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Clinical variants of myocardial involvement in COVID-19-positive patients: a cumulative experience of 2020

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Abstract

Myocardial injury, diagnosed by troponin elevation, is common in COVID-19 patients, but cardiac involvement with clinical manifestations occurs less frequently. We analyzed the literature on COVID-19 (2020) and systematically reviewed the cases where individual patient data were presented. We searched PubMed and Google Scholar for "COVID," "COVID-19," and "coronavirus" in combination with "myocarditis," "heart failure," "takotsubo," "cardiomyopathy," and "cardiogenic shock." We identified 90 cases of COVID-19 with myocardial involvement, mean age 52.9 ± 18.3 years, 54.5% males. Of them, 55 survived (61.1%), 20 died (22.2%), and in 15 (16.7%) the outcome was unknown at the time of publication. Among patients with known outcome, mortality was 26%. The nadir LVEF was 31.7 ± 13.1% and recovered to 50.1 ± 16.0%. Pericardial effusion was a common finding, reported in 21 (23.3%) of patients, including moderate size effusion in 8.9% and large in 7.8%. The effusion caused tamponade in 11 (12.2%) of patients. Out of 83 patients who experienced a decrease in LVEF, 30 could be classified as takotsubo syndrome. The takotsubo patients were older than those with myocarditis, and with relatively high proportion of males. About one third of the cases was complicated by cardiogenic shock. Myocardial involvement in COVID-19 patients most often presents as a new, rapid decrease in LVEF, although normal LVEF or takotsubo-like wall motion pattern does not rule out myocarditis. Moderate and large pericardial effusion is common, and cardiac tamponade occurs in 12.2% of patients. Cardiogenic shock develops in one third of the patients. Mortality appears to be high at 26%.

Keywords COVID-19 · Coronavirus · Myocarditis · Takotsubo · Heart failure · Aortic pulsatility index · Mortality

Introduction

COVID-19, a novel coronavirus infection, which became a pandemic in early 2020, had a profound effect on all spheres of human life and became a tremendous medical and public health challenge. COVID-19 is a single-stranded ribonuclear acid (RNA) highly contagious virus which primarily attacks respiratory system but can also cause multiple effects on other systems and organs.

While it is obvious that the respiratory system is most consistently affected, cardiovascular effects are significant. On the one hand, patients with underlying cardiovascular diseases, such as hypertension, coronary artery disease, heart failure (HF), or diabetes are at increased risk for complications and mortality, which may be up to tenfold higher than in patients without cardiac conditions [1]. On the other hand, COVID-19 is often accompanied by myocardial injury, which may be caused by a direct viral involvement of the myocardium or by a hyperimmune response to the virus. Myocardial injury—defined as elevation in troponin levels to 3 times higher of normal serum concentrations or above their 99th percentile upper reference limit—has been reported in 20–30% of patients hospitalized due to COVID-19 [2]. The final result may also be a product of the both processes when direct viral entry and replication in myocardium may enhance the susceptibility to myocardial injury, which then leads to myocarditis as a part of inflammatory response. Right ventricular dysfunction can also result from the strain caused by increased pulmonary vascular resistance and the workload on the right heart [3]. HF in COVID-19 patients is usually acute and represents de novo cases rather than exacerbation of previously diagnosed condition. Patients developing HF had significantly higher mortality (46.8% vs. 19.7%; $P < 0.001$) [4].

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Although myocardial injury, diagnosed primarily by troponin elevation, is common in COVID-19-positive patients, clinical manifestations of cardiac involvement occur less frequently. The goal of the present review is to summarize the collective experience of 2020 with patients who present with clinical manifestations of myocardial involvement in the course of COVID-19 disease.

Methods

Study design

This study was a systematic review of the literature conducted following PRISMA guidelines [5] to retrieve publications containing data regarding clinical presentations, course, and outcomes of COVID-19-positive patients with myocardial involvement.

Registration of a review protocol was unnecessary because data contained in published literature was used to conduct this study.

Eligibility criteria

The publications included were full-length manuscripts retrieved with our search that contained data on one or more patients 18 years old or older, with a positive test for COVID-19, and with myocardial involvement diagnosed by one or more of the following characteristics: (1) new systolic dysfunction reported as a decrease in left ventricular ejection fraction (LVEF), (2) pericardial effusion in combination with elevated troponin and B-type natriuretic peptides (BNP or NT-proBNP), (3) myocarditis on magnetic resonance imaging with preserved LVEF.

Publications were excluded if these were written in languages other than English, contained pediatric population data (patients younger than 18 years old), or had insufficient data on individual patients.

Search method

Following PRISMA guidelines [5], a systematic search of the literature was conducted in December 2020 using PubMed, Google Scholar, and EMBASE. The keywords "COVID," "COVID-19," and "coronavirus" in combination with "myocarditis," "heart failure," "cardiomyopathy," "takotsubo," and "cardiogenic shock." In relevant papers, the list of references was manually searched as well.

