Original Article

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Clinical and Therapeutic Aspects of Cardiovascular Complications in COVID-19 Patients: A Cross-sectional Study

Pharmacology Section

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ABSTRACT

Introduction: Less is known regarding the Cardiovascular (CV) manifestations in Coronavirus Disease 2019 (COVID-19) patients. Among the complications, in patients with COVID-19 with pre-existing cardiovascular disease, there seem to be worse outcomes with an increased risk of mortality despite treatment. Several therapeutics are still under investigation for COVID-19 patients with cardiovascular impairment, but none of them has shown proven clinical efficacy to date.

Aim: To associate clinical and therapeutic aspects of cardiovascular complications in COVID-19 patients at a tertiary care hospital.

Materials and Methods: The data used for this single-centre cross-sectional study were collected from all the case sheets of COVID-19 positive patients with cardiovascular complications from the Medical Records Department of a Government Stanley Medical College and Hospital, Chennai, Tamil Nadu, India, between May 2020 and December 2020. Parameters like demographic details, co-morbid conditions, time of presentation, clinical presentation, complications, therapy and the outcome of the treatment in terms of mortality rate, Intensive Care Unit (ICU) admission and duration of stay in the hospital were obtained. Chi-square test or Odds Ratio (OR) was used to analyse the data for 97 patients.

Results: The mean age of total 97 patients in the study was 58.48±13.1 years and 30.9% were female. The most common cardiovascular complications include acute coronary syndrome (46.4%), conduction abnormalities (21.6%), cardiac failure (18.6%) and accelerated hypertension (11.3%). Remdesivir use significantly reduced the duration of ICU stay in COVID-19 patients (OR: 8.18; 95% CI: 2.9-22.9). There was no effect found with remdesivir on cardiovascular complications like acute coronary syndrome, conduction abnormalities, cardiac failure and accelerated hypertension. Cardiac drug use significantly reduced the duration of ICU stay in COVID-19 patients (OR: 3.3, 95% CI: 2.4-4.48). There was a significant reduction in cardiovascular complications like thromboembolism and conduction abnormalities with the use of cardiac drugs. In contrast, the use of steroids had no impact on the duration of ICU stay and other cardiovascular complications except for conduction abnormalities (OR: 5.2; 95% CI: 1.1-24.1).

Conclusion: COVID-19 patients presenting with cardiovascular complications were associated predominantly with pre-existing hypertension. The use of remdesivir and cardiac drugs significantly reduced the duration of ICU stay in COVID-19 patients. There was a significant reduction of cardiovascular complications like thromboembolism and conduction abnormalities only with the use of cardiac drugs.

Keywords: Coronavirus disease-2019, Hypertension, Intensive care unit, Remdesivir

INTRODUCTION

The outbreak of Coronavirus Disease 2019 (COVID-19), an infectious disease with the severe acute respiratory syndrome, has now become a worldwide pandemic [1-3]. Coronavirus disease 2019 (COVID-19) presents either asymptomatic or pneumonia-like symptoms (cough, fever, dyspnoea) [4]. The COVID-19 patients with other co-morbidities like diabetes, hypertension, Chronic Obstructive Pulmonary Disease (COPD), Cardiovascular Diseases (CVD), Human Immunodeficiency Virus (HIV), and malignancies, can develop life-threatening complications [5].

Despite the respiratory complication, COVID-19 is also associated with significant multiple organ dysfunction, including severe cardiac impairment. Emerging evidence reveals a direct interplay between COVID-19 and dire cardiovascular complications, including myocardial injury, heart failure, heart attack, myocarditis, arrhythmias as well as blood clots, which are accompanied by elevated risk and adverse outcomes among infected patients, even sudden death [6,7].

Among the complications, in COVID-19 patients with pre-existing cardiovascular disease, there seem to be worse outcomes with an increased risk of mortality [8]. Acute cardiac injury is the most commonly reported cardiac abnormality in COVID-19 that occurs in approximately 8-12% of all patients and there will be a significant elevation of cardiac troponins [9]. COVID-19 itself can induce arrhythmia, myocardial injury, acute coronary syndrome and venous thromboembolism [8].

