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High risk coronavirus disease 2019: The primary results of the CoronaHeart multi-center cohort study

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ABSTRACT

Background: Patients with Coronavirus Disease 2019 (COVID-19) may present high risk features during hospitalization, including cardiovascular manifestations. However, less is known about the factors that may further increase the risk of death in these patients.
Methods: We included patients with COVID-19 and high risk features according to clinical and/or laboratory criteria at 21 sites in Brazil from June 10th to October 23rd of 2020. All variables were collected until hospital discharge or in-hospital death.
Results: A total of 2546 participants were included (mean age 65 years; 60.3% male). Overall, 70.8% were admitted to intensive care units and 54.2% had elevated troponin levels. In-hospital mortality was 41.7%. An interaction among sex, age and mortality was found (p = 0.007). Younger women presented higher rates of death than men (30.0% vs 22.9%), while older men presented higher rates of death than women (57.6% vs 49.2%). The strongest factors associated with in-hospital mortality were need for mechanical ventilation (odds ratio [OR] 8.2, 95% confidence interval [CI] 5.4–12.7), elevated C-reactive protein (OR 2.3, 95% CI 1.7–2.9), cancer (OR 1.8, 95 %CI 1.2–2.9), and elevated troponin levels (OR 1.8, 95% CI 1.4–2.3). A risk score was developed for risk assessment of in-hospital mortality.
Conclusions: This cohort showed that patients with COVID-19 and high risk features have an elevated rate of in-hospital mortality with differences according to age and sex. These results highlight unique aspects of this population and might help identifying patients who may benefit from more careful initial surveillance and potential subsequent interventional therapies.

1. Introduction

Risk prediction in patients hospitalized with Coronavirus Disease 2019 (COVID-19) is of great importance to inform medical

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decisions. Several clinical and laboratory factors have been associated with poor outcomes in COVID-19, especially the involvement of the cardiovascular system [1]. The main cardiovascular (CV) manifestations in patients hospitalized with COVID-19 include myocarditis, acute coronary syndrome and heart failure. Furthermore, myocardial injury, detected by elevated troponin levels, has also been reported and associated with high mortality among these patients during hospital stay [2–4]. Such manifestations may be due to decompensation of pre-existing CV diseases, since these conditions increases the risk of hospitalization due to severe forms of COVID-19 [5], or directly attributable to viral infection. Elevated D-dimer has been found to be an important prognostic tool in COVID-19, as it is a marker of disease severity in this population. Identifying patients with the highest risk of clinical deterioration is critical to enable early treatment strategies in the COVID-19 setting.

In Brazil, the COVID-19 outbreak led to over 540 thousand deaths up to July 2021 since the first case was confirmed on February 26th in 2020. Risk factors for poor prognosis in patients hospitalized with COVID-19 were reported in different Asian, European and North American countries [6,7]. However, COVID-19 patient profiles and clinical outcomes in Latin America need further investigation. Moreover, less is known about factors that may further increase the risk of death in patients who develop high risk features, including CV manifestations, during hospital admission. Using a large nationwide cohort of patients with COVID-19 and high risk features, we aimed to a) describe clinical and laboratory characteristics of these patients, b) describe clinical outcomes of this population, c) evaluate predictors of death, and d) build a risk score to identify patients who are likely to die during hospitalization.

2. Methods

2.1. Study design and participants

This is a multicenter, retrospective, observational study. This study was approved by the National Research Ethics Committee and by the local Institution Review Boards of each site. The informed consent form was waived owing to the use of retrospective data.

We included patients with suspected or confirmed COVID-19 who developed high risk features during hospitalization at 21 sites in Brazil from 10 June 2020 to 23 October 2020. A highly suspected case of COVID-19 was defined as a patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath) and radiological evidence showing lesions compatible with COVID-19. In the confirmed cases, the diagnosis of COVID-19 was performed by either a positive result of a SARS-CoV-2 polymerase chain reaction (PCR) assay for nasal and pharyngeal swab specimens or positive serologic tests (IgM or IgG assays), according to local laboratories and practices. To be enrolled, patients could had been admitted to the general wards or to intensive care units (ICU).

