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Original Article

Cardiovascular complications and its impact on outcomes in COVID-19

Shekhar Kunal [a], Shashi Mohan Sharma [a], Sohan Kumar Sharma [a, *], Dinesh Gautam [a], Harnish Bhatia [a], Himanshu Mahla [a], Sandeep Sharma [a], Sudhir Bhandari [b]

[a] Department of Cardiology, SMS Medical College, Jaipur, Rajasthan, India
[b] Department of Medicine, SMS Medical College, Jaipur, Rajasthan, India

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has led to a widespread morbidity and mortality. Limited data exists regarding the involvement of cardiovascular system in COVID-19 patients. We sought to evaluate the cardiovascular (CV) complications and its impact on outcomes in symptomatic COVID-19 patients.

Methods: This was a single center observational study among symptomatic COVID-19 patients. Data regarding clinical profile, laboratory investigations, CV complications, treatment and outcomes were collected. Cardiac biomarkers and 12 lead electrocardiograms were done in all while echocardiography was done in those with clinical indications for the same. Corrected QT-interval (QTc) at baseline and maximum value during hospitalization were computed.

Results: Of the 108 patients, majority of them were males with a mean age of 51.2 ± 17.7 years. Hypertension (38%) and diabetes (32.4%) were most prevalent co-morbidities. ECG findings included sinus tachycardia in 18 (16.9%), first degree AV block in 5 (4.6%), VT/VF in 2 (1.8%) and sinus bradycardia in one (0.9%). QTc prolongation was observed in 17.6% subjects. CV complications included acute cardiac injury in 25.9%, heart failure, cardiogenic shock and acute coronary syndrome in 3.7% each, "probable" myocarditis in 2.8% patients. Patients with acute cardiac injury had higher mortality than those without (16/28 [57.1%] vs 14/78 [17.5%]; $P < 0.0001$). Multivariate logistic regression analysis showed that acute cardiac injury (OR: 11.3), lymphopenia (OR: 4.91), use of inotropic agents (OR: 2.46) and neutrophil-lymphocyte ratio (OR:1.1) were independent predictors of mortality.

Conclusions: CV complications such as acute cardiac injury is common in COVID-19 patients and is associated with worse prognosis.

1. Introduction

The world is experiencing a never before seen pandemic caused by a novel coronavirus SARS-CoV-2 leading to the coronavirus disease 2019 (COVID-19). Since the first reports of atypical pneumonia originating from Wuhan province of China in December 2019, it was just within few weeks that the virus spread worldwide affecting millions of people.[1] SARS-CoV-2 is a part of the *Coronaviridae* family and is quite similar to the two other coronaviruses SARS and MERS.[2] COVID-19 predominantly affects the respiratory system with pneumonia and acute respiratory distress syndrome (ARDS) being the predominant manifestation. However, recent reports have highlighted the impact of SARS-CoV-2 on the cardiovascular (CV) system.[3–5]

Patients with cardiovascular disease (CVD) risk factors such as hypertension, diabetes and dyslipidemia are at an increased risk of infection as well as adverse outcomes.[6] Cardiovascular complications such as acute myocardial injury, heart failure (HF), cardiac arrhythmias, myocarditis, pericarditis and venous thromboembolism are increasingly being reported.[2–5] In addition, use of multiple QT-interval prolonging drugs such as hydroxychloroquine (HCQ) and azithromycin for the treatment of COVID-19 infection may lead to increased incidence of malignant arrhythmias such as torsades pointes (TdP).[2] Data regarding the CV complications especially from developing countries are limited. The present study aims to determine the CV complications in symptomatic COVID-19 patients and its impact on the disease outcomes.

* Corresponding author.
E-mail address: drsohansharma@gmail.com (S.K. Sharma).