Pre-existing CVD appears to be linked with adverse outcomes and also increased risk of mortality in COVID-19 patients [8]. The mechanisms of cardiac impairment were due to the invasion of coronavirus through angiotensin-converting enzyme-2 into cardiovascular tissue, which leads to endothelial dysfunction, atherosclerotic plaques destabilisation, diminished oxygen supply leading to cardiac stress, myocardial tissue damage, myocardial infarction and stent thrombosis [10]. Several therapeutics are still under investigation for COVID-19 patients with cardiovascular impairment, but none of them has shown proven clinical efficacy to date [7,11]. Less is known regarding the CV manifestations in COVID-19 patients. Though it has been shown that the pre-existing CV disease or development of CVD complications are associated with worse outcomes in COVID-19 patients, it remains unclear [9].

The purpose of the study was to summarise the therapeutic approaches for cardiovascular complications of COVID-19. The study aimed to associate clinical and therapeutic aspects of cardiovascular complications in COVID-19 patients at a tertiary care hospital. Also, the study describes the clinical pattern of COVID-19 positive patients with underlying cardiovascular risk factors and complications and also evaluates the cardiovascular complications and the therapeutic management followed in a tertiary care hospital.

MATERIALS AND METHODS

This study was a single-centre cross-sectional analysis from May 2020 to December 2020 of COVID-19 positive patients >18 years of age. The study was conducted after getting approval from Institutional Ethics Committee (ECR/131/Inst/TN/2013/RR-19). Data were collected from the case sheets in the Medical Records Department of Government Stanley Medical College and Hospital, Chennai, Tamil Nadu, India, for 8 months. In the present study, all the case sheets of COVID-19 positive patients from May 2020 to December 2020 with cardiovascular complications were analysed from the Medical Records Department (MRD).

Inclusion criteria: Case sheets with a confirmed diagnosis of COVID-19 via Reverse Transcriptase-Polymerase Chain Reaction assays (RT-PCR) performed on nasopharyngeal swab specimens were included. The study had included adult (>18 years) COVID-19 positive patients with or without cardiovascular risk factors like hypertension, diabetes and hypercholesterolaemia who developed cardiovascular complications like myocardial infarction, cardiomyopathy, arrhythmias and heart failure.

Exclusion criteria: Patients <18 years old with COVID-19 positive patients were excluded from the study.

The study was done by analysing the case sheets of 100 patients who tested positive via RT-PCR for COVID-19. Three patients were excluded who had incomplete clinical data on outcomes, leaving a final sample of 97 patients. A total of 97 patient's data was obtained from MRD.

Study Procedure

The data obtained from the medical records were demographic details like age (years), gender and other details like Systolic Blood Pressure (BP) (mmHg), diastolic BP (mmHg) and random blood glucose (mg/dL) co-morbid conditions, RT-PCR status, time of presentation, clinical features including chest pain, palpitation, bleeding, breathlessness, vitals like blood pressure, oxygen saturation, pulse rate and laboratory parameters like complete blood count, blood sugar (mg/dL), Electrocardiogram (ECG), D-dimer (ng/mL) (small fibrin degradation product in the blood present due to degradation of a blood clot by fibrinolysis), liver function test, renal function test, C-Reactive Protein (CRP) (mg/L), Interleukin 6 (pg/mL), lactate dehydrogenase (U/mL), coagulation profile (Prothrombin Time/International Normalised Ratio (PT/INR)} and radiographic findings (Chest X-Ray/Computed Tomography).

The therapy given to each patient like remdesivir, steroids, cardiac drugs and/or thrombolytic drugs was obtained from the data and the outcome of the treatment in terms of ICU admission and duration of stay in the hospital was obtained.

STATISTICAL ANALYSIS

Data were analysed using the statistical software package Microsoft Excel and Statistical Package for Social Sciences (SPSS) version 20.0. Demographic and clinical variables were tabulated. Continuous variables were expressed as Mean (M)±Standard Deviation (SD) if normally distributed and non normally distributed data were expressed as median (range). The 95% Confidence Intervals (CI) were used when appropriate. Categorical variables were summarised by frequencies and percentages and Fischer's-exact test or Chi-square test or Odds ratio was used to analyse. A p-value <0.05 was considered to be statistically significant.

