Impact of Age, Sex, and Cardiovascular Disease in Mortality in COVID-19 at the Medical City

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Abstract

INTRODUCTION: COVID-19 (coronavirus disease 2019), which is caused by the human severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), has reached a pandemic level. As a novel disease, local epidemiologic data are important to determine high-risk age groups, as well as risk factors that contribute to mortality. This study is a retrospective cohort study of 182 COVID-19–positive patients confirmed by real-time polymerase chain reaction. Baseline demographics and data on the preexisting cardiovascular comorbidities of 182 COVID-19 patients were collected by chart review and underwent statistical analysis using STATA 14 software (StataCorp, College Station, Texas). In the study, the majority of COVID-19 patients were 61 years or older (44.5%), with a higher prevalence of individuals 61 years or older among those who died (68.4%) compared with survivors (38.2%) ($P = 0.005$). In terms of gender, half of the patients were male (57.7%). In terms of cardiovascular disease, the most prevalent was hypertension (48.3%), followed by diabetes (28.0%). The prevalence of coronary artery disease (CAD) was significantly higher among patients who died (15.8%) compared with survivors (2.8%) ($P = 0.022$). In the univariate logistic regression analysis, older age was significantly associated with increased odds for mortality (odds ratio, 1.06; 95% confidence interval, 1.03–1.09). In terms of comorbidities, having CAD was significantly associated with increased odds for mortality (odds ratio, 6.6; 95% confidence interval, 1.7–24.6). Other variables were not significantly associated with mortality. In our study, advanced age and the presence of underlying CAD have been associated with an increased risk of in-hospital mortality among COVID-19 patients.

KEYWORDS: age, cardiovascular disease, COVID-19, mortality, sex

INTRODUCTION

A disease, first detected in Wuhan, China, with flulike symptoms and with an unknown cause was reported to China's World Health Organization (WHO) Office on December 31, 2019. In only 1 month, the new virus spread fast worldwide, with approximately at least 6000 confirmed cases in January 2020. With this, the WHO declared the outbreak to be a Public Health Emergency of International Concern on January 30, 2020, and in less than 2 months, on March 11, it was then declared to be a pandemic by the WHO Director General. This new coronavirus disease was named COVID-19 (coronavirus disease 2019) on February 11 by the WHO.[1,2] COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2. The spectrum of illness ranges from mild signs and symptoms of flu to severe pneumonia and eventually leading to respiratory failure.[3] The virus has a high rate of transmission and affects all age groups. In new diseases, such as the COVID-19, epidemiological studies are very important to assess its etiology, as well to understand how it affects the population based on specific risk factors. However, local studies are limited as to how it affects the local setting. Early case reports and series from China had associated older age, male sex, and presence of comorbidities with increased risk of death in patients with COVID-19 infections.[4] Presence of coexisting cardiovascular medical conditions was also associated with an increased risk of morbidity and mortality. In the study by Gu et al,[5] the estimated mortality risk in patients with coronary heart disease (CHD) is three times more than those without CHD. In addition, patients with preexisting CHD (65 years old, female, with no other comorbidities) had a lower estimated 30-day survival probability as compared with those without CHD.[5] Studies from 169 hospitals in Asia, Europe, and North America have evaluated the relationship of cardiovascular disease and drug therapy with in-hospital death among hospitalized patients with COVID-19 and also showed that advanced age and cardiovascular diseases, including coronary artery disease (CAD), heart failure, and cardiac arrhythmia, were found independently associated with an increased risk of hospital death.[6] The objectives of this study were to determine the association between mortality and age, sex, or presence of cardiovascular diseases among COVID-19 patients, specifically the in-hospital mortality rate among COVID-19 patients and the risk of in-hospital mortality attributed to age, sex, or presence of cardiovascular disease among COVID-19 patients.

