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# Clinical and epidemiological risk factors for a first episode of acute myocarditis

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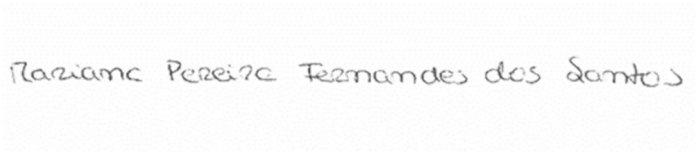

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**Porto, junho de 2025**

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(Lara Peleteiro de Barbosa Paiva)

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## Resumo

**Introdução:** A identificação das características sociodemográgicas e epidemiológicas predisponentes para o desenvolvimento de miocardite aguda pode facilitar o diagnóstico e garantir uma abordagem mais eficaz.

**Métodos**: Foi realizado um estudo observacional retrospetivo que incluiu 161 doentes admitidos consecutivamente no Centro Hospitalar e Universitário de Santo António, com miocardite aguda clinicamente suspeita ou confirmada, entre Janeiro de 2010 e Março de 2023. Pretendeu-se avaliar a incidência de miocardite, as características epidemiológicas e clínicas da população, bem como o prognóstico e a evolução a longo prazo destes pacientes.

**Resultados:** A maioria da população afetada pertencia ao sexo masculino (74.5%), com uma idade mediana de 33 anos. Fatores de risco cardiovasculares tradicionais foram pouco frequentes e apenas o tabagismo apresentou uma prevalência significativa, observada em 32.9% dos doentes. A etiologia viral foi a mais comummente identificada (42.2%), sendo que 39.8% dos doentes teve um episódio de infeção respiratória e 16.1% de infeção gastrointestinal prévia à miocardite. O pico de hospitalizações ocorreu nos meses de Inverno, concordante com os meses do ano em que as infeções respiratórias são mais prevalentes. Relativamente à pandemia por Sars-CoV-2, esta causou um aumento da incidência anual de 42% de miocardite aguda. Comparando os dois grupos de doentes (com e sem infeção por Sars-CoV-2 no mês transato), não foram encontradas diferenças significativas, à exceção do tempo de internamento que foi cerca do dobro nos doentes com Sars-CoV-2 (7.5 dias vs 4 dias). Salientar ainda que as mulheres com miocardite tendem a apresentar uma doença mais grave e com mais complicações, em comparação com os homens.

**Conclusão:** A miocardite aguda é mais prevalente em homens jovens, destacando-se o tabagismo como único fator de risco cardiovascular significativo. Por outro lado, quando se apresenta no sexo feminino tende a ser mais grave. As infeções respiratórias são um dos principais fatores predisponentes identificados, com maior pico de hospitalizações no Inverno. A etiologia viral foi a mais prevalente, sendo que o Sars-CoV-2 se tornou um novo fator de risco, com aumento siginificativo na incidência de episódios de miocardites agudas, e não foi evidente um efeito de risco da vacinação.



**Palavras-chave**: Miocardite aguda; Incidência; Epidemioloiga; Fatores de Risco; Insuficiência Cardíaca;

## Abstract

**Background:** The identification of sociodemographic and epidemiological characteristics predisposing to the development of acute myocarditis may facilitate diagnosis and ensure a more effective approach.

**Methods**: An observational retrospective study was conducted with 161 patients, admitted to the Centro Hospitalar e Universitário de Santo António, diagnosed with clinically suspected or confirmed acute myocarditis, between January 2010 and March 2023. The aim was to assess the incidence of myocarditis, the epidemiological and clinical characteristics of the population, as well as the outcomes and long-term evolution of these patients.

**Results:** The majority of the affected population was male (74.5%), with a median age of 33 years. Traditional cardiovascular risk factors were infrequent, and only smoking showed a significant prevalence (32.9%). Viral aetiology was the most commonly identified (42.2%), with 39.8% of patients experiencing a respiratory tract infection and 16.1% a gastrointestinal infection prior to the onset of myocarditis. The peak of hospitalizations occurred during the winter months, in line with the higher prevalence of respiratory infections during this period. Regarding the Sars-CoV-2 pandemic, it caused a 42% increase in the annual incidence of acute myocarditis. When comparing the two patient groups (with and without Sars-CoV-2 infection in the previous month), no significant differences were found, except for the length of hospitalization, which was approximately double in patients with Sars-CoV-2 (7.5 days vs. 4 days). It is important to highlight that females with myocarditis often experience a more severe clinical course and higher rates of complications, which contribute to less favourable outcomes than those seen in males.

