome (*n* [%])	7 (0.26)	4 (0.34)	3 (0.20)
Obesity (*n* [%])	854 (31.93)	341 (28.90)	513 (34.31)
Presence of 1 morbidity	852 (31.85)	451 (38.22)	401 (26.82)
Presence of 2–3 morbidities	1122 (41.94)	122 (10.34)	1000 (66.89)
Presence of 4 or more morbidities	96 (3.59)	2 (0.17)	94 (6.29)
Death (*n* [%])	695 (25.98)	197 (16.69)	498 (33.31)

Q1-25th percentile; Q3-75th percentile

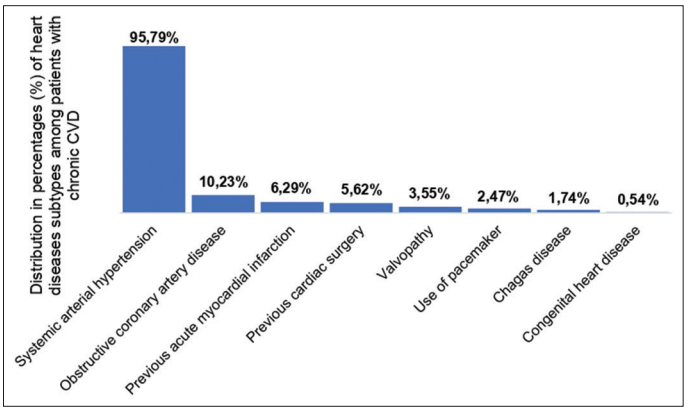

Figure 2. Distribution (in percentages) of heart diseases subcomponents among the total of patients with CVD (*n* = 1495).

in COVID-19, was not an independent predictor of death in the multivariate model.

Regarding laboratory tests, CRP level (OR 1.875; CI 0.413-8.521; *P* = 0.4156), D-dimer (OR 1.365; CI 0.611–3.050; *P* = 0.4478), Creatinine (OR 1.517; CI 0.964–2.387; *P* = 0.0715), and Lymphocytes (OR 1.505; CI 0.956–2.367; *P* = 0.0773) did not appear to explain the clinical outcome of death among patients with chronic CVD. Statistical significance is described in Table 5.

4. Discussion

The high prevalence of chronic heart disease (55.89%) among the total number of patients is consistent with univariate analyses that showed that it may cause greater severity in clinical condition with COVID-19. This study included patients admitted to a tertiary-level hospital with COVID-19. However, reiterating conclusions by Vudathaneni *et al*. [23] and other authors [8,12,14,15,17,22] the results of the present study indicate that chronic CVD cannot be considered as an independent predictor of death from COVID-19, when using multivariate regression analyses, endorsing the

Table 5. Uni- and multi-variate analysis specific to the group of cardiac patients (*n*=489).