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2. Material and methods

2.1. Study design

This was a single center retrospective observational study among COVID-19 patients at a designated tertiary care COVID-19 hospital. Consecutive symptomatic laboratory confirmed COVID-19 patients were enrolled in the study. Asymptomatic patients as well as those subjects without documentation of cardiac biomarkers including cardiac troponin and creatinine kinase-myocardial band (CK-MB) were excluded. Data regarding demographic features, medical history, laboratory findings, treatment and outcomes were collected and evaluated. In all these patients, a baseline neutrophil to lymphocyte ratio (NLR) defined as ratio of absolute neutrophil count to absolute lymphocyte count was computed. Apart from routine laboratory investigations, cardiac biomarkers such as serum CK-MB/cardiac troponins were done in all patients. Two-dimensional (2D) echocardiography was done selectively based on clinical indication. In addition, a 12-lead electrocardiogram was done in all patients and QTc interval were computed both at admission as well as during the course of hospitalization. All the ECG parameters were measured using electronic calipers (EP Calipers v1.6). QT intervals were corrected using the Fridericia method. Delta QTc was determined as difference of maximum QTc during hospitalization to QTc as baseline. Tisdale[7] risk scoring was used retrospectively for prediction of drug-associated QT prolongation in these patients. All the data were collected and analyzed by two independent cardiologists.

In all these patient assessments were done to determine the presence of acute cardiac injury as well other cardiac complications such as acute coronary syndrome (ACS), myocarditis, pericarditis, pericardial effusion, cardiac tamponade, cardiac arrhythmias and CS. Acute cardiac injury was defined as blood levels of cardiac biomarkers above the 99th-percentile upper reference limit irrespective of new findings on ECG or echocardiography.[3] A diagnosis of myocarditis was based on the three-tiered clinical classification on the basis of level of diagnostic certainty (definite, probable and possible).[8] A definite diagnosis requires a histological or immunohistological evidence of myocarditis while probable myocarditis is defined based on the "clinical context of possible myocardial injury with cardiovascular symptoms and at least one of the following: (i) raised cardiac biomarkers; (ii) ECG findings suggestive of cardiac injury, or (iii) abnormal cardiac function on echocardiogram or cardiac MRI even in the absence of histopathological confirmation".[8] Based on the presence or absence of acute myocardial injury, patients were divided into two groups: Group 1: patients with acute myocardial injury and Group 2: patients without acute myocardial injury. A written informed consent was waived off keeping in mind the retrospective nature of this study. The inclusion and use of data complied with the Declaration of Helsinki.

2.2. Outcome

The end point in this study was the occurrence of COVID-19 related death. Successful treatment was defined as improvement in clinical symptoms, normal body temperature, radiological resolution as well as two consecutive negative results on RT-PCR assay for COVID-19.

2.3. Statistical analysis

Descriptive statistics was obtained for all the study subjects with continuous data being expressed as mean ± SD while categorical data represented as proportions. Comparison of means of continuous variables was done using Student's *t*-test while $\chi 2$ test was used for categorical variables. Multivariate logistic regression analysis was done to determine factors associated with worse outcomes. Receiver operating characteristic (ROC) curve was plotted for Tisdale QT risk scoring system predicting QT prolongation and a cut-off score was then determined along with sensitivity and specificity. All statistical analyses were performed on SPSS, version 24.0 (IBM Corp). A *P*-value of ≤ 0.05 was considered to be statistically significant.

3. Results

A total of 108 symptomatic patients were included in the final analysis (28 patients excluded in the absence of documentation of cardiac markers). Of the 108 patients, there were 70 males (64.8%) with a mean age of 51.2 ± 17.7 years. The most common presenting symptoms were fever in 82 (75.9%), cough in 60 (55.6%) and dyspnea in 57 (52.8%) with a mean duration of symptoms being 3.9 ± 2.4 days. Chest pain on presentation was reported in 9 (8.3%) patients of whom four had typical anginal symptoms (all of them had an evidence of raised biomarkers and ECG or echocardiographic changes). Among those with atypical chest pain, raised biomarkers or ECG changes were observed in two of them. A majority of subjects (75.9%) had a history of travel to/resided in an endemic area while international travel was reported in 10 (9.3%) patients. History of contact with a known COVID-19 positive patient was documented in 40 (37.3%) subjects. Co-morbidities were present in 50 (46.3%) patients with hypertension being most common (38%) followed by diabetes (32.4%) and CVD (13%). Chronic lung diseases in the form of chronic obstructive pulmonary disease (COPD) was present in 6 (5.6%), asthma and post-tubercular sequalae in 3 (2.8%) each while interstitial lung disease and bronchiectasis in one patient each. History of smoking was reported in 10 (9.3%) patients. The clinical and demographic profile has been tabulated in Table 1.