**Conclusions:** Acute myocarditis is more prevalent in young men, with smoking standing out as a significant cardiovascular risk factor. On the other hand, when it occurs in females, it tends to be more severe. Respiratory infections are one of the main predisposing factors identified, with a peak in hospitalizations during winter. The viral etiology was the most prevalent, with Sars-CoV-2 becoming a new risk factor, causing a significant increase in the incidence of acute myocarditis episodes, and no clear risk associated with vaccination was observed.



**Key words:** Acute myocarditis; Incidence; Epidemiology; Risk factors; Heart Failure;

## Lista de Abreviaturas

| | |
|---|---|
| **ANA** | Antinuclear Antibodies |
| **ANCA** | Anti-Neutrophilic Cytoplasmic Autoantibodies |
| **Anti-HBc** | Hepatitis B Core Antibody |
| **Anti-HCV** | Hepatitis C Antibody |
| **ASCA** | Anti-Saccharomyces Cerevisiae Antibodies |
| **CDC** | Centers for Disease Control and Prevention |
| **CMR** | Cardiac Magnetic Resonance Imaging |
| **CMV** | Cytomegalovirus |
| **COPD** | Chronic Obstructive Pulmonary Disease |
| **CRP** | C-Reactive Protein |
| **DCM** | Dilated Cardiomyopathy |
| **EBV** | Epstein-Barr virus |
| **ECG** | Electrocardiography |
| **EMB** | Endomyocardial Biopsy |
| **HER-2** | Human epidermal growth factor receptor 2 |
| **HHV6** | Human Herpesvirus 6 |
| **HIV** | Human immunodeficiency virus |
| **ICD** | Implantable Cardioverter Defibrillator |
| **ICD-10** | International Classification of Diseases, Tenth Revision |
| **IQR** | Interquartile Range |
| **LC-1** | Liver Cytosolic Antigen Type-1 |
| **LGE** | Late Gadolinium Enhancement |
| **LV** | Left Ventricle |

| | |
|---|---|
| **LVEF** | Left Ventricular Ejection Fraction |
| **mRNA** | messenger Ribonucleic Acid |
| **NSTEMI** | Non ST Elevation Myocardial Infarction |
| **NT-proBNP** | Pro-brain Natriuretic Peptide |
| **PML** | Promyelocytic leukemia protein |
| **RF** | Rheumatoid factor |
| **SARS-CoV-2** | Severe Acute Respiratory Syndrome Coronavirus 2 |
| **SPSS** | Statistical Package for Social Sciences |
| **STEMI** | ST Elevation Myocardial Infarction |
| **TnI** | Troponin I |
| **TnT** | Troponin T |
| **WHO** | World Health Organization |

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## Introduction

According to the World Health Organization (WHO), myocarditis is an inflammation of the heart muscle, known as the myocardium. [1] It is reported in 4 to 14 people per 100 000 each year globally. [2] However, the true incidence of myocarditis remains unclear, largely due to its frequent subclinical presentation and lack of established non-invasive tests with high sensitivity and specificity. [3]

Studies show that myocarditis has a greater prevalence in men than in women, with a male-to-female ratio ranging from 2:1 to 4:1. It occurs primarily in men under the age of 50, whereas in women, it tends to present more commonly after the age of 50 or during the post-menopausal period. [4]

Myocarditis may present in acute, fulminant, subacute and chronic forms. Although it may be asymptomatic, the predominant cardiac features include chest pain, arrhythmias and dyspnoea. Nevertheless, non-cardiac symptoms associated with infections (such as respiratory, gastrointestinal etc.) may also be present, appearing either before to cardiac symptoms or even exclusively. Considering that, the diagnosis requires a high level of suspicion. [5]