METHODS

This is a retrospective ambispective cohort study. Charts of patients admitted with an impression of COVID-19 were reviewed. Included in the analysis were all adult patients 18 years or older admitted and diagnosed with confirmed COVID-19 infection through a positive real-time polymerase chain reaction nasal and oropharyngeal swab result. Patients with symptoms of possible COVID-19 infection but with a negative real-time polymerase chain reaction swab test, underlying respiratory diseases (eg, asthma, chronic obstructive pulmonary disease), underlying malignancy, chronic renal disease, or acute kidney injury not secondary to COVID-19 infection were excluded from the study. Baseline demographics and preexisting cardiovascular disease of patients were collected. All data collected underwent statistical analysis using STATA 14 software (StataCorp, College Station, Texas). In-hospital mortality rates separated individually by sex and age groups were also computed along with a 95% confidence interval (CI). Bivariate analysis was conducted using a χ^2 test and simple logistic regression prior to multiple logistic regression to determine the association between in-hospital mortality and age, sex, and presence of the cardiovascular diseases among COVID-19 patients.

RESULTS

The majority of patients were 61 years or older (44.5%). Also, there was a significantly higher prevalence of individuals 61 years or older among those who died (68.4%) compared with survivors (38.2%) ($P = 0.005$). Almost half of the participants were male (57.7%). In terms of cardiovascular disease, the most common was hypertension (48.3%), followed by diabetes (28.0%). The prevalence of CAD was significantly higher among patients who died (15.8%) compared with survivors (2.8%) ($P = 0.022$). Also, the prevalence of patients with underlying cardiac arrhythmias was significantly higher among patients who died (13.2%) compared with survivors (0%) ($P = 0.000$). No other significant differences were observed in terms of cardiovascular disease. In terms of cardiovascular drug therapy, the most commonly used was statins (31.4%), followed by angiotensin receptor blocker (19.2%). The prevalence of aspirin use was significantly higher among patients who died (18.4%) compared with survivors (6.9%) ($P = 0.031$). The prevalence of current smoking was found to be 3.8% only, whereas the prevalence of alcohol drinking was 8.2% (Figures 1 and 2). The patients who died and those who survived did not differ significantly in terms of sex ($P = 0.691$), smoking status ($P = 0.293$), and alcohol drinking ($P = 0.315$) (Table 1).

In the univariate logistic regression analysis, older age was significantly associated with increased odds for mortality (odds ratio [OR], 1.06; 95% CI, 1.03–1.09). Also, having CAD was significantly associated with increased odds for mortality (OR, 6.6; 95% CI, 1.7–24.6). Other variables were not significantly associated with mortality (Figures 3–5). In the multiple regression analysis, both age (OR, 1.05; 95% CI, 1.02–1.09) and CAD (OR, 4.9; 95% CI, 1.9–17.2) were significantly associated with increased odds for mortality after controlling for other variables (Table 2).

DISCUSSION

Our study confirms the results of previous epidemiologic studies in the relationship of age and underlying cardiovascular comorbidities to mortality in patients with COVID-19. Age in our study starting from 50 years or older has been associated independently with increased mortality in patients with COVID-19. A possible mechanism for this is that, as usual in aging, there is a gradual decline in immune function called "immunosenescence," which decreases pathogen recognition, alert signaling, and clearance. Another mechanism proposed as to why old age is associated with increased mortality among COVID-19 is the chronic increase in systemic inflammation

Table 1. Characteristics of Patients Included in the Study

Variable	Total No. of Patients N = 182	Survived n = 144 (78.0%)	Mortality n = 38 (22.0%)	*P*
Age				
18–30 y	12 (6.6)	12 (8.3)	0 (0.0)	0.005
31–50 y	39 (21.4)	35 (24.3)	4 (10.5)	
51–60 y	50 (27.5)	42 (29.2)	8 (21.0)	
≥61 y	81 (44.5)	55 (38.2)	26 (68.4)	
Sex				
Male	105 (57.7)	82 (56.9)	23 (60.5)	0.691
Female	77 (42.3)	62 (43.1)	15 (39.5)	
Presence of cardiovascular disease				
Coronary artery disease	10 (5.5)	4 (2.8)	6 (15.8)	0.002
Congestive heart failure	6 (3.3)	4 (2.8)	2 (5.3)	0.606
Atrial fibrillation	7 (3.8)	4 (2.8)	3 (7.8)	0.160
Hypertension	88 (48.3)	65 (45.1)	23 (60.5)	0.091
Hyperlipidemia	15 (8.2)	10 (6.9)	5 (13.2)	0.315
Diabetes	51 (28.0)	38 (26.4)	13 (34.2)	0.417
Other cardiac arrhythmias	5 (2.8)	0 (0.0)	5 (13.2)	0.000
Vascular disease (PE, DVT)	1 (0.5)	0 (0.0)	1 (2.6)	0.209
Valvular heart disease	0 (0.0)	0 (0.0)	0 (0.0)	n/a
Cardiovascular drug therapy				
Aspirin	17 (9.3)	10 (6.9)	7 (18.4)	0.031
P2Y12 inhibitor	6 (3.3)	3 (2.1)	3 (7.9)	0.074
Direct oral anticoagulant	2 (1.1)	1 (0.7)	1 (2.6)	0.375
ARB	35 (19.2)	27 (18.8)	8 (21.0)	0.749
β-Blocker	15 (8.2)	12 (8.3)	3 (7.9)	1.000
Statins	39 (31.4)	27 (18.8)	12 (31.6)	0.118
Smoking				
Current	7 (3.8)	4 (2.8)	3 (7.9)	0.293
Past	7 (3.8)	5 (3.5)	2 (5.3)	
Never	168 (92.3)	135 (93.7)	33 (86.4)	
Alcohol drinking				
Never	167 (91.8)	134 (93.1)	33 (86.8)	0.315
Seldom	15 (8.2)	10 (6.9)	5 (13.2)	

