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A Systematic Review of COVID-19 and Myocarditis

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Abstract

Background.—The COVID-19 infection which emerged in December 2019, is caused by the virus SARS-CoV-2. Infection with this virus can lead to severe respiratory illness, however, myocarditis has also been reported. The purpose of this study is to identify the clinical features of myocarditis in COVID-19 patients.

Methods.—A systematic review was conducted to investigate characteristics of myocarditis in patients infected with COVID-19 using the search term “Coronavirus” or “COVID” and “myocarditis,” “heart,” or “retrospective.” Case reports and retrospective studies were gathered by searching Medline/Pubmed, Google Scholar, CINAHL, Cochrane CENTRAL, and Web of Science databases. 11 articles were selected for review.

Results.—COVID-19 myocarditis affected patients over the age of 50 and incidences among both genders were equally reported. Patients presented with dyspnea, cough, fever with hypotension and chest pain. Laboratory tests revealed leukocytosis with increased C-reactive protein, while arterial blood gas analysis demonstrated respiratory acidosis. All cardiac markers were elevated. Radiographic imaging of the chest showed bilateral ground glass opacities or bilateral infiltrates, while cardiac magnetic resonance imaging produced late gadolinium enhancements. Electrocardiography demonstrated ST-segment elevation or inverted T waves, while echocardiography revealed reduced left ventricular ejection fraction with cardiomegaly or increased wall thickness. Management with corticosteroids was favored in most cases, followed by antiviral medication. The majority of studies reported either recovery or no further clinical deterioration.

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Conclusion.—Current available data on COVID-19 myocarditis is limited. Further research is needed to advance our understanding of COVID-19 myocarditis.

Keywords

COVID-19; SARS-CoV-2; Myocarditis; echocardiogram; cardiac MRI; electrocardiography

1. Introduction

A newly identified viral illness emerged in late December 2019 that has subsequently spread rapidly throughout the world [1]. A new coronavirus, later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the pathogen that caused severe respiratory illness also known as coronavirus disease 2019 or COVID-19 [2].

SARS-CoV-2 binds with high affinity to human angiotensin-converting enzyme 2 receptor (ACE 2) [3]. ACE-2 is widely expressed throughout the body, including in the lungs and the heart [4]. Although scarce, serious systemic infections such as myocarditis have been reported in connection with COVID-19.

Myocarditis, an inflammatory condition affecting the myocardium, results from a wide spectrum of both infectious and non-infectious causes. Many different viruses have been implicated, including the Middle East Respiratory Syndrome (MERS) coronavirus [5], which closely resembles SARS-CoV-2. Myocarditis is suspected on the basis of elevated troponins in the patient's blood, cardiac arrythmias or diffuse ST elevation on electrocardiogram (ECG) and left ventricular wall motion abnormalities (regional or global hypokinesis) on echocardiogram. The clinical presentations of myocarditis include subclinical, subacute, acute and fulminant forms, and abrupt-onset myocarditis is known to be associated with significant severity [6].

The annual incidence of acute myocarditis from all causes is approximately 22 cases per 100,000 population, with heart failure occurring in 0.5% to 4.0% of these cases [7]. Myocarditis can occur in 1% to 5% of all patients with acute viral infections [8]. To date, clinical data on myocarditis caused by SARS-CoV-2 is scarce. Patient characteristics, clinical course, degree of severity, imaging and electrocardiographic features, management and outcomes of myocarditis are just some of relevant data clinicians should have access to when treating patients with COVID-19 myocarditis. Therefore, we conducted a systematic review of myocarditis in COVID-19 patients to evaluate clinical features, diagnostic tests and current therapeutic management.

2. Methods

2.1. Protocol and Registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was adhered to for this systematic review [9]. The protocol was not registered.

2.2. Eligibility Criteria

2.2.1. Inclusion Criteria—Only articles that reported myocardial inflammation or myocarditis in association with COVID-19 were included.

2.2.2. Exclusion Criteria—Studies were excluded if: 1) Articles were not case reports, case series or observational studies, or 2) Articles were reviews or editorials. The language the article was written in was not a limitation.