Pathogenetically, it occurs as a result of the immune system's response to a specific agent. Viral infection is the most common trigger, but a broad range of other infectious and non-infectious causes can also be identified. The most common viruses associated with inflammatory cardiomyopathy include adenoviruses and enteroviruses, however, in the last two decades, Parvovirus B19 and HHV6 have been more frequently detected. Other viruses that can be implicated include Epstein–Barr virus, Cytomegalovirus, HIV, and influenza A and B. [5-7] More recently, COVID-19 has emerged as a significant risk factor for myocarditis, with infected individuals being 16 times more likely to develop the condition. The association between COVID-19 and myocarditis is particularly pronounced in children under 16 years of age and in older adults, especially those over 50 years. Approximately 30% of patients have multiple viral infections. [8] Bacteria, fungi, protozoa, and helminths are also recognized as infectious causes of myocarditis. On the other hand, regarding non-infectious causes, it is important to consider systemic diseases such as systemic lupus erythematosus or sarcoidosis, as well as exposure to drugs, alcohol, and radiation. [6]

There has been growing concern about the potential development of myocarditis after vaccination. Concerning influenza vaccination, studies have shown no significantly increased risk of myocarditis, regardless of timing or individual characteristics [9] However, in the case of COVID-19,

myocarditis has been identified as a rare serious adverse effect of mRNA vaccines. The incidence remains extremely low, with an excess of only 1.2–1.9 cases per 100,000 individuals above the baseline rate of myocarditis. The risk is notably higher in young males aged 18 to 24 years, particularly following the second dose and when shorter intervals between doses are used, with approximately 90% of cases occurring within the first seven days post-vaccination. Importantly, most cases are mild and resolve quickly. [10, 11]

As previously mentioned, the diagnosis of myocarditis can be particularly challenging. The suspicion is raised when we are dealing with a young individual, presenting with new-onset cardiac symptoms, with a recent history of viral infection and in the absence of cardiovascular risk factors. [12] Although endomyocardial biopsy (EMB) is the gold standard, it is not commonly performed in clinical practice. Consequently, myocarditis is diagnosed if at least one clinical criteria and one criteria from auxiliary diagnostic tests (ECG/Holter/stress test/troponins/imaging) are present, in the absence of other clinical conditions that could explain the findings. [13, 14]

Concerning the treatment of myocarditis, the main principles focus on optimal management of heart failure and arrhythmia. The outcome and prognosis depend on the aetiology, clinical presentation and severity of the disease. In approximately 50% of cases, it resolves in the first 2 to 4 weeks, while in 25% of cases, persistent cardiac dysfunction develops. Unfortunately, up to 25% of patients may progress to end-stage dilated cardiomyopathy (DCM), requiring a heart transplant or resulting in death. [13]

## Methods

### Studied population and definitions

A retrospective observational study was conducted using an initial sample of consecutive patients with possible myocarditis (patients identified via the International Classification of Diseases, Tenth Revision [ICD-10] with the diagnostic codes: A3953, B3323, I010, I092, I30, I300, I301, I308, I309, I310, I311, I32, M3212, A381, A3952, B2682, B3322, B5881, D8685, I012, I090, I40, I400, I40.1, I408, I409) admitted our hospital between 01 January 2010 and 21 March 2023.

Only patients with a “definitive diagnosis” of acute myocarditis (i.e., with histopathological criteria on endomyocardial biopsy) or with criteria to be considered "clinically suspected" [13] were included. The diagnosis of "clinically suspected" myocarditis was considered if ≥1 clinical presentation (A) and ≥ 1 criteria from auxiliary diagnostic tests (B) were present, in the absence of other clinical conditions that could explain the findings (without coronary stenosis ≥ 50% and without known pre-existing cardiovascular disease or extra cardiac causes that could explain the syndrome).

(A) Clinical criteria: acute chest pain; new-onset (days up to 3 months) or worsening of dyspnoea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs; palpitations and/or unexplained arrhythmia symptoms and/or syncope and/or aborted sudden cardiac death; unexplained cardiogenic shock;

(B) Criteria from anciliary diagnostic tests: abnormalities on ECG/Holter/stress test; elevated troponin T (TnT) or troponin I (TnI) levels; functional and structural abnormalities on cardiac imaging; or presence of Lake Louise criteria (original [15] or modified [16]) on cardiac magnetic resonance imaging.