The search was limited to the articles published in English in 2020 (January 1 to December 31). All the identified publications were screened to excluded duplicates by comparing titles, authors, and digital object identifiers. After removing duplicates, all the remaining publications were screened for exclusion criteria by reading titles and abstracts. After removing publications that met exclusion criteria, the reminding publications were further screened for inclusion and exclusion criteria by reading the full-text publications. The list of references for each relevant publication was manually examined. Through this searched method, the publications to include in the analysis were identified (Fig. 1).

Data extraction process

The included publications were analyzed in a qualitative manner for authors' names, date of publication, medical center where they were treated, country, and the timeline of the events. These publications were used to identify our subjects of interest. Once identified, subjects were labeled, and their data extracted. These data were used to perform quantitative analyses of comorbidities, biomarkers, symptoms on presentation, dynamical changes of LVEF, wall motion abnormalities, presence of cardiogenic shock, treatment modalities, and outcomes (survival to discharge).

Results

Literature search

The search identified 657 publications. After removing duplicates and screening for exclusion and inclusion criteria, 68 publications were included in the analysis (Fig. 1).

Patient characteristics

We identified 90 cases of COVID-19 with myocardial involvement with data available on individual patients, mean age was 52.9 ± 18.3 years, and 54.5% were males. The reports came from 17 countries, including 42 (46.7%) from North America, 34 (37.8%) from Europe, 12 (13.3%) from Asia, and 2 (2.2%) from South America. Myocardial involvement was diagnosed by (1) new systolic dysfunction (92%), (2) pericardial effusion with elevated troponin and B-type natriuretic peptides with normal LVEF (1%), and (3) myocarditis on magnetic resonance imaging with preserved LVEF (6.8%). Of them, 55 survived (61.1%), 20 died (22.2%), and in 15 (16.7%), the outcome was either unknown at the time of publication or not reported.

In the whole cohort, cardiac risk factors such as diabetes, hypertension, or hyperlipidemia were common. Diabetes was reported in 24.4%, hypertension in 35.6%, and other risk factors in 26.7%. These conditions were frequently combined in the same patients.

In clinical presentation, fever (60%) and dyspnea (58.9%) were the most prevalent symptoms, followed by cough (44.4%), general weakness/fatigue/malaise (43.3%), chest