RESULTS

Among 97 patients, the mean age was 58.48±13.1 years, 30 (30.9%) were female and 67 (69.1%) were male [Table/Fig-1]. Chronic medical conditions of these patients included hypertension 75 (77.3%), known case of Coronary Artery Disease (CAD) 58 (59.8%) and diabetes mellitus 51 (52.6%). Total 86 (88.7%) patients presented early to the hospital. Dyspnoea was seen in 80 (82.5%) patients and chest pain in 42 (43.3%) patients, were the common clinical presentations [Table/Fig-2]. Laboratory Investigations for markers like ferritin, CRP, Interleukin-6, D-dimer and Lactate Dehydrogenase (LDH) were higher than their normal limits.

Characteristics	Value (N=97)
Age (mean±SD)	58.48±13.1 years
Sex (M/F)	67/30
Systolic blood pressure (mean and range)	133 (80-220) mmHg
Diastolic blood pressure (mean and range)	82 (40-120) mmHg
Random blood glucose (mean±SD)	199±92.5 mg/dL

[Table/Fig-1]: Demographic details of the patients.

Characteristics	Number and percentage
Co-morbidities	
Hypertension	75 (77.3%)
Diabetes	51 (52.6%)
Known case of coronary artery disease	58 (59.8%)
Time of presentation	
Early	86 (88.7%)
Late	11 (11.3%)
Clinical presentation	
Chest pain	42 (43.3%)
Dyspnoea	80 (82.5%)
Both chest pain and dyspnoea	30 (30.9%)
Cardiovascular complications	
Acute coronary syndrome	45 (46.4%)
Conduction abnormalities (Atrial fibrillation, Bundle branch block)	21 (21.6%)
Cardiac failure	18 (18.6%)
Accelerated hypertension	11 (11.3%)
Thromboembolic complications (acute coronary syndrome, Deep vein thrombosis, Pulmonary embolism)	52 (53.6%)
Renal complications	7 (7.2%)
Therapy	
Remdesivir	51 (52.5%)
Steroids	68 (70.1%)
Cardiac drugs	96 (99%)
Thrombolytic drugs	41 (42.3%)
Duration of ICU stay	
Lesser than 5 days	67 (69.1%)
Greater than or equal to 5 days	30 (30.9%)
Laboratory investigations (mean±SD)	
Ferritin (10 to 250 ng/mL)	483±353 ng/mL
C-reactive protein (<3 mg/L)	57±47 mg/L
IL6 (<1.8 pg/mL)	105±173 pg/mL
D-dimer (<250 ng/mL)	2035±1561 ng/mL
Lactate dehydrogenase (140-280 U/mL)	737±207 U/mL

[Table/Fig-2]: Clinical characteristics of the patients.
ICU: Intensive care unit

The most common cardiovascular complications include acute coronary syndrome 45 (46.4%), conduction abnormalities 21 (21.6%), cardiac failure 18 (18.6%) and accelerated hypertension 11 (11.3%). Thromboembolic complications (acute coronary syndrome, deep vein thrombosis, pulmonary embolism) were seen in 52 (53.6%) patients. Renal complications like acute kidney injury was seen in 7 (7.2%) of patients. Around 99% of patients were treated with cardiac-related drugs. The other drugs used in the treatment were steroids 68 (70.1%), remdesivir 51 (52.5%) and thrombolytic drugs 41 (42.3%) [Table/Fig-2].

There was a statistically significant difference found between CAD patients on remdesivir treatment as compared to those patients with CAD without remdesivir treatment in terms of reduction in the duration of ICU stay to <5 days (p-value <0.001). Remdesivir treatment reduced the duration of ICU stay by <5 days in patients without CAD as compared to those patients without CAD who did not receive remdesivir treatment (p-value <0.01) [Table/Fig-3].

