



Myocarditis during SARS-CoV-2 Infection: A Series of 15 Cases

**A. Benhlime^{a*}, I. Bouzekraoui^a, A. Taj^a, A. Bouchaala^a,
H. Elhamzaoui^a and M. Alilou^a**

^a *Emergency Department, Faculty of Medicine and Pharmacy in Rabat, Ibn Sina Hospital – Rabat, Morocco.*

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJMAH/2023/v21i9861

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/98987>

Original Research Article

Received: 20/02/2023

Accepted: 24/04/2023

Published: 23/06/2023

ABSTRACT

COVID-19 is a global health problem responsible for significant morbidity and mortality and a major socioeconomic impact. While the major manifestation is respirator with a risk of acute respiratory distress syndrome, several extrapulmonary aspects, particularly cardiovascular, have emerged over time.

The aim of this work is to study the clinical, biological, radiological, therapeutic, and evolutionary characteristics of acute myocarditis associated with SARS-CoV-2 infection in comparison to data from the literature.

This is a prospective cohort study conducted at the Ibn Sina University Hospital in Rabat over a period of 9 months (from January 1, 2021, to September 30, 2021) and included patients hospitalized in different departments managing COVID-19 and diagnosed with acute myocarditis confirmed by cardiac MRI.

Fifteen patients were included during the study period. The average age of patients was 40 years old with a slight male predominance (sex ratio M/F-1.14). The average time between the onset of COVID-19 infection and the appearance of myocarditis symptoms was 17 days. The symptoms

*Corresponding author: E-mail: abdel.benhlime@gmail.com;

were mainly dominated by chest pain (40% of cases), unexplained cardiogenic shock (40% of cases), and palpitations (20% of cases). ECG revealed diffuse repolarization abnormalities in more than half of the cases (53%) and supraventricular tachycardia (27%). The inflammatory markers were significantly disturbed (CRP = 102 +/-47.30 mg/L and ferritin - 510 +/-336.45 ng/mL). Troponin I was elevated with myocarditis kinetics in all patients. Cardiac MRI showed T2 hypersignal corresponding to edema with early and late subepicardial enhancement, mainly located at the level of the left ventricular lateral wall.

The evolution was marked by the occurrence of death in 5 patients (33.33%) in the days following hospitalization for cardiogenic shock and dilated cardiomyopathy in only one case (6.67%). It was favourable for the rest of the patients (60%).

The results of this study have highlighted several characteristics of myocarditis associated with SARS-CoV-2. Firstly, there is a delayed interval between virus infection and the onset of cardiac symptoms. Additionally, the kinetics of myocardial injury markers are distinct, and there is significant disruption of inflammatory markers at the time of diagnosis. Moreover, fulminant forms of myocarditis are associated with a reserved prognosis and high mortality.

Furthermore, the study emphasizes the crucial importance of cardiac MRI availability for confirming the diagnosis in the absence of histological evidence from endomyocardial biopsy.

Keywords: Myocarditis; SARS-CoV-2; COVID-19; anti-COVID treatment; anti-COVID vaccination.

1. INTRODUCTION

Acute myocarditis presents a diagnostic challenge for clinicians, given its clinical polymorphism, differential diagnoses, and estimated annual incidence of 10 to 100 cases per 100,000 inhabitants [1-2].

Nevertheless, its impact on morbidity and mortality is significant. Acute myocarditis is responsible for 6% to 44% of sudden unexpected deaths in young populations, 14% to 32% of rhythm and conduction disorders, and 12% to 46% of non-ischemic dilated cardiomyopathies [3-4].

Numerous and diverse etiologies of myocarditis are dominated by infectious causes, with viral pathogens being the most prevalent [5].

Since the beginning of 2020, the world has been ravaged by the 2019 Coronavirus pandemic. It has been responsible for more than 470 million confirmed cases and more than six million deaths, mostly due to pulmonary involvement via acute respiratory distress syndrome.