High risk features during hospitalization were defined as presenting with any of the following: a) troponin levels above the 99 percentile the upper reference value, b) brain natriuretic peptide (BNP) levels > 300 pg/mL, c) NT-proBNP levels > 1500 pg/mL, d) D-dimer levels>3 times the upper limit of normal, e) new alterations in the echocardiogram (myocardial dysfunction, pericardial effusion or segmental dysfunction), f) alterations in the electrocardiogram suggestive of myocardial ischemia or pericarditis, and g) occurrence of bradyarrhythmias, tachyarrhythmias, cardiogenic shock, heart failure or acute coronary syndromes.

2.2. Data collection and follow-up

Data on demographic characteristics, medical history, clinical presentation, laboratory results within the first 48 hours of hospital admission, and clinical outcomes were assessed through medical records and collected in a case report form by local investigators who were trained by the study team. Participants had their data collected until hospital discharge and/or in-hospital death. No intervention was carried out through this study. All data collected was reviewed by the study team, to assure data quality. The registry utilized a web-based case report form in the RedCap System.

2.3. Clinical outcomes

We describe in-hospital events including all-cause death, admission to the ICU, need for mechanical ventilation, vasopressor use, need for dialysis, hospitalization length of stay and length of ICU stay.

2.4. Statistical analysis

Categorical variables were reported as percentages and continuous variables as mean and standard deviation or median (interquartile range). The cohort was described comparing male and female patients. Their profile was compared using chi-square tests for categorical variables and Mann-Whitney tests for most continuous variables, unless highlighted otherwise in the tables.

Baseline characteristics were completed in 2496 (98.1%) patients, and missing data were imputed via chained equations method, using the package *mice* [8]. The interaction between sex and age on mortality was identified in Kaplan-Meier curves and bar charts according to age quantiles. Multivariate logistic regression analysis for in-hospital mortality were presented considering baseline factors and laboratory findings. As not all baseline laboratorial tests were available in the whole population, the multivariable analysis was carried out with a subsample of 1.323 patients. Additional models including the overall population are available in the supplemental material. A nomogram was formulated based on the results of the final model using the *rms* package [9]. All analyses were done with R 4.0.2 software (R Core Team, Vienna, Austria, 2020) [10].

3. Results

3.1. Study population

A total of 2546 participants were included, of whom 90.5% had COVID-19 diagnosis confirmation by either PCR or serologic assays. The remaining 241 cases were defined as highly suspected cases that fulfilled inclusion criteria for clinical symptoms and chest tomography results. Demographical and clinical characteristics in the overall cohort and stratified by sex are presented in Table 1. The mean age was 64.8 years and 60.3% were male. The median time between symptom onset and hospital admission was 7 (3 – 10) days. Initial symptoms such as fever and cough were more frequent in men than women, while fatigue, anosmia, and gastrointestinal symptoms were more common in women. A total of 66.6% had prior history of hypertension, 39.5% diabetes, 20.0% obesity, 19.7% prior smoking, 16.2% heart failure, and 15.2% coronary artery disease. Women had more frequently hypertension and obesity than men, while men were more frequently current or prior smokers and had more commonly coronary artery disease than women. Overall, 68.7% needed oxygen therapy at admission.

Table 1
Demographic and clinical characteristics stratified by sex.