Drugs	Characteristics	n,%	Odds ratio (95% CI)
Remdesivir (n=51)	ICU stay <5 days	45 (88.2%)	8.18 (2.9-22.9)*
	ICU stay >5 days	6 (11.8%)	
	Thromboembolic disease	27 (52.9%)	0.94 (0.42-2.1)
	Conduction defect	13 (25.5%)	1.6 (0.6-4.3)
	Cardiac failure	9 (17.6%)	0.88 (0.3-2.4)
	Accelerated hypertension	5 (9.8%)	0.72 (0.2-2.5)
Cardiac drugs (n=96)	ICU stay <5 days	67 (69.8%)	3.3 (2.4-4.48)*
	ICU stay >5 days	29 (30.2%)	
	Thromboembolic disease	52 (54.2%)	2.18 (1.7-2.7)*
	Conduction defect	20 (20.8%)	4.8 (3.2-7.08)*
	Cardiac Failure	18 (18.8%)	NA
	Accelerated hypertension	11 (11.5%)	NA
Steroids (n=68)	ICU stay <5 days	46 (67.6%)	0.797 (0.3-2.08)
	ICU stay >5 days	22 (32.4%)	1.25 (0.48-3.2)
	Thromboembolic disease	36 (52.9%)	0.91 (0.38-2.1)
	Conduction defect	19 (27.9%)	5.2 (1.1- 24.1)*
	Cardiac failure	13 (19.1%)	1.1 (0.36-3.53)
	Accelerated hypertension	5 (7.4%)	0.3 (0.08-1.09)

[Table/Fig-3]: Association between therapy for COVID-19 and other clinical characteristics with respect to drug therapy.
NA: Not applicable; ICU: Intensive care unit; Please note that the patients only with accelerated hypertension have been included in the table; Statistical test: Odds Ratio, *p-value <0.05

Remdesivir use significantly reduced the duration of ICU stay in COVID-19 patients (OR: 8.18; 95%CI: 2.9-22.9). There was no effect found with remdesivir on cardiovascular complications like Acute coronary syndrome, conduction abnormalities, Cardiac failure and accelerated hypertension [Table/Fig-3].

Cardiac drugs significantly reduced the duration of ICU stay in COVID-19 patients (OR: 3.3; 95% CI: 2.4-4.48). There was a significant reduction in cardiovascular complications like thromboembolism (OR: 2.18; 95% CI: 1.7-2.7) and conduction abnormalities (OR: 4.8; 95% CI: 3.2-7.08) with the use of cardiac drugs (p-value <0.05) [Table/Fig-3].

In contrast, the use of steroids had no impact on the duration of ICU stay and other Cardiovascular (CV) complications except for conduction abnormalities (OR, 5.2; 95% CI, 1.1-24.1). Duration of ICU stay for lesser than 5 days was seen in 67.6% of patients [Table/Fig-3].

In a subgroup analysis, the majority of patients who were known cases of CAD were staying for <5 days in ICU than patients who did not had a history of CAD (OR: 0.37; 95%CI: 0.15-0.90). Complications at presentations related to thromboembolism were seen both in patients with a history of CAD and without a history of CAD. While conduction defects and cardiac failure were common among patients with a known case of CAD. In contrast, accelerated hypertension was common among those who did not had a history of CAD [Table/Fig-4].

Characteristics	Known case of CAD (n)	Not known case of CAD (n)	Odds ratio (95% CI)
ICU stay <5 days	45	22	0.37 (0.15-0.90)*
ICU stay >5 days	13	17	
Thromboembolic disease	26	26	0.4 (0.17-0.94)*
Conduction defect	18	3	5.4 (1.4-19.8)*
Cardiac failure	12	6	1.4 (0.48-4.2)*
Accelerated hypertension	4	7	0.34 (0.09-1.2)

[Table/Fig-4]: Association showing clinical characteristics of COVID-19 patients in relation to coronary artery disease.
CAD: Coronary artery disease; ICU: Intensive care unit
Statistical test: Odds Ratio; *p-value <0.05

[Table/Fig-5,6] shows association showing a reduction in ICU stay in relation with/without CAD patients and remdesivir respectively. The result was significant at a p-value <0.05.