Univariate			Final model of multivariate		
Variables	**Cardiac patients death (*n*=193)**	**Cardiac patients discharge (*n*=296)**	***P***	**ODDS Ratio 95%IC**	***P***
Age in years (median; [Q1–Q3])	71 (63–79)	62 (53.5–71)	<0.0001	1.038 (1.020–1.056)	<0.0001
Troponin T (median; [Q1–Q3])	33.88 (15.16–104)	11.52 (7.28–18.76)	<0.0001	4.073 (2.601–6.376)	<0.0001
Lactate dehydrogenase (median; [Q1–Q3])	498 (393–657)	381 (297–472)	<0.0001	3.962 (1.788–8.780)	0.0007
Hemoglobin (median; [Q1–Q3])	13.1 (11.5–14.2)	13.35 (12.1–14.4)	0.0177	1.600 (1.015–2.520)	0.0428
O2 saturation<95% (n [%])	177 (91.71)	247 (83.45)	0.0126	2.346 (1.202–4.577)	0.0124
Creatinine (median; [Q1–Q3])	1.3 (1–2.2)	1 (0.75–1.3)	<0.0001		
D-dimer (median; [Q1–Q3])	1.98 (0.98–4.98)	1.09 (0.66–1.885)	<0.0001		
Reactive C Protein (median; [Q1–Q3])	15.74 (9.4–24.13)	9.18 (5.02–15.49)	<0.0001		
Lymphocytes (median; [Q1–Q3])	720 (490–960)	890 (650–1250.0)	<0.0001		
Dyspnea (*n* [%])	166 (86.01)	230 (77.70)	0.03		
Male sex (*n* [%])	120 (62.18)	162 (54.73)	0.2142		
Fever (*n* [%])	92 (47.67)	141 (47.64)	>0.9999		
Cough (*n* [%])	133 (68.91)	193 (65.20)	0.4518		
Sore throat (*n* [%])	24 (12.44)	29 (9.78)	0.4423		
Diarrhea (*n* [%])	15 (7.77)	26 (8.78)	0.8199		
Vomit (*n* [%])	9 (4.66)	25 (8.45)	0.154		
Abdominal pain (*n* [%])	4 (2.07)	14 (4.73)	0.2007		
Loss of smell (*n* [%])	8 (4.15)	19 (6.42)	0.3824		
Loss of taste (*n* [%])	5 (2.59)	15 (5.07)	0.2635		

Q1-25th percentile, Q3-75th percentile, CI: confidence interval, Multivariate logistic equation: logit DEATH = −5.852544+0.037406 age +0.852527 oxygen saturation above 95% +1.404269 troponin T +1.376706 lactate dehydrogenase +0.469787 hemoglobin

importance of other variables in explaining the clinical outcome analyzed.

Patients with CVD (*n* = 1495) had a higher average age compared with the overall group of participants, in excess of 6.23 years. This finding was in line with that of O'Gallagher *et al*. [24], who reported that patients with chronic heart disease were older than those without heart disease. However, the study revealed that at the age of 70 years, prior CVD was not an independent risk factor for death, highlighting the relevance of advanced age being associated with a greater probability of death from COVID-19 [8,10,13-15,17,20-22].

Furthermore, the majority of the patients with chronic CVD (53.04%) were male, which was associated with a 46.6% increase in the chance of death. Accordingly, there is a growing body of evidence that suggests a higher mortality rate in men compared with women [14,22,25-27]. Differences in men regarding immunological phenotypes (lower T-cell response) [25], behaviors (higher rates of alcoholism and smoking) [26], and receptor expressions (ACE2) of SARS-CoV-2 have been noted [27].

Another aspect of note was the prevalence of comorbidities in patients with chronic CVD [24], particularly diabetes [14,15,20] and obesity [28,29], both of which have been considered as independent risk factors for death in previous studies. These findings have also been reported in relation to chronic kidney [5], neurological [11], and lung diseases [11,14,20,21] as well as immunosuppression [29]. Supporting this evidence was the larger amount of comorbidities in patients with chronic CVD compared with the control group (patients without chronic CVD). Of those with heart disease, 66.89% had 2–3 comorbidities and 6.29% had 4 or more. In non-cardiac patients, these numbers were 10.34% and 0.17%, respectively.

These results are in accordance with CAPACITY-COVID/LEOSS study [30], a retrospective cohort with 16,511 patients. This multicenter trial has found that patients with a history of heart disease were older, more frequently male and had more comorbidities beyond CVD. Also, chronic CVD as a unique group ("history of heart disease") was not independently associated with in-hospital mortality. Although, based on ACC/AHA heart failure (HF) classification [31], we did not consider appropriated in our study's design to include HF as an isolated diagnosis of CVD, since it is a clinical syndrome, and thus, by definition, already accompanies the entirely cases of various degrees of structural alterations (e.g., valvar, coronary, or myocardial), they analyzed the syndrome as an isolated heart disease and found its significance with death.

