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Cardiac Complications in COVID-19 Infected Patients Admitted in a Tertiary Care Hospital in Karachi

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Abstract: The objective of the current cross-sectional study was to determine the frequency, types, associations, and outcome of cardiac complications in hospitalized COVID-19 infected patients. This study was conducted at Dr. Ziauddin University Hospital, Clifton campus, Karachi, from 1st April 2020 to 31st March 2021. A total number of 1,050 patients were included in the study through consecutive sampling with the diagnosis of COVID-19 infection. Patients were labeled as having complications secondary to COVID pneumonia only after comparing their hospital's clinical course with their baseline status. The independent variables were age, gender, cardiovascular risk factors (smoking status, diabetes mellitus, and hypertension), while the dependent variables were cardiac complications including acute coronary syndrome, myocarditis, pericarditis, and arrhythmias. The Association of complications with independent variables was analyzed by applying the Chi-Square test and statistical significance was set at a P-value of ≤0.05. There were 599 (57.0%) males and 451 (43.0%) females with the mean age of the participants being 55.1 years (± 13.08) years. Diabetes and hypertension were present in 451 (43.0%) and 490 (46.6%) patients respectively. Out of 1050 patients, the primary endpoint occurred in 55.6% of patients, including 23.1% acute coronary syndrome, 19.3% arrhythmias, 10.8% myocarditis, and 2.2% pericarditis. Analysis of secondary endpoint showed that 31.1% of patients had severe disease out of which the mortality was 39.4%. Acute coronary syndrome and atrial fibrillation are frequent complications, especially in those with severe disease and multi-organ dysfunction. Furthermore, the incidence of these complications is higher in patients with multiple co-morbidities. Considering the devastating impact this pandemic has had globally, it is important to know the cardiac involvement this condition can have along with the debilitating outcome so that healthcare facilities can be upgraded to provide better care to save lives.

Keywords: COVID-19, myocarditis, pericarditis, acute coronary syndrome, myocardial infarction.

卡拉奇三级医院收治的 COVID-19 感染患者的心脏并发症

摘要：当前横断面研究的目的是确定住院新冠肺炎感染患者心脏并发症的频率、类型、关联和结果。这项研究于2020年4月1日至2021年3月31日在卡拉奇克利夫顿校区的齐奥丁大学医院进行。通过连续采样诊断为新冠肺炎感染，共有1,050名患者被纳入研究。只有在将医院的临床过程与其基线状态进行比较后，患者才被标记为患有继发于冠状病毒病肺炎的并发症。自变量是年龄、性别、心血管危险因素（吸烟状况、糖尿病和高血压），而因变量是心脏并发症，包括急性冠状动脉综合征、心肌炎、心包炎和心律失常。通过应用卡方检验分析并发症与自变量的关联，并将统计学显着性设定为P值≤0.05。男性599人（57.0%），女性451人（

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43.0%），平均年龄55.1岁（±13.08）岁。糖尿病和高血压分别出现在451(43.0%)和490(46.6%)患者中。在1050名患者中，主要终点发生在55.6%的患者中，包括23.1%的急性冠状动脉综合征、19.3%的心律失常、10.8%的心肌炎和2.2%的心包炎。次要终点分析显示，31.1%的患者患有重症，其中病死率为39.4%。急性冠状动脉综合征和心房颤动是常见的并发症，尤其是在患有严重疾病和多器官功能障碍的患者中。此外，在患有多种合并症的患者中，这些并发症的发生率更高。考虑到这种流行病在全球范围内造成的破坏性影响，重要的是要了解这种情况可能会导致心脏受累以及使人衰弱的结果，以便可以升级医疗设施以提供更好的护理以挽救生命。

关键词：新冠肺炎、心肌炎、心包炎、急性冠状动脉综合征、心肌梗塞。

1. Introduction

Coronavirus disease started in Wuhan, the city of China in November 2019. COVID-19 is caused by severe acute respiratory syndrome coronavirus. It was considered a Public Health Emergency in January 2020 but due to the rising magnitude and spread of infection throughout 191 countries over the world, it was labeled as a pandemic by World Health Organization on 11th March 2020 [1]. This outbreak was supposed to be limited to zoonotic transmission arising from the seafood market which is involved in trading wild animals but the person-to-person transmission was also observed [2].

