FREQUENCY OF MYOCARDITIS IN COVID-19 PATIENTS

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ABSTRACT

Objective: To determine frequency of myocarditis in COVID-19 patients.

Study Design: Cross-sectional study.

Place and Duration of Study: Armed Forces Institute of Cardiology-National Institute of Heart Diseases (AFIC-NIHD), Rawalpindi and Pak Emirates Military Hospital (PEMH), Rawalpindi, from Dec 2020 to May 2021.

Methodology: A total of 143 hospitalized patients who had tested positive for COVID-19 infection via RT-PCR were included in the study. Patients with pre-existing cardiac conditions were excluded. All patients underwent transthoracic echocardiography and their ejection fractions were recorded. Meticulous testing for the inflammatory markers including CRP, serum ferritin, procalcitonin and interleukin-6 (IL-6) and cardiac biomarker (NT-pro-BNP) was carried out. The data was recorded on a specially designed questionnaire and later transferred to SPSS-23 for analysis. Myocarditis was diagnosed on the basis of reduced Ejection Fraction or raised NT pro BNP or both in a person without any known cardiac pathologies before getting COVID-19.

Results: Out of total 143 COVID-19 patients included in the study, 24 patients (16.8%) developed myocarditis. The frequency of myocarditis in COVID-19 positive male population was 14.6% (10.5% of all myocarditis cases) and that of female population was 22.5% (6.3% of all myocarditis cases). The raised pro-inflammatory markers IL-6 and CRP were significantly associated with development of myocarditis while ferritin was not significantly associated. Only 28% of the study population recovered and got discharged from the hospital, however, there were no survivors among those who developed myocarditis.

Conclusion: Myocarditis is a serious complication of COVID-19 and directly linked to increased mortality risk. There is an increasing need to perform serial assays for the inflammatory as well as cardiac biomarkers including IL-6, Trop-I and NT-pro-BNP for early detection and prompt treatment of this not so uncommon complication.

Keywords: COVID-19, Echocardiography, IL-6, Myocarditis, NT-pro-BNP, Transthoracic.

INTRODUCTION

An outbreak of pneumonia of uncertain origin occurred in the Wuhan city of China by the end of year 2019 which was discovered to be due to a novel coronavirus thus given the name nCoV-19, later to be called Corona virus disease - COVID-19[1]. The disease turned out to be highly infectious and started to spread quickly around the world attaining the status of Public Health Emergency of international Concern (PHEIC) by WHO on Jan 30, 2020 and later declared a pandemic on 11thMarch, 2020[2]. The causative agent of COVID-19 is Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), which belongs to the family of beta-corona viruses but has a significantly higher human-to-human transmission rate than other coronaviruses (SARS, MERS).

SARS-CoV-2 is an air-borne virus and spreads mostly through aerosol and droplet infection. The viral entry into target cells is facilitated by binding of receptor site on the outer coat of the virus to the ACE2 receptors on the host cells. In humans, the ACE2 receptors are found predominantly on type II alveolar cells in the lungs and also on cardiovascular, renal and gastrointestinal tissues, thus, accounting for the multi-system organ dysfunction in cases of severe COVID-19[3].

The severity of COVID-19 ranges from asymptomatic but carrier infection to mild symptoms like flu like illness to a severe and systemic disease characterized by treatment resistant fever, acute respiratory distress syndrome (ARDS), cardiovascular complications (ACS, myocarditis, arrhythmias, heart block, cardiogenic shock), coagulation abnormalities, multi organ failure and even death[4].

The disease affects more severely the older male populations with comorbidities as compared to healthy individuals without comorbidities[5]. Age is the most important predictor of poor prognosis in COVID-19 but fatalities are not uncommon even in younger age group and most of them are due to cardiovascular origin specially Myocardial Infarction due to thromboembolic complications and myocarditis leading to acute and, most of the times, fatal heart failure.

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Myocarditis is the inflammation of cardiac myocytes and is a recognized complication of COVID-19. The pathophysiology of COVID-associated myocarditis can be attributed to direct viral injury as well as to the cytokine storm syndrome (CSS) which is the host's immunological response to SARS-CoV-2[6]. The clinical findings include electrocardiogram and cardiac biomarker changes and impaired cardiac function. Cardiac function impairment due to myocarditis as a result of coronavirus infection could be diagnosed through transthoracic echocardiography, cardiac magnetic resonance imaging and in most specialized centers via endomyocardial biopsy. The frequency of myocarditis in COVID-19 patients is largely unknown and there is scanty data available in literature.

