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Coronary artery disease in patients hospitalised with Coronavirus disease 2019 (COVID-19) infection

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ABSTRACT

Objective Among patients with Coronavirus disease 2019 (COVID-19), coronary artery disease (CAD) has been identified as a high-risk condition. We aimed to assess the clinical outcomes and mortality among patients with COVID-19 according to CAD status.

Methods We retrospectively analysed data from patients with COVID-19 admitted to the Cremona Hospital (Lombardy region, Italy) between February and March 2020. The primary outcome was all-cause mortality. CAD was defined as a history of prior myocardial infarction (MI), prior percutaneous coronary intervention (PCI), prior coronary artery bypass grafting (CABG) or CAD that was being medically treated.

Results Of 1252 consecutive patients with COVID-19, 124 (9.9%) had concomitant CAD. Patients with CAD were older and had a higher prevalence of comorbidities compared with those without CAD. Although patients with CAD had a higher risk of all-cause mortality than patients without CAD (HR 3.01, 95% CI 2.27 to 3.99), this difference was no longer significant in the adjusted model (HR 1.14, 95% CI 0.79 to 1.63). Results were consistent among patients with prior MI (adjusted HR (aHR) 0.87, 95% CI 0.54 to 1.41), prior PCI (aHR 1.10, 95% CI 0.75 to 1.62), prior CABG (aHR 0.91, 95% CI 0.45 to 1.82), or CAD medically treated (aHR 0.84, 95% CI 0.29 to 2.44). Multivariable analysis showed that age (aHR per 5 year increase 1.62, 95% CI 1.53 to 1.72) and female sex (aHR 0.63, 95% CI 0.49 to 0.82) were the only two independent correlates of mortality.

Conclusion Patients with COVID-19 and CAD have an exceedingly higher risk of mortality, which is mainly attributable to the burden of comorbidities rather than to a direct effect of CAD per se.

Key questions

What is already known about this subject?

- Coronary artery disease (CAD) has been identified as a high-risk condition among patients with Coronavirus disease 2019 (COVID-19).
- However, the real impact of CAD on mortality among patients with COVID-19 is not well understood.

What does this study add?

- Among 1252 consecutive COVID-19 patients, patients with CAD (9.9%) were older and had a higher prevalence of comorbidities compared with those without CAD. Patients with CAD also had a higher risk of all-cause mortality, but this difference was not significant in the adjusted model.

How might this impact on clinical practice?

- Patients with COVID-19 and CAD have an exceedingly higher risk of mortality, which is mainly attributable to the burden of comorbidities rather than to a direct effect of CAD per se.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains a global pandemic affecting more than 5.5 million persons worldwide with 356 000 deaths as of the end of May 2020.

Coronary artery disease (CAD) is the leading cause of death and the most common cardiovascular disease worldwide.[1] Accordingly, CAD is a prevalent condition among patients with COVID-19, varying between 2.5% and 10% of cases.[2 3] Since the early reports from China, where the outbreak of COVID-19 originally began, CAD has been identified as a risk factor for severe COVID-19. Among 72 314 cases of COVID-19 reported by the Chinese Centre for Disease Control and Prevention, the case-fatality rate increased from 2.3% to 10.5% in patients with pre-existing cardiovascular disease.[3] However, a complete characterisation of CAD status among patients with COVID-19 is still lacking, and whether CAD should be recognised as an independent risk factor for mortality in the setting of COVID-19 remains to be further elucidated. Indeed, there are important limitations to previous studies, including the lack of a standardised definition of CAD, incomplete accounting for other coexisting conditions frequently intertwined with CAD, and short-term follow-up.

Against this background, we investigated the impact of CAD among patients with COVID-19 and evaluated its association with the risk of all-cause mortality.

METHODS

The present retrospective, observational, single-centre study included all consecutive patients admitted to the Cremona hospital in the Lombardy region, Italy, with a confirmed diagnosis of pneumonia caused by SARS-CoV-2 according to the Interim Guidance from WHO on the clinical management of severe acute respiratory infection when COVID-19 is suspected (published online on 13 March 2020). Specifically, patients were eligible for the analysis if they had the following two criteria: (1) a confirmed clinical and radiological diagnosis of SARS-CoV-2 pneumonia, according to the criteria proposed by Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (seventh edition, published online on 4 March 2020); and (2) a positive reverse transcriptase–polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 in a respiratory tract sample.

