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Original Article

Non-Obstructive Coronary Artery Disease due to COVID-19 Infection: St-Segment Elevation due to Endothelial Dysfunction

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ABSTRACT

The ongoing inflammatory process in COVID infection is reported to cause acute cardiac injury either due to direct cytotoxicity or oxidative stress injury to myocytes. Hypercoagulability and endothelial dysfunction are the two main events resulting in the transient thrombotic process. **Objective:** To assess the coronary artery occlusion in COVID infected patients presenting with ST-elevation myocardial injury. **Methods:** A descriptive case series study was conducted on 52 patients presenting with ST-elevation myocardial infarction along with COVID infection. Data was collected regarding demographic profile, Troponin levels, COVID PCR, changes in ECG, Echocardiographic findings and coronary arteries were assessed angiographically. Data were analyzed using SPSS software and various percentages were calculated. **Results:** Of all the 52 patients studied, 46 patients (88%) tested positive for COVID -19 on RT-PCR done via nasopharyngeal swab. Other 6 patients tested negative initially but they had findings on their CXR and HRCT suggestive of interstitial pneumonia. All the patients were in age group 30-60 years with 32 patients (62%) being males and 20 being females (38%). None of the patients previously had any history of angina or myocardial infarction. Inflammatory markers were raised in about 43 patients (82.7%). ECG showed ST segment elevation in anterior leads in 35 patients (67%) and in inferior leads in 9 patients (17%) and in lateral leads in 2 patients (3.8%). Qualitative Troponin I test was positive in all the patients, whereas, about 41 patients (78%) had Quantitative Troponin I test in high probability range. About 50 patients (96%) had Ejection Fraction greater than 45% and normal segmental wall motion analysis. The coronary arteries were reported to be normal or recanalized in 40 patients (76%) and mild-moderate disease in single or two vessels are present in rest of the 12 patients. None of the patients had shown culprit artery severe disease or clot burden on angiograms. **Conclusions:** Acute Cardiac injury in previously asymptomatic patients may be related to the pro-thrombotic state created by COVID-19 infection resulting in endothelial dysfunction and mimicking ST-elevation myocardial injury raising Troponin levels indicated by raised D-Dimers and CRP level. The auto-recanalization of the coronary arteries and normal echocardiographic findings, are good prognostic factors for the post cardiac injury rehabilitation.

INTRODUCTION

COVID-19 virus, since its outbreak in Wuhan China, has taken many discourses in its presentation as viral pneumonia, affecting the gastrointestinal, nervous, cardiovascular systems and creating a hypercoagulable state in the body, raising D-Dimers and acute phase proteins. This novel disease has not only affected the patients with pre-existing cardiovascular disease but also those who had no previous presentation or risk factors (e.g. diabetes, hypertension, hyperlipidemia) [1]. It affected the first case in Pakistan on 26th Feb, 2020 raising the count to 692,231 confirmed cases locally till 05th April 2021, with second highest number of confirmed cases (233,348) in Punjab [2]. The signs and symptoms have changed with each passing phase spanning from simple flu, headache,