Regarding asthma, Lee *et al*. [32] found different results from our study results. In addition, regarding DS, there was a lack of information to confirm or deny that it was an independent predictor of mortality. Furthermore, it is important to highlight that the weight of DS in this study, consistent with the genetic disease severity in COVID-19 evidenced by Espinosa *et al*. [33], was disproportionate to the scarcity of other studies on the topic. This may indicate the need for further analysis to address DS in the context of SARS-CoV-2 infection.

Finally, in line with Guo *et al*. [5], multivariate analyses conducted in our study showed that TnT levels were found to be a significant independent risk factor and predictor of death in

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patients with CVD in a Brazilian multicenter study (21 centers) with 2546 patients [34].

In consideration of the study performed and population analyzed, it may be inferred that acute cardiovascular injury, not chronic CVD, is of greater importance for the clinical outcome studied [11]. In addition to TnT, lactate dehydrogenase [11,35], anemia [36], desaturation [6], age [10], and polycythemia (including changes in hemoglobin values concomitant with anemia) comprised the independent predictors of death found in patients with prior heart disease.

4.1. Study limitations

This single-center, retrospective study, multiple inferential, and exploratory analyses were performed. Due to the review of electronic medical records of all those hospitalized patients during the study period, no sample calculation was performed for the priori statistical hypotheses. Furthermore, due to the lack of data on clinical and laboratory variables analyzed as predictive factors, the study restricted to patients with chronic CVD included a small number of participants. Moreover, we did not conduct a specific analysis for cumulative CVD as happens in HF, considering that the different stages of the syndrome had already been covered by the confirmed cases of heart diseases.

5. Conclusions

The results of the present study showed that, despite the current thinking that chronic CVD is an important morbidity in predicting death in COVID-19, neither overall CVD nor its subcomponents were shown to be independent risk factors of COVID-19 mortality when multivariate analyses were performed. In the study population, death may have been better explained by other underlying morbidities. In particular, advanced age, acute cardiovascular injury (TnT >14 pg/mL), lactic dehydrogenase > 250 U/L, hemoglobin outside the range of 12–17 g/dL, and oxygen saturation <95% – all measured within 24 h of hospital admission – independently predicted death in patients with chronic CVD.

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Conflicts of Interest

The authors declare that there is no conflicts of interest.

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ORIGINAL ARTICLE

The impact of chronic cardiovascular disease on COVID-19 clinical course

Supplementary File

Supplementary Table 1. Complete multivariate analysis (*n*=2675).

Model	Variables	Coefficient	ODDS Ratio 95%CI	*P*
1.1	Age	0.056	1.058 (1.049–1.066)	<0.0001
	Male sex	0.395	1.484 (1.215–1.813)	0.0001
	Diabetes	0.443	1.558 (1.262–1.923)	<0.0001
	Chronic cardiovascular disease	0.185	1.203 (0.959–1.509)	0.1097
	Chronic neurological disease	0.921	2.513 (1.832–3.446)	<0.0001
	Chronic kidney disease	0.550	1.733 (1.126–2.667)	0.0125
	Chronic lung disease	0.581	1.788 (1.248–2.562)	0.0016
	Obesity	0.340	1.405 (1.118–1.766)	0.0036
	Immunosuppression	1.050	2.857 (1.914–4.264)	<0.0001
	Asthma	0.695	2.004 (1.161–3.455)	0.0126
	Down syndrome	3.970	53.030 (9.514–295.581)	<0.0001
1.2	Age	0.058	1.059 (1.051–1.067)	<0.0001
	Male sex	0.386	1.471 (1.205–1.797)	0.0002
	Diabetes	0.484	1.626 (1.325–1.994)	<0.0001
	Chronic neurological disease	0.922	2.515 (1.833–3.540)	<0.0001
	Chronic kidney disease	0.582	1.789 (1.162–2.753)	0.0082
	Chronic lung disease	0.590	1.803 (1.259–2.583)	0.0013
	Obesity	0.359	1.432 (1.141–1.798)	0.0019
	Immunosuppression	1.055	2.871 (1.925–4.282)	<0.0001
	Asthma	0.690	1.995 (1.158–3.437)	0.0129
	Down syndrome	4.007	54.980 (9.703–311.528)	<0.0001

CI: confidence interval

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Supplementary Table 2. Complete multivariate analysis considering chronic cardiovascular diseases by subcomponents(*n*=2675).