3.1. Laboratory parameters

Lymphopenia was observed in 35 (32.4%) patients, C-reactive protein (CRP) positivity in 43 (39.8%) patients while D-dimer was positive in 38 of the 79 patients where it was done. A normal chest radiograph was reported in 37 (34.2%) patients while unilateral opacities were present in 10 (9.2%) subjects and bilateral opacities in 61 (56.5%). The common ECG findings in our study were sinus tachycardia in 18 (16.9%) followed first degree Atrioventricular (AV) block in 5 (4.6%), ventricular tachycardia/ventricular fibrillation [VT/VF] in 2 (1.8%) and sinus bradycardia in one (0.9%) patient. On serial ECGs, persistent sinus tachycardia was found in 12/18 (66.7%) patients and persistent sinus bradycardia in one (100%) patient. ST-T segment changes were observed in 17 (15.7%) patients while bundle branch block was reported in 5 (4.6%) subjects. Both the patients with VT/VF had a normal baseline QTc interval.

It was observed that there was a significant prolongation of QTc from a baseline value of 418.6 ± 31.2 ms to a maximal average value of 444.5 ± 37.8 ms ($P < 0.0001$) following therapy for COVID-19 infection. QTc prolongation (defined as QTc $\geq$ 470 ms in men and $\geq$480 ms in women) post therapy was reported in 19/108 (17.6%) subjects. Severe prolongation of the QTc ($\geq$500 ms) occurred in 7/108 (6.5%) patients while significant increase in QTc (Delta QTc $\geq$ 60 ms) post therapy for COVID-19 was reported in 9 (8.3%) patients. However, none of the patients including those with a severely prolonged QTc had TdP events. The mean Tisdale QT score was 7.02 ± 3 with no significant difference between survivors or deceased. Of the 108 patients, 53 (49.1%) had a Tisdale score <6, 38 (35.2%) had a Tisdale score between 7 and 10 while 17 (15.7%) had a score >11. There was a significant correlation between Tisdale QT

Table 1
Clinical and demographic features in patients with COVID-19 infection.

	No. of patients ($n = 108$)
Age (mean ± SD)	51.2 ± 17.7
Sex (M/F)	70/38 (64.8%/35.2%)
Symptomatology	
Fever	82 (75.9%)
Cough	60 (55.6%)
Dyspnoea	57 (52.8%)
Sore throat	12 (11.1%)
Fatigue	12 (11.1%)
Chest pain	9 (8.3%)
Headache	8 (7.4%)
Rhinorrhoea	7 (6.5%)
Diarrhoea	7 (6.5%)
Altered sensorium	5 (4.6%)
Myalgias	4 (3.7%)
Anorexia	3 (2.8%)
Pain abdomen	3 (2.8%)
Duration of symptoms (mean ± SD)	3.9 ± 2.4
Presence of co-morbidities	60 (55.5%)
Co-morbidities	
Hypertension	41 (38%)
Diabetes Mellitus	35 (32.4%)
Diabetes status (controlled/uncontrolled)	11 (31.4%)/24 (68.6%)
Cardiovascular disease	14 (13%)
Dyslipidaemia	6 (5.6%)
Heart Failure	1 (0.9%)
Chronic lung diseases:	14 (13%)
Chronic obstructive pulmonary disease	6 (5.6%)
Asthma	3 (2.8%)
Post-tubercular sequalae	3 (2.8%)
Interstitial Lung Disease	1 (0.9%)
Bronchiectasis	1 (0.9%)
Chronic Kidney Disease	9 (8.3%)
Malignancy	3 (2.8%)
Smoking	10 (9.3%)
Use of ACEi/ARBs	13 (12%)
Duration of hospital stay	8.7 ± 6.1 days
Time to COVID-19 negativity	7.04 ± 3.9 days