ARB=angiotensin receptor blocker; DVT=deep vein thrombosis; PE=pulmonary embolism.

Table 2. Association of Age, Sex, and Cardiovascular Disease With Mortality Among COVID-19 Patients

	Univariate Regression		Multiple Regression	
Variable	**Odds Ratio (95% Confidence Interval)**	***P***	**Odds Ratio (95% Confidence Interval)**	***P***
Age	1.06 (1.03–1.09)	0.000	1.05 (1.02–1.09)	0.002
Sex				
Male	Reference	—	Reference	—
Female	0.9 (0.4–1.8)	0.691	0.8 (0.3–1.9)	0.581
Presence of cardiovascular disease				
None	Reference	—	Reference	—
Coronary artery disease	6.6 (1.7–24.6)	0.005	4.9 (1.9–17.2)	0.042
Congestive heart failure	1.9 (0.3–11.0)	0.453	0.4 (0.04–5.4)	0.520
Atrial fibrillation	3.0 (0.6–14.0)	0.163	2.2 (0.3–14.2)	0.408
Hypertension	1.9 (0.9–1.9)	0.094	0.9 (0.4–2.2)	0.883
Hyperlipidemia	2.0 (0.6–6.3)	0.223	1.2 (0.3–4.6)	0.781
Diabetes	1.5 (0.7–3.1)	0.341	1.2 (0.5–2.9)	0.664

ARB=angiotensin receptor blocker; DVT=deep vein thrombosis; PE=pulmonary embolism.

called "inflammaging," which arises from an overactive, yet ineffective alert system.[7] In COVID-19, the ability to control the viral load and regulate the immune response is one of the best prognosticators of whether a patient will have mild or severe symptoms, and with aging, this regulation of the immune response is decreased.[8]

In our study, the majority of our patients who had cardiovascular disease are in the older age group. Hypertension and diabetes were the major cardiovascular comorbidities present among COVID-19 patients. However, there were no associations with mortality among COVID-19 patients with hypertension, diabetes mellitus, and other cardiovascular comorbidities except for CAD. This somehow shows some contrasts with findings in the previous studies suggesting that COVID-19 patients with underlying cardiovascular comorbidities, particularly heart failure, type 2 diabetes mellitus, and arrhythmias, are at increased risk of mortality.[6] This could be probably due to the small sample size of our study, which was done in a single-center institution as compared with some previous studies that included multiple institutions and database and therefore had a bigger sample sizes. Also, we did not include in our analysis the level of control of these cardiovascular comorbidities, which in previous studies was associated with the increased mortality (eg, blood pressure, glycemic control). Stable CAD in patients with COVID-19 may have an increased mortality due to a possible progression to acute coronary syndrome due to aggravation of the systemic inflammation causing disruption in a stable plaque, coronary spasm, or thromboembolism.[9] Therefore, disruption in the control of a previously stable cardiovascular comorbidity might suggest the increased risk of mortality in patients with both cardiovascular disease and COVID-19.