Study population

For the purpose of this analysis, the study cohort was stratified according to CAD status. At baseline, patients with a history of previous myocardial infarction (MI), or previous percutaneous coronary intervention (PCI), or previous coronary artery bypass grafting (CABG), or angiographically documented CAD treated with medical therapy (ie, without myocardial revascularisation) were identified as having CAD.

The study was approved by the Ethics Committee of the Cremona Hospital that authorised us to retrospectively collect and publish data from patients admitted since February 2020. All the data were fully anonymised. This observational analysis was conducted in accordance with the Declaration of Helsinki.

Data collection

We collected information on sex, age, coexisting conditions including obesity (body mass index ≥30 kg/m^2), cardiovascular risk factors (smoking, hypertension, hyperlipidaemia, diabetes mellitus), chronic kidney disease, prior cerebrovascular event, history of heart failure with reduced left ventricular ejection fraction <35%, atrial fibrillation, chronic obstructive pulmonary disease, asthma, and active cancer. Clinical and radiological data, complete blood chemistry tests, cardiovascular drug therapy at the time of hospital admission (antiplatelet therapy, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, β-blockers, oral anticoagulant therapy) were reviewed from electronic clinical records. Lung involvement was visually classified at chest X-ray or at high resolution chest computed tomography (CT scan) in terms of evidence of parenchymal abnormalities in one (unilateral) or both lungs (bilateral). Information about pericardial effusion and pneumomediastinum at CT scan were also collected.

Study outcomes

The primary outcome of this study was all-cause death. Additional outcomes included: acute respiratory distress syndrome (ARDS), the need for non-invasive ventilation with continuous positive air pressure (CPAP), invasive mechanical ventilation, and in-hospital death. ARDS was defined as a ratio between arterial oxygen partial pressure (PaO_2) and fractional inspired oxygen (FiO_2) ≤300 mm Hg according to the interim guidance from WHO about the clinical management of severe acute respiratory infection when COVID-19 is suspected. For discharged patients, a telephonic follow-up was performed in order to ascertain their vital status. All study outcomes were monitored up to 4 May 2020, the final date of follow-up.

Statistical analysis

Continuous variables are summarised by their means and SD and categorical variables are summarised by the corresponding counts and percentages. Differences in baseline and in-hospital data between patients with and without CAD are shown as absolute risk differences (RD) with 95% confidence intervals (95% CI). For the primary outcome of death, we used a flexible parametric survival model proposed by Royston-Parmar-Lambert to obtain both unadjusted and adjusted results for patients with versus without CAD.[4] This model provides hazard ratios (HRs) with 95% CI that are similar to the Cox regression model, although the baseline cumulative hazard in the flexible parametric approach is modelled with restricted cubic splines functions. We tested different numbers of knots, affecting the number of splines being used and where they connect, and four knots were adequate for our data. We assumed that the HR for death was constant over time because the log-log plots and Schoenfeld residuals confirmed that the proportionality assumption was satisfied. A multivariable model, with adjusted HR and 95% CI, was fitted by including in the regression equation the presence or absence of CAD by default and any other baseline demographic and clinical variable that was associated with all-cause death (as conservatively defined by a value of $p<0.1$). Age was included as a continuous variable and modelled linearly. Time-to-event curves for both unadjusted and adjusted analyses were visually estimated by plotting the standardised survival functions stratified by CAD status after using the flexible parametric survival models. Standardised survival curves predict a survival curve for each individual and then take the average of these curves (whereas adjusted Kaplan-Meier curves provide a prediction for an individual who has the mean value of each covariate which might not be reflective of the average in the population). All analyses were done using Stata, version 14 (StataCorp).

RESULTS

Between 21 February and 31 March 2020, 1252 consecutive patients were admitted with COVID-19, caused by laboratory-confirmed SARS-CoV-2 infection, and were included in this report. A history of CAD was present in

124 patients (9.9%). In the CAD group, 61 patients (49%) had a prior MI, 100 (81%) a prior PCI, 20 (16%) a prior CABG, and 10 (8%) had angiographically-confirmed CAD that was medically treated. CAD was documented in the context of a chronic coronary syndrome in 57 patients (46%), whereas in the remaining 67 patients (54%) with a history of acute coronary syndrome, 20 (30%) had ST-segment elevation MI and 47 (70%) presented a non-ST-segment elevation acute coronary syndrome. CAD severity was defined according to the number of obstructive coronary arteries corresponding to 50% or more narrowing and reported in online supplemental table S1.