The presence of isolated pericarditis will not be considered for patient inclusion, but patients with coexisting pericarditis (i.e., with myopericarditis or perimyocarditis) will be considered. [17]

Patients were followed up until 31 August 2024, using information from the electronic medical records and the integrated access management system of the “Serviço Nacional de Saúde” (namely, SClínico and Processo Clínico Eletrónico), including demographic characteristics, comorbidities, symptoms, laboratory and test results, as well as therapeutic interventions. All data was anonymized.

We seek to evaluate the incidence of acute myocarditis, the clinical and epidemiological characteristics of the affected population, the impact of modifiable risk factors, clinical outcomes (including mortality, heart failure and arrhythmic events), and the long-term evolution of these patients.

**Statistical Analysis**

Statistical analysis was performed using SPSS® software (Statistical Package for Social Sciences, version 29.0), with $p<0.05$ considered statistically significant. Continuous variables were described as mean ± standard deviation for normal distributions, or median and interquartile range (75th percentile - 25th percentile) for non-Gaussian distributions. Categorical variables will be presented as absolute frequencies (n) and percentages (%) and were compared using $\chi 2$ test or Fisher's exact test. In continuous variables we used the Student's t-test or Mann-Whitney U test , as appropriate. Normality was checked with the Shapiro-Wilks test.

## Results

### Baseline characteristics

From 01 January 2010 to 21 March 2023, a total of 849 patients were assessed, of whom only 161 met the inclusion criteria for this study, having been diagnosed with clinically suspected acute myocarditis. Among these, 120 (74.5%) were male and 41 (25.5%) were female. The median age was 33 years for males and 40 years for females (p = 0.009).The majority (90.7%) were admitted through the Cardiology department, and the median length of hospital stay was 5 days.

Baseline characteristics of patients are shown in Table I.

Regarding relevant cardiac medical history, 5 (3.1%) patients had a history of heart failure, 8 (5.0%) had coronary artery disease, and 3 (1.9%) had valvular disease (exclusively present in women). Additionally, 13 (8.1%) had diabetes, 26 (16.1%) had hypertension (10.8% of men vs 31.7% of women, p=0.003), cerebrovascular disease was present in 4 (2.5%) patients and 14 (8.7%) had chronic kidney disease (with a prevalence of 5.8% in men and 17.1% in women, p=0.048). It is noteworthy that 53 patients (32.9%) had smoking habits, with 44 being male and 9 female (36.7% of all male patients vs 21.0% of all female patients, p=0.123). Furthermore, 6 (3.7%) had a history of cancer, while 15 (9.3%) had autoimmune disorders (7.5% among males and 14.6% among females, p=0.213) and 9 (5.6%) were immunocompromised (3.3% among men and 12.2% among women, p=0.048). Hyperthyroidism and anemia also had a higher prevalence in female patients (p=0.016 and p=0.003, respectively). 10 (6.2%) patients had a previous episode of myocarditis before 2010 and one patient (0.6%) had received an influenza vaccine in the month prior to diagnosis. Regarding aetiology, the main causes identified were viral (42.2%), *Streptococcus* tonsillitis (8.7%), and unknown (41.6%). In fact, 39.8% reported a recent respiratory infection, while 16.1% mentioned gastroenteritis.

The initial diagnoses at admission varied primarily between myocarditis (66.5%), STEMI (12.4%), and NSTEMI (14.3%). A total of 148 patients (91.9%) presented with chest pain, 13 (8.1%) with heart failure (prevalence in women of 17.1% vs 5% in men, p=0.022), and 1 (0.6%) with arrhythmia. Electrocardiographically, this was reflected in 74 (46%) patients showing ST-segment elevation and 32 (19.9%) with T-wave inversion. Biochemically, the median troponin T level was 0.59 µg/L, while the median PCR level was 63.83 mg/L.

At presentation, 118 patients (73.7%) had preserved LVEF, while 24 (14.9%) had mild depression and 9 had moderate to severe LVEF (11.8%). 10 (2.6%) patients presented with

cardiogenic shock. Additionally, 92 (57.1%) patients showed concomitant pericarditis, whereas 33 patients (20.5%) exhibited pericardial effusion, the majority (90.9%) of which were characterized as mild.