METHODOLOGY

This descriptive cross-sectional study was conducted at AFIC-NIHD, Rawalpindi and COVID-19. ITC of Pak-Emirates Military Hospital, Rawalpindi after approval from the ethics committee of the institutes. Non probability consecutive type of sampling technique was used from December 2020 to May 2021.A total number of 143 patients were included in the study. Sample size was calculated using open epi calculator with confidence interval of 95% and margin of error of 6.5% and prevalence of response 20% (an average from previous international research). Inclusion criteria for the study population consisted of both male and female patients above 18 years of age, admitted to hospital for treatment of COVID-19. Patients with pre-existing cardiac conditions (congenital cardiac defects, previous history of myocardial infarction, valve diseases and heart failure) were excluded from the study. All the data of patients consisting of haematological investigations relevant to severity of cytokine storm (including CRP, serum ferritin and IL-6,), cardiac bio-markers (NT-pro BNP), radiological investigations (ejection fraction estimated by transthoracic echocardiography) and results of cardiac MRI (where available) were included in a specially designed questionnaire. Normal values for all the said markers are given in table-II. The data was then transferred to SPSS-23 and analyzed.

Myocarditis was diagnosed on the basis of reduced Ejection Fraction or raised NT pro BNP or both in a person without any known cardiac pathologies before getting COVID-19.

RESULTS

Out of 143 patients included in the study, out of 103 (72%) were males and 40 (28%) were females. The mean age of study population was 63.4 ± 12.763 *p* years. Among 143 patients, 58 (40.6%) had DM while HTN was present in 89 patients (62.6%). The mean ejection fraction of the study population was 52.2% (table-I).

Table-I: Demographic data of the study population.

Variable	Mean ± SD
Age	63.4 ± 12.7
Gender	
Male	103 (72%)
Female	40 (28%)
DM	58 (40.6%)
HTN	89 (62.6%)
EF %	52.2%

A total of 24 patients developed COVID related myocarditis (16.8%) (fig-1). The frequency of myocarditis in COVID-19 positive male population was 14.6% (10.5% of all myocarditis cases) and that of female population was 22.5% (6.3% of all myocarditis cases) (fig-2).

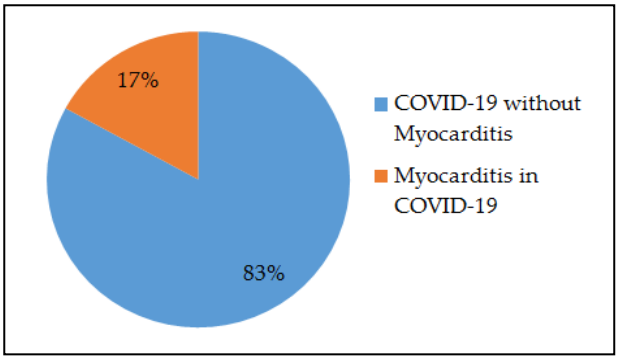

Figure-1: Frequency of myocarditis in COVID-19.

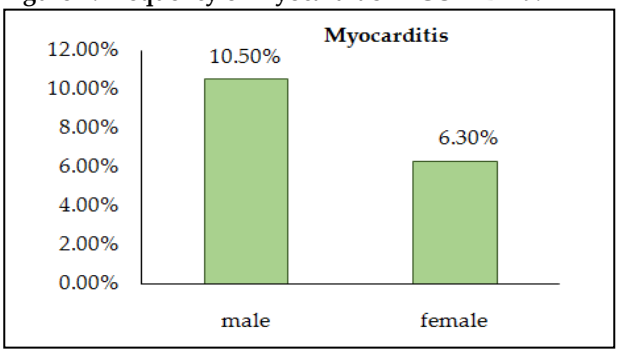

Figure-2: Gender wise distribution of myocarditis in COVID-19.

The pro inflammatory markers included in the study were CRP, IL-6 and serum Ferritin. The mean CRP level of myocarditis patients was 126.5 ± 122.8. Mean IL-6 level was found to be 411.8 ± 699.2. While the mean ferritin of myocarditis patients was 936.16 ±

777.5. Cardiac investigations included transthoracic echocardiography and NT-pro BNP. Echocardiography revealed that the mean ejection fraction of myocarditis patients was 35.0 ± 9.6% while mean NT-pro BNP level was 8501.9 ± 10097. In addition, Cardiac MRI was performed on 25 COVID-19 patients with suspicion of myocarditis and out of those 25 patients, 100% were identified to be having acute myocarditis. A total of 28% patients included in the study recovered from COVID-19 while 72% had in-hospital death. There were no survivors among the patients who developed myocarditis.

Table-II: Association of various biomarkers with COVID-19 related myocarditis.