Known case of CAD	ICU stay <5 days	ICU stay >5 days	Total
Patients with remdesivir	33	3	36
Patients without remdesivir	12	10	22
Total	45	13	58

[Table/Fig-5]: Association showing a reduction in ICU stay in relation to CAD patients and remdesivir.
CAD: Coronary artery disease; ICU: Intensive care unit
Statistical test: The Chi-square statistic is 10.8204. The p-value is 0.001004.
The result is significant at a p-value <0.05

Not known case of CAD	ICU stay <5 days	ICU stay >5 days	Total
Patients with remdesivir	12	3	15
Patients without remdesivir	10	14	24
Total	22	17	39

[Table/Fig-6]: Association showing a reduction in ICU stay in relation to non-CAD patients and remdesivir.
CAD: Coronary artery disease; ICU: Intensive care unit
Statistical test: The Chi-square statistic is 5.5163. The p-value is 0.01884.
The result is significant at a p-value <0.05

DISCUSSION

Pre-existing CV manifestations or development of CVD complications are associated with worse outcomes in COVID-19 patients. In this single-centre cross-sectional study, the clinical pattern of COVID-19 positive patients with underlying cardiovascular risk factors and complications were associated with the therapeutic management followed in a tertiary care hospital. In the final sample of 97 patients, the mean age was 58.48±13.1 years and 30 (30.9%) were female. This is in contrast to a study by Petersen E et al., where the mean age was more than 60 years with a predominantly female population [11].

Dyspnoea (82.5%) and chest pain (43.3%) were the common clinical presentation. A study by Peng Y et al., showed that in CV patients with COVID-19, apart from fever and cough, chest pain and dyspnoea were the common symptoms [7].

Among 97 patients, 54% of patients had hypertension with CAD and 39% of patients had hypertension with diabetes mellitus, 41% of patients had CAD with diabetes mellitus, 35% of patients had hypertension with diabetes mellitus with CAD and 40% of patients were not a known case of CAD. This is in accordance with Ejaz H et al., and Lee S et al., where hypertension being the most common comorbidity associated with COVID-19 [5,12].

About 88.7% of patients presented early within 7 days of COVID-19 infection and 11.3% of patients presented late after 7 days of COVID-19 infection. Of the 97 patients, 46.4% of patients presented with the acute coronary syndrome, 21.6% of patients presented with conduction abnormalities and 18.6% of patients presented with cardiac failure [6]. Total 86% of patients accounted for myocardial injury out of 97 patients as inferred by the study by Bardaji A et al., stating that myocardial injury was detected in one in every five patients with confirmed or ruled out COVID-19 cases [10,13].

Laboratory markers like ferritin, C-reactive protein, IL-6, D-dimer and lactate dehydrogenase were higher than their normal limits. Out of 97 patients, 84 patients had elevated CRP whose mean value was 57, which is inferred by the study by Ali N, stating that elevated CRP might be linked to the overproduction of inflammatory cytokines in

severe patients with COVID-19 but remains to be a non specific marker. Out of 84 patients with elevated CRP, 38 patients had acute coronary syndrome, 20 patients had conduction abnormalities and 13 patients had a cardiac failure [14].

In a pooled analysis of nine studies, Henry BM et al., showed that elevated LDH levels were associated with a ~6-fold increase in odds of developing the severe disease in patients with COVID-19 [15] which goes with this study where 19 patients had elevated LDH with a mean value of about 737 indicating the severity like acute coronary syndrome (five patients), conduction abnormalities (13 patients) and cardiac failure (three patients) accounting for myocardial injury.

As stated by Qeadan F et al., higher values of serum ferritin and D-dimer was associated with diffusing thrombosis which might require ICU [16], 57 patients had elevated serum ferritin and 11 patients had elevated D-dimer out of which 11 patients developed pulmonary embolism and deep vein thrombosis.