The clinical manifestations of COVID-19 infection vary from asymptomatic, mild respiratory symptoms to severe viral pneumonia. It was initially thought to affect only the respiratory system but according to several studies, gastrointestinal, neurological, and cardiovascular complications were also experienced by infected patients. The literature revealed that patients with co-morbidities like diabetes mellitus, hypertension, and a history of cardiovascular disease have worse outcomes and are more likely to require intensive care units as compared to their counterparts with no co-morbidities [3]. Several pieces of the research reported that Middle East Respiratory Syndrome can cause acute myocarditis and heart failure. Both MERS-COV and SARS-COV belong to the same family of viruses and share similar pathogenicity towards a cardiac system which leads to difficulty in treatment and recovery of infected patients. Myocardial injury was reported among 5 out of the first 41 patients infected in Wuhan. On assessment, infected patients had higher levels of troponin I > 28pg/ml [4, 5].

A meta-analysis, conducted on 1527 patients with COVID-19 infection, determined the prevalence of cardiovascular diseases in infected patients. Studies reported 17.1%, 16.4%, and 9.7% prevalence of diabetes mellitus, cardiac and cerebrovascular diseases, respectively [6]. Another study conducted at Grady Memorial Hospital of United States on a cohort of diabetes mellitus and non-diabetes mellitus patients identified that diabetic patients had a higher odds ratio or are more likely to develop composite cardiovascular endpoint (OR 3.0, CI 1.0-8.9), acute heart failure (OR 7.9, CI 1.6-40.3) and new-onset atrial fibrillation (OR 28.7, CI 1.3-647.9) [7]. The report published by Qiuorang et al. on 150 patients of Wuhan City on clinical predictors identified that among 68 deaths, 53% died due to respiratory failure followed by 7% by myocardial injury, 33% due to both causes, and 7% by unknown causes. The study also confirmed the existence of fulminant myocarditis in SARS-CoV-2 infected patients. Moreover, the study concluded with bringing the concentration of physicians towards cardiac complications which could lead to worse outcomes in infected patients [8]. Another research was conducted on registered cases from 28th March 2020 to 3rd July 2020 by CAPACITY COVID international patient registry to determine the cardiovascular complications. This registry contains a record of 13 European countries on confirmed COVID-19 patients. Research reported that among 3011 patients, 31% of patients had a cardiac history with predominant coronary artery disease. Out of 19.8% of patients who died during hospitalization, 2.7% had cardiac causes. Cardiac complications were observed in 11% patients, which included 4.7% atrial fibrillation followed by 1.8% heart failure, 0.5% acute coronary syndrome, 0.5% ventricular arrhythmia, 0.1% bacterial endocarditis and 0.03% pericarditis [9].

Existing literature from other countries reported a significant association of cardiac complications with COVID-19 infected patients but there are limited studies available in our region to present evidence-based results on these findings. The current study will fill this gap by conducting a study on existing data to determine the cardiac complications in patients hospitalized with COVID-19 infection. The objective

of this study is to determine the frequency, types, associations, and outcome of cardiac complications in hospitalized COVID-19 infected patients. The relevant results can aid in the design and implementation of strategies to anticipate these complications in advance, and introduce therapeutic measures to combat these devastating effects that increase both morbidity and mortality.

2. Material and Methods

This is a cross-sectional descriptive study conducted at Dr. Ziauddin Hospital, Clifton campus, which is a 150 bedded tertiary care teaching hospital in Karachi. It was conducted from 1st April 2020 to 31st March 2021. A total of 1,050 patients admitted during this period were included in the study. The inclusion criterion was all patients aged 18 years or older admitted with laboratory or radiological diagnosis of COVID-19 infection. The exclusion criteria included patients with a previous history of cardiovascular diseases (LV dysfunction, ischemic heart disease, congenital or valvular diseases) or patients who left against medical advice (LAMA). Patients were labeled as having complications secondary to COVID pneumonia only after comparing their hospital's clinical course with their baseline status. The approval from the ethical review committee (ERC) of the hospital was taken with reference number 3690421GHCAR, dated 17th May 2021. Informed consent was waived off due to minimal risk to the privacy of individuals; however, patients' identity was kept anonymous and confidentiality was maintained throughout the study. The stated hospital's electronic medical records were reviewed for the given time to identify patients with the diagnosis of SARS-CoV-2 infection. A structured questionnaire was used to obtain detailed information on socio-demographic characteristics, co-morbidities, cardiac biomarkers, echocardiography, ECG findings, previous cardiac history, and cardiac outcomes.