During hospitalization, 8 (5.0%) developed atrial fibrillation, 5 (3.1%) developed ventricular tachycardia and 4 (2.5%) developed bundle branch block. One patient (0.6%) underwent electrical cardioversion and three patients (1.9%) passed away during hospitalization.

On the other hand, 52 (32.3%) patients were tested for autoantibodies, with 39 (75%) showing negative results and 6 (11.5%) testing positive for antinuclear antibodies (ANA). Regarding serologies, 80 (49.7%) patients were tested, with 69 (86.3%) revealing negative results and 9 (11.3%) testing positive for various viral serologies.

116 (72%) patients underwent cardiac magnetic resonance, approximately 15 days (IQR:3.0-27.0) after admission, with 84 (72.4%) showing late gadolinium enhancement, 12 (10.3%) presenting with early gadolinium enhancement, and 60 (51.7%) demonstrating oedema. Endomyocardial biopsy was conducted in only three patients, reflecting its use in a very limited subset of the cohort.

Regarding treatment, 12 (7.5%) patients received specific therapy, 8 (66.7%) with immunosuppressants (prednisolone and methylprednisolone) and 4 (33.3%) with antivirals (oseltamivir and valganciclovir). Furthermore, beta-blockers were prescribed to 78 patients (48.4%), and antiarrhythmic drugs were used in 7 cases (4.3%).

As shown in supplementary Table I, women appear to have a worse disease course than men, with higher PCR (p=0.048) and NT-pro-BNP levels (p=0.024), but with lower troponin T levels (p=0.03). Pericarditis is more common in women (75.6% vs. 50.8%, p=0.006), as is pericardial effusion (41.5% vs. 13.0%, p<0.01), with cardiogenic shock (17.1% vs. 2.5%, p=0.003) and atrial fibrillation (14.6% vs. 1.7%, p=0.004) also being more frequent in female patients. In-hospital mortality occurred exclusively in women (7.3%, p=0.016). Conversely, men more often present with preserved LVEF (79.2% vs. 56.1%, p = 0.007) despite showing a greater prevalence of late gadolinium enhancement (p < 0.01).

**Impact of SARS-CoV-2 infection in myocarditis**

Considering that the first case of COVID-19 in Portugal occurred on March 1st, 2020, the incidence of myocarditis in our study population, from January 1st, 2010, until February 2020, was 11.02 cases per year. However, after the onset of the SARS-CoV-2 pandemic, and up through March 2023, the incidence increased to 15.6 cases per year, reflecting a 42% rise in the disease occurrence rate.

Table III compares the baseline characteristics of the 6 patients with SARS-CoV-2 infection up to 1 month prior to myocarditis and the 42 patients without known SARS-CoV-2 infection in the month preceding myocarditis, during this time period (March 2020 – March 2023).

Regarding age, sex, and personal medical history, no statistically significant differences were found between the two patient groups. On the other hand, with respect to the length of hospitalization, the group of patients with SARS-CoV-2 infection had a longer hospital stay, with a median of 7.5 days, compared to 4 days in the other patient group.

In addition, considering only cases after the start of the national COVID-19 vaccination campaign on December 27th, 2020, 5 patients (13.8%) reported receiving a vaccine within the month preceding the onset of myocarditis. Among these, the median time from vaccination to symptom onset was 4 days (IQR: 3.0–5.5).

**Temporal Pattern of Hospitalizations**

As observed in Figure 1, January and February recorded the highest number of hospitalizations, with a notable peak in February. Following this initial period, there was a decline in hospitalizations in March. In July, hospitalizations increased again, followed by a decline in August and September. In the last months of the year, a relative increase was observed in October, followed by stabilization in November and December.

**Follow-up data**

A total of 141 patients from the initial cohort were included in the follow-up analysis, with 17 patients lost to follow-up and 3 deaths during hospitalization. Of these, 132 (92.3%) continued

attending Cardiology consultations, being discharged approximately 13.5 months after the initial episode. A reevaluation of LVEF, conducted at a median of 14.0 months, showed preserved LVEF in 106 patients (94.6%). CMR revaluation was performed in 18 patients (12.8%), revealing partial resolution in 9 cases (50.0%) and complete resolution in 8 cases (44.4%). Adverse outcomes during follow-up included heart failure in 9 (6.4%) cases, recurrence of pericarditis in 7 (5.0%), recurrence of myocarditis in 5 (3.5%), and arrhythmias in 3 (2.1%). One patient (0.6%) received an implantable cardioverter-defibrillator two years after the initial episode. At follow-up, 9 patients (6.4%) had died, with a median time to death of 39.0 months. The overall median duration of follow-up was 15.0 months.