Baseline characteristics and clinical presentation

In the overall cohort, the mean (SD) age was 64.7±15.5 years and 36.3% were female. However, patients with CAD were on average 12.4 years older and less likely to be female (RD −20.6% percentage points). Patients in the CAD group were more likely to be smokers, to be obese, and to have hypertension, hyperlipidaemia, diabetes mellitus, chronic kidney disease, heart failure with reduced ejection fraction, atrial fibrillation, and chronic obstructive pulmonary disease (table 1). At hospital admission, patients with CAD had a lower heart rate and PaO_2 compared with those without CAD (table 2). Radiological exams were similarly employed in both CAD and non-CAD patients, and the pattern of lung involvement consisted of bilateral lung infiltrates in almost all patients irrespective of CAD status. With respect to in-hospital medications (table 3), patients with CAD were more likely to receive ACE inhibitors, β-blockers and antiplatelet therapy. Moreover, patients in the CAD group were less likely to receive darunavir/ritonavir, levofloxacin, and

Table 1 Baseline demographic and clinical characteristics

	All patients (n=1252)	CAD (n=124)	No CAD (n=1128)	Difference (95% CI)
Age, years	64.7±15.5	75.9±9.4	63.5±15.6	12.4 (9.6 to 15.2)
Female sex	454 (36.3%)	22 (17.7%)	432 (38.3%)	−20.6 (−29.4 to 11.7)
Smokers	97 (7.7%)	34 (27.4%)	63 (5.6%)	21.8 (17.0 to 26.7)
Obesity	46 (3.7%)	10 (8.1%)	36 (3.2%)	4.9 (1.4 to 8.4)
Hypertension	498 (39.8%)	98 (79.0%)	400 (35.5%)	43.6 (34.8 to 52.3)
Hyperlipidaemia	93 (7.4%)	39 (31.5%)	54 (4.8%)	26.7 (22.0 to 31.3)
Diabetes mellitus	191 (15.3%)	37 (29.8%)	154 (13.7%)	16.2 (9.6 to 22.8)
Chronic kidney disease	104 (8.3%)	26 (21.0%)	78 (6.9%)	14.1 (9.0 to 19.1)
Prior CVE	103 (8.2%)	13 (10.5%)	90 (8.0%)	2.5 (−2.6 to 7.6)
LVEF*	54.8±9.6	49±9	59±7	10 (8.1 to 11.9)
LVEF <35%	38 (3.0%)	20 (16.1%)	18 (1.6%)	14.5 (11.5 to 17.6)
Atrial fibrillation	108 (8.6%)	18 (14.5%)	90 (8.0%)	6.5 (1.3 to 11.7)
COPD	75 (6.0%)	15 (12.1%)	60 (5.3%)	6.8 (2.4 to 11.2)
Asthma	19 (1.5%)	1 (0.8%)	18 (1.6%)	−0.8% (−3.1% to 1.5%)
Active cancer	35 (2.8%)	5 (4.0%)	30 (2.7%)	1.4 (−1.7 to 4.4)
Coronary artery disease	124 (9.9%)	124 (100%)	–	–
Prior MI	61 (49%)	61 (49%)	–	–
Prior PCI	100 (81%)	100 (81%)	–	–
Prior CABG	20 (16%)	20 (16%)	–	–
CAD medically treated	10 (8%)	10 (8%)	–	–
CAD presentation				
Chronic coronary syndrome	57 (4.6%)	57 (46%)	–	–
Prior ACS	67 (5.3%)	67 (54%)	–	–
NSTE-ACS	47 (70%)	47 (70%)	–	–
STEMI	20 (30%)	20 (30%)	–	–
Days from symptoms onset	5.8±3.8	5.8±3.9	5.8±3.8	0.1 (−0.6 to 0.8)

Data are expressed as n (%) or mean±SD.
Obesity was defined as a body mass index ≥30 kg/m^2. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2.
*LVEF data were available in 204/1252 (16%) of no CAD group and in 100% of CAD group.
ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVE, cerebrovascular event; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation ACS; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Table 2 In-hospital data