2.3. Information Sources and Search Strategies

A comprehensive literature search was completed using Medline/Pubmed, Google Scholar, CINAHL, Cochrane CENTRAL and Web of Science databases up to and including 29 April 2020, using the terms “Coronavirus” or “COVID” and “myocarditis,” “heart” or “retrospective.”

2.4. Study Selection

Articles were triaged based on whether titles or abstracts met the inclusion criteria. Full-text articles were then read, and those that did not satisfy the inclusion criteria or fit exclusion criteria were excluded. A summary of study characteristics is included in Table 1.

2.5. Data Collection Process and Data Items

Data extracted from articles included the name of first author, year and country of publication and study design. Patient variables including age, sex and presenting complaints on admission were sought from all studies. Laboratory tests and diagnostic studies, as well as myocarditis management strategies and patient outcomes, including complications, were obtained from case studies.

2.6. Synthesis of Results and Summary of Measures

Information was assessed if it was reported by two or more articles. Data were tabulated, evaluated and summarized. From the retrospective studies, for Deng et al. [10] the diagnosis of myocarditis was assumed, while Ruan et al. [11] gathered patient profiles and presenting symptoms from the deceased population.

2.7. Risk of Bias of the Included Studies

Potential biases of the included studies were analyzed utilizing the study characteristics. Two independent reviewers evaluated the methodological quality of the eligible studies. A third reviewer evaluated papers for which no decision regarding bias could be reached. The Joanna Briggs Institute critical appraisal tool for case reports was selected for use in this systematic review [12]. The presence of a bias was determined for each article using a checklist the eight questions included in Table 1. The articles received scores to indicate their degree of biases; low (included), high (excluded) or uncertain (more information is required). For the purpose of this study, if “yes” was answered for half or more of the eight questions on the checklist, the study was considered to be at low risk of bias. Similarly, an answer of “no” to half or more of the eight questions meant the study was determined to be at high risk of bias. Whereas “unclear” answers were equal to or greater than 50% response.

3. Results

3.1. Study Selection

Five databases were used to find the 1076 articles related to COVID-19 and myocarditis. Eleven studies were then deemed eligible for inclusion in this review [10,11,13,14,15,16,17,18,19,20,21]. A PRISMA flow diagram detailing the process of identification, inclusion and exclusion of studies is shown in Figure 1.

3.2. Study Characteristics

Of the 11 included articles, nine were case reports [13,14,15,16,17,18,19,20,21] and two were retrospective studies [10,11]. All but one [21] were peer-reviewed. All articles were published in 2020. Five studies were conducted in Asia [10,11,14,17,21] and six were conducted in Europe [13,15,16,18,19,20]. China produced the most articles [10,11,14,21] followed by Italy [15,19,20].

3.3. Risk of Bias within the Studies

In comparison of the case reports, the majority of articles were determined to have low risk of bias [13,14,15,16,18,19,20,21]. Only one study was identified as having high risk of bias [17]. Both retrospective studies were rated as having high risk of bias [10,11]. These results are included in Table 1.

3.4. Results of Individual Studies

Nine case reports were selected for the systematic review. In the French study by Doyen et al. [13], the authors described a 69-year-old Italian man who tested positive for COVID-19, developed elevated troponins and ECG changes and was managed with hydrocortisone. Hu et al. [14] reported a case of a 37-year-old COVID-19 male from China with fulminant myocarditis who was treated with glucocorticoids and intravenous human immunoglobulin. Inciardi et al. [15] reported a 53-year-old Italian woman with COVID-19 with acute myopericarditis with evidence of systolic dysfunction on echocardiogram. In the only article not written in English, Irabien-Ortiz et al. [16] described a 59-year-old woman from Spain with COVID-19 and fulminant myocarditis in the absence of initial respiratory symptoms. In the study by Kim et al. [17], a 21-year-old woman from South Korea presented with COVID-19 and myocarditis. In the French study by Paul et al. [18], the authors reported a 35-year-old male positive for COVID-19 with acute myocarditis without fever, cough or pulmonary involvement. The article by Sala et al. [19] described a 43-year-old Italian woman diagnosed with COVID-19 and acute virus-negative lymphocytic myocarditis. Tavazzi et al. [20] described a case of a 69-year-old Italian woman with COVID-19 and low-grade myocardial inflammation; viral particles were seen in the patient's myocardium and the she required venous-arterial extracorporeal membrane oxygenation. Finally, Zeng et al. [21] reported a 63-year-old Chinese man with COVID-19 complicated by fulminant myocarditis.