Other extra-pulmonary pathological aspects of COVID-19 have been revealed as the global understanding of the pathogenic agent progressed. The universality and accumulation of reports indicating the occurrence of myocarditis following SARS-CoV-2 infection, in the absence of any other diagnostic element that could explain myocardial damage, provide strong

causality, although the pathogenesis of this condition is still poorly understood.

The aim of this work is to study the correlation between myocarditis and concomitant SARS-CoV2 infection, as well as the clinical, paraclinical, prognostic and therapeutic characteristics of this condition.

2. MATERIALS AND METHODS

2.1 Aim of the Work

The main objective of this work is to study the clinical, paraclinical, therapeutic, and evolutionary characteristics of acute myocarditis during SARS-CoV2 infection.

2.2 Study Population

The study population is represented by all patients who meet the inclusion criteria and are hospitalized in the different departments of Ibn Sina Hospital in Rabat, taking care of COVID-19, over a period of 9 months from January 1, 2021, to September 30, 2021.

Inclusion Criteria:

- Individuals aged between 15 and 45 years for males and 55 years for females.
- SARS-Cov-2 infection is confirmed by RT-PCR.
- The diagnosis of myocarditis is confirmed in accordance with the international consensus of learned societies.

Exclusion Criteria:

- The presence of a congenital or acquired cardiovascular disease history that may cause or contribute to myocardial involvement.
- The presence of a cardiovascular risk factor:
 - Tobacco smoke
 - Alcohol consumption
 - Diabetes
 - High blood pressure
 - High blood cholesterol
 - Obesity
 - Insufficient physical activity.
- The presence of a known pathology as a cause of myocarditis.
- Incomplete or non-exploitable records.

2.3 Methodology

This is a prospective longitudinal cohort study conducted on the study population over a period of nine months. All data was collected on an exploitation sheet containing anamnestic, clinical, biological, radiological, therapeutic, and evolutionary elements during the entire hospitalization period, and then follow-up in consultation after discharge at 3 months, 6 months, and 1 year.

2.4 Data Analysis and Statistical

Methods Statistical data entry was carried out using Excel Office 365 software, then analyzed using Epi-Info version 7.1.5 software (March 19, 2015).

3. RESULTS

3.1 Socio-demographic Data

During the nine-month period, 15 patients were included in the study. The mean age was 37 ± 10 years, with a median age of 40 years and extremes ranging from 17 to 52 years. 53.3% of the patients were male and 46.7% were female, resulting in a sex ratio of 1.17.

3.2 Clinical Data

3.2.1 Initial clinical severity of COVID-19

Respiratory-wise, 47% of patients had correct oxygen saturation in ambient air, while 53% required respiratory support. Thus, 20% of our patients were on oxygen glasses, 13% on High Concentration Mask (HCM), and 20% were undergoing non-invasive ventilation sessions.

On the scanographic level, two-thirds of this patients (67%) had tissue damage classified as CORADS-5.

3.2.2 Time between COVID-19 diagnosis and onset of suggestive symptoms of acute myocarditis

In this study, the time between the date of confirmation of SARS-CoV-2 infection and the onset of suggestive symptoms of myocardial involvement ranged from 5 to 25 days, with an average delay of 17 days.

3.2.3 Initial clinical presentation

The clinical symptoms were dominated by three presentations: Chest pain, infarcted or pericarditic, was found in 40% of cases, 40% presented an unexplained cardiogenic shock, and 20% reported palpitations.

3.3 Paraclinical Data

3.3.1 ECG abnormalities

All our patients presented ECG abnormalities at the time of myocarditis diagnosis. These were mainly ventricular repolarization disorders (53% of cases). 62% had diffuse ST-segment elevation and 38% had T-wave abnormalities.

Supraventricular tachycardia was found in 27% of cases, diffuse microvoltage in 13% of cases, and ventricular extrasystoles in one patient.

3.3.2 Biological characteristics

Inflammatory markers were disturbed in all patients with a mean CRP value of 125 mg/L and a ferritin level of 508 ng/mL (Table 1).

3.3.3 Evolution of cardiac biomarkers

High levels of Troponin I US were found at the time of diagnosis in all cases. They ranged from 0.15 ng/mL to 10.4 ng/mL with a median of 2.47 ng/mL (reference value < 0.040 ng/mL). The kinetics of troponin showed a rapid regression and normalization by the 5th day (Table 2).