Characteristics at follow-up are shown in table II.

## Discussion

The present study included a sample of 161 participants, of whom 74.5% were male, corresponding to a male-to-female ratio of 2.9:1. This parallels other studies showing that myocarditis has a greater prevalence in men than in women, with a male-to-female ratio ranging from 2:1 to 4:1.[4]

The median age of male participants in our study was 33 years, which aligns with the literature showing that myocarditis typically affects men under the age of 50. In contrast, the median age of female participants was 40 years, which appears to be slightly lower than what is reported in the literature, where myocarditis is described as being more frequent in the post-menopausal period.[4] Regarding their medical history, no significantly prevalent cardiovascular disease or significant cardiovascular risk factors were identified, with the exception of tobacco use. Although 32.9% of patients reported smoking habits, with a higher prevalence among males (36.7%) than females (21.0%), these figures are comparable to those observed in the general portuguese population, where smoking prevalence is around 33% in men and 22% in women [18]. Therefore, smoking does not appear to be a distinguishing feature of the myocarditis population in this cohort, suggesting that its presence may reflect general population trends rather than a specific association with the disease. In terms of recent infections, a notable proportion of patients reported a preceding respiratory (39.8%) or gastrointestinal infection (16.1%) prior to the development of myocarditis, which suggests a potential viral trigger. Indeed, according to the literature, viral infection is the most commonly identified cause [2], accounting for 42.2% of the identified etiologies in our study, while 41.6% remained idiopathic. Additionally, 6.2% of patients had a previous episode of myocarditis before 2010, which is consistent with the literature reporting that recurrence of myocarditis is not uncommon, reaching up to 10% during follow-up.[19]

Concerning the impact of SARS-CoV-2 infection on myocarditis, our study data show an increase in incidence from 11.02 to 15.6 cases per year after the onset of COVID-19, which can be explained by the fact that COVID-19 has become a significant risk factor for the development of this disease. These findings are consistent with information published by the CDC (Centers for Disease Control and Prevention), which reported a 42% increase in myocarditis cases from 2019 to 2020 [8]. In the comparison between patients with and without a previous SARS-CoV-2 infection, the only statistically significant difference observed was in the length of hospital stay. Patients with a prior COVID-19 infection had a significantly longer median stay, with a duration of 7.5 days, compared to 5 days for those without a history of infection. No significant differences were found between the two groups regarding demographic characteristics or medical history. Furthermore, there were no

differences in terms of disease progression or complications during hospitalization that could account for the extended length of stay. Therefore, the increased hospitalization period in the COVID-positive group may possibly be explained by the nature of COVID-19 as a new infection with unknown characteristics or due to the extended symptom period of COVID-19. Moreover, given the uncertainty and the potential for complications, a more prolonged observation period may have been adopted out of caution. [20, 21] Concerning vaccination, our study revealed that after the initiation of the vaccination campaign in Portugal, 13.8% of myocarditis cases in our cohort were preceded by the administration of a SARS-CoV-2 vaccine dose in the month before, with the median interval between vaccination and symptom onset being 4 days. This suggests that the interval between vaccination and clinical manifestation is generally short, typically not exceeding the first week, which aligns with previously reported temporal patterns.[10] This observation is consistent with the extant literature, which indeed identifies myocarditis as a potential complication of vaccination. Nevertheless, it is important to note that, according to these studies, the majority of these cases are typically mild and self-limiting, underscoring that the risk-benefit profile of vaccination substantially outweighs the mortality associated with COVID-19.[22] Conversely, vaccination against the influenza virus appears to be considerably less associated with the development of myocarditis, indicating it as a much rarer adverse event; in our cohort, this was observed in only one patient. [9]

Regarding the period of hospitalization, the highest peak was observed between January and February, which aligns with epidemiological data from temperate climates, such as Portugal, where respiratory infections like influenza, coronavirus and human respiratory syncytial virus typically reach peak incidence between October and April. Subsequently, a decline in admissions was observed from March, followed by a secondary increase in July. This latter rise may be attributed to the persistence of certain respiratory infections that circulate throughout the year, such as adenovirus, bocavirus, metapneumovirus and rhinovirus, as well as the occurrence of gastrointestinal infections, and the presence of cases with unknown aetiology [23, 24]. These factors highlight the complex and multifactorial nature of the triggers associated with the clinical presentations observed in this cohort.