ACEi: angiotensin converting enzyme inhibitor; ARBs: Angiotensin receptor blockers; COVID-19: coronavirus disease 2019; F: female; M: male; No.: number; SD: standard deviation.

score and QTc maximal (R = 0.56; $P < 0.0001$). ROC curve plot showed that the cut-off of Tisdale QT score identifying risk of QT prolongation was >6 with a sensitivity of 85% and a specificity of 57% (AUC:0.83; 95% CI: 0.74–0.93; $P < 0.0001$). Echocardiogram was done in 28/108 patients based on the clinical indication with an abnormal echocardiogram being reported in 20 patients. The abnormal echocardiographic findings included diastolic dysfunction in 17, left ventricular systolic dysfunction in 11, concentric left ventricular hypertrophy in nine, regional wall motion abnormality (RWMA) confined to a single coronary territory in eight patients (four patients had a prior echocardiogram suggesting RWMA in the past), moderate or greater tricuspid regurgitation (TR) in six patients (moderate TR: four, severe TR: two), mitral regurgitation (MR) in five patients (moderate MR: three and severe MR: two), global left ventricular hypokinesia in three and pericardial effusion in two patients. Right ventricular systolic dysfunction was present in only one patient. Among the patients with elevated cardiac biomarkers, new findings on ECG or echocardiography were reported in 22 (78.6%) of them.

3.2. Management

Majority of patients received supportive care along with HCQ and azithromycin. HCQ was administered to 99 (90.7%) patients, azithromycin to 79 (73.1%), 71(65.7%) received both HCQ and azithromycin while HCQ alone was prescribed to 28 (25.9%) patients. In the patients who received both HCQ and azithromycin, there was a significant prolongation of QTc following therapy (452.5 ± 41.7 ms vs 427.2 ± 22.6 ms; $P = 0.003$) as compared to those who received HCQ alone. QTc prolongation was seen in 17/71 (23.9%) patients who received both HCQ and azithromycin as compared to one patient (3.5%) with HCQ alone ($P = 0.009$). HCQs and azithromycin were discontinued in patients with QTc prolongation or those who had a Delta QTc ≥60 ms in follow-up ECGs. Of the 108 patients, 25 (23.1%) required invasive mechanical ventilation while 13 (12.4%) were given a trial of non-invasive ventilation. The mean time to RT-PCR negativity was 7.04 ± 3.9 days (range: 3–25 days).

3.3. Complications

3.3.1. Cardiovascular complications

Acute cardiac injury was the most common cardiovascular complication reported in 28 (25.9%) subjects followed by HF, cardiogenic shock (CS) and ACS in 4 (3.7%) patients each, “probable myocarditis” in three patients (2.8%) while pericardial effusion was reported in two patients (1.9%). Patients who presented with acute cardiac injury were significantly older, had greater frequency of co-morbidities including hypertension, diabetes and cardiovascular diseases, higher total leucocyte count, liver enzymes, cardiac troponins and CK-MB levels. In addition, these patients had greater D-dimer positivity, higher lactate dehydrogenase (LDH) levels and increased use of IMV (Table 2). No significant difference was found in terms of NLR among subjects with cardiac injury than those without (7.2 ± 5.1 vs 6.5 ± 8.1; $P = 0.68$). There was no correlation between use of angiotensin converting enzymes inhibitors (ACEi)/angiotensin receptor blockers (ARBs) and cardiac injury in these subjects (ACEi/ARBs in cardiac injury vs no cardiac injury: 5 (17.8%) vs 8 (10%); $P = 0.27$).