Baseline characteristics	Overall (n = 2546)	Women (n = 1011)	Men (n = 1535)	p-value
Age (years)	64.8 ± 14.9	65.8 ± 15.5	64.2 ± 14.5	0.01*
Symptoms				
Cough	1585 (62.3)	600 (59.3)	985 (64.2)	0.02
Fever	1295 (50.9)	482 (47.7)	813 (53)	0.01
Dyspnea	1772 (69.6)	683 (67.6)	1089 (70.9)	0.08
Chest pain	159 (6.2)	70 (6.9)	89 (5.8)	0.29
Myalgia	529 (20.8)	221 (21.9)	308 (20.1)	0.30
Fatigue	484 (19)	220 (21.8)	264 (17.2)	0.01
Anosmia	70 (2.7)	43 (4.3)	27 (1.8)	<0.01
Rhinorrhea	210 (8.2)	78 (7.7)	132 (8.6)	0.47
Sore throat	84 (3.3)	25 (2.5)	59 (3.8)	0.08
Loss of taste	162 (6.4)	70 (6.9)	92 (6)	0.39
Gastrointestinal symptoms	367 (14.4)	172 (17)	195 (12.7)	<0.01
Comorbidities				
Hypertension	1696 (66.6)	705 (69.7)	991 (64.6)	<0.01
Diabetes	1006 (39.5)	416 (41.1)	590 (38.4)	0.18
Smoking	154 (6)	49 (4.8)	105 (6.8)	0.05
Previous smoking	502 (19.7)	158 (15.6)	344 (22.4)	<0.01
Obesity	509 (20)	254 (25.1)	255 (16.6)	<0.01
Renal disease on dialysis	120 (4.7)	45 (4.5)	75 (4.9)	0.68
Prior coronary disease	390 (15.3)	123 (12.2)	265 (17.3)	<0.01
Heart Failure	412 (16.2)	181 (17.9)	231 (15.0)	0.06
Atrial fibrillation	326 (12.8)	131 (13.0)	195 (12.7)	0.90
Prior cardiovascular disease	829 (32.6)	316 (31.3)	513 (33.4)	0.27
Cancer	242 (9.5)	100 (9.9)	142 (9.3)	0.64
Chronic obstructive pulmonary disease	187 (7.3)	67 (6.6)	120 (7.8)	0.29
Prior stroke	169 (6.6)	69 (6.8)	100 (6.5)	0.82
Oxygen support at admission				
None	575 (22.6)	230 (22.7)	345 (22.5)	0.88
Oxygen by nasal cannula	1087 (42.7)	425 (42.0)	662 (43.1)	
Non-invasive ventilation	46 (1.8)	21 (2.1)	25 (1.6)	
High-flow devices	22 (0.9)	9 (0.9)	13 (0.8)	
Mechanical ventilation	593 (23.3)	231 (22.8)	362 (23.6)	
Prior medications				
ACE inhibitors/ ARBs	946 (37.2)	387 (38.3)	559 (36.4)	0.36
Statins	665 (26.1)	269 (26.6)	396 (25.8)	0.68
Aspirin/Clopidogrel	485 (19.0)	171 (16.9)	314 (20.5)	0.03
Beta-blocker	711 (27.9)	289 (28.6)	422 (27.5)	0.58
Diuretics	645 (25.3)	304 (30.1)	341 (22.2)	<0.01

(*) T-test
ACE denotes angiotensin-converting enzyme; ARB aldosterone receptor blocker.

Regarding the high risk criteria, a total of 54.2% had troponin elevation, 10.2% had BNP/NT-proBNP elevation, 12.6% presented with decompensated heart failure, 9.3% atrial fibrillation, 6.0% alterations in the echocardiogram, 5.7% acute coronary syndromes, 4.5% arrhythmias, and 2.1% cardiogenic shock. In addition, 57.7% had D-dimer elevation.

3.2. Laboratory findings at hospital admission

The laboratory findings at hospital admission stratified by sex are presented in Table 2. The median elevation in C reactive protein levels was 21.2 (9 – 41.5) times the upper limit of normal (ULN), while for troponin levels it was 2.1 (1 – 6.5) times the ULN and for D-dimer levels it was 3.3 (1.6 – 9.4) times the ULN. Among patients with troponin measures available within 48 hours from admission (n = 1816), the median (25th and 75th percentiles) elevation was 2.1 (1.0 – 6.5) times the ULN. Among patients included in the study with cardiovascular manifestations other than troponin elevation (n = 1165), 593 had troponin values available with median (25th and 75th percentiles) of 1.0 (0.7–3.8) times the ULN.

3.3. Clinical outcomes

Clinical outcomes are presented in Table 3. Median hospitalization was 14 (8–24) days. Overall, admission to the ICU occurred in 70.8% and median length of ICU stay was 6 (0–14) days. Length of ICU stay among survivors was 2 (0–11) days and among non-survivors was 9 (4–18) days. Need for mechanical ventilation

Table 2
Laboratory findings stratified by sex.

Laboratory findings	Overall	Women	Men	p-value*
Creatinine	1.2 (0.9–2)	1.1 (0.8–1.9)	1.2 (0.9–2.1)	<0.01
Hemoglobin	12.3 (10.6–13.7)	11.5 (10.0–12.9)	12.8 (11.0–14.2)	<0.01
Lymphocytes	910 (599.2–1304.5)	980 (662.2–1416.8)	870 (560.0–1236.2)	<0.01
Neutrophils	6600 (4097.8–10268.8)	6680 (4160–10126)	6570 (4071.5–10295.5)	0.75
Platelets ($x10^3$)	200.7 (147.0–270.0)	215.5 (163.0–287.0)	192.0 (138.6–257.0)	<0.01
C-reactive protein(x ULN)	21.2 (9.0–41.5)	19.6 (8.4–39.3)	22.2 (10.1–42.6)	0.06
Troponin (x ULN)	2.1 (1.0–6.5)	2.1 (1.0–6.6)	2.1 (1.0–6.4)	0.96
D-dimer (x ULN)	3.3 (1.6–9.4)	3.3 (1.6–8.5)	3.3 (1.6–10.4)	0.77

(*) Mann-Whitney Test.
ULN denotes upper limit of normal.