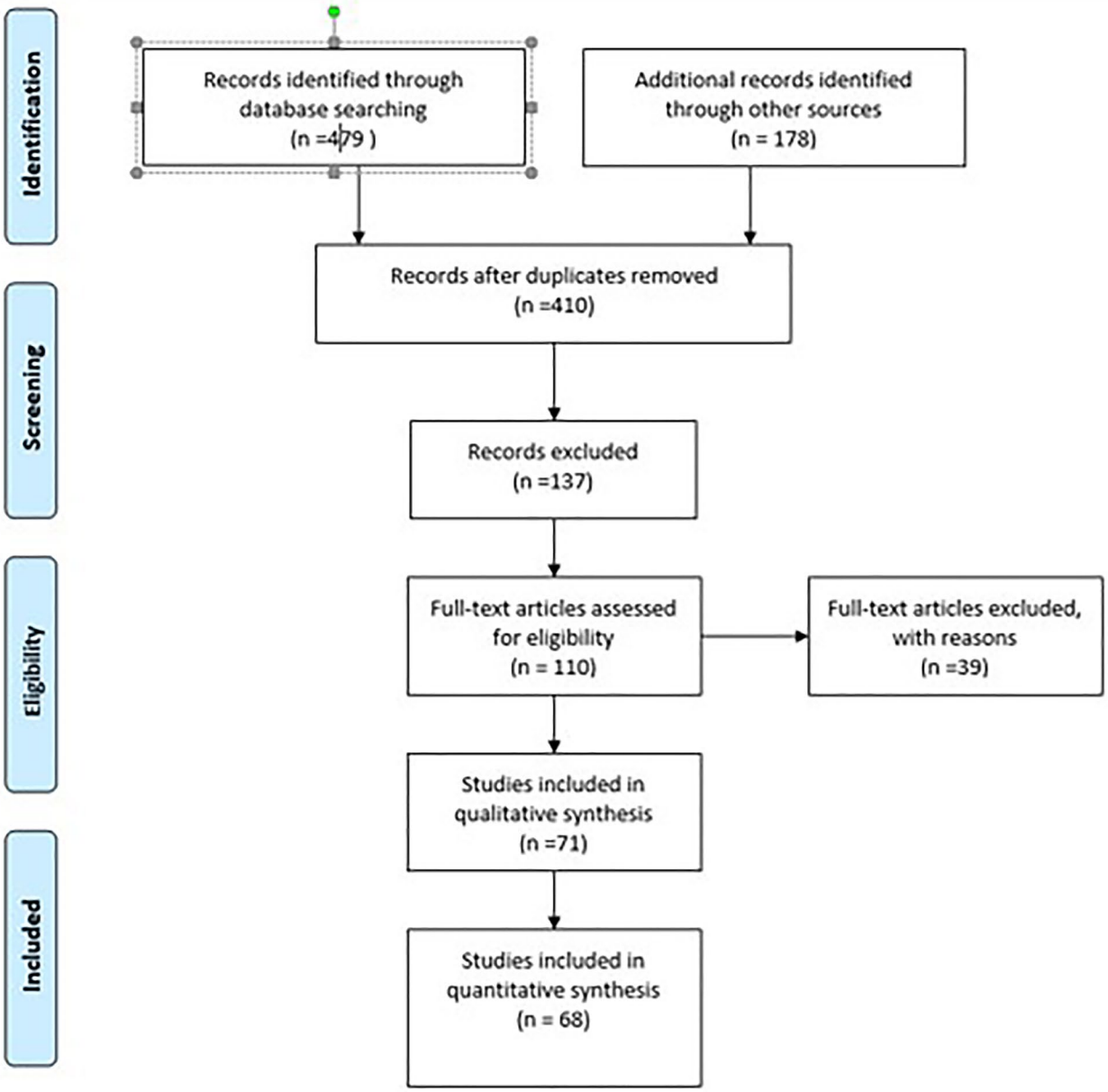

Fig. 1 Study selection flowchart

pain (21.1%), and abdominal symptoms (nausea, vomiting, diarrhea) (14.4%). Upper respiratory symptoms were reported in a minority of patients (1.1%). Bilateral pulmonary infiltrates on chest X-ray (CXR) were present in 64.4% of patients, absent in 14.4%, and not reported in the rest.

In terms of elevated biomarkers or inflammatory factors, troponin was elevated in 80%, within normal limits in 6.7%, and not reported in 13.3%. The corresponding percentages of elevated, normal, and not reported values for other tests were as follows: B-type natriuretic peptide or NT-pro-BNP, 57.8%, 3.3%, 41.9%; ferritin, 36.7%, 6.7%, 56.6%; C-reactive protein (C-RP), 61.1%, 2.0%, 369%; and interleukin-6 (IL-6), 21.1%, 0%, 78.9%, respectively.

The quantitative analysis of the levels of biomarkers was not feasible because of a wide variety of assays and reference values utilized by different centers.

In almost all patients, there were some abnormalities on the electrocardiogram (ECG), but they were mostly nonspecific. Prolonged QT interval was observed in 6.7% of cases, and ST segment elevation was seen in 30.0% of patients.

Pericardial effusion was a relatively common finding, reported in 21 (23.3%) of patients, including moderate size effusion in 8.9% and large in 7.8%. The effusion caused tamponade in 11 (12.2%) of patients.

Many patients required vasopressors and/or inotropes (46.7%), and 11 (12.2%) were placed on venoarterial

extracorporeal membrane oxygenation (VA ECMO). In terms on anti-inflammatory, antiviral therapies, and immunomodulators, hydroxychloroquine was used most (36.7%), steroids were given to 28.9%, tocilizumab to 12.2%, and remdesevir, convalescent plasma, intravenous immunoglobulin were utilized in a very small number of cases. The comparison between males and females is presented in Table 1.

Among 75 patients with known outcome, 55 survived and 20 died (mortality was 26.7%). Except for older age (65.1 ± 13.8 vs 49.8 ± 18.4, $p = 0.0018$), nonsurvivors were not different from survivors by the prevalence of cardiac risk factors or symptoms.

Comparison of survivors vs nonsurvivors is shown in Table 2.

Listed as causes of death were cardiogenic shock, septic shock, cardiac arrest, multiorgan failure, and respiratory failure.

Table 1 Patient characteristics: males vs females

	M		F		Total	
Total	49	100.0%	41	100.0%	90	100.0%
Symptoms						
Fever	32	65.3%	22	53.7%	54	60.0%
General	18	36.7%	21	51.2%	39	43.3%
Dyspnea	34	69.4%	19	46.3%	53	58.9%
Cough	25	51.0%	15	36.6%	40	44.4%
Abdominal pain	8	16.3%	5	12.2%	13	14.4%
Chest pain	13	26.5%	6	14.6%	19	21.1%
Upper respiratory	0	0.0%	1	2.4%	1	1.1%
Lung infiltrates	31	63.3%	27	65.9%	58	64.4%
Elevated biomarkers						
Troponin	39	79.6%	33	80.5%	72	80.0%
Natriuretic peptides	28	57.1%	24	58.5%	52	57.8%
QT	3	6.1%	3	7.3%	6	6.7%
ST elevation	13	26.5%	14	34.1%	27	30.0%
Cardiac risk factors						
Diabetes	12	24.5%	10	24.4%	22	24.4%
Hypertension	17	34.7%	15	36.6%	32	35.6%
Echocardiographic findings						
Left ventricular ejection fraction, %	33.6 ± 13.1		31.9 ± 14.0			
Pericardial effusion	5	10.2%	16	39.0%	21	23.3%
• Moderate	0	0.0%	8	19.5%	8	8.9%
• Large	3	6.1%	4	9.8%	7	7.8%
• Tamponade	3	6.1%	8	19.5%	11	12.2%
	0	0.0%	0	0.0%	0	0.0%
Hydroxychloroquine	17	34.7%	16	39.0%	33	36.7%
Steroids	12	24.5%	14	34.1%	26	28.9%
Lopinivir/ritonavir	3	6.1%	6	14.6%	9	10.0%
Tocilizumab	7	14.3%	4	9.8%	11	12.2%
IVIG	3	6.1%	4	9.8%	7	7.8%
Plasma	2	4.1%	2	4.9%	4	4.4%
Remdesivir	1	2.0%	2	4.9%	3	3.3%
Combination of several agents	19	38.8%	15	36.6%	34	37.8%
	0	0.0%	0	0.0%	0	0.0%
Vasopressors/inotropes	20	40.8%	22	53.7%	42	46.7%
VA ECMO	5	10.2%	6	14.6%	11	12.2%
IABP	2	4.1%	3	7.3%	5	5.6%