Two retrospective studies were selected for the systematic review. In the first study, Deng et al. [10] described 14 of the original 112 patients hospitalized with COVID-19 in a major tertiary teaching hospital in China, who presented with cardiac abnormalities similar to

myocarditis. In the second retrospective study Ruan et al. [11] reported that some of the 150 COVID-19 positive patients from two hospitals in China died of fulminant myocarditis. A summary of findings from all studies is presented in Table 2.

3.5. Synthesis of Results

3.5.1. Patient Profiles—Among the nine case reports, COVID-19 patients with myocarditis were 51.8 ± 16.9 years of age, and males and females were equally affected [13,14,15,16,17,19,20,21]. In contrast, the retrospective studies described the typical myocarditis patient as male and older than 55 years of age [10,11]. The youngest patient described with COVID-19-related myocarditis was a 21-year old woman [17].

3.5.2. Presenting Complaints—The predominant complaint on presentation was dyspnea [10,11,13,14,16,17,19,20,21], followed by coughing [10,11,15,17,20,21], fever [10,11,13,14,15,17,21], and chest pain [10,13,16,19,21]. The mean temperature recorded was 37.53 ± 1.3°C [10,15,19,20,21], and the mean blood pressure was 85/58.3 ± 22.4/14.6 [10,14,15,16,19,20]. The distribution of presenting complaints and associated symptoms is found in Table 3.

3.5.3. Past Medical History—There were insufficient data regarding past medical history.

3.5.4. Laboratory Tests—A summary of laboratory tests is found in Table 4. Mean white blood cell (WBC) count was elevated at 17,383 ± 4,947 cells/mm^3 [16,20], and C-reactive protein (CRP) levels were increased at 31.2 ± 20.0 mg/L [13,15,19,20]. Arterial blood gas analyses showed respiratory acidosis with a mean pH of 7.24 ± 0.17 [13,15,20,21] and mean pCO_2 of 51.2 ± 8.2 mmHg [13,15,21]. Average oxygen saturation was 94.6 ± 4.1% [13,15,16,19,21], with a pO_2 of 91.0 ± 37.2 mmHg [13,15,20,21]. All studies reported either increased troponin-I [13,17,20,21] or troponin-T [14,15,16,19], along with elevated creatinine kinase-myocardial band (CK-MB) [14,15,21] and brain natriuretic peptide (BNP) [14,15,16,17,19,20,21].

3.5.5. Diagnostic Studies—A list of the diagnostic tests and imaging techniques utilized in the studies is provided in Table 5. All patients were confirmed COVID-19 positive. Bilateral infiltrates were discovered in 50% of chest radiographs [17,19,21] and bilateral ground glass opacities were seen in all patients who underwent chest computed tomography (CT) [13,14,17,19,20,21].

Cardiac magnetic resonance imaging (MRI) revealed late gadolinium enhancement [13,15,17,18,19] in all of the patients, while myocardial edema was identified in more than half of the images [15,17,19]. Fifty percent of the imaging studies revealed cardiomegaly or vascular redistribution [14,16,17]. Coronary artery stenosis was not appreciated on the CT angiography studies [14,17,19].

Electrocardiograms revealed ST-segment elevation in five cases [14,15,16,18,19], and inverted T waves in three cases [13,15,20]. In six of the studies, 2-D echocardiography revealed decreased left ventricular ejection fraction (LVEF) [14,15,17,19,20,21], and in

the same number of cases, cardiomegaly or increased wall thickness were observed [13,14,15,16,20,21]. Pericardial effusion was present in only three patients [14,15,16]. Two studies reported the results of endomyocardial biopsies [19,20]; both samples revealed active inflammation, and only one found viral particles within the myocardium [20].