	All patients (n=1252)	CAD (n=124)	No CAD (n=1128)	Difference (95% CI)
Clinical presentation				
Systolic blood pressure, mm Hg	121±19	121±21	121±19	−0.7 (−4.3 to 2.8)
Heart rate, bpm	90.4±15.9	84.0±14.4	91.1±19.1	−7.1 (−10.0 to −4.2)
PaO_2, mm Hg	63.6±15.7	59.9±15.7	64.0±15.7	−4.2 (−7.1 to −1.3)
Chest X-ray	1003 (80.1%)	97 (78.2%)	906 (80.3%)	−2.1 (−9.5 to 5.3)
Bilateral lung infiltrate	964 (96.4%)	94 (96.9%)	870 (96.3%)	0.6 (−3.3 to 4.5)
Chest CT scan	980 (78.3%)	92 (74.2%)	888 (78.7%)	−4.5 (−12.2 to 3.1)
Bilateral lung infiltrate	954 (97.3%)	87 (94.6%)	867 (97.6%)	−3.1 (−6.5 to 0.4)
Pericardial effusion	37 (3.8%)	1 (1.1%)	36 (4.1%)	−3.0 (−7.1 to 1.1)
Pneumomediastinum	6 (0.6%)	0 (0.0%)	6 (0.7%)	−0.7 (−2.4 to 1.0)
Clinical outcomes				
ARDS	615 (49.2%)	91 (73.4%)	524 (46.5%)	26.9 (17.7 to 36.1)
Time from hospitalisation to ARDS, days	1.6±3.8	2.5±5.7	1.5±3.4	1 (0.1 to 1.8)
Time from symptoms onset to ARDS, days	7.4±5.5	8.0±6.6	7.3±5.3	0.7 (−0.5 to 1.9)
CPAP	480 (38.3%)	71 (57.3%)	409 (36.3%)	21.0 (12.0 to 30.0)
Time from hospitalisation to CPAP, days	2.8±11.3	3.2±6.2	2.7±11.9	0.5 (−2.4 to 3.3)
Time from symptoms onset to CPAP, days	8.7±11.8	8.7±7.0	8.7±12.4	0 (−2.9 to 3.0)
Intubation	120 (9.6%)	12 (9.7%)	108 (9.6%)	0.1 (−5.4 to 5.6)
Time from hospitalisation to intubation, days	3.5±5.5	8.2±9.2	3.0±4.7	5.2 (2.1 to 8.4)
Time from symptoms onset to intubation, days	9.3±6.5	16.4±10.1	8.5±5.6	7.8 (4.2 to 11.5)
Death	252 (20.1%)	55 (44.4%)	197 (17.5%)	26.9 (19.6 to 34.2)
Time from hospitalisation to death, days	9.2±6.7	10.1±7.7	8.9±6.4	1.2 (−0.8 to 3.2)
Time from symptoms onset to death, days	15.0±7.9	16.2±8.6	14.7±7.7	1.5 (−0.8 to 3.9)

ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; CPAP, continuous positive airway pressure; PaO_2, arterial oxygen partial pressure.

hydroxychloroquine, whereas they more frequently received lopinavir/ritonavir and other antibiotics.

Clinical outcomes

As reported in table 2, ARDS developed in 73.4% of patients with CAD compared with 46.5% of those without CAD (RD 26.9 percentage points, 95% CI 17.7 to 36.1 percentage points). Non-invasive ventilation with CPAP was needed in 57.3% and 36.3% of patients with CAD versus without CAD, respectively (RD 21 percentage points, 95% CI 12 to 30 percentage points). Intubation was required in 9.7% and 9.6% of patients with CAD versus without CAD, respectively (RD 0.1 percentage point, 95% CI −5.4 to 5.6 percentage points). In-hospital death occurred in 44.4% of patients with CAD compared with 17.5% of patients without CAD (RD 26.9 percentage points, 95% CI 19.6 to 34.2 percentage points).

Overall, a total of 1000 patients were discharged: 69 (55%) and 931 (82%) patients with CAD and without CAD, respectively. At follow-up, a total of 43 patients (4.3%) died after being discharged alive, nine (13%) in the CAD group and 34 (3.6%) in the no-CAD group. Rehospitalisation was needed in 21 (2.1%) patients; of these, one (1.5%) was in the CAD group and 20 (2.2%) in the no-CAD group. The two main causes of rehospitalisation were new-onset dyspnoea (16 patients) and pulmonary embolism (five patients).