IVIG intravenous immunoglobulin, *VA ECMO* venoarterial extracorporeal oxygenation, *IABP* intraaortic balloon pump

Table 2 Patient characteristics between survivor and nonsurvivors

	Survivors		Nonsurvivors	
N	*N*	%	*N*	%
	55		20	
Fever	32	58.2%	15	75.0%
General	24	43.6%	11	55.0%
Dyspnea	31	56.4%	12	60.0%
Cough	22	40.0%	12	60.0%
Abdominal	10	18.2%	0	0.0%
Chest pain	12	21.8%	3	15.0%
Lung infiltrates	36	65.5%	12	60.0%
Elevated biomarkers				
Troponin	41	74.5%	19	95.0%
Natriuretic peptides	31	56.4%	11	55.0%
Ferritin	18	32.7%	11	55.0%
C-reactive protein	33	60.0%	14	70.0%
Interleukin-6	12	21.8%	4	20.0%
Electrocardiogram				
Prolonged QT	4	7.3%	1	5.0%
ST elevation	14	25.5%	6	30.0%
Cardiac risk factors				
Diabetes	12	21.8%	6	30.0%
Hypertension	14	25.5%	12	60.0%
Other risk factors	12	21.8%	7	35.0%
Cardiogenic Shock	15	27.3%	0	0.0%
Echocardiographic findings				
Left ventricular ejection fraction, %	33.6 ± 13.1		28.6 ± 12.2	
Wall motion abnormality				
*Apical	11	20.0%	8	40.0%
*Basal	6	10.9%	3	15.0%
*Diffuse	7	12.7%	3	15.0%
*Other	4	7.3%	0	0.0%
Right ventricular dysfunction	6	10.9%	6	30.0%
Pericardial effusion	13	23.6%	4	20.0%
• Moderate	5	9.1%	1	5.0%
• Large	4	7.3%	3	15.0%
• Tamponade	7	12.7%	4	20.0%
Therapy				
• Hydroxychloroquine	19	34.5%	7	35.0%
• Steroids	17	30.9%	3	15.0%
• Lopinavir/ritpnavir	6	10.9%	1	5.0%
• Tocilizumab	9	16.4%	1	5.0%
• IVIG	4	7.3%	1	5.0%
• Plasma	3	5.5%	0	0.0%
• Remdesivir	2	3.6%	0	0.0%
• Combination of agents	21	38.2%	7	35.0%
• Vasopressors/inotropes	23	41.8%	10	50%

Left ventricular ejection fraction changes

In majority of patients, LVEF was assessed at least once, and in many repeatedly. The nadir LVEF in the whole study cohort was 31.7 ± 13.1% and recovered to 50.1 ± 16.0%.

The time between the nadir LVEF and recovered LVEF varied widely because the repeat echocardiographic evaluation was not done according to any protocol. In some patients, recovered LVEF was measured or estimated only several months after the discharge at routine follow-ups. Nevertheless, if we limit the cohort to subjects in whom the echocardiogram was repeated during the same admission, the range to LVEF recovery was 2 to 54 days, median 10 days.

There was no difference between the lowest LVEF between men and women (Table 1) or between survivors and nonsurvivors (Table 2). In regard to wall motion characteristics, takotsubo pattern was present in 43.9%, reversed takotsubo in 24.4%, and diffuse or unspecified hypokinesis in 26.8%. Moderate or large pericardial effusion was present in 16% of patients, with tamponade in 12.5%. Cardiogenic shock developed in 31 patients (32.5%). Except for older age (65.1 ± 13.8 vs 49.8 ± 18.4, $p = 0.0018$), nonsurvivors were not different from survivors by the prevalence of cardiac risk factors or symptoms.