Table 3
Clinical Outcomes by sex.

Outcomes	Overall n (%)	Women n (%)	Men n (%)	p-value
In-hospital mortality	1062 (41.7)	410 (40.6)	652 (42.5)	0.36
Admission to intensive care unit	1802 (70.8)	677 (67.0)	1125 (73.3)	<0.01
Need for mechanical ventilation	1169 (45.9)	448 (44.3)	721 (47)	0.20
Vasopressor use	1313 (51.6)	498 (49.3)	815 (53.1)	0.06
Dialysis	654 (25.7)	220 (21.8)	434 (28.3)	<0.01
Length of stay*	14 [8 –24]	13 [8 –24]	14 [8 –25]	0.07
Length of ICU stay*	6 [0–14]	5 [0–14]	6 [0–15]	<0.01

*Length of hospital stay and length of ICU stay are presented as median [25th and 75th percentiles], and compared with Mann-Whitney test.
ICU denotes intensive care unit.

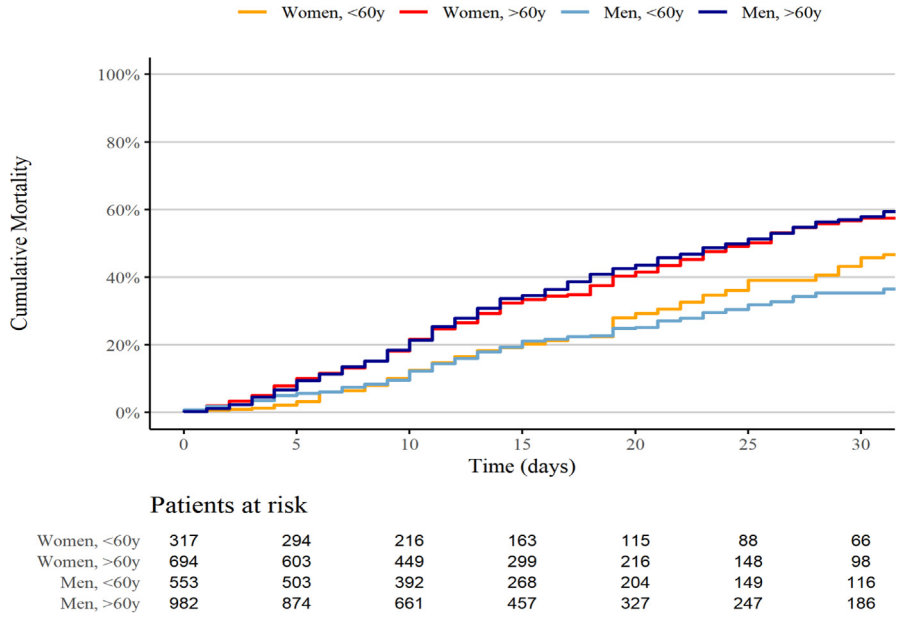

Fig. 1. In-hospital mortality rates by age categories and sex.

occurred in 45.9%, for vasopressors in 51.6%, and for dialysis in 25.7%. The overall in-hospital mortality rate was 41.7%. Men were more frequently admitted to the ICU than women (73.3% vs 67.0%; p = 0.001), and more commonly needed dialysis (28.3% vs 21.8%; p < 0.001). Kaplan Meier curves for in-hospital mortality stratified by age (>or < 60 years) and sex are presented in Fig. 1.

3.4. Predictors of in-hospital mortality

Several clinical and laboratory variables were associated with in-hospital mortality in the univariate analysis (Supplemental Tables 1 and 2). The cutoff points with the highest discrimination for in-hospital mortality prediction among biomarkers were: 2.17 times ULN for troponin levels, 4.34 times ULN for D-dimer and 22.7 times ULN for CRP (Supplemental Fig. 1).