Model	Variables	Coefficient	Odds ratio (95% CI)	P
2.1	Age	0.057	1.059 (1.050–1.067)	<0.0001
	Male sex	0.384	1.467 (1.197–1.797)	0.0002
	Diabetes	0.4938	1.639 (1.323–2.030)	<0.0001
	Systemic arterial hypertension	−0.004	0.996 (0.795–1.247)	0.9698
	Obstructive coronary artery disease	0.114	1.120 (0.742–1.691)	0.59
	Previous acute myocardial infarction	−0.186	0.827 (0.494–1.387)	0.4718
	Chagas disease	0.334	1.398 (0.598–3.269)	0.4396
	Previous cardiac surgery	0.232	1.261 (0.665–2.391)	0.4769
	Valvopathy	0.408	1.499 (0.770–2.916)	0.2334
	Congenital heart disease	1.647	5.187 (0.636–42.324)	0.1243
	Use of pacemaker	0.475	1.607 (0.664–3.890)	0.293
	Chronic neurological disease	0.921	2.510 (1.827–3.449)	<0.0001
	Chronic kidney disease	0.529	1.701 (1.096–2.642)	0.0179
	Chronic lung disease	0.577	1.779 (1.239–2.554)	0.0018
	Obesity	0.378	1.460 (1.160–2.642)	0.0012
	Immunosuppression	1.048	2.845 (1.904–4.251)	<0.0001
	Asthma	0.677	1.962 (1.133–3.399)	0.0162
	Down syndrome	3.397	30.864 (5.124–185.916)	0.0002
2.2	Age	0.057	1.059 (1.050–1.067)	<0.0001
	Male sex	0.384	1.467 (1.199–1.797)	0.0002
	Diabetes	0.493	1.637 (1.332–2.013)	<0.0001
	Obstructive coronary artery disease	0.112	1.119 (0.743–1.686)	0.5907
	Previous acute myocardial infarction	−0.187	0.827 (0.494–1.385)	0.4699
	Chagas disease	0.334	1.398 (0.598–3.268)	0.4396
	Previous cardiac surgery	0.232	1.261 (0.665–2.389)	0.4773
	Valvopathy	0.407	1.498 (0.771–2.909)	0.2334
	Congenital heart disease	1.647	5.185 (0.636–3.890)	0.1243
	Use of pacemaker	0.475	1.607 (0.664–3.890)	0.2929
	Chronic neurological disease	0.921	2.510 (1.827–3.449)	<0.0001
	Chronic kidney disease	0.528	1.700 (1.097–2.636)	0.0176
	Chronic lung disease	0.577	1.779 (1.239–2.554)	0.0018
	Obesity	0.377	1.459 (1.161–1.833)	0.0012
	Immunosuppression	1.048	2.846 (1.905–4.252)	<0.0001
	Asthma	0.677	1.962 (1.133–3.399)	0.0162
	Down syndrome	3.398	30.886 (5.129–185.978)	0.0002
2.3	Age	0.057	1.059 (1.050–1.067)	<0.0001
	Male sex	0.389	1.475 (1.206–1.804)	0.0002
	Diabetes	0.498	1.646 (1.340–2.022)	<0.0001
	Previous acute myocardial infarction	-0.133	0.872 (0.540–1.407)	0.5742
	Chagas disease	0.335	1.399 (0.599–3.269)	0.4377
	Previous cardiac surgery	0.261	1.297 (0.690–2.438)	0.4191
	Valvopathy	0.395	1.479 (0.762–2.871)	0.247
	Congenital heart disease	1.636	5.134 (0.630–41.829)	0.1264
	Use of pacemaker	0.455	1.576 (0.653–3.807)	0.312
	Chronic neurological disease	0.926	2.523 (1.837–3.464)	<0.0001
	Chronic kidney disease	0.537	1.716 (1.108–2.657)	0.0156
	Chronic lung disease	0.582	1.787 (1.245–2.565)	0.0016
	Obesity	0.378	1.459 (1.162–1.834)	0.0012
	Immunosuppression	1.053	2.860 (1.915–4.272)	<0.0001

(*Contd...*)

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Supplementary Table 2. (*Continued*).