Of the four patients who presented with ACS, anterior wall myocardial infarction (MI) was seen in 2/3, inferior wall and right ventricular (IW + RV) MI in one patient and non-ST segment elevation MI in one patient. Successful fibrinolysis was reported in two patients while the third one had a delayed presentation and hence managed on antiplatelets and parenteral anti-coagulation in the form of low molecular weight heparin for the duration of hospital stay. One of the patients with IW + RVMI succumbed on third day of presentation following multiple episodes of VT/VF. Of the three patients with “probable myocarditis”, complete recovery was documented in two while one patient developed CS and died on 9th day of hospital admission. Moderate pericardial effusion with no evidence of tamponade was seen in one patient while the other patient had mild effusion. Of the 15 patients who underwent CT pulmonary angiogram (CTPA), pulmonary embolism was reported in one patient.

3.3.2. Other complications

Other complications reported in this cohort of patients included sepsis in 25 (23.1%), ARDS in 12 (11.1%) and acute kidney injury in 8/108 patients. In addition, three patients developed diabetic ketoacidosis while one had an intracranial hemorrhage.

3.4. Outcomes

A total of 30 (27.8%) symptomatic critically ill patients died during the course of hospitalization. The patients in the deceased group as compared to the survivors were older, had significantly higher frequency of co-morbidities, hypertension, diabetes, chronic lung diseases, acute cardiac injury, cardiogenic shock and VT/VF. In addition, non-survivors had higher levels of ESR, NLR, troponin T, serum LDH and CK-MB levels (Table 3). There was no significant

Table 2
Comparison of clinical and laboratory parameters between COVID-19 patients with acute cardiac injury and those without acute cardiac injury.

	Acute cardiac injury present ($n = 28$)	Acute cardiac injury absent ($n = 80$)	*P*-value
Age (years)	60.9 ± 15.1	47.9 ± 17.4	**0.001**
Sex (M/F)	14/14 (50%/50%)	56/24 (70%/30%)	0.06
Duration of symptoms (in days)	4.4 ± 3.1	3.9 ± 2.1	0.31
Presence of co-morbidities	23 (82.1%)	37 (46.3%)	**0.001**
Hypertension	18 (64.3%)	23 (30%)	<**0.0001**
Diabetes	20 (71.4%)	15 (18.6%)	**0.005**
Cardiovascular disease	7 (25%)	7 (8.7%)	**0.03**
Heart Rate (per min)	94.4 ± 16.4	88.2 ± 14.1	0.06
Systolic blood pressure (mmHg)	118.5 ± 23.2	122.9 ± 17.5	0.29
Haemoglobin (gm/dl)	12.2 ± 2.9	12.8 ± 2.2	0.29
Total leucocyte count (per mm^3)	10430.4 ± 5640.9	8195.8 ± 5062.4	**0.05**
Lymphopenia	8 (28.6%)	27 (33.7%)	0.61
Platelet count (10^5/mL)	1.79 ± 0.87	2.17 ± 0.84	**0.04**
Aspartate aminotransferase (U/L)	177.7 ± 445.4	37.5 ± 30.3	**0.006**
Alanine aminotransferase (U/L)	114.1 ± 312.6	31.1 ± 25.1	**0.02**
Serum urea (mg/dl)	58.4 ± 40.9	34.8 ± 31.6	**0.002**
Serum creatinine (mg/dl)	2.1 ± 2.1	1.3 ± 1.4	**0.03**
Delta QTc (milliseconds)	26.1 ± 19.8	25.9 ± 27	0.96
Maximum QTc (milliseconds)	453.37 ± 32.7	441.5 ± 39.1	0.15
ST-T changes on ECG	9 (32.1%)	7 (8.7%)	**0.01**
Tisdale QT score	8.96 ± 2.98	6.34 ± 2.70	<**0.0001**
CK-MB (U/L)	55.7 ± 30.1	23.8 ± 7.9	<**0.0001**
Troponin-T (μg/L)	0.66 ± 1.28	0.01 ± 0.0008	**0.001**
D-dimer positivity[a]	16/19 (84.2%)	22/60 (36.6%)	<**0.0001**
Serum LDH (U/L)	1403 ± 1491.8	661.8 ± 298.8	**0.002**
VT/VF	0/78 (0%)	2/30 (6.67%)	**0.02**
SOFA score	5.21 ± 3.03	1.98 ± 2.30	<**0.0001**
Mortality	16 (57.1%)	14 (17.5%)	<**0.0001**