In the multivariable analysis, increasing age, oxygen support at admission, active or prior cancer, presence of myalgia at admission, D-dimer levels > 4.4 times the ULN, troponin levels > 2 times the ULN, CRP levels > 20 times the ULN, and decreasing platelets levels were associated with higher in-hospital mortality (Table 4). The AUC was 0.78. Other two models were built with similar findings and are presented in Supplemental Tables 3 and 4, including the overall cohort (N = 2546) and the cohort with biomarkers available (N = 1395).

Table 4
Multivariate logistic regression model for prediction of in-hospital death in patients with COVID-19 and CV manifestations with laboratory tests available.

Variables	OR [95 %CI]	p-value
Male sex	0.32 [1.00–1.08]	0.07
Age, years	1.02 [1.00–1.03]	0.01
Oxygen need at admission*		
Oxygen by nasal cannula	3.58 [2.46–5.30]	<0.01
Non-invasive ventilation	5.45 [2.16–14.03]	<0.01
High-flow devices	5.89 [1.60–22.45]	0.01
Mechanical ventilation	8.22 [5.44–12.65]	<0.01
Cancer	1.87 [1.20–2.91]	<0.01
Myalgia at admission	0.64 [0.48–0.87]	<0.01
D-dimer elevated > 4.4 × ULN	1.29 [0.99–1.69]	0.06
Troponin elevated > 2.0 × ULN	1.77 [1.37–2.29]	<0.01
C-reactive protein elevated > 20 × ULN	2.25 [1.72–2.94]	<0.01
Platelets	0.10 [1.00–1.00]	<0.01
Interaction between sex and age	1.02 [1.00–1.04]	0.04
Area under curve	0.78	

(*) No oxygen support as reference.
OR denotes odds ratio; ULN upper limit of normal.

A significant interaction between sex, age and mortality was found (interaction p = 0.007). Younger women presented higher rates of death than men (30.0% vs 22.9%), while older men presented higher rates of death than women (57.6% vs 49.2%) (Fig. 2).

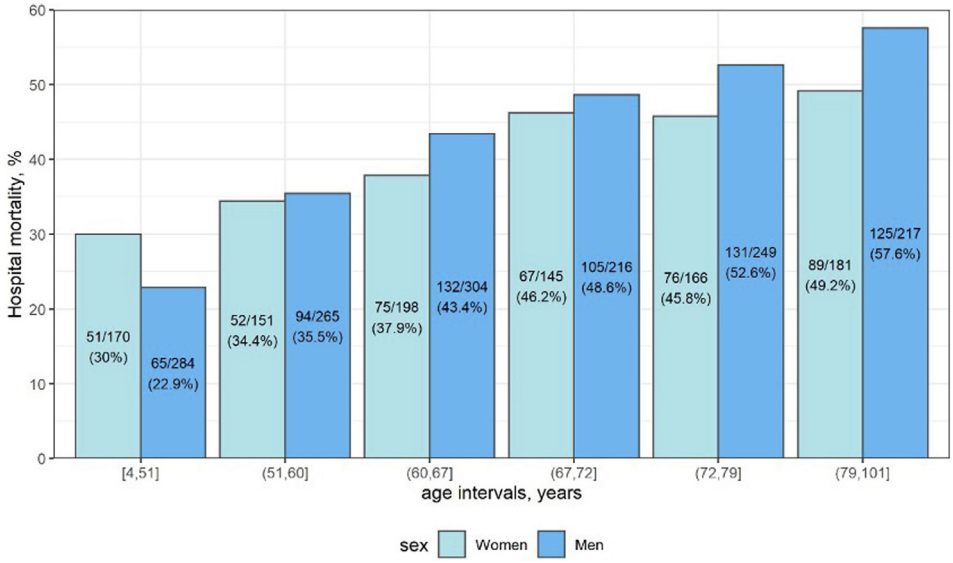

Fig. 2. In-hospital mortality rates by sex and age intervals.