3.3.4 Transthoracic echocardiography

All the patients underwent a transthoracic echocardiography. It showed global hypokinesia with impaired ejection fraction in 4 patients (26.67%), minimal pericardial effusion in three

patients (20%), ventricular dilation (6.67%) in one case, and septal hypertrophy (6.67%) in one case. The transthoracic echocardiography was normal in 6 patients (40%).

3.3.5 Cardiac MRI

Cardiac MRI was performed in 8 patients, accounting for 53.33% of cases. It revealed the presence of non-ischemic subepicardial late gadolinium enhancement in all these patients, T2 hyperintensity in five patients (33.33%), and an increase in extracellular volume on TI in four patients (26.26%). Cardiac MRI could not be performed in seven patients, six of whom were in cardiogenic shock and one patient under continuous non-invasive ventilation.

Cavity measurements and systolic and diastolic ventricular functions of our patients were normal with good segmental kinetics and preserved intrinsic contractility. Pericardial effusion was present in two patients at the time of MRI.

4. TREATMENT, FOLLOW-UP, AND OUTCOME

4.1 Modality and Duration of Follow-up

All the patients were hospitalized. After discharge, follow-up was carried out through scheduled consultations at the consultation center at 3 months, 6 months, and 1 year.

Table 1. Summary table of the biological assessment of the patients

| Biological characteristic | Average value per unit corresponding \pm ET |
|--------------------------------|---|
| K+ | 4,2 +/-0,47 |
| alkaline reserve | 24 +/- 2,98 |
| Urea | 0,39 +/-0,24 |
| Creatinine | 9,85 +/- 2,69 |
| Blood glucose level | 0,98 +/- 0,11 |
| Protides | 65 +/- 8,05 |
| CRP | 125 +/- 89,90 |
| Ferritine | 508 +/- 236,58 |
| Hemoglobin | 14 +/- 1,36 |
| White blood cells | 7121 +/- 1745 |
| neutrophilic polynuclear cells | 4350 +/- 1171 |
| Blood platelets | 203500 +/-76652 |

Table 2. Troponin I us kinetics during the first five days

| Patients | Baseline Troponin (ng/mL) | D1Troponin (ng/mL) | D2Troponin (ng/mL) | D3Troponin (ng/mL) | D4Troponin (ng/mL) | D5Troponin (ng/mL) |
|----------|---------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| P1 | 0,005 | 10,4 | 2,463 | 0,71 | 0,121 | 0,041 |
| P2 | 0,02 | 1,519 | 0,654 | 0,21 | 0,055 | 0,009 |
| P3 | 0,01 | 0,891 | 0,351 | 0,092 | 0,038 | 0,007 |
| P4 | 0,01 | 0,783 | 0,066 | 0,023 | 0,011 | 0,004 |
| P5 | 0,01 | 0,76 | 0,251 | 0,05 | 0,018 | 0,002 |
| P6 | 0,008 | 1,776 | 0,678 | 0,101 | 0,043 | 0,01 |
| P7 | 0,008 | 0,446 | 0,104 | 0,015 | 0,01 | 0,008 |
| P8 | 0,035 | 0,162 | 0,06 | 0,033 | 0,01 | 0,004 |
| P9 | 0,01 | 6,619 | 1,05 | 0,08 | 0,042 | 0,036 |
| P10 | 0,033 | 0,15 | 0,06 | 0,01 | 0,01 | 0,01 |
| P11 | 0,01 | 0,469 | 0,152 | 0,085 | 0,026 | 0,01 |
| P12 | 0,02 | 1,48 | 0,523 | 0,062 | 0,015 | 0,01 |
| P13 | 0,025 | 4,01 | 1,756 | 0,811 | 0,04 | 0,022 |
| P14 | 0,008 | 6,68 | 2,255 | 0,761 | 0,08 | 0,04 |
| P15 | 0,033 | 0,896 | 0,122 | 0,04 | 0,016 | 0,008 |
| Median | 0,02 | 0,896 | 0,351 | 0,080 | 0,035 | 0,008 |

4.2 Treatment

The management of patients was based on symptomatic treatment, including titration oxygen therapy, vitamin therapy combining vitamin C and vitamin D, zinc, injectable glucocorticoids, antibiotic therapy in case of bacterial superinfection, anticoagulation, and adequate hydration.