3.5.6. Management of Myocarditis—Corticosteroids were utilized in attempted treatment in 75% of studies [13,14,15,16,20,21], while the use of the antiviral medications lopinavir-ritonavir was reported in 62.5% of studies [14,15,16,19,20,21]. The utilization of hydroxychloroquine [15,19,20], human immunoglobulin [14,16,21], piperacillin-tazobactam [14,20,21], and extracorporeal membrane oxygenation [16,20,21] each as single therapeutic interventions was described in 37.5% of case reports. The use of inotropes and/or vasopressors was reported in 50% of studies [14,15,16,20].

3.5.7. Outcome—Patient outcomes were included in the majority of the case reports [13,14,17,18,19,20,21]. Only one death was reported, and it was non-myocarditis-related [20]. The remaining articles reported either recovery [14,15,16,19,21] or no further impairment of LVEF [20].

3.6. Risk of Bias across the Studies

Due to the nature of the descriptive studies, the results presented are liable to investigator bias, selection procedure bias and selection bias.

3.6.1. Limitation of the Study—Statistical analyses were not performed as there were no control/comparison groups in the included studies.

4. Discussion

In order of prevalence, the clinical manifestations of the severe acute respiratory syndrome due to COVID-19 are fever, cough and fatigue [22]. Typically, myocarditis presents with fever, dyspnea and/or chest pain [23], which hampers the recognition and clinical diagnosis of myocarditis during the COVID-19 pandemic. We have identified through this systematic review that patients with COVID-19 myocarditis will commonly present with dyspnea, followed by coughing, fever and chest pain.

Serum biomarkers are conventionally used to confirm suspected acute myocarditis. While troponin was elevated in a few patients with acute myocarditis [24], elevated serum cardiac troponins were almost always seen in fulminant myocarditis [6]. Heightened levels of troponins have been described in many patients infected with COVID-19, with particular differences observed between deceased and surviving patients [25]. The absence of increased serum cardiac troponins, however, does not rule out myocarditis [6]. Elevated CK-MB and BNP were often elevated in myocarditis and can provide insight into prognosis [26]. CRP was commonly elevated, although normal levels did not exclude myocarditis [27]. CRP has been shown to be above the normal range in most COVID-19 patients as well [22]. This systematic review revealed increases in troponins, CK-MB, BNP, and CRP in COVID-19 myocarditis.

ST-segment abnormalities on ECG were demonstrated in 71.4% of patients. The ECGs of most patients with myocarditis demonstrated non-specific features including sinus tachycardia, ST-wave and T-wave abnormalities, and occasional atrioventricular or bundle branch block [28]. While ST-segment elevations in contiguous leads in a segmental fashion or in a nonvascular distribution are common electrocardiographic signs of myocarditis, they can often be mistaken for coronary occlusion [6].

Echocardiographic patterns of dilated, hypertrophic, restrictive and ischemic cardiomyopathies, particularly increased sphericity and left ventricular volume, have been described in histologically proven myocarditis [29]. Impaired LVEF on presentation is an independent predictor of a fulminant disease course [30]. This systematic review found that the majority of COVID-19 myocarditis patients had cardiomegaly, pleural effusion and reduced LVEF.

Dilated ventricles are typical of acute myocarditis, although the fulminant form can lead to increased left ventricular wall thickness as a result of active inflammation [29]. The majority of the cases of COVID-19 myocarditis reviewed here displayed cardiomegaly. Furthermore, the development of pneumonia seen as ground glass opacities on chest CT, the characteristic feature of COVID-19, was found in all patients in this systematic review [22,31].

There are only a few prospective blinded randomized trials that have specifically targeted viral infections or the associated inflammatory cascades in myocarditis. Presently, evidence does not support the routine use of corticosteroids or intravenous immunoglobulin alone [32,33], although combined treatment of corticosteroids with immunosuppressants has shown non-significant increases in LVEF [32]. The use of extracorporeal membrane oxygenation, however, has been shown to provide favorable outcomes for patients with myocarditis and sepsis [34], as well as fulminant myocarditis [35].

Among COVID-19 patients, there is limited evidence of the effectiveness of current management and treatment strategies. A recently published systematic review concluded that treatment with corticosteroids, mainly methylprednisolone, in patients infected with a coronavirus like COVID-19, SARS, MERS, etc., is associated with higher mortality, longer hospitalization, and higher rates of bacterial infection and electrolyte abnormalities [36]. A combination treatment of steroids with immunomodulatory therapy and antibiotics was used in a minority of studies. Extracorporeal membrane oxygenation was used in three studies with mixed results.