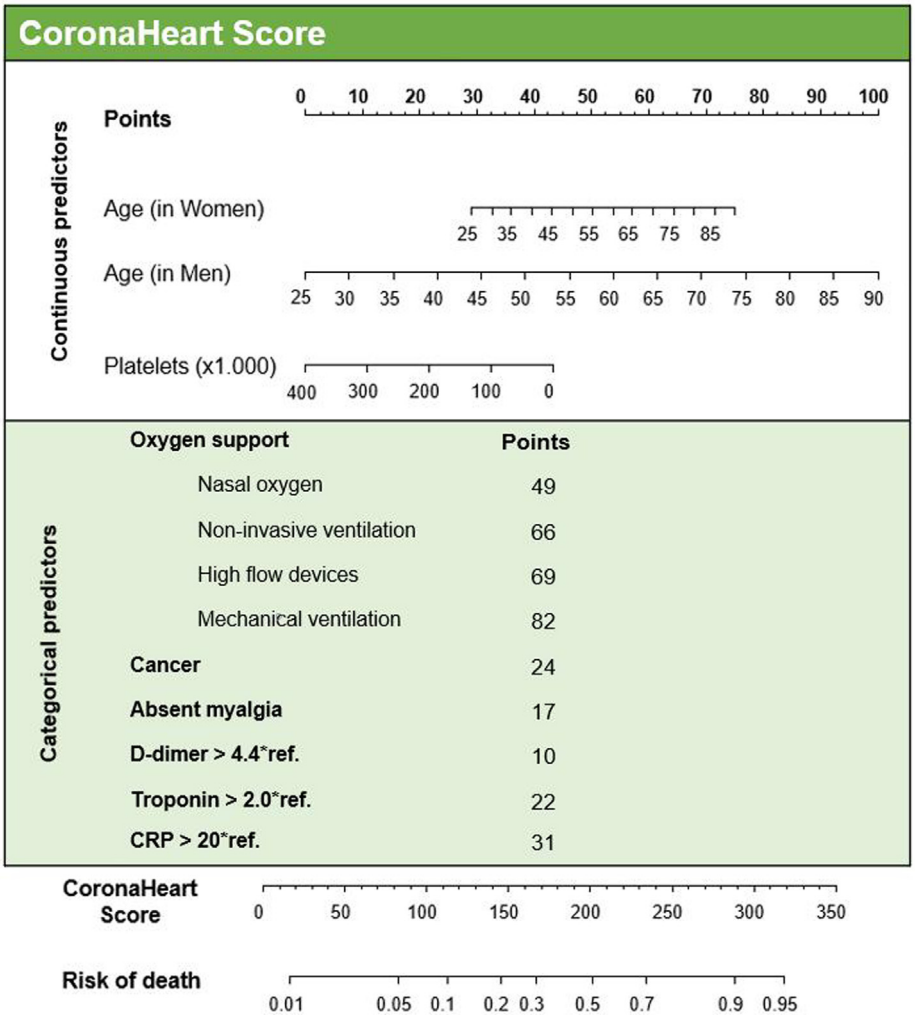

Fig. 3. The CoronaHeart Risk Score. CRP denotes C-reactive protein; ref., reference value.

3.5. Risk score for in-hospital mortality

The CoronaHeart Risk Score was constructed based on the coefficients from the logistic model. A nomogram was developed to help clinicians to calculate the likelihood that a patient with COVID-19 and high risk features will have a poor outcome (Fig. 3).

4. Discussion

Our study has four main findings. First, we observed a high mortality rate among COVID-19 patients who present with high risk features during hospitalization. Second, although the overall mortality was not different between males and females, younger women presented higher rates of death than men, while older men presented higher rates of death than women. Third, several variables were independently associated with in-hospital mortality. Finally, a risk score was built in order to help clinicians identifying patients at higher risk of adverse outcomes.

In Chinese cohorts, the mortality rate among COVID-19 patients with elevated troponin levels varied from 51.2 to 59.6%, reaching 69.4% in those who had history of CV diseases [11,12]. In Italy, a death rate of 37.4% was observed in 614 patients admitted due to COVID-10 who presented with elevated troponin levels [13]. In Brazil, we found a 41.7% mortality rate among patients with COVID-19 and high risk features, including CV manifestations at hospitalization. In our study, however, only 54.2% had troponin elevation. One can assume that our mortality rate could be inferior to those studies. On the other hand, the present study had over 16% of patients with prior heart failure and over 27% with previous CV disease. Therefore, our fatality rate was equivalent to the one seen in these other cohorts. Lala et al. showed that troponin levels were generally mildly elevated at admission in a large cohort of New York City patients hospitalized with COVID-19 [14]. Our results are in accordance with this finding, since troponin levels were in median 2.1 times the ULN elevated in our cohort. The pathophysiological mechanisms to explain myocardial injury in COVID-19 are not entirely elucidated. For instance, the direct viral damage in the myocardial tissue, marked systemic inflammatory response, hypoxia, endothelial injury, and thrombogenesis have been suggested as possible explanations [1].