Aspirin and colchicine were used in forms of perimyocarditis, while Tocilizumab and Anakinra were administered in patients with elevated IL-6 levels. No patient received antivirals. The use of antiarrhythmics, particularly beta-blockers, was initiated in some supraventricular tachycardias.

4.3 Outcome

The average length of stay was 6 days with extremes ranging from 2 to 30 days. The overall mortality rate was 33.33% (5 cases) related to cardiogenic shock referred to fulminant myocarditis.

After one year, only one patient developed dilated cardiomyopathy (CMD) with an ejection fraction of 30%. The other patients had a satisfactory clinical and paraclinical outcome.

5. DISCUSSION

5.1 Myocarditis during SARS-CoV-2 Infection

Cardiac involvement during COVID-19 and its implication in the worsening of prognosis were suspected from the early months of the pandemic. Myocardial injury defined by a significant elevation of myocytary lysis markers [6] was suggested by Chinese authors from January 2020.

In their study of 671 cases of COVID-19. Shi et al. found a rate of 15.8% of patients presenting concomitant myocardial injury, which was responsible for the death of 30.6% of cases. This study also highlighted the remarkable disruption of inflammatory markers in these patients, thus suggesting a probable link between a disproportionate inflammatory response and myocardial injury [7].

Guo et al. reported a rate of 27.8% of concomitant myocardial injury among hospitalized patients for the management of COVID-19 (52 cases out of a total of 187) with a six-fold higher mortality rate compared to other patients whose troponin value was normal (59.6% vs 8.9%) [8].

Other studies estimated this rate between 7.2% to 22.2% of all hospitalized patients for SARS-CoV-2 pneumonia and those admitted to the ICU, respectively [9,10].

Although the first studies highlighted the presence of myocardial injury and suggested it as a prognostic factor, they were hesitant about the nature or etiopathogenic mechanisms, given the frequent presence of cardiovascular comorbidities that could attribute or explain myocardial injury.

The diagnosis of myocarditis as the cause of this myocardial injury was first suggested in the context of fulminant myocarditis. Hu et al. reported the case of a 37-year-old man presenting with unexplained cardiogenic shock concomitant to COVID-19 pneumonia. The patient's condition improved with symptomatic treatment, and the diagnosis of fulminant myocarditis due to SARS-CoV-2 was retained [11]. Three months later, the first confirmed myocarditis due to SARS-CoV-2 was diagnosed in Italy in a 60-year-old woman with unexpected cardiogenic shock.

Globally, cardiac MRI was limited for COVID-19 positive patients in whom myocarditis was highly likely, which could be explained by the risk of exposure of radiological equipment and personnel, the duration of the examination, and its modality, which might not be tolerated by SARS-CoV-2-infected patients [12].

Huang et al. reported the results of 26 patients, with a median age of 36 years, without notable cardiovascular history, recovering from moderate COVID-19 pneumonia and presenting with a clinical picture suggestive of acute myocarditis. Cardiac MRI was performed within 47 days of the onset of clinical symptoms [13].

Fifteen patients in this study (58% of cases) showed T2 hypersignal and/or late gadolinium enhancement signals. Cardiac edema was observed in 14 patients (54%), while eight patients (31%) had subepicardial late enhancement. This study also highlighted the clinical and biological disparity of concomitant myocarditis in SARS-CoV-2.

5.2 Etiopathogenic Mechanisms

Direct viral multiplication Viral infection of the myocardium is a well-established cause of acute myocarditis, and is even considered the primary etiology of it. Keeping in mind previous

experiences with viruses from the same family, including MERS-CoV and SARS-CoV-1, which are implicated in acute myocarditis through direct viral replication, by exploiting the affinity to angiotensin 2 conversion enzymes ACE2 [9, 13, 14]. This has raised the hypothesis of the presumption of the same mechanism with the new coronavirus.