Takotsubo syndrome versus myocarditis

Out of 83 patients who experienced a decrease in LVEF, 30 could be classified as takotsubo syndrome (Table 3), and 53 as acute myocarditis (Table 4), based on the reported wall motion pattern. The takotsubo patients were older than

Table 3 COVID-19-positive patients with takotsubo pattern of the wall motion abnormality

Author, date	Age	Sex	Baseline EF	Recovered EF	Time to recovery, days	Wall motion: location of hypokinesis/akinesis	Outcome
Chao et al. [29]	49	M	40	55	6	Basal	Survived
Coyle et al. [31]	57	M	35–40	82	18	Basal	Survived
Faqihi et al. [32]	40	M	30			Basal	Survived
Hedge et al. [33]	70	F	45			Basal	Survived
Hedge et al. [33]	58	M	40	Recovered		Basal	Survived
Solano-López et al. [34]	50	M	Decreased	Recovered	10	Basal	Survived
Demetriz et al. [35]	76	F	40			Basal	Died
Panchal et al. [36]	65	M				Basal	Died
Bhattacharyya et al. [37]	32	F	38	51	13	Distal/apical	Survived
Bottiroli et al. [38]	76	F	25	38	14	Distal/apical	Survived
Dabbagh et al. [39]	67	F	40			Distal/apical	Survived
Li et al. [40]	60	M	15–20	Normal	5	Distal/apical	Survived
Oyarzabal et al. [41]	82	M	Very depressed			Distal/apical	Survived
Pasqualetto et al. [30]	84	M	53			Distal/apical	Survived
Pasqualetto et al. [30]	81	M	42			Distal/apical	Survived
Roca et al. [42]	87	F	48			Distal/apical	Survived
Sattar et al. [43]	67	F	30			Distal/apical	Survived
Taza et al. [44]	52	M	45			Distal/apical	Survived
Trpkov et al. [45]	62	F	24	54	14	Distal/apical	Survived
Hedge et al. [33]	71	F	15			Distal/apical	Died
Hedge et al. [33]	78	F	20			Distal/apical	Died
Hedge et al. [33]	56	M	45	Recovered		Distal/apical	Died
Karyanna et al. [46]	72	F	Depressed			Distal/apical	Died
Park et al. [47]	78	F	Severely depressed	Improved with no ballooning apex	7	Distal/apical	Died
Park et al. [47]	73	F				Distal/apical	Died
Pasqualetto et al. [30]	85	F	30			Distal/apical	Died
Torabi et al. [48]	42	F	20			Distal/apical	Died
Minhas et al. [49]	58	F	20	55	6	Distal/apical	Unknown
Khalid et al. [50]	76	F	55	59		Distal/apical	Unknown
Bernardi et al. [51]	74	M	22	57	14	Distal/apical	Unknown

Table 4 COVID-19-positive patients with diffuse or unspecified pattern of the wall motion abnormality

Author, date	Age	Sex	Baseline LVEF	Recovered LVEF	Days to recovery	Outcome
Anupama et al. [52]	66	M	32	60–65	10	Survived
Ashok and Loke [53]	53	M	Mildly depressed			Survived
Bernal-Torres et al. [54]	38	F	30	Normal	14	Survived
Blaivas [55]	46	M	40–45	50	7	Survived
Blaivas [55]	21	M	25–30			Survived
Bonnet et al. [56]	27	M	20	40	30	Survived
Chitturi et al. [57]	65	F	25	64	2	Survived
Cuomo et al. [58]	49	F	45	55	7	Survived
Dalen et al. [59]	55	F	46	60	10	Survived
De Vito et al. [60]	35	F	20	20	4	Survived
Garau	18	F	10	20	45	Survived
Garot et al. [61]	18	M	30	54	14	Survived
Gay et al. [62]	56	M	5	50	4	Survived
Gomez et al. [63]	54	F	25–30	70–75	13	Survived
Gomila-Grange et al. [64]	39	M	30	Normal	10	Survived
Khalid et al. [65]	48	M	45			Survived
Khalid et al. [65]	34	F	25	Normal	3	Survived
Luetkens et al. [66]	79	M	49			Survived
Naneishvili et al. [67]	44	F	37	Normal	2	Survived
Oleszak et al. [68]	52	M	15–20	20–25	5	Survived
Parsova et al. [69]	58	F	30	50	180	Survived
Paul et al. [70]	35	M				Survived
Pavon et al. [71]	64	M	42	47	3	Survived
Yeleti et al. [21]	25	F	10	50	2	Survived
Richard et al. [72]	28	F	25–30	55	3	Survived
Rubartelli et al. [73]	43	M	20	23	56	Survived
Sala et al. [8]	43	F	43			Survived
Salamanca et al. [74]	44	M	15	75	14	Survived
Sampaio et al. [75]	45	F	Decreased	Improved		Survived
Tsao et al. [76]	59	F	36	Normal	10	Survived
Vilaro et al. [77]	50	M	40	Normal	8	Survived
Yuan et al. [78]	33	M	Slightly decreased			Survived
Gomez et al. [63]	53	M	35			Died
Hakmi et al. [79]	56	M	20			Died
Hakmi et al. [79]	55	M	Decreased			Died
Hedge et al. [33]	88	M	30	Recovered		Died
Kazi et al. [80]	73	M	25	70	14	Died
Khatri and Wallach [81]	50	M	Severely decreased			Died
Radbel et al. [82]	40	M	Mildly decreased			Died
Sang et al. [13]	58	F	Severely decreased			Died
Tavazzi et al. [7]	69	M	25	Normal	4	Died
Zeng et al. [83]	63	M	32	68	14	Died
Hussain et al. [84]	51	M	20			Unknown
Inciardi et al. [85]	53	F	35	44	6	Unknown
Fried et al. [86]	38	M	20–25			Unknown
Fried et al. [86]	64	F	30	50	10	Unknown
Kim et al. [87]	21	F	Severely decreased			Unknown
Hu et al. [88]	37	M	27			Unknown