The primary endpoint was defined as a composite of cardiac complications developing on a background of COVID-19 infection; namely acute coronary syndrome, arrhythmias, myocarditis, and pericarditis. The secondary endpoint was to investigate the impact of disease severity and cardiac complications on the morbidity and mortality of the patient.

The diagnosis of COVID-19 was made on findings of High-Resolution Computed Tomography (HRCT) such as consolidation, bilateral and peripheral disease, greater total lung involvement, linear opacities "crazy paving" and the reverse "halo sign" [10], Chest X-ray findings like peripheral haze and bilateral infiltration [11] and positive COVID-19 nasopharyngeal swab PCR test [12-14]. Acute Coronary Syndrome is defined according to the fourth universal definition of myocardial infarction [15]. It was diagnosed if serum levels of cardiac biomarkers such as troponin, I was above the 99th percentile upper reference limit, or new abnormalities (ST-segment changes or new-onset bundle branch block) were seen in electrocardiography and echocardiography. New-onset arrhythmias were diagnosed based on electrocardiographic changes. Acute myocarditis is defined as an inflammatory disease of the myocardium diagnosed based on troponin I greater than 0.03 ng /ml and established histological, immunological, and immunohistochemical criteria. Pericarditis or inflammation of the pericardium was diagnosed based on chest pain, pericardial friction rub, ECG changes (new widespread ST elevation or PR depression), and pericardial effusion. ARDS is defined using the Berlin Definition developed by the European Society of Intensive Care Medicine, The American Thoracic Society, and the Society of Critical Care Medicine in 2013 [13]. ARDS was classified as mild, moderate, and severe based on the ratio of arterial oxygen tension (PaO2) over inspired oxygen fraction (FiO2). AKI is defined according to the kidney disease improving global outcomes classification, as an abrupt decrease in kidney function, which encompasses both structural damage and loss of function, leading to decreased glomerular filtration rate (GFR), an acute rise in serum creatinine levels, and decline in urine output over a given time interval. The shock was defined according to the interim guidance of WHO for novel coronavirus.

Data were analyzed using SPSS 23. The independent variables were age, gender, cardiovascular risk factors (smoking status, diabetes mellitus, and hypertension), while the dependent variables were cardiac complications including acute coronary syndrome, myocarditis, pericarditis, and arrhythmias. Descriptive statistics of socio-demographic variables were presented as mean, standard deviation, or frequency percentages. The Association of complications with independent variables was analyzed by applying the Chi-Square test. Statistical significance was set at a P-value of ≤ 0.05 and where necessary, Bonferroni's correction was used to adjust for multiple comparisons with a corrected P-value (P′) of <0.05.

3. Results

The study population included 1,050 patients who were admitted to the hospital with laboratory or radiologically confirmed diagnosis of SARS-CoV-2 infection. There were 599 (57.0%) males and 451 (43.0%) females with the mean age of the participants being 55.1 years (± 13.08) years. In the cohort, 451 (43.0%) patients had pre-existing diabetes mellitus, 490 (46.6%) patients were hypertensive and 397 (37.8%) were active smokers. Of the 1050 patients, 723 (68.8%) were admitted to the isolation units whereas 327 (31.1%) were transferred to intensive care units because of severe hypoxemia (requiring high flow oxygen or mechanical ventilation), multi-organ

dysfunction, and/or hemodynamic instability.

Table 1 shows the baseline characteristics and cardiac complications encountered in our patients. The acute coronary syndrome was found to be the most common cardiac complication. Out of 1050 COVID-19 infected patients, 243 (23.1%) had ACS. ST-elevation myocardial infarction, characterized by acute chest pain or ST-segment elevation on EKG, was present in 86 (8.1%) patients, whereas non-ST elevation myocardial infarction, characterized by elevated cardiac biomarkers, occurred in 157 (14.9%) patients. Cardiac arrhythmias were the second most common complication, encountered in 203 (19.3%) patients, out of which atrial fibrillation accounted for 72.4% of the arrhythmias (14.0% cases), followed by supraventricular tachycardia (4.0%), ventricular tachycardia (0.8%), atrial flutter (0.2%) and ventricular fibrillation (0.1%). Myocarditis occurred in 114 (10.8%) patients whereas the incidence of pericarditis was 2.2%.