All-cause mortality and multivariable analysis

Figure 1 shows the predicted population averaged probability curves for all-cause mortality in CAD and no-CAD groups, without and with adjustment for baselines variables associated with all-cause mortality at the univariable model (online supplemental table S2). The Royston-Parmar-Lambert model for mortality, with CAD status as the only variable, showed an unadjusted HR of 3.01 (95% CI 2.27 to 3.99), suggesting a higher risk of mortality for patients with CAD compared with those without CAD. The unadjusted probability of death was 0.49 versus 0.20 in patients with CAD versus without CAD (figure 1, panel A). However, the multivariable model showed that CAD was not associated with all-cause death (adjusted HR (aHR) 1.14, 95% CI 0.79 to 1.63, with an adjusted probability of death of 0.25 and 0.20 in patients with CAD versus without CAD (figure 1, panel B). Multivariable analysis showed that female sex (aHR 0.63, 95% CI 0.49 to 0.82) and age (aHR per 5 year increase 1.62, 95% CI 1.53 to 1.72) were significantly associated with all-cause mortality (figure 2).

Table 3 In-hospital medications

	All patients (n=1252)	CAD (n=124)	No CAD (n=1128)	Difference (95% CI)
ACE inhibitors	160 (12.8%)	25 (20.2%)	135 (12.0%)	8.2 (2.0 to 14.4)
ARBs	156 (12.5%)	19 (15.3%)	137 (12.1%)	3.2 (–3.0 to 9.3)
β-blockers	380 (30.4%)	92 (74.2%)	288 (25.5%)	48.7 (40.6 to 56.8)
Aspirin	239 (19.1%)	113 (91.1%)	126 (11.2%)	80 (74.2 to 85.8)
Clopidogrel	31 (2.5%)	16 (12.9%)	15 (1.3%)	11.6 (8.8 to 14.4)
Ticagrelor/prasugrel	6 (0.5%)	6 (4.8%)	0 (0.0%)	4.8 (3.6 to 6.1)
Warfarin	41 (3.3%)	5 (4.0%)	36 (3.2%)	0.8 (–2.5 to 4.1)
NOAC	29 (2.3%)	5 (4.0%)	24 (2.1%)	1.9 (–0.9 to 4.7)
Darunavir/ritonavir	958 (76.5%)	61 (49.2%)	897 (79.5%)	–30.3 (–38.0 to –22.6)
Remdesevir	9 (0.7%)	0 (0.0%)	9 (0.8%)	–0.8 (–2.4 to 0.8)
Lopinavir/ritonavir	87 (6.9%)	27 (21.8%)	60 (5.3%)	16.5 (11.8 to 21.1)
Levofloxacin	597 (47.7%)	42 (33.9%)	555 (49.2%)	–15.3 (–24.6 to –6.1)
Other antibiotics	555 (44.3%)	63 (50.8%)	492 (43.6%)	7.2 (–2.0 to 16.4)
Tocilizumab	23 (1.8%)	2 (1.6%)	21 (1.9%)	–0.2 (–2.7 to 2.2)
Hydroxychloroquine	996 (79.6%)	87 (70.2%)	909 (80.6%)	–10.4 (–17.9 to –3.0)
Steroids	763 (60.9%)	76 (61.3%)	687 (60.9%)	0.4 (–8.7 to 9.4)
Enoxaparin	723 (57.8%)	78 (63.4%)	645 (57.2%)	6.2 (–3.0 to 15.4)
Hydration	852 (68.1%)	84 (67.7%)	768 (68.1%)	–0.3 (–9.0 to 8.3)
Oxygen therapy	1049 (83.8%)	101 (81.5%)	948 (84.0%)	–2.6 (–9.4 to 4.3)

ACE, angiotensin-converting enzyme; ARBs, angiotensin-receptor blockers; CAD, coronary artery disease; NOAC, novel oral anticoagulant.