Cytokine storm and autoimmune response Also called "cytokine storm", this inflammatory state is the most severe form of cytokine release syndrome (CRS), characterized by an uncontrolled inflammatory response involving continuous activation of macrophages and lymphocytes [9].

This mechanism is considered the primummovens of the pathogenesis of diffuse lung injury, responsible for acute respiratory distress syndrome [13,15,16]. Prolonged inflammatory activation appears to be responsible for triggering an autoimmune response and perpetuating myocardial damage [15,17].

5.3 Comorbidities

This study excluded all patients with comorbidity or cardiovascular risk factors in order to limit interference with other diagnostics. The studies by Luetkens Esposito followed a similar method. Cardiovascular catheterization was systematic in patients to rule out coronary artery disease [18, 19].

Other studies have reported the presence of cardiovascular risk factors and comorbidities. In Huang's study, 8% of patients had only isolated hypertension, while the rates of diabetes and hypertension in Puntmann's study were 22% and 18%, respectively [13, 20].

The low rates of comorbidities and cardiovascular risk factors can be explained by the fact that the population frequently affected by acute myocarditis is a young population [5].

5.4 Clinical and Paraclinical Features of COVID-19-Associated Myocarditis

5.4.1 The interval between COVID-19 infection and the onset of cardiac symptoms

Prior to the COVID-19 era, the median time between the onset of flu-like symptoms and

acute myocarditis was between one to two weeks [21]. This duration was considered necessary for viruses to replicate within the myocardium and/or trigger an inflammatory or autoimmune response capable of initiating or maintaining acute myocarditis [5]. This variability can be explained by the fact that some authors use the onset of flu-like symptoms as a reference point, while others consider it from the confirmation of SARS-CoV-2 infection.

In this study, the median time from the onset of symptoms of SARS-CoV-2 infection to the appearance of suggestive symptoms of myocarditis was 17 days. This timeframe aligns with findings from various studies currently available.

5.4.2 Clinical presentation

Chest pain was reported in 17% to 80% of cases with concurrent acute myocarditis and SARS-CoV-2 [13, 18, 20]. This symptom predominates the clinical presentation with mostly angina-like symptoms, which explains the indication for coronary angiography to rule out acute coronary syndrome [5].

Unexplained and sudden cardiogenic shock following acute myocarditis is characteristic of the fulminant form. Bajaj et al. reported a rate of 33% (3 out of 9 patients), while Wong et al. reported a rate of 47% [22, 23].

Palpitations were a frequent symptom reflecting rhythm and/or conduction disorders. Its incidence varied in the literature between 20% and 88% [13, 20].

In this series, acute myocarditis was manifested by "infarctoid or pericarditic" chest pain in 40% of cases, 40% of cases presented with unexplained cardiogenic shock, and the remaining 20% had palpitations. The clinical presentations reported in the current study are consistent with those documented in the literature.

5.4.3 ECG

Repolarization abnormalities illustrated by diffuse concave ST-segment elevation, ST-segment depression, and T-wave inversion represent the majority of ECG abnormalities reported in acute myocarditis concurrent with COVID-19. They were followed in second place by conduction disorders: atrioventricular block and bundle branch blocks [18, 24].

The predominance of ST-segment or T-wave abnormalities, associated with angina-like chest

pain, requires the elimination of coronary artery disease before considering myocarditis, which was done in all the aforementioned studies [13, 20-25] in compliance with recommendations [5].

Approximately half of the cases in our study (53%) exhibited diffuse repolarization disorder, while the remaining patients presented with supraventricular tachycardia, diffuse microvoltage, or ventricular extrasystoles, which were found in 27%, 13%, and 7% respectively.

5.5 Laboratory Tests

5.5.1 Troponin kinetics

The kinetics of cardiac troponin following acute myocarditis has been of interest to several scientific societies, to determine if this kinetics follows a particular pattern allowing differentiation between acute myocarditis and other cardiac diseases, particularly myocardial infarction.