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and sore throat, high grade fever to dizziness, encephalopathy, diarrhea and interstitial lung disease. Many studies have reported the ongoing inflammatory process in COVID-19 infection causing acute cardiac injury either due to direct cytotoxicity or oxidative stress injury to myocytes. The elevated levels of Troponin I have been reported in about 19.7% COVID-19 patients by Shi *et al.*, among 416 hospitalized patients with mortality rate of 51.2% compared to 4.5% in those who showed no evidence of myocardial injury [3]. The major causes of raised troponin levels have been reported to be hypotension, microthrombi, cytotoxic insult, vasospasm and raised level of inflammatory markers [2, 3]. A New York based case series has reported 18 COVID-19 patients with non-obstructive coronary arteries on angiography with new onset ST-segment elevation myocardial injury [2]. A case report showing diffuse ST-elevation on ECG has been reported by Inciardi *et al.*, in which elevated troponin and Pro-BNP levels were found with normal chest X-ray and no signs and symptoms of interstitial pneumonia [4]. A study done by Chinese authors, Chen C. et al. shows cardiac manifestation of arrythmia, myocarditis, heart failure and pericardial effusion observed in a number of patients with a poor survival prognosis [5]. Xu X. *et al.*, reported development of cardiomyopathy in a cohort of 41 severely sick patients with signs and symptoms of COVID-19 infection and heart failure [6]. ICU admitted patients with normal electrolytes and tissue injury induced arrythmia (44.5%) have been retrospectively assessed and reported by Wang C. *et al.*, [7]. Alteration of the Angiotensin-converting enzyme 2 pathways have been implicated in causing direct myocardial injury too [2, 3]. Kamil B. *et al.*, reported a case, in which COVID-19 infection was shown to mimic the STEMI as there was no obstructed lesion on coronary angiography of the patient, whereas ECG showed ST segment elevation in inferior leads. Upon taking complete history, patient revealed influenza-like symptoms in the entire family, 2 weeks back and tested herself positive for CCOVI-19 PCR later [8]. Two case reports of Takotsubo cardiomyopathy and spontaneous coronary artery dissection have also been reported in COVID-19 patients [2, 3]. Mustafa S. *et al.*, reported a case of myocarditis in COVID-19 patient showing ST elevation changes in anterior leads with raised troponin levels and diffuse hypokinesia of Echo [9]. Thrombotic process ongoing in this infection is also reported to cause idiopathic central vein occlusion and left ovarian thrombosis apart from cardiological manifestations [2, 3]. Mayo Hospital Lahore, being a referral center for COVID-19 infected patients, enabled us to come across unusual and atypical cardiovascular findings in them. This study was mainly focused on reviewing the endothelial dysfunction in the coronary arteries in our local society, caused by inflammatory flare and hypercoagulability in COVID-19 infection affecting the patients with no previous cardiac history, presenting in the form of ST-segment changes and cardiac enzymes elevation with minimum abnormal findings on echocardiography and coronary angiography, as evidenced by a number of case reports and studies available internationally.

METHODS

A descriptive case series study was conducted by enrolling about 52 patients presenting to Cardiology department, Mayo Hospital, Lahore, referred from various medical wards for ECG changes i.e. ST-segment elevation in anterior, inferior or lateral leads, from June, 2020 to October, 2020. These patients were tested for COVID-19 by RT-PCR done on nasopharyngeal swab and initial presentation was mostly due to fever, cough, sore throat dyspnea and chest pain. All the patients shifted to Cardiology department underwent quantitative Troponin test, echocardiography and coronary angiography. The angiographic images were assessed for categorization of any coronary artery lesion and wall motion along with Ejection Fraction analysis, done on echocardiography. The findings were reported by well qualified consultants in the department. The detailed medical history of the patients was taken after informed consent, using a pre-tested questionnaire. CXR, ECG, D-dimers, CRP, HBA1c and other basic blood reports were retrieved after proper consent. Data was analyzed and stratified according to age, risk factors like hypertension, diabetes, duration of symptoms, findings on Echo and angiography. Percentages were calculated for different sub-groups using SPSS 21 software.

RESULTS

Of all the 52 patients studied, 46 patients (88%) tested positive for COVID -19 on RT-PCR done via nasopharyngeal swab. Other 6 patients tested negative initially but they had findings on their CXR and HRCT suggestive of interstitial pneumonia. Most of the patients (38 out of 46) were shifted to Cardiology department within 72 hours of their initial presentation. The 6 patients who tested negative but had typical high-risk findings were shifted after a stay of about 7-8 days in COVID-19 ward or ICU (Table 1 and Figure 1).