CK-MB: creatine kinase myocardial band; CRP: C-reactive protein; ECG: electrocardiogram; F: female; gm/dl: gram per deciliter; LDH: Lactate dehydrogenase; M: male; μg/L: microgram per litre; mg/dl: milligram per deciliter; mL: milliliter; SOFA: sequential organ function assessment; U/L: units per liter; VT/VF: ventricular tachycardia/ventricular fibrillation.
A P-value ≤0.05 was considered as statistically significant (highlighted in bold).
[a] Done in 79 patients.

Table 3
Comparison of clinical and laboratory parameters between survivors and non-survivors.

	Survivors ($n = 78$)	Non-Survivors ($n = 30$)	*P*-value
Age	48.8 ± 17	57.5 ± 18.1	**0.02**
Sex (M/F)	51/27 (65.4%/34.6%)	19/11 (63.3%/36.7%)	0.84
Duration of symptoms (in days)	3.9 ± 2.1	4.3 ± 3.1	0.41
Presence of co-morbidities	31 (39.7%)	19 (63.3%)	**0.03**
Hypertension	24 (30.7%)	17 (56.7%)	**0.01**
Diabetes	21 (26.9%)	14 (46.7%)	**0.05**
Cardiovascular disease	9 (11.5%)	5 (16.7%)	0.47
Heart Rate (per min)	86.3 ± 11.6	98.8 ± 18.5	<**0.0001**
Systolic blood pressure (mm Hg)	124.6 ± 17.8	105.6 ± 21.2	<**0.0001**
Haemoglobin (gm/dL)	12.8 ± 2.3	12.2 ± 2.6	0.18
Total leucocyte count (per mm^3)	7948.3 ± 3968.4	10924.7 ± 7387.6	**0.008**
Absolute lymphocytic count (per mm^3)	1650.4 ± 771.1	1059.5 ± 642.2	**0.0001**
Lymphopenia	17 (21.8%)	18 (60%)	<**0.0001**
NLR	4.75 ± 4.66	11.81 ± 10.37	<**0.0001**
Platelet count (10^5/mL)	2.19 ± 0.79	1.77 ± 0.96	**0.02**
Admission blood sugar (mg/dl)	120.3 ± 55.8	184.5 ± 125.8	<**0.0001**
ESR (mm/hr)	41.0 ± 29.1	58.9 ± 30.6	**0.024**
Aspartate aminotransferase (U/L)	32.2 ± 17.2	182.1 ± 428.6	**0.002**
Alanine aminotransferase (U/L)	30.9 ± 21	108.9 ± 303.2	**0.025**
Blood Urea (mg/dl)	33.2 ± 26.8	61.1 ± 46.8	<**0.0001**
Serum Creatinine (mg/dl)	1.4 ± 1.7	1.7 ± 1.5	0.36
CK-MB (U/L)	23.4 ± 14.3	38.8 ± 29.4	**0.01**
Troponin T (μg/L)	0.10 ± 0.49	0.61 ± 1.31	**0.02**
D-dimer positivity[a]	26/65 (40%)	12/14 (85.7.%)	**0.01**
Serum LDH (U/L)	638.1 ± 261.6	1530.2 ± 1455.4	<**0.0001**
SOFA score	1.65 ± 2.04	5.83 ± 2.53	<**0.0001**
Acute cardiac injury	12 (15.4%)	16 (53.3%)	<**0.0001**

CK-MB: creatine kinase myocardial band; CRP: C-reactive protein; ECG: electrocardiogram; ESR: erythrocyte sedimentation rate; F: female; gm/dl: gram per deciliter; LDH: Lactate dehydrogenase; M: male; μg/L: microgram per litre; mg/dl: milligram per deciliter; mL: milliliter; mm per hr: millimeter per hour; NLR: neutrophil to lymphocyte ratio; SOFA: sequential organ function assessment; U/L: units per liter.
A P-value ≤0.05 was considered as statistically significant (highlighted in bold).
[a] Done in 79 patients.

difference in outcomes in those using ACEi/ARBs than those without [5 (17.8%) vs 8 (10%); $P = 0.27$].