As shown in Fig. 1, patients were divided into six groups, based on their age. Table 1 demonstrates that most of the patients (28.6%) lied in the age group of 61 to 70 years, followed by 27.6% in the age group of 51 to 60 years. The occurrence of complications was directly related to the advancing age of the patient. This is especially significant for STE-ACS where the incidence was 2.3% in patients less than 50 years of age compared to 97.6% in patients greater than 50 years of age. This was also true for NSTE-ACS where 63.05% of the cases were encountered in patients above 50 years of age (p-value = 0.000). Arrhythmias occurred more in the elderly as compared to their young counterparts (p-value = 0.000). Only 32 out of 203 (15.7%) patients had new-onset arrhythmias from less than 50 years age group whereas 171 (84.2%) patients who had the same presentation were greater than 50 years of age. 57.0% cases of myocarditis were encountered in patients older than 50 years. The incidence of pericarditis was more in the younger population – 79.1% of the patients who had pericarditis were less than 50 years old (p-value = 0.000).

Table 1 also shows that the incidence of STEMI and arrhythmias was more in the male patients as compared to their female counterparts (72.0% and 67.4% in males compared to 27.9% and 32.5% in females respectively) (p-value = 0.003 and 0.001 respectively). In contrast, 56.1% and 70.8% cases of myocarditis and pericarditis occurred in the female population compared to 43.8% and 29.1% in the males respectively (p-value = 0.003 and 0.005 respectively).

The incidence of acute coronary syndrome in the background of SARS-CoV-2 infection was strongly associated with the co-morbidities of the patients. Out of 451 diabetics, 61 (13.5%) patients had STEMI, 93 (20.6%) had NSTEMI while 297 (65.8%) did not have ACS. This is in contrast with the non-diabetic population where the incidence of STEMI and NSTEMI was 4.1% and 10.6% respectively (p-value = 0.000). Results were quite similar in those with hypertension or a history of smoking where 165 out of 490 (33.6%) and 164 out of 397 (41.3%) patients developed acute coronary syndrome respectively (p-value = 0.000 and 0.000 respectively). No significant association was found between diabetes, hypertension, or tobacco smoking with the occurrence of arrhythmias, myocarditis, or pericarditis.

Table 2 depicts the incidence of cardiac complications concerning the severity of COVID-19 infection and its impact on the outcome of the disease. In patients developing severe ARDS, multi-organ involvement characterized by acute renal injury, and/or hemodynamic instability, the incidence of complications was comparatively higher. The incidence of ACS in patients with severe ARDS, AKI, and shock was 76.7%, 31.0%, and 65.3% as compared to 20.1%, 21.0%, and 21.0% in patients with mild to moderate lung disease, no organ involvement, and no hemodynamic instability respectively (p-value = 0.000, 0.003 and 0.000 respectively). Severe disease was associated with a significantly increased mortality rate (p-value = 0.000).

Table 3 describes the association of the complications with the patient's outcome. Patients who had acute coronary syndrome had a poor outcome as the mortality rate was 38.6% in the ACS group as compared to 2.7% in the non-ACS group (p-value = 0.000). Similar results were found in those who had ventricular tachycardia and ventricular fibrillation as the mortality was 100% and 77.7% respectively.