Our study also investigated the association of sex with mortality of patients with COVID-19. Our study showed that the absolute number of patients with COVID-19 was male. Also, the majority of cardiovascular comorbidities are present in male patients in all age groups. This could be attributed to the behavioral differences between sexes where male patients as compared with female patients have more high-risk behaviors (eg, smoking, drinking), and female patients have a more responsible attitude toward safety protocols than do male patients.[10] Previous studies have also associated male sex with an increased risk of mortality among COVID-19 patients. This was hypothesized because of hormonal differences, in which females, because of the presence of estrogen, have a protective effect by stimulating B-cell development, leading to humoral antiviral response. Also, testosterone has been implicated to have a role in coagulation in which it augments platelet activation and aggregation by increasing platelet expression of thromboxane A_2 receptors. Also, some have implicated that males have a higher expression of TMPRSS2 (transmembrane protease serine 2) that cleaves the viral S protein at two sites, allowing better penetration of the virus into the cells.[11] However, in our analysis, it showed that sex did not have an association with an increased risk of mortality in COVID-19 patients.

CONCLUSION

Our study showed that in patients admitted due to COVID-19 there were no observed differences in characteristics and between sexes. Presence of cardiovascular morbidities tends to increase with age. Advanced age and presence of CAD were significantly associated with in-hospital mortality. Closer monitoring along with more intensive and appropriate medical interventions may be needed for these patients at higher risk.

LIMITATIONS AND RECOMMENDATIONS

This single-center retrospective cohort study is in contrast with other studies that included multiple centers, which therefore have a larger sample size for analysis. This study also did not investigate the level of control of certain cardiovascular comorbidities (eg, hypertension, diabetes, dyslipidemia) and its risk of mortality. Further analysis in the level of control of these cardiovascular comorbidities such as blood pressure control, heart failure status, or glycemic control could provide additional understanding of the roles of cardiovascular diseases in the in-hospital mortality of patients with COVID-19.

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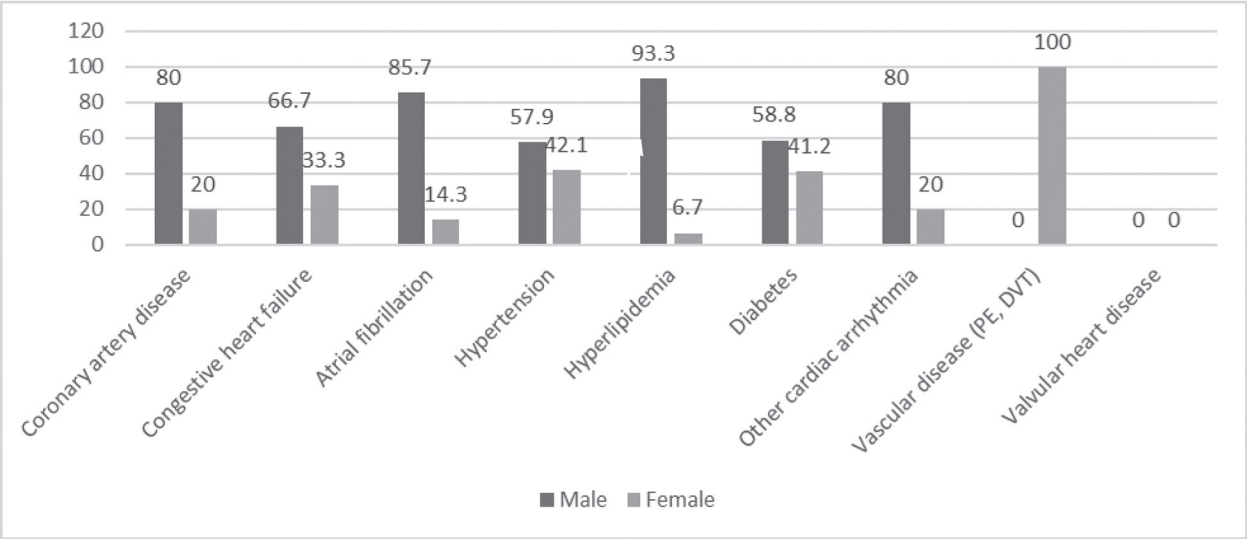

Figure 1. Cardiovascular comorbidity by sex among COVID-19 patients.