Model	Variables	Coefficient	Odds ratio (95% CI)	P
	Asthma	0.676	1.961 (1.132–3.396)	0.0162
	Down syndrome	3.389	30.615 (5.080–184.482)	0.0002
2.4	Age	0.057	1.058 (1.050–1.067)	<0.0001
	Male sex	0.386	1.469 (1.202–1.797)	0.0002
	Diabetes	0.499	1.647 (1.341–2.023)	<0.0001
	Chagas disease	0.322	1.380 (0.591–3.227)	0.4568
	Previous cardiac surgery	0.240	1.269 (0.678–2.375)	0.4553
	Valvopathy	0.406	1.496 (0.772–2.902)	0.2329
	Congenital heart disease	1.643	5.169 (0.635–42.078)	0.1246
	Use of pacemaker	0.453	1.572 (0.651–3.799)	0.3149
	Chronic neurological disease	0.926	2.524 (1.838–3.465)	<0.0001
	Chronic kidney disease	0.527	1.699 (1.098–2.628)	0.0173
	Chronic lung disease	0.578	1.781 (1.241–2.557)	0.0017
	Obesity	0.377	1.458 (1.161–1.832)	0.0012
	Immunosuppression	1.054	2.8621 (1.916–4.274)	<0.0001
	Asthma	0.679	1.966 (1.135–3.404)	0.0159
	Down syndrome	3.390	30.655 (5.093–184.506)	0.0002
2.5	Age	0.057	1.059 (1.051–1.067)	0.0002
	Male sex	0.382	1.463 (1.197–1.788)	<0.0001
	Diabetes	0.496	1.642 (1.337–2.017)	<0.0001
	Previous cardiac surgery	0.238	1.267 (0.677–2.371)	0.4588
	Valvopathy	0.418	1.515 (0.782–2.935)	0.2184
	Congenital heart disease	1.637	5.138 (0.631–41.813)	0.126
	Use of pacemaker	0.492	1.634 (0.6802–3.926)	0.2721
	Chronic neurological disease	0.925	2.520 (1.836–3.460)	<0.0001
	Chronic kidney disease	0.526	1.696 (1.096–2.624)	0.0177
	Chronic lung disease	0.577	1.778 (1.239–2.551)	0.0018
	Obesity	0.375	1.455 (1.158–1.828)	0.0013
	Immunosuppression	1.052	2.857 (1.912–4.268)	<0.0001
	Asthma	0.674	1.957 (1.130–3.390)	0.0165
	Down syndrome	3.394	30.784 (5.115–185.251)	0.0002
2.6	Age	0.057	1.059 (1.051–1.795)	0.0001
	Male sex	0.386	1.469 (1.202–1.795)	0.0002
	Diabetes	0.500	1.649 (1.343–2.025)	<0.0001
	Valvopathy	0.502	1.647 (0.880–3.085)	0.1189
	Congenital heart disease	1.700	5.454 (0.0664–44.824)	0.1144
	Use of pacemaker	0.676	1.964 (0.946–4.079)	0.0703
	Chronic neurological disease	0.917	2.501 (1.823–3.432)	<0.0001
	Chronic kidney disease	0.526	1.696 (1.096–2.623)	0.0177
	Chronic lung disease	0.576	1.776 (1.238–2.549)	0.0018
	Obesity	0.373	1.454 (1.157–1.826)	0.0013
	Immunosuppression	1.053	2.859 (1.913–4.273)	<0.0001
	Asthma	0.677	1.963 (1.134–3.398)	0.0159
	Down syndrome	3.441	32.301 (5.377–194.035)	0.0001
2.7	Age	0.057	1.059 (1.051–1.0667)	0.0001
	Male sex	0.386	1.469 (1.202–1.795)	0.0002
	Diabetes	0.488	1.630 (1.328–2.000)	<0.0001
	Congenital heart disease	1.834	6.240 (0.797–48.887)	0.0813
	Use of pacemaker	0.718	2.048 (0.987–4.251)	0.0544

(*Contd...*)

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Supplementary Table 2. (*Continued*).