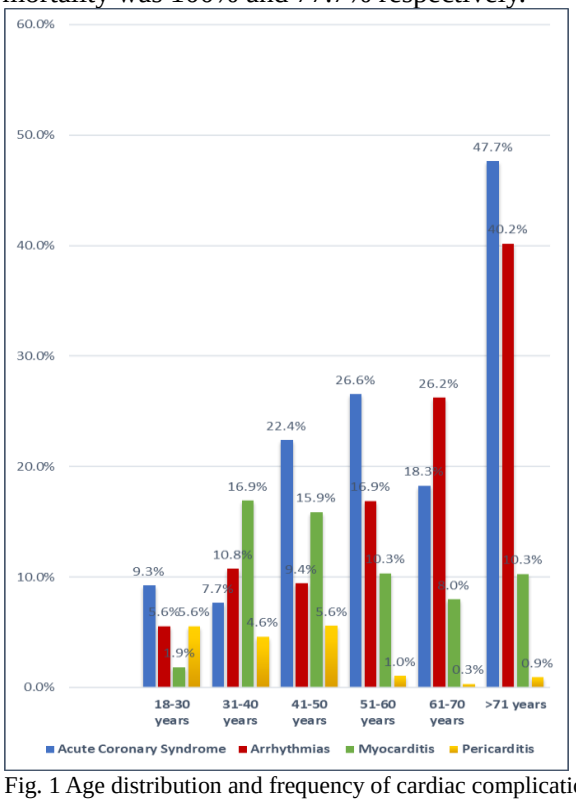

Fig. 1 Age distribution and frequency of cardiac complications in each age group

Table 1 Baseline characteristics and frequency of cardiac complications in COVID-19 infected patients

Age Group	Total	Acute Coronary Syndrome				Arrhythmias							Myocarditis			Pericarditis		
		STEMI (a)	NSTEMI (b)	No	p-value	AF (c)	VF (d)	SVT (e)	Atrial Flutter	VT (f)	No	p-value	Yes	No	p-value	Yes	No	p-value
18-30 years	54 (5.1%)	0	5	49		0	0	0	2	1	51		1	53		3	51	
31-40 years	65 (6.1%)	0	5	60		5	0	0	1	1	58		11	54		3	62	
41-50 years	233 (22.1%)	2	48	183		19	0	2	0	1	211		37	196		13	220	
51-60 years	290 (27.6%)	22	55	213	0.000	36	0	9	0	4	241	0.000	30	260	0.008	3	287	0.000
61-70 years	301 (28.6%)	23	32	246		56	1	21	0	1	222		24	277		1	300	
>71 years	107 (10.1%)	39	12	56		31	1	10	0	1	64		11	96		1	106	
Total	1050 (100%)	86 (8.1%)	157 (14.9%)	807 (76.8%)		147 (14.0%)	2 (0.1%)	42 (4.0%)	3 (0.2%)	9 (0.8%)	847 (80.6%)		114 (10.8%)	936 (89.1%)		24 (2.2%)	1026 (97.7%)	
Gender																		
Male	599 (57.0%)	62	78	459		96	2	33	3	3	462		50	549		7	592	
Female	451 (43.0%)	24	79	348	0.003	51	0	9	0	6	385	0.001	64	387	0.003	17	434	0.005
Total	1050 (100%)	86 (8.1%)	157 (14.9%)	807 (76.8%)		147 (14.0%)	2 (0.1%)	42 (4.0%)	3 (0.2%)	9 (0.8%)	847 (80.6%)		114 (10.8%)	936 (89.1%)		24 (2.2%)	1026 (97.7%)	
Diabetes																		
Yes	451 (43.0%)	61	93	297		62	0	20	0	6	363		53	398		10	441	
No	599 (57.0%)	25	64	510	0.000	85	2	22	3	3	484	0.283	61	538	0.419	14	585	0.898
Total	1050 (100%)	86 (8.1%)	157 (14.9%)	807 (76.8%)		147 (14.0%)	2 (0.1%)	42 (4.0%)	3 (0.2%)	9 (0.8%)	847 (80.6%)		114 (10.8%)	936 (89.1%)		24 (2.2%)	1026 (97.7%)	
Hypertension																		
Yes	490 (46.6%)	55	110	325		76	2	20	1	4	387		46	444		11	479	
No	560 (53.3%)	31	47	482	0.000	71	0	22	2	5	460	0.500	68	492	0.152	13	547	0.934
Total	1050 (100%)	86 (8.1%)	157 (14.9%)	807 (76.8%)		147 (14.0%)	2 (0.1%)	42 (4.0%)	3 (0.2%)	9 (0.8%)	847 (80.6%)		114 (10.8%)	936 (89.1%)		24 (2.2%)	1026 (97.7%)	
Smoking																		
Yes	397 (37.8%)	72	92	233		61	2	18	0	3	313		37	360		5	392	
No	653 (62.1%)	14	65	574	0.000	86	0	24	3	6	534	0.239	77	576	0.212	19	634	0.083
Total	1050 (100%)	86 (8.1%)	157 (14.9%)	807 (76.8%)		147 (14.0%)	2 (0.1%)	42 (4.0%)	3 (0.2%)	9 (0.8%)	847 (80.6%)		114 (10.8%)	936 (89.1%)		24 (2.2%)	1026 (97.7%)	