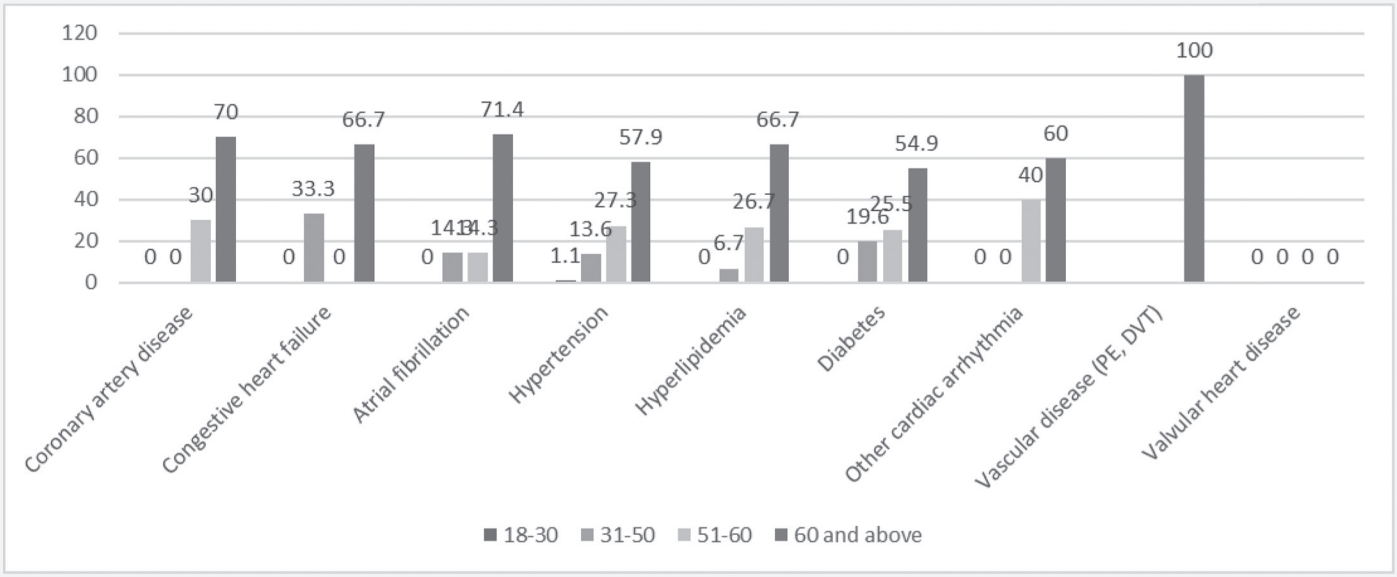

Figure 2. Cardiovascular comorbidity by age group among COVID-19 patients.

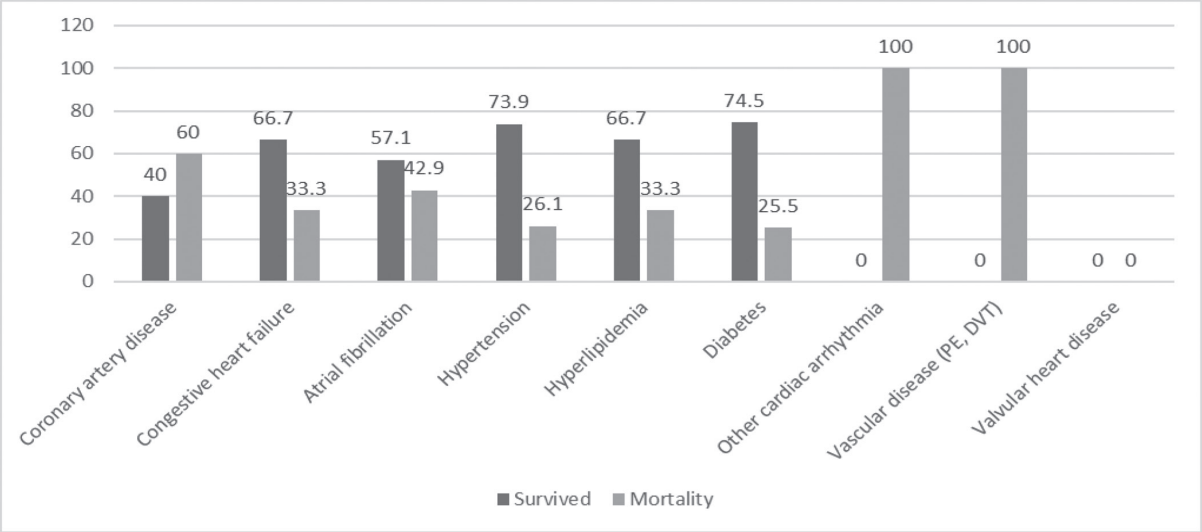

Figure 3. Cardiovascular comorbidity by survival among COVID-19 patients.