Table 4 (continued)

Author, date	Age	Sex	Baseline LVEF	Recovered LVEF	Days to recovery	Outcome
Spano et al. [89]	49	M	Severely decreased			Unknown
Juusela et al. [90]	45	F	40			Unknown
Juusela et al. [90]	26	F	40–45			Unknown
Irabien-Ortiz et al. [91]	59	F	Severely decreased	Normal	4	Unknown
Rassaf et al. [92]	30	M	23			Unknown

those with myocarditis, with mean age 65.0 ± 14.8 years versus 47.2 ± 15.5, respectively ($p < 0.001$). In the myocarditis cohort, 31 (58.5%) were males. In the takotsubo cohort, 13 (43.3%) were males.

The LVEF was not different between takotsubo and myocarditis (32.8 ± 11.2% vs 29.3 ± 9.1%, respectively), nor was the time to LVEF recovery (10.7 ± 10.0 days vs 9.8 ± 9.1 days, respectively) (Table 5).

Cardiogenic shock

We considered that the patients had cardiogenic shock if they required vasopressors, inotropes, and/or mechanical circulatory support (MCS), and no positive blood cultures/septic shock was reported. By these criteria, cardiogenic shock occurred in 33 (33.6%) patients in the whole cohort. The mean age was 53.5 ± 17.5 years of age, which was similar to the whole cohort, and there was almost equal representation of males (48.5%) and females. In majority of them (19/57.6%), cardiogenic shock was either present on admission, or developed in the first hours after the admission, but in some, this condition developed later in the course of the disease, up to 2 weeks. Fifteen survived, 9 died, and in the rest, the outcome was either unknown at the time of publication or not reported. Thus, from the patients with known outcomes, 57.6% survived to discharge. VA ECMO was used in 9 cases, including five patients who also were supported with intraaortic balloon pump or Impella, and in three more cases, either balloon pump or Impella were used without ECMO, bringing the use of mechanical circulatory support devices to 36.4%. Six patients, supported by MCS, survived, 3 died, in the rest the outcomes are unknown. Twelve of the 33 patients had wall motion abnormality in the pattern of either apical or basal hypokinesis/akinesis (takotsubo and reverse takotsubo), and in the rest, hypokinesis was diffuse. There were survivors and nonsurvivors in any pattern of wall motion abnormality: 4 and 4 in the takotsubo subset and 11 and 5 in the diffuse hypokinesis subset.

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) results were available for 25 patients. This diagnostic study was performed almost exclusively in patients with diffuse hypokinesis of the left ventricle (as opposed to takotsubo or reverse takotsubo pattern). Interestingly, six of these patients had completely normal LVEF (≥ 50%). There are three MRI sequences that are critical in the diagnosis of myocarditis. They can identify edema (T2-weighted images), hyperemia (T1-weighted images, early gadolinium enhancement), and necrosis (late gadolinium enhancement (LGE)). While the first two methods mostly reflect reversible injury related to inflammation, LGE identifies irreversible damage such as necrosis and fibrosis [6].

In 7 patients, all three CMR criteria for myocarditis were met. Two out of three features were found in 9 patients, either edema T2 and late gadolinium enhancement (6) or only edema and hyperemia (3), and in 8 only one criterion was present, either myocardial edema (5) of late gadolinium enhancement (3). In one patient, no signs of myocarditis could be found.

Endomyocardial biopsy

Among survivors, 6 biopsied were performed, two demonstrated lymphocytic myocarditis with no COVID-19 genome and one with parvovirus and three were negative for any diagnostic findings including myocarditis. In two patients with negative biopsy, CMR was also performed and was consistent with myocardial edema in one case and the presence of necrosis by late gadolinium enhancement in 45 days after the presentation. In one of the two cases with lymphocytic myocarditis, the CMR was positive for myocardial edema and hyperemia, with no late gadolinium enhancement. In one more case, Tavazzi et al. [7] identified COVID-19 particles in the bioptate; however, no viral genome analysis was reported.