Model	Variables	Coefficient	Odds ratio (95% CI)	P
	Chronic neurological disease	0.925	2.521 (1.838–3.457)	<0.0001
	Chronic kidney disease	0.547	1.732 (1.122–2.674)	0.0132
	Chronic lung disease	0.575	1.775 (1.238–2.546)	0.0018
	Obesity	0.370	1.449 (1.154–1.819)	0.0014
	Immunosuppression	1.069	2.907 (1.947–4.339)	<0.0001
	Asthma	0.674	1.956 (1.131–3.383)	0.0164
	Down syndrome	3.402	31.063 (5.192–185.855)	0.0002
2.8	Age	0.057	1.059 (1.051–1.798)	<0.0001
	Male sex	0.387	1.471 (1.204–1.798)	0.0002
	Diabetes	0.486	1.626 (1.325–1.995)	<0.0001
	Use of pacemaker	0.722	2.054 (0.987–4.274)	0.0542
	Chronic neurological disease	0.924	2.519 (1.837–3.456)	<0.0001
	Chronic kidney disease	0.558	1.750 (1.135–2.699)	0.0113
	Chronic lung disease	0.584	1.791 (1.250–2.566)	0.0015
	Obesity	0.359	1.4334 (1.142–1.799)	0.0019
	Immunosuppression	1.063	2.888 (1.935–4.309)	<0.0001
	Asthma	0.691	1.990 (1.154–3.430)	0.0133
	Down syndrome	3.945	54.208 (9.605–305.935)	<0.0001
2.9	Age	0.058	1.059 (1.051–1.067)	<0.0001
	Male sex	0.386	1.471 (1.205–1.797)	0.0002
	Diabetes	0.484	1.626 (1.325–1.994)	<0.0001
	Chronic neurological disease	0.922	2.515 (1.833–3.540)	<0.0001
	Chronic kidney disease	0.582	1.789 (1.162–2.753)	0.0082
	Chronic lung disease	0.590	1.803 (1.259–2.583)	0.0013
	Obesity	0.359	1.432 (1.141–1.798)	0.0019
	Immunosuppression	1.055	2.871 (1.925–4.282)	<0.0001
	Asthma	0.690	1.995 (1.158–3.437)	0.0129
	Down syndrome	4.007	54.980 (9.703-311.528)	<0.0001

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Supplementary Table 3. Complete multivariate analysis excluding arterial hypertension as a sole CVD diagnose (*n*=2675).