3.5. Predictors of mortality

Univariate logistic regression analysis showed that age (OR: 1.03; 95% CI: 1.01–1.05; $P = 0.02$), presence of co-morbidities (OR: 2.61; 95% CI: 1.10–6.25; $P = 0.03$), hypertension (OR: 2.94; 95% CI: 1.23–7.00; $P = 0.015$), lymphopenia (OR: 5.38; 95% CI: 2.17–13.30; $P < 0.0001$), use of inotropes (OR: 10.71; 95% CI: 3.06–37.40; $P < 0.0001$), NLR (OR: 1.16; 95% CI: 1.07–1.26; $P < 0.0001$) and acute cardiac injury (OR: 6.28; 95% CI: 2.44–16.17; $P < 0.0001$) were predictors of mortality. Multivariate logistic regression analysis showed that only acute cardiac injury (OR: 11.3; 95% CI:2.31–55.54; $P = 0.003$), lymphopenia (OR: 4.91; 95% CI:1.18–20.45; $P = 0.028$), use of inotropic agents (OR: 2.46; 95% CI:1.22–14.40; $P = 0.04$) and NLR (OR:1.1; 95% CI: 1.01–1.20; $P = 0.05$) were the independent predictors of mortality in this subset of patients. In this model, age (OR:1.02; 95% CI:0.99–1.06; $P = 0.16$) and hypertension (OR:0.33; 95% CI:0.09–1.21; $P = 0.95$) were not found to be independent predictors of mortality.

4. Discussion

This study provides a detailed understanding of cardiovascular implications of COVID-19 infection and its impact on the outcomes. Patients with co-morbidities such as hypertension, diabetes and CVD are often prone to COVID-19 infection and portends a bad prognosis.[6,9] In the series of 44,672 COVID patients, hypertension was documented in 2683 (12.8%), diabetes in 1102 (5.3%) while CVD in 873 (4.2%) subjects.[10] Similarly, in a meta-analysis, most common comorbidities reported were hypertension (17%), diabetes (8%) and CVD (5%).[11] In our series too, hypertension, diabetes and CVD were most common co-morbidities associated with COVID-19.

4.1. CV complications and COVID-19

In this study, acute cardiac injury was the most common cardiovascular complication in COVID-19 patients. Previous studies have documented prevalence of acute cardiac injury to be 7–44%.[3,4,12–15] Shi et al[3] had documented that acute cardiac injury was independently associated with increased mortality in COVID-19 patients. Similarly, Guo et al[4] reported myocardial injury in 52 (27.8%) of his 187 COVID-19 patients. Mortality rates were significantly higher in patients with increased cardiac troponins than those with normal levels (59.6% vs 8.9%). In addition, patients with co-morbidities such as hypertension, coronary artery disease and diabetes had higher troponin-T levels, a finding seen in our study too. There is no clarity regarding the exact mechanisms responsible for acute cardiac injury with the plausible hypothesis being i) direct viral invasion of the myocardium, ii) hypoxemia leading to acute cardiac injury, iii) "cytokine storm" and immune mediated cardiac injury and iv) stress cardiomyopathy.[2]

Other cardiovascular complications include myocarditis, ACS, HF, pericarditis, venous thromboembolism.[2] The data on myocarditis in COVID-19 is sparse with the reported prevalence ranging up to 12%.[5,16,17] while in our series "probable myocarditis" was present in 2.8%. HF in COVID-19 patients can either develop de novo as a result of myocardial injury or can be an exacerbation of pre-existing HF. In our series, 3.7% of patients had HF while Zhou and colleagues[14] documented HF in 23% patients. CS was reported in 3.7% of our patients and was associated with a poor outcome. Often these patients may have right sided cardiac involvement which can go unnoticed.[18] CS in these patients is associated with poor prognosis and a veno-arterial ECMO may be the last resort in these cases.[19] VTE is increasingly being recognised in COVID-19 patients and is often due to an underlying coagulopathy. Grillet et al[20] recently reported the prevalence of acute pulmonary embolism on CTPA in 23% of severe cases. We too had a case of acute pulmonary embolism in an elderly male however, the exact prevalence might be underrepresented in our series as only 15 patients underwent CTPA.