	Myocarditis	n	Mean ± SD	Normal Value	*p*-value
CRP	Yes	24	126.5 ± 122.8	<10mg/ml	0.022
	No	119	77.9 ± 86.8		
IL6	Yes	24	411.8 ± 699.2	0-7pg/ml	0.014
	No	109	144.4 ± 412.3		
NT-pro-BNP	Yes	23	8501.9 ± 10097.2	0-125pg/ml	0.001
	No	92	1558.8 ± 4140.7		
EF	Yes	24	35.0 ± 9.6	60-70%	0.001
	No	119	55.0 ± 6.9		

DISCUSSION

By the end of 2019, a new disease, pneumonia of uncertain origin was being reported in Wuhan city of China. It was declared a pandemic by WHO on 11th March 2020. Till date it has affected 176 million people and claimed lives of 3.8 million and continues to wreak HAVOC among the lives of many. The culprit behind COVID-19 is Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). With extensive research all around the world, it was found out that COVID-19 is not just disease of respiratory system, rather it is a diverse syndrome which affects various systems and in its most severe form causes multi-organ failure and death.

Among the many potential sequelae of COVID-19[7], one of the most concerning is myocarditis, which is defined as inflammation of the heart muscle and is commonly caused by a viral infection, according to the American Heart Association[8].

The common symptoms of myocarditis include chest pain and shortness of breath, as well as arrhythmias and fatigue. In more severe cases, myocarditis can lead to heart failure, an ischaemic event including myocardial infarction or stroke, and even sudden cardiac arrest[9]. The connection between COVID-19 and myocarditis is currently only theoretical and point to either the virus itself or potentially the immune response to the virus (the cytokine storm syndrome). The former theory was presented by Siripanthong and colleagues in September 2020 and states that virus enters the heart tissues via the ACE-2 receptors[6], while the immune mediated response was considered the cause of myocarditis in COVID-19 by Tschöpe and colleagues and was published in Nature[10]. However, both theories need further evaluation in relation to COVID-19. In our study we found a strong association of raised pro-inflammatory markers (IL-6 and CRP) in patients suspected of myocarditis. Serum ferritin, although an inflammatory marker was raised in almost all the patients and was not significantly associated with development of myocarditis.

The frequency of COVID-19 induced myocarditis is not well-known[3,6]. Most of the data about frequency of myocarditis is available on studies done on young athletes. One study found that the incidence of myocarditis in athletes was 1.4%[11]. Another study showed the incidence to be 2.3%[12]. A study published in JAMA Cardiology suggested that after being screened via cardiac magnetic resonance imaging, 60% of COVID-19 survivors had developed myocarditis[13]. It was a surprising finding and thus prompted further research. Because of these variable results, it could be deduced that development of myocarditis in COVID-19 patients is some what dependent on multiple individual, ethnic or genetic factors and that area of research remains unexplored. There is a need to find the frequency in our local context to tailor the treatment regimen according to the risk present.

A large number of COVID-19 patients have mild to moderate symptoms[14], and they continue to treat themselves at home. Due to this reason, proper screening of the patient investigations cannot be done. Hence if the findings of our study are to be extrapolated to the general population, then there might be many cases who are at risk of developing cardiac complications without knowing and it is an alarming situation as it can lead to long term negative outcomes for the patients as well burden on the already strained healthcare

system. Among all diagnostic investigations, cardiac MRI is the most sensitive investigation modality to detect myocarditis[15]. In our study, cardiac MRI could be done on 25 suspected cases of myocarditis on the basis of raised NT-pro BNP and 100% were found to be having myocarditis.

This study further investigated various inflammatory markers to predict their association of the cytokine storm syndrome to the development of myocarditis in COVID-19. The pro-inflammatory markers included CRP, IL-6 and serum ferritin. All the patients who developed myocarditis had raised level of CRP and IL-6 and it was significantly associated (p-value<0.05). Findings of raised IL-6 levels in myocarditis were consistent with international research[16]. Serum ferritin level was not found to be significantly associated with myocarditis (p-value=0.91). Cardiac biomarker in our study was NT-pro-BNP and was significantly associated with myocarditis (p-value<0.05)[17]. The mean value of ejection fraction in patients with myocarditis was 35% (p-value <0.05).

Many studies suggest that myocarditis develops after COVID-19 and its incidence need to be further investigated[18], however, myocarditis is challenging to diagnose, further research is needed to screen covid patients for this potentially lethal complication.

LIMITATION OF STUDY

The limitations of this study were scarcity of resources to perform expensive investigations like cardiac MRI for all the patients.

CONCLUSION

Myocarditis is a serious complication of COVID-19 and directly linked to increased mortality risk, especially in younger population. Its incidence is inversely related to advancing age. There is an increasing need to perform serial assays for the inflammatory as well as cardiac biomarkers including IL-6, serum ferritin Trop-I and NT-pro-BNP for early detection and prompt treatment of this not so uncommon but potentially fatal complication of COVID-19.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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