Table 1: Time of Shifting to Cardiology Department

Total enrolled Patients = 52		
Time of shifting to Cardiology department	**RT-PCR +ve for COVID-19**	**RT-PCR -ve for COVID-19**
Within 72hrs	38	-
After 72 hrs	8	-
At 7th-8th day	-	6

All the patients were in age group 30-60 years with 32 males (62%) and 20 females (38%). None of the patients

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previously had any history of angina or myocardial infarction. Diabetes was reported in 31 patients (59%) and HBA1c levels were correlated. Only 12 patients (23%) had history of hypertension and 31% had diabetes previously (Figure 2). Atypical, mild to moderate chest pain was present in only 20 (38%) of the total patients. Other symptoms reported were high grade fever in 4 patients (7%), low grade fever of 99-100°F in 24 patients (46%), grade II-III dyspnea in 32 patients (61.5%) and cough in 37 patients (71%) (Figure 3). Inflammatory markers like D-dimers, CRP and Ferritin levels were raised in about 43 patients (82.7%). ECG showed ST segment elevation in anterior leads in 35 patients (67%), in inferior leads in 9 patients (17%), in lateral leads in 2 patients (3.8%) and T inversions with non-specific ST-T changes in 6 patients (11%). Qualitative Troponin I test was positive in all the patients, whereas, about 41 patients (78%) had Quantitative Troponin I test in high probability range and 11 patients (21%) had the quantitative values in borderline range. In Echocardiography 50 patients (96%) had Ejection Fraction greater than 45% with normal segmental wall motion analysis. The coronary arteries were reported to be normal or recanalized in 40 patients (76%) and mild-moderate disease in single or two vessels was present in rest of the 12 patients (23%) (Figure 4, 5). None of the patients had shown culprit artery severe disease or clot burden on angiograms. All the patients were managed medically and ECG changes started resolving in most of the patients with Ischemia Guided Medical Therapy while being hospitalized. Follow up was advised after two weeks for any worsening anginal symptoms or persistent ECG changes (Table 2).

Table 2: Signs, Symptoms and Demographics

Variables	Our Study
Demographics	
Age distribution	30-60 years (87% in b/w 30-45yrs
Gender distribution	Males: 62%, Females: 38%
Signs and Symptoms	
Chest pain with or without dyspnea	38%
Risk Factor Profile	
Previous episode of angina or MI	None
Diabetes	59%
Hypertension	12%
Investigations	
Rise in acute Inflammatory markers	82%
Quantitative Troponin I levels in high probability range	78%
ECG: ST-Segment elevations	87% (Anterior leads: 67%)
Ejection fraction <45%	96%
Segmental motion wall abnormality	0%
Angiography	Culprit related artery was normal or re-canalized
Patients who underwent Thrombolysis	80%
Investigations	
Patient outcome	Good prognosis & low mortality (Owing to low risk factor profile, less critical Pneumonia, early resolution of respiratory findings and early mobility of patients)