Table 2 Association of cardiac complications with different parameters of disease severity and its impact on the outcome

	Total	Acute Coronary Syndrome				Arrhythmias							Myocarditis			Pericarditis			Patients' Outcome		
ARDS (g)		STEMI (a)	NSTEMI (b)	No	p-value	AF (c)	VF (d)	SVT (e)	Atrial Flutter	VT (f)	No	p-value	Yes	No	p-value	Yes	No	p-value	Death	Discharged	p-value
Mild	820 (78.0%)	14	81	725		82	0	27	2	2	707		89	731		19	801		31	789	
Moderate	174 (16.5%)	49	56	69		44	1	12	1	3	113		19	155		3	171		52	122	
Severe	56 (5.3%)	23	20	13	0.000	21	1	3	0	4	27	0.000	6	50	0.999	2	54	0.718	33	23	0.000
Total	1050 (100%)	86 (8.1%)	157 (14.9%)	807 (76.8%)		147 (14.0%)	2 (0.1%)	42 (4.0%)	3 (0.2%)	9 (0.8%)	847 (80.6%)		114 (10.8%)	936 (89.1%)		24 (2.2%)	1026 (97.7%)		116 (11.0%)	934 (88.9%)	
AKI (h)																					
Yes	222 (21.1%)	28	41	153		43	2	13	0	6	158		56	166		5	217		52	170	
No	828 (78.8%)	58	116	654	0.003	104	0	29	3	3	689	0.000	58	770	0.000	19	809	0.970	64	764	0.000
Total	1050 (100%)	86 (8.1%)	157 (14.9%)	807 (76.8%)		147 (14.0%)	2 (0.1%)	42 (4.0%)	3 (0.2%)	9 (0.8%)	847 (80.6%)		114 (10.8%)	936 (89.1%)		24 (2.2%)	1026 (97.7%)		116 (11.0%)	934 (88.9%)	
Shock																					
Yes	49 (4.6%)	20	12	17		9	0	3	0	3	34		5	44		2	47		44	5	
No	1001 (95.3%)	66	145	790	0.000	138	2	39	3	6	813	0.002	109	892	0.880	22	979	0.389	72	929	0.000
Total	1050 (100%)	86 (8.1%)	157 (14.9%)	807 (76.8%)		147 (14.0%)	2 (0.1%)	42 (4.0%)	3 (0.2%)	9 (0.8%)	847 (80.6%)		114 (10.8%)	936 (89.1%)		24 (2.2%)	1026 (97.7%)		116 (11.0%)	934 (88.9%)	

Table 3 Association of cardiac complications with patients' outcome

ACS (i)	Patients' Outcome			
	Death	Discharged	Total	p-value
STEMI (a)	53	33	86 (8.1%)	0.000
NSTEMI (b)	41	116	157 (14.9%)	
No	22	785	807 (76.8%)	
Total	116 (11.0%)	934 (88.9%)	1050 (100%)	
Arrhythmias				
AF (c)	25	122	147 (14.0%)	0.000
VF (d)	2	0	2 (0.1%)	
SVT (e)	6	36	42 (4.0%)	
Atrial Flutter	0	3	3 (0.2%)	
VT (f)	7	2	9 (0.8%)	
No	76	771	847 (80.6%)	
Total	116 (11.0%)	934 (88.9%)	1050 (100%)	
Myocarditis				
Yes	10	104	114 (10.8%)	0.412
No	106	830	936 (89.1%)	
Total	116 (11.0%)	934 (88.9%)	1050 (100%)	
Pericarditis				
Yes	3	21	24 (2.2%)	0.818
No	113	913	1026 (97.7%)	
Total	116 (11.0%)	934 (88.9%)	1050 (100%)	

*(a) = ST elevation myocardial infarction; (b) = Non-ST elevation myocardial infarction; (c) = Atrial Fibrillation; (d) = Ventricular Fibrillation; (e) = Supraventricular Tachycardia; (f) = Ventricular Tachycardia; (g) = Acute Respiratory Distress Syndrome; (h) = Acute Kidney Injury; (i) = Acute Coronary Syndrome;