It is difficult to evaluate the effectiveness of the various treatment strategies currently being attempted in cases of COVID-19 given the lack of randomized control trial results to date. While current evidence shows no significant difference in the prognosis of virus-positive and virus-negative patients with myocarditis [37], that may change within the COVID-19 climate.

In conclusion, our systematic review provides a comprehensive characterization of clinical features among COVID-19 patients with myocarditis. Data are presently limited, therefore more research, particularly of the epidemiological type, is needed to improve our understanding of COVID-19 myocarditis.

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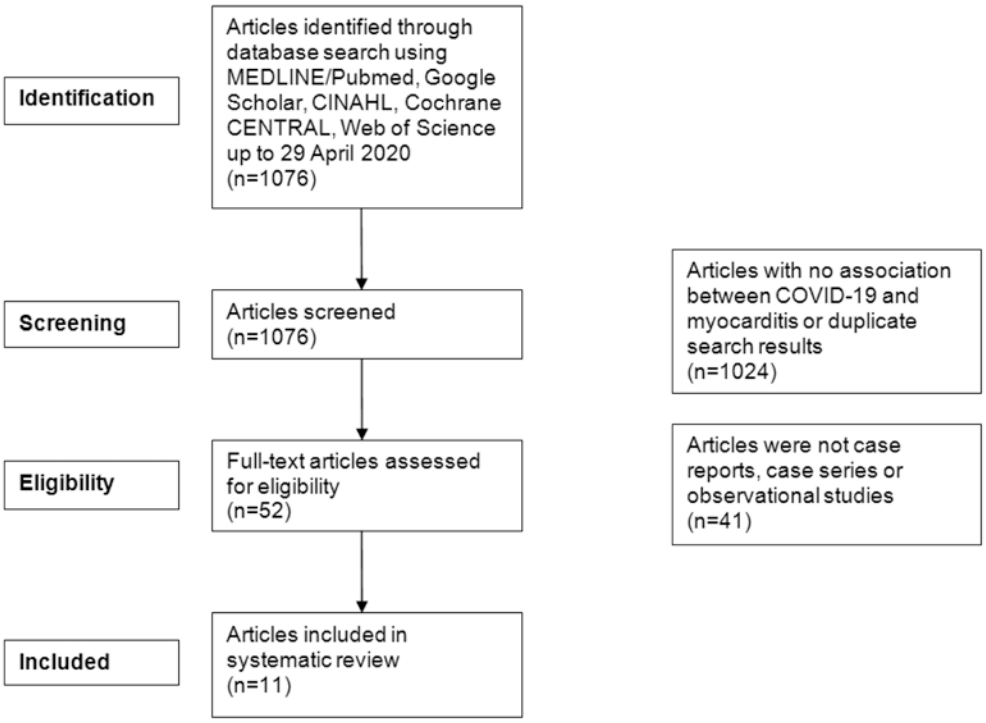

Figure 1.

Flow diagram of literature search and selection criteria adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Table 1.

Summary Assessment of the Risk of Bias for the Included Studies

Reference, publication year	Were the patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the patient's clinical condition on presentation clearly described?	Were diagnostic tests or assessment methods and results clearly described?	Was the intervention or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?	Total score
Deng et al., 2020 [10]	✓	Medical hx unknown	✓	All laboratory tests not included	No	No	No	✓	37.50%
Doyen et al., 2020 [13]	✓	✓	✓	All laboratory tests not included	✓	✓	✓	✓	87.50%
Hu et al., 2020 [14]	✓	Medical hx unknown	✓	All laboratory tests not included	✓	✓	✓	✓	75%
Inciardi et al., 2020 [15]	✓	✓	✓	✓	✓	Outcome unknown	✓	✓	87.50%
Irabien-Ortiz et al., 2020 [16]	✓	✓	✓	All laboratory tests not included	✓	Outcome unknown	✓	No	62.50%
Kim et al., 2020 [17]	✓	Medical hx unknown	✓	All laboratory tests not included	No	No	No	No	25%
Paul et al., 2020 [18]	✓	✓	✓	All laboratory tests not included	✓	✓	✓	No	75%
Ruan et al., 2020 [11]	No	No	No	✓	✓	No	No	✓	37.50%
Sala et al., 2020 [19]	✓	✓	✓	All laboratory tests not included	✓	✓	✓	No	75%
Tavazzi et al., 2020 [20]	Sex Missing	✓	✓	All laboratory tests not included	✓	✓	✓	✓	75%
Zeng et al., 2020 [21]	✓	✓	Admission vitals missing	All laboratory tests not included	Dosage missing	✓	✓	✓	63%

Table 2.