The American Heart Association (AHA) has highlighted the differences in troponin kinetics following acute myocarditis and myocardial infarction. This kinetics tends to normalize rapidly after 2 to 3 days in acute myocarditis, compared to slow normalization in myocardial infarction [26, 27].

In the study by Bajaj et al., the troponin level was high at the time of diagnosis with values ranging from 6 to 208 times the upper limit of normal and normalization of this level within two to five days following the initial peak [22].

In this study, ultra-sensitive troponin I was employed as a marker to assess and monitor myocardial injury. All the patients had an initial elevated troponin value at the time of diagnosis of acute myocarditis, with a fast return to normal value within two to three days following the initial increase.

5.5.2 Inflammatory markers

Various studies have reported disproportionate inflammation during acute myocarditis appearing following SARS-CoV-2 infection, thus suggesting the hypothesis of cytokine storm as a probable mechanism for this condition. The main marker used to assess and monitor inflammation was CRP. The measurement of ferritin, interleukins, and procalcitonin was not systematic [22].

In the present study, the disturbance of inflammatory markers was significant with initial

mean CRP and Ferritin values of 102 mg/L and 510 ng/mL respectively.

5.6 Cardiac Imaging

5.6.1 Transthoracic echocardiography

Bearse's study was the first to provide an anatomical-echocardiographic comparison of myocarditis in SARS-CoV-2. In this study, the ejection fraction was normal in all patients with proven myocarditis, while the ejection fraction was reduced in patients without myocarditis but with detectable viral genome in the myocardium [24]. Although Bajaj et al. reported a decrease in left ventricular ejection fraction in all patients with acute myocarditis, with a mean value of 24% (10%-34%) [23], Wong's study found higher values of LVEF during fulminant and non-fulminant myocarditis [23].

In this study, transthoracic echocardiography showed global hypokinesia with impaired ejection fraction (LVEF<40%) in 26.67% of cases, minimal pericardial effusion in 20% of cases, ventricular dilatation and septal hypertrophy in 6.67% of cases respectively. In 40% of the cases the transthoracic echocardiography came back without any particularity.

5.6.2 Cardiac MRI

Huang's study was the first to detail the results of cardiac MRI in patients with acute myocarditis related to SARS-CoV-2. The systolic ejection fraction was preserved (EF = 60.7 +/- 6.4%), and the functions of the LV and RV were similar to those of the non-affected control group [13]. The same results have been reported by other studies, highlighting the absence of disparity in the systolic and diastolic functions of both ventricles [20,25].

Cardiac MRI in all patients of this study revealed findings consistent with modified Lake Louise criteria, confirming the diagnosis of myocarditis. Similar to other studies reporting myocarditis in the context of COVID-19, cardiac MRI was utilized as a valuable tool, especially in the absence of specialized centers for endomyocardial biopsy during this pandemic.

6. THERAPEUTIC, EVOLUTIONARY AND PROGNOSTIC CHARACTERISTICS

6.1 Therapeutic Characteristics

All the patients received symptomatic treatment based on titrated oxygen therapy, injectable

glucocorticoids, antibiotics in case of bacterial superinfection, preventive or therapeutic anticoagulation depending on the patient's risk of thromboembolism, along with vitamin therapy (vitamin C, vitamin D), zinc and adequate hydration. Tocilizumab and Anakinra were used in patients with high IL-6 levels, while no patients received antivirals.

Similar protocols in compliance with WHO recommendations were adopted by other studies similar to ours. Huang's study provided the first therapeutic data of patients with acute myocarditis using early antivirals such as Kaletra and Umifenovir (Arbidol) [13]. The use of antivirals was limited in patients with myocarditis attributed to SARS-CoV-2 with no major differences in outcomes [20, 24].

6.2 Evolutionary and Prognostic Characteristics

The current literature does not provide precise data regarding the evolution of patients with acute myocarditis caused by SARS-CoV-2, considering the recent nature of the different studies.

Although Bearn's study was based on pathological reports of deceased patients, the cause of death was acute respiratory distress in relation to COVID-19 without evidence of fulminant myocarditis [24]. In addition, other studies similar to ours did not provide clarification on the short- and long-term evolution of patients.