4. Discussion

SARS-CoV-2 is an enveloped, non-segmented, single-stranded, RNA virus [14-17]. The entry site for SARS-CoV-2 is proposed to be angiotensin-converting enzyme 2 (ACE2), which is present on the surface of lung alveolar epithelial cells and enterocytes of the small intestine, which subsequently breaks down angiotensin II, a pro-inflammatory factor in the lung. The binding of viral S Protein to ACE-2 is a critical phenomenon for infection and disease progression. The cytokine release resulting in systemic inflammation is a significant feature of coronavirus infection and is attributed to the inhibition of ACE-2. This leads to multi-organ dysfunction and acute respiratory distress syndrome (ARDS).

The cause of cardiovascular injury in COVID-19 infection seems to be multifactorial. The virus may cause direct damage to the heart utilizing ACE2 receptors located within cardiac tissue [18, 19]. Systemic inflammatory response on the other hand can destabilize vascular plaques while the cytokine activity increases cardiac demand, thus inducing ischemia in the myocardial tissue. Hence, disruption in immune system regulation increased metabolic demand and pro-coagulant activity likely accounts for some of the increased risks of adverse outcomes in those with COVID-19 related cardiovascular disease (CVD) [18].

Although not yet fully understood, several cardiovascular manifestations of COVID-19 have been described. COVID-19 may present with acute myocardial infarction, myocarditis, cardiomyopathies (including stress cardiomyopathy), coronary spasms, etc [20, 21]. It is still challenging to define the true incidence of cardiac complications, and particularly to determine what proportion relates specifically to COVID-19, rather than more generally to critical illness or even coincidence [22]. Interestingly, amongst the COVID positive cases reported by the National Health Commission of China (NHC), a few of them first presented to their local physicians with cardiovascular symptoms like palpitations and chest tightness, rather than respiratory symptoms typical of COVID. In fact, of all the infected individuals who died, 11.8% of them had no previous cardiovascular disease but an autopsy showed substantial heart damage during hospitalization, further emphasizing the high incidence of cardiac complications in this disease entity [5]. Several risk factors have been identified that predict the susceptibility to SARS-CoV-2 infection and disease severity. According to the Centers for Disease Control and Prevention, the elderly population was more prone to get infected with the virus, especially those with a previous history of ischemic heart disease, hypertension, or diabetes [20, 23].

An increased risk of an acute coronary syndrome (ACS) is found in viral illnesses, with the greatest risk within the first week of illness due to systemic inflammation resulting in atherosclerotic plaque disruption [24]. Myocardial damage caused by such viruses undoubtedly increases the complexity of patients' treatment. Literature suggests acute MI may occur in 7–17% of hospitalized patients and over 20% of ICU patients with COVID-19, but the true prevalence is difficult to determine due to underreporting [25, 26]. Wang et al. in one of his research studied 138 hospitalized COVID-19 patients in Wuhan, China. In his study population, 7.2% of patients encountered acute cardiac injury during the

course of illness, 16.7% had arrhythmias whereas 8.7% developed shock, requiring vasopressor support [1]. It was also found that patients in the intensive care unit had a higher frequency of complications compared to their counterparts who were admitted in the isolation units with mild to moderate disease. On comparing these statistics with our study, it is evident that the occurrence of complications was more in our setup. 23.1% of the patients in our cohort developed acute coronary syndrome whereas the rate of arrhythmias was also as high as 19.3%. However, only 4.6% of patients in our study required vasopressor support. It is also interesting to note that in our study, 13.1% of ACS occurred in those with shock, 39.0% in those with ARDS, and 28.3% in those with acute kidney injury. In our study, mortality was high in those with cardiac injury as compared to those who did not encounter any cardiac complication during the course of the disease – 38.6% vs. 2.7% in patients with and without ACS respectively, and 19.7% vs. 8.9% in those with and without arrhythmias respectively. Similar results were found in another study where mortality was 51.2% in those with cardiac injury compared to 4.5% in those without it [17].