Model	Variables	Coefficient	Odds ratio (95% CI)	*P*
3.1	Age	0.056	1.058 (1.049–1.066)	<0.0001
	Male sex	0.372	1.451 (1.186–1.775)	0.0003
	Diabetes	0.470	1.601 (1.296–1.976)	<0.0001
	Chronic cardiovascular disease (without isolated arterial hypertension)	0.276	1.317 (0.959–1.810)	0.0891
	Isolated arterial hypertension	0.045	1.046 (0.829–1.321)	0.7028
	Chronic neurological disease	0.914	2.495 (1.819–3.423)	<0.0001
	Chronic kidney disease	0.527	1.693 (1.095–2.618)	0.0178
	Chronic lung disease	0.576	1.779 (1.241–2.550)	0.0017
	Obesity	0.357	1.428 (1.136–1.796)	0.0023
	Immunosuppression	1.044	2.842 (1.904—4.242)	<0.0001
	Asthma	0.692	1.997 (1.157–3.448)	0.013
	Down syndrome	3.914	50.117 (9.025–278.307)	<0.0001
3.2	Age	0.057	1.058 (1.050–1.067)	<0.0001
	Male sex	0.369	1.446 (1.183–1.768)	0.0003
	Diabetes	0.480	1.617 (1.318–1.983)	<0.0001
	Chronic cardiovascular disease (without isolated arterial hypertension)	0.246	1.279 (0.967–1.692)	0.0843
	Chronic neurological disease	0.914	2.495 (1.819–3.423)	<0.0001
	Chronic kidney disease	0.532	1.702 (1.102–2.631)	0.0166
	Chronic lung disease	0.576	1.780 (1.241–2.551)	0.0017
	Obesity	0.362	1.436 (1.143–1.803)	0.0018
	Immunosuppression	1.044	2.842 (1.904–4.241)	<0.0001
	Asthma	0.691	1.996 (1.156–3.445)	0.0131
	Down syndrome	3.918	50.306 (9.038–280.008)	<0.0001
3.3	Age	0.058	1.059 (1.051–1.067)	<0.0001
	Male sex	0.386	1.471 (1.205–1.797)	0.0002
	Diabetes	0.484	1.626 (1.325–1.994)	<0.0001
	Chronic neurological disease	0.922	2.515 (1.833–3.540)	<0.0001
	Chronic kidney disease	0.582	1.789 (1.162–2.753)	0.0082
	Chronic lung disease	0.590	1.803 (1.259–2.583)	0.0013
	Obesity	0.359	1.432 (1.141–1.798)	0.0019
	Immunosuppression	1.055	2.871 (1.925–4.282)	<0.0001
	Asthma	0.690	1.995 (1.158–3.437)	0.0129
	Down syndrome	4.007	54.980 (9.703-311.528)	<0.0001

CI: confidence interval

Multivariate regression analysis (models 1.2, 2.9, and 3.3)

- Accuracy = 1.000000E-007
- Log likelihood with all covariates = −1.249.044457
- Deviance with all covariates = 2.064.897119 df = 2128 rank = 11
- Akaike information criterion = 2.086.897119
- Schwartz information criterion = 2.156.914243
- Deviance with no covariates = 2.606.208712
- Deviance (likelihood ratio) Chi-square = 541.311593 df = 10 $P < 0.0001$
- Pseudo (McFadden) R-square = 0.207701
- Pseudo (likelihood ratio index) R-square = 0.178098
- Pearson Chi-square goodness of fit = 2.270.903793 df = 2128 $P = 0.0156$
- Deviance goodness of fit = 2.064.897119 df = 2128 $P = 0.8332$
- Hosmer–Lemeshow test = 11.319129 df = 8 $P = 0.1843$.

Final multivariate logistic equation

logit DEATH = −5.488214 +0.386201 male sex +0.057663 AGE +4.006971 Down syndrome +0.690494 Asthma +0.485909 diabetes +0.922279 chronic neurological disease +0.589728 chronic lung disease +1.054624 immunossuppresion +0.581579 chronic kidney disease +0.35937 obesity.

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Supplementary Table 4. Complete multivariate analysis specific to cardiac patients group(*n*=489).