Post-myocarditic complications, such as dilated cardiomyopathies, are mainly reported in case reports, with no major studies detailing this frequent complication of myocarditis [28, 29].

Although the prognosis of acute myocarditis related to SARS-CoV-2 is still unclear, the presence of myocardial injury is a negative prognostic factor. This injury was found in 7% to 23% of COVID-19 cases and in 50% of patients who died from the disease [9, 15, 17].

6.3 Study limitations

This study presented several limitations:

- The literature on acute myocarditis due to SARS-CoV-2 is still limited.
- Small study sample.
- Delayed diagnosis of myocarditis in COVID-19 patients.

- Incomplete investigations, and therefore, incomplete medical records of COVID-19 patients with a clinical probability of concomitant myocarditis.

7. CONCLUSION

Acute myocarditis is a public health problem, given the epidemiological estimation of this pathology remains poorly understood, it affects a predominantly young population, and its main complications are sudden death and dilated cardiomyopathy.

This study has allowed us to examine the clinical, biological, radiological, therapeutic, and evolutionary peculiarities of acute myocarditis during SARS-CoV-2 infection, in comparison to data from the literature, and to discuss plausible etiopathogenic mechanisms of this condition, mainly represented by direct viral multiplication, cytokine shock, and induced autoimmune response.

In this regard, this work has revealed certain characteristics of concomitant myocarditis with SARS-CoV-2, such as the delayed interval between infection and onset of cardiac symptoms, the specific kinetics of myocardial injury markers, significant disturbance of the inflammatory balance at the time of diagnosis, and poor prognosis, especially for fulminant forms with high mortality.

Furthermore, the study has highlighted the importance of the availability of cardiac MRI, a key element for confirming the diagnosis in the absence of histological evidence on endomyocardial biopsy.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Golpour A, Patriki D, Hanson PJ, McManus B, Heidecker B. Epidemiological

- impact of myocarditis. *J Clin Med.* 2021; 10(4):603.
2. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015;386(9995):743-800.
 3. Lyng TH, Nielsen TS, Gregers Winkel B, Tfelt-Hansen J, Banner J. Sudden cardiac death caused by myocarditis in persons aged 1-49 years: a nationwide study of 14 294 deaths in Denmark. *Forensic Sci Res.* 2019;4(3):247-256.
 4. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, Messere J, Cox GF, Lurie PR, Hsu D, Canter C, Wilkinson JD, Lipshultz. Incidence, causes, and outcomes of dilated cardiomyopathy in children. *JAMA.* 2006;296:1867-187.
 5. Caforio ALP, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J.* 2013;34(33):2636-48.
 6. Kristian Thygesen, Joseph S Alpert, Allan S Jaffe, Bernard R Chaitman, Jeroen J Bax, David A Morrow, Harvey D White. ESC scientific document group, fourth universal definition of myocardial infarction (2018), *European Heart Journal.* 2019;40(3):237-269.
 7. Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, Cao S, Liu X, Xiang Y, Zhao Q, Huang H. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *European heart journal.* 2020 Jun 7;41(22):2070-9.
 8. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA cardiology.* 2020;5(7):811-8.
 9. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiology.* 2020;5(7):802-810.
 10. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* 2020;323(11):1061-9.
 11. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, Sepe PA, Resasco T, Camporotondo R, Bruno R, Baldanti F. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *European journal of heart failure.* 2020;22(5):911-915.
 12. Salerno M, Kwong RY. CMR in the era of COVID-19: evaluation of myocarditis in the subacute phase. *Cardiovascular Imaging.* 2020;13(11):2340-2342.
 13. Huang L, Zhao P, Tang D, Zhu T, Han R, Zhan C, Liu W, Zeng H, Tao Q, Xia L. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. *Cardiovascular Imaging.* 2020;13(11):2330-9.
 14. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, Butany J. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *European Journal of Clinical Investigation.* 2009;39(7):618-25.
 15. Pirzada A, Mokhtar AT, Moeller AD. COVID-19 and myocarditis: what do we know so far?. *CJC open.* 2020;2(4):278-285.
 16. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang X, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical and immunological features of severe and moderate coronavirus disease 2019. *The Journal of clinical investigation.* 2020;130(5):2620-2629.
 17. Shchendrygina A, Nagel E, Puntmann VO, Valbuena-Lopez S. COVID-19 myocarditis and prospective heart failure burden. Expert review of cardiovascular therapy. 2021;19(1):5-14.
 18. Esposito A, Palmisano A, Natale L, Ligabue G, Peretto G, Lovato L, Vignale D, Fiocchi F, Marano R, Russo V. Cardiac magnetic resonance characterization of myocarditis-like acute cardiac syndrome in COVID-19. *JACC. Cardiovascular imaging.* 2020;13(11):2462-5.