Interestingly, one of the cases with acute myocarditis confirmed on both endomyocardial biopsy and CMR was initially considered to represent reverse takotsubo based on the wall motion pattern [8].

Table 5 Takotsubo/reversed takotsubo versus diffuse wall motion abnormality

	Takotsubo		Myocarditis	
Total	30	100.0%	53	100.0%
Symptoms				
• Fever	18	60.0%	23	43.4%
• General	12	40.0%	27	50.9%
• Dyspnea	20	66.7%	32	60.4%
• Cough	16	53.3%	14	26.4%
• Abdominal pain	3	10.0%	5	9.4%
• Chest pain	6	20.0%	11	20.8%
Upper respiratory	0	0.0%	2	3.8%
Lung infiltrates	19	63.3%	37	69.8%
QT	4	13.3%	1	1.9%
ST elevation	11	36.7%	11	20.8%
Cardiac risk factors				
• Diabetes	11	36.7%	11	20.8%
• Hypertension	18	60.0%	18	34.0%
Pericardial effusion				
• Moderate	2	6.7%	7	13.2%
• Large	1	3.3%	5	9.4%
• Tamponade	2	6.7%	8	15.1%
Treatment				
Hydroxychloroquine	14	46.7%	20	37.7%
Steroids	8	26.7%	18	34.0%
Lopinavir/ritpnavir	3	10.0%	6	11.3%
Tocilizumab	4	13.3%	8	15.1%
IVIG	1	3.3%	4	7.5%
Plasma	0	0.0%	3	5.7%
Remdesivir	0	0.0%	3	5.7%
Combination of agents	14	46.7%	21	39.6%
Vasopressors/inotropes	14	46.7%	26	49.1%
VA ECMO	1	3.3%	6	11.3%
IABP	1	3.3%	3	5.7%
Impella	0	0.0%	1	1.9%
Outcomes				
Survived	17	56.7%	32	60.4%
Died	10	33.3%	10	18.9%
Unknown	3	10.0%	10	18.9%

IVIG intravenous immunoglobulin, *VA ECMO* venoarterial extracorporeal oxygenation, *IABP* intraaortic balloon pump

Discussion

In this systematic literature review, we summarized the collective worldwide experience with myocardial involvement in COVID-19-infected patients. The overwhelming effect of the pandemic mandated expedited publication process as the professional community struggled to understand this new entity. As a result, many case reports and case series were published, but a significant proportion of them lacks important details. Moreover, many cases were submitted and published while the patient remained hospitalized, and the outcomes was unknown. Nevertheless, the sum experience is valuable.

Subclinical changes in cardiac structure and function occur in many patients with COVID-19. Such changes manifest as reduced longitudinal strain observed predominantly in basal LV segments, resembling a reversed takotsubo pattern (71%), or alterations in radial and circumferential strain [9]. Acute and remote significance of such changes are unknown, we also do not know yet whether they resolve completely with the recovery from the acute viral process.

On CMR, patients who survived COVID-19 with pulmonary symptoms, no signs of HF, and elevated troponin levels, had pericardial effusions in 7% of cases, and myocarditis-like pattern on late gadolinium enhancement in 45% of cases [10]. In another study, 54% of patients with COVID-19 and nonspecific symptoms of chest discomfort or palpitations had myocardial edema, and 31% of cases had evidence of small focal subepicardial and patchy mid-wall LGE in a pattern consistent with myocarditis. All of them had normal troponin levels at the time of CMR, and only half of them had elevated troponin during the acute infection [11].

However, in clinical practice, it is important to know what happens to the patients who have clinical evidence of myocardial involvement.

Majority of cases with clinically relevant myocardial involvement (> 60%) had acute bilateral pulmonary process typical for COVID-19. Other investigators reported that ECG changes, such as ST depression, T-wave inversion, ST-T changes, and the presence of fractionated QRS in COVID-19 are closely associated with severity of the viral infection [12].

In terms of clinical entities, most authors, reporting the cases or case series, categorized their patients into two categories based on the pattern of wall motion abnormality: myocarditis or stress-induced cardiomyopathy. A distinct pattern of the wall motion abnormality, specifically predominantly distal and apical akinesis/hypokinesis, or basal hypokinesis/akinesis, usually placed patients into the takotsubo or reversed takotsubo syndrome, respectively. Diffuse hypokinesis or decreased LVEF with no specific pattern reported, typically was reported as myocarditis. This division has to be interpreted with caution, because such distinctions are not absolute, and in at least one patient, who was thought to have a takotsubo cardiomyopathy based on the wall motion pattern, the CMR confirmed acute myocarditis [8]. Nevertheless, we compared patients based on the wall motion pattern. Doing this, we did not always go with the authors' diagnosis. For instance, Sang et al. [13] reported a case of takotsubo cardiomyopathy, but they described a diffuse pattern of severe LV hypokinesis with some apical predominance and signs

of myocarditis on the autopsy. We analyzed this case as presumed myocarditis with diffuse LV hypokinesis.