The analysis of different subtypes of CAD (figure 1, panels C and D, and figure 3) showed that, in the unadjusted models, patients with prior MI (unadjusted HR 2.52, 95% CI 1.69 to 3.76), prior PCI (unadjusted HR 2.91, 95% CI 2.13 to 3.96), prior CABG (unadjusted HR 3.66, 95% CI 2.04 to 6.54), and medically treated CAD all had a higher risk of mortality compared with patients without CAD. However, no subtype of CAD was associated with a higher hazard of all-cause mortality in the multivariable models.

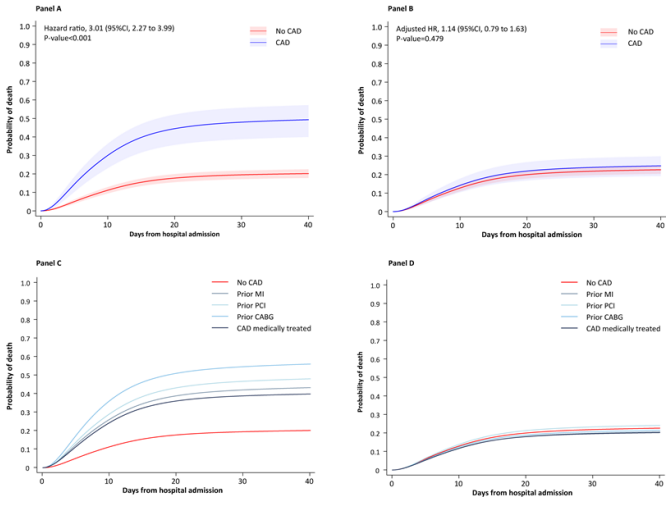

Figure 1 Unadjusted (panel A) and adjusted (panel B) population averaged probability curves for all-cause mortality in patients with CAD and without CAD. Unadjusted (panel C) and adjusted (panel D) population averaged probability curves for all-cause mortality according to subtypes of CAD. 95% CI are shown as coloured areas in panel A and B, whereas they have been omitted in panels C and D. CABG, coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

DISCUSSION

The principal findings of this study can be summarised as follows: a concomitant CAD is present in approximately 1 in 10 patients hospitalised for COVID-19; in the context

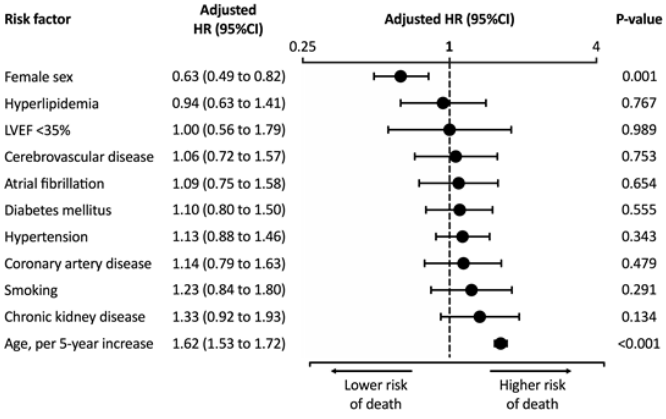

Figure 2 Multivariable analysis for death. LVEF, left ventricular ejection fraction.

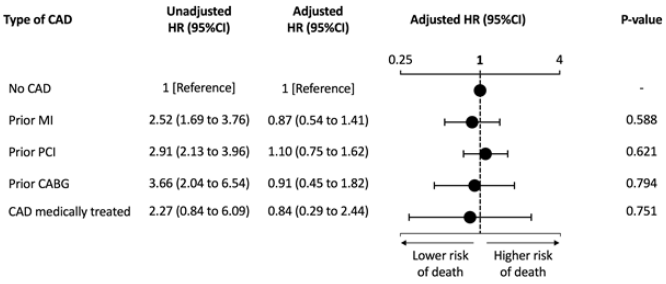

Figure 3 Risk of all-cause mortality according to the type of CAD. CABG, coronaryartery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

of COVID-19, patients with CAD have a threefold higher probability of all-cause death compared with those without CAD; much of this difference is, however, likely attributable to demographic and patient factors, with age and burden of comorbidities greater among patients with CAD; the two factors independently associated with all-cause mortality were female sex and ageing, which resulted in a protective factor and risk factor, respectively.