In a meta-analysis of four studies including 341 patients, troponin I levels was significantly higher in those with severe COVID-19 related illness compared to those with non-severe disease [23]. Reports have also suggested that such cardiac injury is associated with a poor prognosis. Cohort studies from hospitalized patients in China estimate that myocardial injury is more common in patients admitted to ICU and in those who died [3]. However, it is important to consider that high troponin levels do not always correlate to myocardial infarction. More than often, COVID infected patients have a renal impairment which delays the excretion of troponins thus resulting in high serum levels.

Prior studies in coronavirus species have demonstrated fulminant myocarditis in the setting of high viral load with autopsy findings of inflammatory mononuclear infiltrate in myocardial tissue [3]. In fact, in a case series of 150 patients, 7% of deaths were attributed to viral myocarditis [8]. The mortality in our cohort secondary to myocarditis was estimated to be 8.7%.

Cardiac arrhythmias were yet another very common cardiovascular manifestation of SARS-CoV-2 infection. In a cohort of 137 patients admitted with COVID-19 infection, 7.3% had arrhythmias on presentation [23]. Our study investigates the specifics of these arrhythmias in detail and concluded that atrial fibrillation was the most frequently occurring arrhythmia, followed by supraventricular tachycardia. The mortality associated with arrhythmias in our study was 19.7%. The development of such irregular rhythm may be attributable to the metabolic disarray, hypoxia, or inflammatory stress on the background of viral infection. However, if arrhythmias occur in the setting of troponin elevation, then myocarditis must be ruled out.

It is no wonder that acute respiratory distress syndrome (ARDS) and severe parenchymal lung disease caused by SARS-CoV-2 can lead to pulmonary hypertension and subsequently right-sided heart failure. Zhou et al. in one of his studies reported the incidence of heart failure to be as high as 23.0%; 51.9% out of these patients died during hospitalization [2]. This disease entity could arise as an exacerbation of pre-existing left ventricular dysfunction or new-onset myocarditis or stress cardiomyopathy. However, the development of heart failure or cardiomyopathy was not studied in detail in our cohort.

4.1. Strengths

There are several strengths to this study. First, this study reflects the association between the disease severity and the occurrence of cardiac complications and also establishes an association of the former with the rate of mortality. Second, by removing the patients with preexisting cardiovascular disease, we were able to see the true effects that the SARS-CoV-2 virus has on the heart. Lastly, the laboratory results that were used in this study for diagnostic purposes were seen on admission and also followed throughout hospitalization to determine the course of the illness.

4.2. Limitations

We acknowledge several limitations to this study. First, a sample size of 1,050 is smaller as compared to other studies that have been conducted but are still relevant to show a significant occurrence of cardiac complications. Furthermore, the cases were all from a single hospital in a certain demographic of Pakistan, which may not show a proper representation of the disease and its effects on the cardiovascular system on a country-wide basis**.**

6. Conclusion

The study demonstrates that myocardial infarction is a frequently encountered complication in COVID pneumonia, partly because of the SARS-CoV-2 virus inducing a pro-thrombotic state in the body. The occurrence of arrhythmias and myocarditis can be attributed to the virus causing direct cellular injury to the myocardial cells or indirectly as a result of multi-organ dysfunction and hypoxemia caused by the virus. Furthermore, the incidence of these complications is higher in patients with multiple co-morbidities. Such complications impact the overall prognosis of patients and affect mortality. Our study was prototype research in the above-stated domain because no data is available from local setups that highlighted the occurrence of cardiac complications in the setting of COVID-19

pneumonia. Although international data is available, the results may vary given the difference in the race, ethnicity, and genetic predisposition of the individuals. Furthermore, the selection of cohort was carefully done by excluding the patients with the known cardiovascular ailment. By doing this, we were able to determine more accurately the true impact of coronavirus on the cardiovascular system. This study was conducted over a period of one year during which the world was affected by multiple strains of SARS-CoV-2 which means we were able to see the cumulative results of all the mutated strains of this virus on the heart. The results of our study can help the scientific community in anticipating the cardiac complications of the coronavirus in advance so that preventive measures can be taken beforehand and better healthcare facilities can be provided to the general population. The scientific community still needs further large-scale investigations to better understand the underlying mechanism of these pathologies. Other studies should also be done to assess the effect of the coronavirus on other physiological mechanisms. By understanding how this virus causes multisystem effects, we may be able to eliminate the root cause at the genetic level in the coming years and prevent these complications from happening altogether, thus improving both morbidity and mortality in the future.

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