Takotsubo cardiomyopathy in COVID-19 is not infrequent. Other studies summarizing reported cases had a female predominance of 66% and mean age of 70.8 ± 15.2 years [14]—not too different from our cohort, likely because the same cases from the literature were included. Other reports had an almost even representation of males and females in takotsubo syndrome in COVID-19 [15], which is unusual because typical takotsubo cohorts have an overwhelming female predominance. Thus, in a large Japanese registry, female patients accounted for 77.2% [16], while in the Western countries, the share of women reaches 91% [17]. Interestingly, the stressful event that triggered this stress-induced cardiomyopathy was identified in only 3 of 12 cases [14]. One can speculate that the very fact of being diagnosed with COVID-19 could be that stressful event. On the other hand, there is at least one known case where a characteristic echocardiographic pattern suggested the diagnosis of takotsubo, while the CMR and biopsy confirmed acute myocarditis. Because CMR and endomyocardial biopsy are rarely done—in fact, neither was performed in a single other case where clinical diagnosis, based on presentation and imaging, suggested takotsubo syndrome—we were reluctant to upfront categorize the published cases into takotsubo versus myocarditis and analyzed the whole cohort with myocardial involvement instead. Some other cases classified as takotsubo could, in fact, represent myocarditis. Other researchers also cautioned that in the absence of CMR, myocarditis can be misinterpreted as takotsubo [15].

Acute lymphocytic myocarditis is not uncommon in COVID-19. On the autopsy of 21 consecutive COVID-19 patients, myocarditis, defined as the presence of multiple foci of inflammation with associated myocyte injury, was present in 14% of the cases. Pericarditis and acute right ventricular injury were also identified [18].

The mechanism of myocardial inflammation in COVID-19 is not well established. The virus can trigger immune response in the form of cytokine storm releasing IL-6, IL-10, and TNF-alpha causing myocarditis. In two cases, there was an evidence of the viral presence in the myocardium [7, 19]. The unique affinity of COVID-19 to angiotensin-converting enzyme 2 receptor creates the potential for direct viral infection of the myocardium [20].

Another potential mechanism is that COVID-19 makes patients more susceptible to myocarditis caused by other pathogens. We reported a case of fulminant myocarditis, confirmed by CMR, in a young COVID-19-positive patient. Should we have not sent the sample for a viral genome, we would have little doubt that the myocarditis was due to COVID-19; however, the genome test returned positive for parvovirus [21]. This observation is not unique. Shah et al. noticed a high (22%) co-infection rate in patients with coronavirus [22, 23]. Of course, some patients could have false-positive tests for COVID-19 as well.

It is known that patients, who die as a result of COVID-19, have more comorbidities, more severe inflammation and active coagulation factors, and higher levels of myocardial biomarkers [24]. However, in the present study, we could not confirm that in patients with decreased LVEF.

It is interesting that the degree of LV dysfunction and the pace of recovery did not differ between patients with a takotsubo/reversed takotsubo pattern of wall motion abnormality and diffuse LV hypokinesis.

Another characteristic feature of COVID-19-related cardiac injury is a high prevalence of pericardial effusion (23.3%), and most importantly the cardiac tamponade (12.2%).

It was reported before that the presence of pericardial effusion often signifies systemic and myocardial inflammation and may predict poor prognosis [25]. The presence of COVID-19 in pericardial fluid has been recently reported [26]. Also, viral particles in pericardial effusion were seen on electron microscopy [27]. From our standpoint, this is a sufficient reason to include early echocardiography into the standard work-up of symptomatic COVID-19 patients.

The autopsy of 9 patients with COVID-19 who either died suddenly or had cardiogenic shock demonstrated lymphomononuclear infiltrates in the myocardium with focal necrosis of adjacent myocytes and pericardial effusion. There were also inflammatory changes in the subepicardial ganglia and His-Purkinje system. No viral genomes were identified.[28].

Finally, it is important to note that pharmaceutical management of the patients does not reflect currently approved regimen. The most common regimen included hydroxychloroquine as well as steroids, but remdesevir and convalescent plasma have only been used in few. There was no noticeable use of monoclonal antibodies, that ultimately gained emergency approval in November 2020. The multinational origin of the reports and scatter of the cases throughout the whole calendar year of 2020 with rapidly changing recommendations likely account for this.

In summary, COVID-related myocardial involvement occurs in patients with severe respiratory damage, manifests as a rapid and mostly reversible left ventricular systolic dysfunction, and may have a pattern of selective distal, selective proximal, or diffuse hypokinesis. Preservation of normal left ventricular ejection fraction or presence of wall motion abnormalities rather than diffuse hypokinesis does not rule out myocarditis. Pericardial effusion is common, and tamponade occurs in 12% of the patients, justifying early echocardiographic evaluation. Cardiogenic shock complicates one third of the cases and often requires mechanical circulatory support.

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