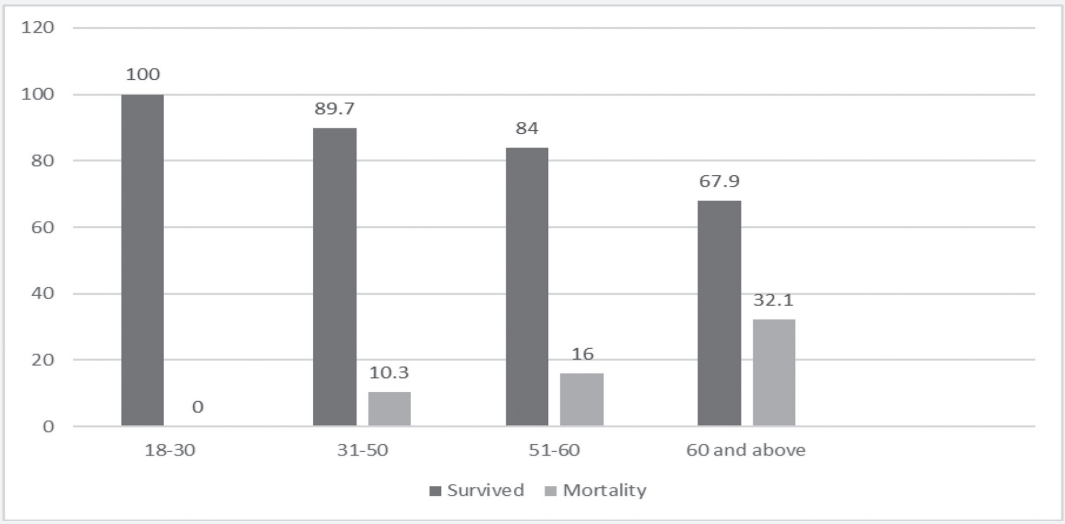

Figure 5. Age distribution by survival among COVID-19 patients.

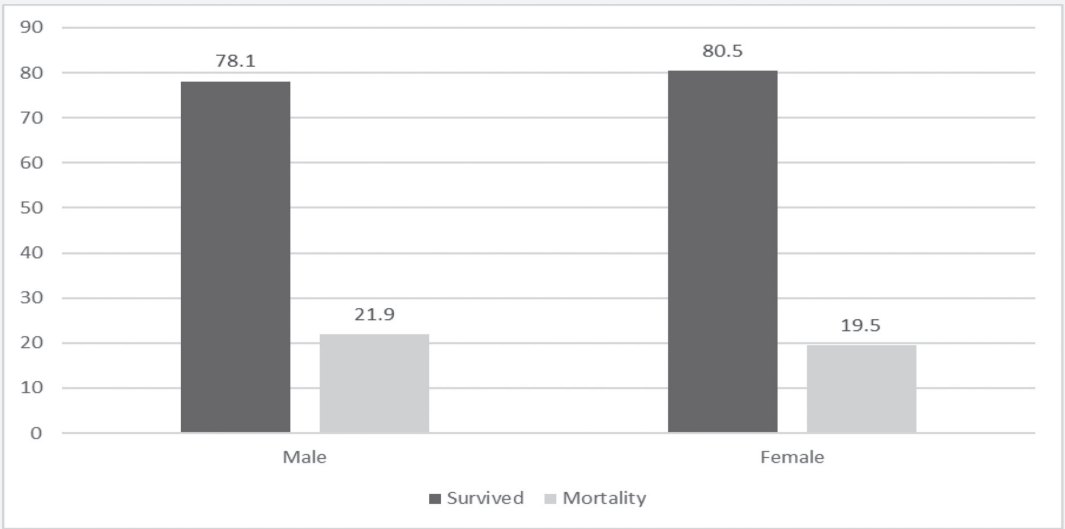

Figure 4. Sex distribution by survival among COVID-19 patients.