4.2. ECG abnormalities in COVID-19

ECG abnormalities reported in patients with COVID-19 include ST-T changes, QT prolongation and cardiac arrhythmias.[2] Sinus tachycardia has been reported as the most common ECG finding in COVID-19 patients, a finding seen in our series too.[21] First degree AV block was documented in five of our patients while one had sinus bradycardia. Recently, Peigh et al[22] reported sinus node dysfunction among two COVID-19 patients and proposed "myocardial inflammation or direct viral infiltration" as a plausible hypothesis.

Treatment of COVID-19 infection with HCQ, azithromycin and antivirals often leads to an increased risk of QT-interval prolongation and drug-induced TdP.[23] In a series of 84 patients receiving HCQ/azithromycin, there was a significant prolongation of QTc.[24] In nine patients, there was a severe prolongation of QTc to >500 ms however, none had an evidence of TdP. Similarly, in our series too, there was a significant increase in QT-interval following therapy with HCQ/azithromycin and 6.5% patients reported a severe prolongation of QTc >500 ms. Patients on HCQ and azithromycin combination had far more greater QT-interval prolongation than on HCQ alone, a finding similar to that reported by Bessière et al[25] and Mercuro et al.[26]

4.3. Outcomes and use of ACE inhibitors/ARBs in COVID-19

Previous studies have reported elderly patients with multiple co-morbidities had a poor outcome. In our study too, elderly patients with diabetes, hypertension had a worse prognosis. In addition, lymphopenia, leucocytosis, serum LDH, elevated cardiac biomarkers, D-dimer, interleukin-6 (IL-6) and serum creatinine have been considered as poor prognostic markers.[2,9] Patients with acute cardiac injury have been shown to have a worse outcomes.[3,4] Similar findings were observed in our series too. In our series, NLR was significantly higher among non-survivors and was an independent predictor of mortality. Similar findings have been reported by Yan et al[27] and Liu et al[28] wherein they found NLR to be an independent risk factor for in-hospital mortality. There has been lots of concern and speculation regarding the use of ACEi in these patients since the initial reports of an adverse outcomes with these medications.[29,30] However, we did not find any relationship between the usage of ACE inhibitors/ARBs and cardiac injury or worse outcomes, a finding which has been replicated in multiple studies.[2,31]

This was a single centre observational study including symptomatic patients over a short period of time with relatively small sample size. In addition, being retrospective in nature, not all laboratory investigations such as serum IL-6 were done in all patients. Owing to the resource limitations, only single measurements of cardiac troponins were obtained in our patients. Logistic issues hampered our ability to perform echocardiography in all patients and was limited to only those with a clinical indication for the same. A lack of cardiac magnetic resonance imaging and an endomyocardial biopsy owing to the logistic issues further prevented us to better characterise the patients with myocarditis. Larger multicentric studies are further warranted to further characterise the

CV outcomes and to confirm the role of cardiac injury in these patients.

5. Conclusions

Recent clinical and epidemiological studies have suggested that CV complications are common in COVID-19 patients however, the exact mechanism regarding the cardiovascular involvement is still unclear. Acute cardiac injury is a frequently encountered complication in COVID-19 patients and is associated with an increased mortality. Cardiac biomarkers can be used for risk stratification of critically ill patients in order to identify those who need intense monitoring. Currently advocated treatment regimens comprise QT-interval prolonging drugs such as HCQ and azithromycin which calls for strict cardiac monitoring especially in those who are critically ill. Risk stratification needs to be done to identify those with an increased risk for QT prolongation.

Ethics approval

This retrospective observational study was conducted in accordance with all relevant guidelines and procedures.

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Patient consent for publication

Not applicable.

Declaration of competing interest

Authors have no conflict of interest to disclose.

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