Model	Variables	Coefficient	Odds ratio (95% CI)	*P*
4.1	Age	0.031	1.032 (1.013–1.050)	0.0006
	Troponin T	1.248	3.482 (2.147–5.648)	<0.0001
	Lactate dehydrogenase	1.267	3.551 (1.590–7.931)	0.002
	Hemoglobin	0.443	1.557 (0.983–2.464)	0.0589
	O2 saturation<95%	0.782	2.187 (1.109–4.313)	0.0239
	Creatinine	0.417	1.517 (0.964–2.387)	0.0715
	D-dimer	0.311	1.365(0.611–3.050)	0.4478
	Reactive C Protein	0.629	1.875 (0.413–8.521)	0.4156
	Lymphocytes	0.409	1.505 (0.956–2.367)	0.0773
	Dyspnea	0.312	1.366 (0.771–2.422)	0.2854
4.2	Age	0.032	1.033(1.014–1.051)	0.0004
	Troponin T	1.281	3.604 (2.238–5.806)	<0.0001
	Lactate dehydrogenase	1.283	3.607 (1.615–8.057)	0.0018
	Hemoglobin	0.445	1.560 (0.986–2.469)	0.0577
	O2 saturation<95%	0.776	2.173 (1.102–4.284)	0.0250
	Creatinine	0.410	1.507 (0.959–2.367)	0.0754
	Reactive C Protein	0.611	1.842 (0.405–8.383)	0.4294
	Lymphocytes	0.414	1.513 (0.962–2.381)	0.0729
	Dyspnea	0.315	1.370 (0.774–2.426)	0.2802
4.3	Age	0.033	1.033 (1.015–1.052)	0.0003
	Troponin T	1.259	3.523 (2.195–5.654)	<0.0001
	Lactate dehydrogenase	1.303	3.679 (1.654–8.184)	0.0014
	Hemoglobin	0.450	1.560 (0.986–2.470)	0.0575
	O2 saturation<95%	0.771	2.162 (1.099–4.255)	0.0256
	Creatinine	0.411	1.508 (0.960–2.368)	0.0746
	Lymphocytes	0.428	1.534 (0.977–2.409)	0.0629
	Dyspnea	0.315	1.370 (0.775–2.422)	0.2786
4.4	Age	0.033	1.034 (1.016–1.053)	0.0002
	Troponin T	1.268	3.554 (2.218–5.695)	<0.0001
	Lactate dehydrogenase	1.361	3.901 (1.757–8.662)	0.0008
	Hemoglobin	0.455	1.576 (0.997–2.492)	0.0517
	O2 saturation<95%	0.817	2.265 (1.160–4.420)	0.0166
	Creatinine	0.391	1.479 (0.944–2.318)	0.0878
	Lymphocytes	0.412	1.510 (0.962–2.368)	0.0728
4.5	Age	0.036	1.036 (1.018–1.054)	<0.0001
	Troponin T	1.392	4.025 (2.566–6.314)	<0.0001
	Lactate dehydrogenase	1.367	3.925 (1.768–8.713)	0.0008
	Hemoglobin	0.455	1.576 (0.999–2.487)	0.0505
	O2 saturation<95%	0.812	1.252 (1.151–4.405)	0.0177
	Lymphocytes	0.400	1.492 (0.953–2.338)	0.0804
4.6	Age	0.037	1.038 (1.020–1.056)	<0.0001
	Troponin T	1.404	4.073 (2.601–6.376)	<0.0001
	Lactate dehydrogenase	1.377	3.962 (1.788–8.780)	0.0007
	Hemoglobin	0.470	1.600 (1.015–2.520)	0.0428
	O2 saturation<95%	0.853	2.346 (1.202–4.577)	0.0124

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Multivariate regression analysis (model 4.6)

- Accuracy = 1.000000E-007
- Log likelihood with all covariates = −269.393055
- Deviance with all covariates = 243.737794 df = 233 rank = 6
- Akaike information criterion = 255.737794
- Schwartz information criterion = 282.073039
- Deviance with no covariates = 360.990989
- Deviance (likelihood ratio) Chi-square = 117.253195 df = 5 $P < 0.0001$
- Pseudo (McFadden) R-square = 0.324809
- Pseudo (likelihood ratio index) R-square = 0.178729
- Pearson Chi-square goodness of fit = 234.760647 df = 233 $P = 0.4553$
- Deviance goodness of fit = 243.737794 df = 233 $P = 0.3013$
- Hosmer-Lemeshow test = 7.548898 df = 8 $P = 0.4787$.

Final multivariate logistic equation

logit Death = −5.852544 +0.037406 age +0.852527 oxygen saturation above 95% +1.404269 troponin t +1.376706 lactate dehydrogenase +0.469787 hemoglobin.

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