Summary of Included Articles

Reference number & publication year	Country	Type of study	Patient profile (age in years, sex)	Diagnosis
Deng et al., 2020 [10]	China	Retrospective study, single center	74, male	Possible myocarditis
Doyen et al., 2020 [13]	France	Case report	69, male	Acute myocarditis
Hu et al., 2020 [14]	China	Case report	37, male	Fulminant myocarditis
Inciardi et al., 2020 [15]	Italy	Case report	53, female	Acute myopericarditis
Irabien-Ortiz et al., 2020 [16]	Spain	Case report	59, female	Fulminant myocarditis
Kim et al., 2020 [17]	South Korea	Case report	21, female	Acute myocarditis
Paul et al., 2020 [18]	France	Case report	35, male	Acute myocarditis
Ruan et al., 2020 [11]	China	Retrospective study, multi-center	Unknown	Possible fulminant myocarditis
Sala et al., 2020 [19]	Italy	Case report	43, female	Acute virus-negative lymphocytic myocarditis
Tavazzi et al., 2020 [20]	Italy	Case report	69, female	Myocardial localization of virus in cardiogenic shock
Zeng et al., 2020 [21]	China	Case report, non-peer reviewed	63, male	Fulminant myocarditis

Table 3.

Most common clinical manifestations among patients with COVID-19 and myocarditis on admission as reported from all articles

Symptom	%
Dyspnea	81.8 [10,11,13,14,16,17,19,20,21]
Fever	54.6 [10,11,13,15,17,21]
Cough	54.6 [10,11,15,17,20,21]
Chest pain	54.6 [10,14,16,18,19,21]

Table 4.

Trends of laboratory values of COVID-19 patients with myocarditis

	Trends	(Standard range)
Vitals		
Temperature, Celsius	Elevated [13,15,19,20,21]	(<37.5)
Systolic blood pressure, mmHg	Decreased [14,15,16,19,20]	(90-120)
Diastolic blood pressure, mmHg	Decreased [14,15,16,19]	(60-80)
Arterial blood gas		
pH	Low [13,15,20,21]	(7.35-7.45)
pCO2, mmHg	High [13,15,21]	(35-45)
pO2, mmHg	Normal [13,15,20,21]	(75-100)
SaO2, %	Normal [13,15,16,19]	(>94)
Inflammatory markers		
WBC, cells/mm3	Elevated [13,16,20]	(4,500-11,000)
CRP, mg/L	Elevated [15,19,20]	(<8.0)
Cardiac markers		
Troponin-I, ng/mL	Elevated [13,17,18,20,21]	(<0.04)
Troponin-T, ng/mL	Elevated [14,15,16,19]	(<0.01)
CK-MB, ng/mL	Elevated [14,15,21]	(<5.0)
BNP, pg/mL	Elevated [14,15,16,17,19,20,21]	<125

Table 5.

Common findings on diagnostic tests of COVID-19 patients with myocarditis

Tests	Proportion Recorded from Articles Reviewed
Imaging (X-ray, CT, MRI)	
Late gadolinium enhancement	100 [13,15,17,18,19]
Bilateral infiltrates/ground glass opacities	66.7 [13,14,17,19,20,21]
Cardiomegaly	33.3 [14,15,17]
Echocardiography	
Decreased LVEF	66.7 [14,15,17,19,20,21]
Cardiomegaly or wall thickness	66.7 [13,14,15,16,20,21]
Pericardial effusion	33.3 [14,15,16]
Electrocardiography	
ST-segment elevation	55.6 [14,15,16,18,19]
T-wave inversion	33.3 [13,15,20]