Prior studies with COVID-19 patients observed higher rates of death among men, compared with women [15,16]. A potential protective role of elevated estrogen levels has been suggested. In our study, with adequate representativity of female patients, the overall in-hospital mortality was similar between men and women. Rates of death were also similar among men and women admitted due to Covid-19 in Italy [17]. However, interestingly, in our study, younger women presented higher rates of death than men, while older men presented higher rates of death than women. The reasons behind these findings are unknown, but could be explained, at least in part, by a potential protected effect of testosterone in younger men. It has been previously shown that lower levels of testosterone were associated with worse prognosis in men admitted due to COVID-19 [18]. Our results may suggest that a special medical attention should be given to younger female and older male patients when admitted with COVID-19 and high risk features are present. However, these findings deserve further exploration in other studies.

Studies showed that biomarker elevation, imaging results, and several clinical characteristics predict poor outcomes in patients with COVID-19[2]. Increasing age, elevated troponin levels and the presence of hypoxia are variables commonly associated with mortality in COVID-19 [19–21]. In addition to these variables, we found that elevated CRP and history of cancer at admission were associated with death. The presence of pulmonary hypertension, as defined by an estimated systolic pulmonary artery pressure>35 mmHg, was associated with worse in-hospital outcomes in COVID-19 patients [22]. Coronary artery calcium and thoracic aortic calcium assessed by chest computed tomography (CT) were also predictors of death in patients admitted due to COVID-19 undergoing chest CT for assessment of pneumonia [23].

Liang et al. utilized data from 1590 patients with COVID-19 in China to build a risk score to predict the risk for developing critical illness, defined as admission in the ICU, need for mechanical ventilation or death [24]. Increasing age and history of cancer were common predictors of poor outcomes among their cohort and ours. The role of smoking in respiratory deterioration in COVID-19 patients has been debated. Our cohort comprised 6% of patients who were active smokers, which is somewhat lower than the observed rate of smoking in the overall Brazilian population [25].

We developed the CoronaHeart Risk Score to help clinicians in the early assessment of risk for poor prognosis and guide level of care for patients with COVID-19 and high risk features. Using this risk score, a man aged 60 years, with platelet levels of 200.000, admitted with need for oxygen via nasal cannula, and elevated D-dimer levels would have a 15% likelihood of in-hospital death. On the other hand, a woman aged 35 years, admitted with need for mechanical ventilation, platelet levels of 100.000, elevated troponin and CRP would have a 50% likelihood of death.

5. Limitations

We recognize some important limitations of this study. As an observational study, our results should be interpreted as hypothesis-generating. Some participants were included without a PCR or serologic confirmation of COVID-19 infection. However, we do not believe this has a major impact on our results, since these patients represent only 9.5% of our study population. Not all participants had laboratory results available, since the study was observational in nature, which reflects clinical practice throughout the country. Biomarkers were available for around half of the participants and were used for the risk score development. Also, different assays were used at each hospital, therefore we could only categorize patients by how many times the ULN the test result was elevated. Conversely, this categorization may be more useful in clinical practice for risk prediction than establishing a specific cutoff for each biomarker. In addition, we did not collect systematically treatments administered during hospitalization. The total number of patients admitted due to COVID-19 in the participant hospitals was not systematically collected either. Finally, medical care varied across the country and recommended therapies for COVID-19 changed during the study period.

6. Conclusions

This large cohort showed that patients with COVID-19 and high risk features have an elevated rate of in-hospital mortality with important differences according to age and sex. We developed the CoronaHeart risk score with 9 variables to help clinicians in identifying patients who may benefit from more careful initial surveillance and potential subsequent interventional therapies.

7. Sources of funding

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8. Disclosures

R.D.L. reports receiving consulting fees from Bayer, Bristol-Myers Squibb, Boehringer Ingleheim, Daiichi Sankyo, Glaxo Smith Kline, Medtronic, Merck, Portola, Sanofi, and Pfizer, and receiving institutional grant support from Bristol-Myers Squibb, Glaxo Smith Kline, Medtronic, Pfizer and Sanofi. F. A. C. reports receiving honoraria from Bayer. D.C. reports receiving honoraria from Bayer, Janssen, Daiichi Sankyo and Stago. E.F. reports receiving research fees from AstraZeneca, Pfizer, Novartis, Bayer and Amgen. All other authors have no disclosures.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100853.

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