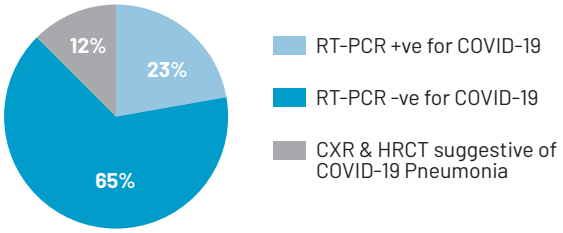

Figure 1: COVID-19 status at the time of Angiography

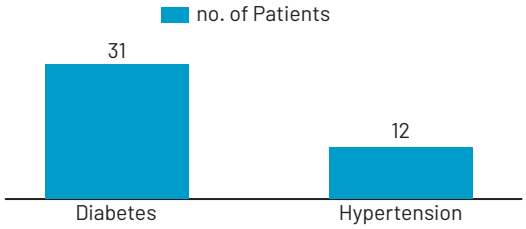

Figure 2: Frequency of co-morbidity

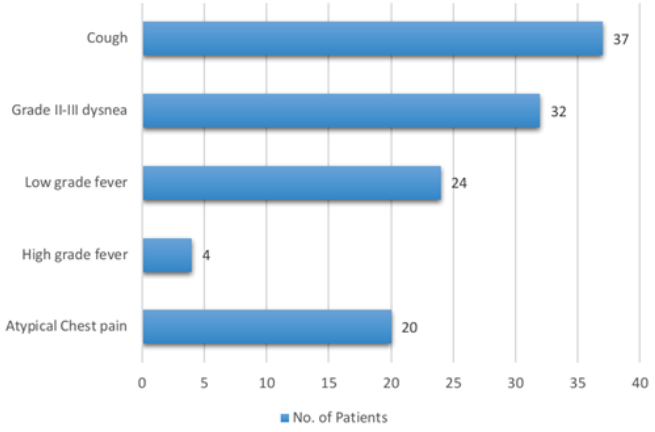

Figure 3: Clinical presentation of patients

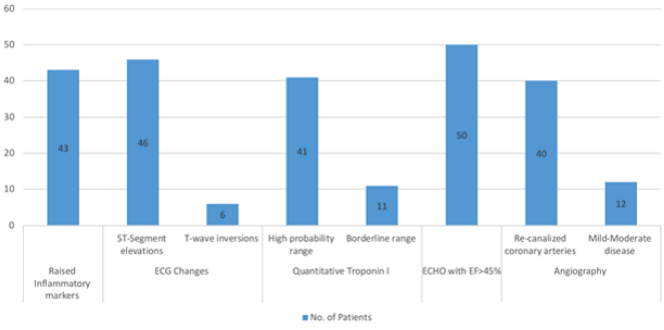

Figure 4: Clinical investigations of the patients

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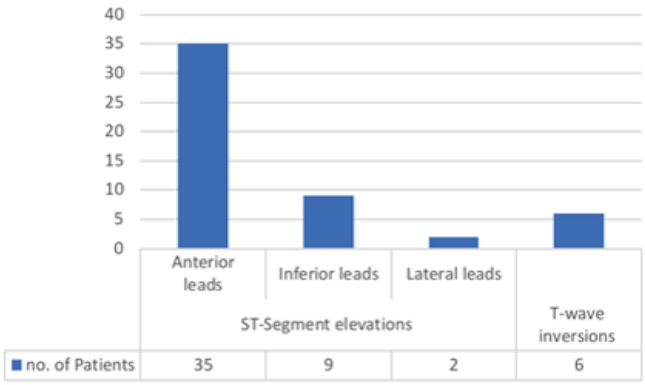