Italy is one of the countries most heavily affected by the COVID-19 pandemic, and the Lombardy region accounted for approximately 40% of cases and more than 50% of deaths in the country. The hospital of Cremona was at the centre of the pandemic with the area served by the hospital having one of the highest densities of COVID-19 cases per inhabitants across the country. Since the initial reports on the disease, cardiovascular risk factors and CAD emerged as important comorbidities carrying a poor prognosis in patients with COVID-19. In several observational studies, even including larger populations, CAD among patients with COVID-19 has been associated with an increased risk of death. These findings are similar to those previously described with the Middle East respiratory syndrome (MERS), in which an increased risk of adverse events was observed among patients with pre-existing cardiovascular disease.[5] What has not been clear from these studies is the extent to which the increased risk of death is directly attributable to CAD and the extent to which it is due to confounding effects from features intertwined with CAD, such as age, male sex, and other common cardiovascular risk factors. Mechanistically, the pathobiological processes underlying the development of a more severe course of COVID-19 in patients with CAD could be related to the systemic inflammatory response that occurs in any viral infection, favouring platelet activation, endothelial dysfunction, and a prothrombotic milieu.[6]

In the present study, we found no evidence that CAD is independently associated with a higher risk of all-cause mortality among patients hospitalised with COVID-19. Although the crude hazards for death were higher in patients with CAD, adjustment according to variables associated with death substantially altered the hazard ratios for patients with CAD and its subtypes. Another important aspect pertains to the definition of CAD. We defined CAD as at least prior MI, prior PCI, prior CABG, or CAD being medically treated, whereas CAD was not defined in other reports showing its role as an independent risk factor for mortality in patients with COVID-19. Of interest, the adjusted risk estimates for the subtypes of CAD consistently indicate the lack of an independent effect of CAD in increasing the risk of death compared with the group of patients without CAD, although in the subgroup with the smallest number of participants (ie, CAD being medically treated) there was imprecision in risk estimates.

In addition to the analysis of mortality risk, the present study provides additional insights into other important clinical outcomes. We found that patients with CAD had an absolute increase of about 27% and 21% in the occurrence of ARDS throughout hospitalisation and non-invasive ventilation, respectively. In contrast, the rate of mechanical ventilation was similar, 9.7% and 9.6%, among patients with and without CAD, respectively. This discrepancy in similar rates of invasive mechanical ventilation despite higher rates of ARDS should be also considered when interpreting deaths from COVID-19 in patients with CAD. It suggests that these patients were preferentially managed with non-invasive ventilation and that, in case of further deterioration, mechanical ventilation was not pursued. This could be explained by the rationing of healthcare resources during the pandemic, resulting in a lower priority of patients with CAD compared with those without CAD who were more likely to recover if treated.[7] Although the study does not address the allocation of healthcare resources among patients with COVID-19, the burden of comorbidities and more advanced age among patients with CAD could again explain the increased mortality rate observed in patients with CAD.

The two factors having independent association with all-cause mortality in our report were age and female sex. Although there is overwhelming evidence showing that ageing is a risk factor for mortality among patients with COVID-19,[3 8 9] the effect of gender on clinical outcomes remains more controversial.[9–11] Sex differences have already been described for other coronavirus-related infections, including in animal studies on severe acute respiratory syndrome (SARS),[12 13] showing men more susceptible to respiratory viral infections than women because of hormonal and epigenetic mechanisms involving innate immunity.[14]

This study has several limitations. First, this is a single-centre and retrospective study. Second, CAD encompasses a wide spectrum of clinical entities. Although we did not find a specific association between the type of CAD and the risk of mortality, our findings should be considered hypothesis-generating in view of the relatively small sample of CAD subgroups. However, our analysis still follows the rule of thumb of at least 10 outcome events per predictor variable (15 candidate predictors per 293 events).[15] Furthermore, we were unable to measure the effects of other important features, such as anatomic complexity and incomplete revascularisation, on clinical

outcomes. Third, we included all consecutive patients admitted to the hospital from the onset of COVID-19. Hence, despite the all-comer nature of the study, there have been variations on disease knowledge and management over time. Fourth, although we extended the follow-up among discharged patients, its length remains short. Whether patients with CAD derive additional long-term complications from COVID-19 deserve further investigation.

CONCLUSION

In conclusion, we found that patients with COVID-19 and CAD have an exceedingly higher risk of mortality, which is attributable, however, to the burden of comorbidities rather than to a direct effect of CAD per se on the risk mortality.

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