In the current study, remdesivir use significantly reduced the duration of ICU stay in COVID -19 patients (OR: 8.18; 95% CI: 2.9-22.9). This finding is consistent with the study by Garibaldi BT et al., which inferred that remdesivir recipients had a shorter time to clinical improvement than matched controls without remdesivir treatment (median, 5.0 days (interquartile range: 4.0-8.0 days) vs 7.0 days (interquartile range: 4.0-10.0 days); adjusted hazard ratio: 1.47 [95% CI: 1.22-1.79] [17].

While remdesivir therapy is correlated with each cardiovascular complications like acute coronary syndrome, conduction abnormalities, cardiac failure and accelerated hypertension, there was no effect found. This was similar to a study by Wang Y et al., which showed that in adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits [18].

Cardiac drug use in COVID-19 patients with cardiovascular complications significantly reduced the duration of ICU stay in COVID-19 patients (OR: 3.3; 95% CI: 2.4-4.48) and significantly reduced cardiovascular complications like thromboembolism and conduction abnormalities. Therefore, the addition of cardiac drugs to remdesivir therapy renders benefit in improving cardiovascular complications in COVID-19 patients.

There was a statistically significant difference found between CAD patients on remdesivir treatment as compared to those patients with CAD without remdesivir treatment in terms of reduction in the duration of ICU stay to <5 days (p-value <0.001). Steroids had no impact on the duration of ICU stay and other CV complications except for conduction abnormalities (OR: 5.2; 95% CI: 1.1-24.1). This is consistent with a study by Garibaldi et al., where the addition of remdesivir and corticosteroid did not reduce the time to death compared with remdesivir alone (Hazard Ratio: 1.94; 95% CI: 0.67-5.57) [17].

In subgroup analysis, the majority of patients who were known cases of CAD were staying for <5 days in ICU compared to those who did not had a history of CAD. The reason might be in patients with a history of CAD, the regular intake of cardiac drugs might have significantly reduced the duration of ICU stay in COVID-19 patients.

The pre-existing cardiovascular disease seems to be linked with worse outcomes and increased risk of death in patients with COVID-19. Whereas, COVID-19 itself can also induce myocardial injury, arrhythmia, acute coronary syndrome and venous thromboembolism [8]. Potential contributors to acute cardiac injury in the setting of COVID-19 include [13]:

- Acute changes in myocardial demand and supply due to tachycardia, hypotension, and hypoxemia resulting in type 2 myocardial infarction
- Acute coronary syndrome due to acute atherothrombosis.
- Microvascular dysfunction due to diffuse microthrombi or vascular injury
- Stress-related cardiomyopathy (Takotsubo syndrome)
- Non ischaemic myocardial injury due to a hyperinflammatory cytokine storm
- Direct viral cardiomyocyte toxicity and myocarditis.

This study signifies that the early diagnosis, prevention and treatment of predisposing conditions might reduce cardiovascular complications in COVID-19 patients.

So, it was very important for good and appropriate management of cardiovascular diseases as the COVID-19 pandemic was associated with a significant worsening of the mental health and mortality of patients with CVD [7,19].

Limitation(s)

This is a single-centre cross-sectional study with predominantly South Indian patients which may limit its generalisability. The sample population with CAD was relatively small. This study included only patients with documented evidence of CAD, which may underestimate CAD prevalence in this study. This study did not include patients who were still admitted at the time of analysis due to a lack of outcome data such as mortality and other potentially significant clinical outcomes such as length of stay were not taken into account. Compliance with guideline-recommended therapies for CAD was not considered and may influence clinical outcomes.

CONCLUSION(S)

The COVID-19 is associated with cardiovascular complications like acute myocardial infarction, heart failure, dysrhythmia, cardiogenic shock and hypertensive urgency. Patients presenting with cardiovascular complications post-COVID-19 infection were associated predominantly with pre-existing hypertension. The use of remdesivir significantly reduced the duration of ICU stays in COVID-19 patients. Also, patients with a history of CAD and intake of cardiac drug use significantly reduced the duration of ICU stay in COVID-19 patients. However, CAD in itself was not independently associated with an increase in ICU stay. Other covariates may play an important role in the poor outcomes and increased ICU stay in these COVID-19 patients.

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