Figure 5: Electrocardiogram Changes

DISCUSSION

This is a first case series study conducted locally to assess related thrombotic cardiovascular events in COVID-19 patients. A lot of cases have been reported internationally showing probable hypercoagulable state in these patients and mimicking ST-elevation myocardial infarction. All the cases under study were discharged on medical management of anti-ischemic therapy and anticoagulation for short time. All the patients remained stable and no mortality was recorded due to cardiovascular cause. As evidenced by different case reports by Mustafa *et al.*, and Mengal *et al.*, our patients were also in the age group of 30-60year, but the striking factor was that most of the patients (87%) were in the 30-45 years of age group [9, 10]. The distribution of gender was same as various studies in literature review show, having a greater proportion of males (62%) than females (38%). Stefanini *et al.*, have discussed that most of the patients (78%) had a complaint of chest pain with or without dyspnea whereas, our patients reported chest pain in only 38%. However, 46% of the patients reported low grade fever with a median time of 5-10 days before the other symptoms or ECG changes [11]. We observed the raised D-Dimers and CRP level in these cardiac patients in about 82% cases as evidenced by studies conducted by Karbalai *et al.*, in China, and Tahir *et al.*, which also show a comparative rate of rise of acute inflammatory markers in 90% of the cases [12, 13]. All the patients were tested for COVID RT-PCR before proceeding in line with the guidelines of COVID-19 diagnosis supported by study on the epidemiological and clinical features of Corona virus disease conducted by and Xu *et al.*, and Wang *et al.*, [6, 7]. Out of these cases, about 12 patients (23%) were known positive before proceeding for angiography and underwent procedure after stabilization. Almost 34 patients (65%) were positive on PCR about 2 weeks before and were negative on PCR at the time of the coronary angiography. Whereas the rest of 06 patients were under high suspicion for their typical CXR and HRCT findings for COVID-19 pneumonia and were proceeded for angiography after initial stabilization for pneumonia. None of the patients had previous episode of angina or myocardial infarction but 59% of the patients had diabetes in their comorbid risk factors and only 12 patients had hypertension which is consistent with the results of the studies by Xu *et al.*, Wang *et al.*, He *et al.*, and Xiong *et al.*, [6, 7, 14, 15]. Total 87% of the patients had findings of ST-segment elevation in either anterior, inferior or lateral leads with more (67%) being in anterior leads, which is further supported by the studies and case report by Inciardi *et al.*, and Stefaninin *et al.*, Haussner *et al.*, where is the ration is about 70% for the anterior lead changes [4, 11, 16]. However, T wave inversions were only found in 06 of our patients. As per criteria of diagnosis of Myocardial infarction and AHA guidelines, all patient with ECG changes were tested for quantitative Troponin levels and levels were raised for all of them. Our 78% patients had high probability values as compared to 92% rates in other studies by Vetta *et al.*, Chen C *et al.*, and Bujak *et al.* [2, 5, 8]. The Echocardiographic findings of normal segmental wall motion analysis and ejection fraction greater than 45% reported in our study is in contrast to other studies available by Inciardi *et al.*, Bujak *et al.*, Stefaninin *et al.*, Tahir *et al.*, Bangalore *et al.*, which reported about 25-35% patients with some motion wall abnormality and 14-20% patients with ejection fraction less than 45 [4, 8, 11, 13, 17]. A striking finding of this study is all of the patients recruited underwent coronary angiography and the culprit related artery was normal or recanalized with no obstructive lesion, which is strongly supported by all the studies and case reports by Bujak *et al.*, Tahir *et al.*, and Stefanini *et al.*, Haussner *et al.*, Banagalore *et al.*, in which COVID-19 virus is reported to be causing ST elevation myocardial infarction [8, 13, 11, 16, 17]. However, none of the patients in these studies underwent thrombolysis but our 42 patients underwent thrombolysis with streptokinase in Emergency department. In accordance with the studies mentioned, all the patients were kept on Heparin infusion in the pre-procedure phase and direct Xa inhibitor anticoagulants were given for 6 weeks post procedure along with single antiplatelet agent as outlined in the guidelines erected in the study by Bikdeli *et al.* [18]. The good prognosis and low mortality rate in our patients can be supported by low risk factor profile and less critical pneumonia in term of intermittent low flow oxygen inhalation need, early resolution of respiratory findings and early mobility of the patients as compared to poor outcomes reported in cardiovascular complications by Shi *et al.*, Yang *et al.*, and Li *et al.*, [3, 19, 20].

CONCLUSIONS

We can conclude that acute Cardiac injury in previously asymptomatic patients may be related to the pro-thrombotic and hypercoagulable state created in the body

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by COVID-19 infection which leads to endothelial dysfunction and mimics ST-elevation myocardial injury raising Troponin levels. The raised D-dimer and CRP levels indicate that oxidative stress, cytokines and inflammatory interleukins might be involved in the pathophysiology. The auto-recanalization of the coronary arteries and normal echocardiographic findings, are good prognostic factors for the post cardiac injury rehabilitation, which can further be enhanced by timely management and careful monitoring along with guideline directed therapy.

Authors Contribution

Conceptualization: AT
Methodology: AJ, AF
Formal analysis: ZZ, SN. YK
Writing-review and editing: AT, AJ, AF, ZZ, SN, YK

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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