19. Luetkens JA, Isaak A, Öztürk C, Mesropyan N, Monin M, Schlabe S, Reinert M, Faron A, Heine A, Velten M, Dabir D, Boesecke C, Strassburg CP, Attenberger U, Zimmer S, Duerr GD, Nattermann J. Cardiac MRI in suspected acute COVID-19 myocarditis. *Radiology. Cardiothoracic Imaging.* 2021;3(2): e200628.
20. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA cardiology.* 2020;5(11): 1265-73.
21. Rroku A, Kottwitz J, Heidecker B. Update on myocarditis - what we know so far and where we may be heading. *Eur Heart J Acute Cardiovasc Care.* 2020; 2048872620910109.
22. Bajaj R, Sinclair HC, Patel K, Low B, Pericao A, Manisty C, Guttman O, Zemrak F, Miller O, Longhi P, Proudfoot A, Lams B, Agarwal S, Marelli-Berg FM, Tiberi S, Cutino-Moguel T, Carr-White G, Mohiddin SA. Delayed-onset myocarditis following COVID-19. *The Lancet Respiratory Medicine.* 2021;9(4):e32-4.
23. Christopher Wong, Amtul Mansoor, Thomas Mc Ginn. A cross-sectional study of clinical COVID-19 myocarditis: differences in biomarkers in fulminant and non-fulminant cases medrxiv 2021;06(06): 21258423.
24. Bearse M, Hung YP, Krauson AJ, Bonanno L, Boyraz B, Harris CK, Helland TL, Hilburn CF, Hutchison B, Jobbagy S, Marshall MS, Shepherd DJ, Villalba JA, Delfino I, Mendez- Pena J, Chebib I, Newton-Cheh C, Stone JR. Factors associated with myocardial SARS-CoV-2 infection, myocarditis, and cardiac inflammation in patients with COVID-19. *Modern Pathology.* 2021;34(7):1345-57.
25. Knight DS, Kotecha T, Razvi Y, Chacko L, Brown JT, Jeetley PS, Goldring J, Jacobs M, Lamb LE, Negus R, Wolff A, Moon JC, Xue H, Kellman P, Patel N, Fontana M. COVID-19: Myocardial Injury in Survivors. *Circulation.* 2020;142(11):1120-1122.
26. Mahajan VS, Jarolim P. How to interpret elevated cardiac troponin levels. *Circulation* 2011;124(21):2350-2354.
27. Wereski R, Kimenai DM, Taggart C, Doudesis D, Lee KK, Lowry MT, Bularga A, Lowe DJ, Fujisawa T, Apple FS, Collinson PO. Cardiac troponin thresholds and kinetics to differentiate myocardial injury and myocardial infarction. *Circulation.* 2021;144(7):528-38.
28. Komiyama M, Hasegawa K, Matsumori A. Dilated cardiomyopathy risk in patients with coronavirus disease 2019: how to identify and characterise it early?. *European Cardiology Review.* 2020;15.
29. Azeka E, Arshad A, Martins C, Dominguez AC, Siqueira A, Loss AS, Jatene M, Miura N. Case report: dilated cardiomyopathy in a newborn, a potential association with SARS-COV-2. *Frontiers in pediatrics.* 2021;9:674300.

© 2023 Benhlima et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:
<https://www.sdiarticle5.com/review-history/98987>