Although EMB remains the gold standard for the diagnosis of myocarditis, it is rarely performed in low-risk patients due to its invasive nature and the associated procedural risks [25, 26]. This is consistent with the findings of our study, in which only 1.9% of patients underwent biopsy. As a result, clinical criteria and complementary diagnostic methods have been developed to facilitate the establishment of a diagnosis. Clinically, chest pain is the most frequently reported symptom, with 91.9% of patients in our study presenting with this complaint. Among the tests

available, biomarkers typically demonstrate elevated levels, reflecting the presence of inflammation (CRP)[27], myocardial injury (TnT)[28], and cardiac dysfunction (NT-proBNP)[29]. This pattern was also observed in our study, supporting the association between these biomarkers and cardiac inflammation. ECG does not present specific changes for myocarditis, however, ST-T segment abnormalities are the most frequently observed findings, occurring in up to 48% of patients [3, 30], which aligns with the results observed in our cohort, in which 46% presented with ST elevation and 20% with T wave inversion. Regarding imaging techniques, CMR should be performed in all hemodynamically stable patients with suspected acute myocarditis or in cases of chest pain with a normal coronary angiography, in order to differentiate myocarditis from an ischemic process. Ideally, CMR should be conducted 2 to 3 weeks after symptom onset, as this timing optimizes diagnostic accuracy. This approach was reflected in our study, in which CMR was performed approximately 15 days following hospital admission. [30] The updated Lake Louise Criteria define the diagnosis of myocarditis as the presence of at least one positive marker from each of the following two categories: a T2-based marker indicating myocardial oedema, and a T1-based marker indicating associated myocardial injury.[16] In fact, among the 161 patients diagnosed with myocarditis in our study, 72% underwent CMR, of whom 72% exhibited late gadolinium enhancement (LGE) and 51% showed evidence of myocardial oedema.

During hospitalization, the majority of patients did not experience significant complications, with the average length of stay being 5 days, which is consistent with some reports in the literature, although variability is observed across studies.[5, 31] These differences may reflect variations in patient characteristics or healthcare settings.

Regarding the observed data comparing the two sexes, females seem to have a worse prognosis. Although myocarditis is clearly more prevalent in males, who exhibit higher troponin levels and a greater prevalence of LGE, when it occurs in females, it appears to manifest in a more severe form, with a greater burden of complications, including mortality.[32,33] This disparity may be explained by the fact that women had more comorbidities and present at an older age. On the other hand, we cannot exclude the hypothesis that women may be underdiagnosed and that the diagnosis is recognised only later at more advanced and severe stages of the disease, resulting in poorer outcomes.

**Limitations**

This study presents several limitations that must be acknowledged. Firstly, since the sample includes patients hospitalized since January 2010, there were significant gaps in the electronic medical records, particularly regarding follow-up data, notably 12.4% of patients had no follow-up data. This limitation constrains the interpretation of certain results and restricts the analysis of some variables to an even smaller subset of cases. Errors in coding the diseases may also have occurred. Our CMR studies also lacked T1 and T2 mapping.

Another major limitation relates to the small number of patients with a diagnosis of SARS-CoV-2 infection in the month prior to the diagnosis of myocarditis. This significantly limits the statistical robustness of comparisons between the COVID-19 and non-COVID-19 groups, reducing the discriminatory power of the analyses performed.

Furthermore, as this is a retrospective study, there are inherent methodological constraints, including the potential for bias in establishing a relationship between the occurrence of myocarditis and clinical outcomes.

Finally, it should be noted that the sample consists exclusively of patients from the Centro Hospitalar e Universitário de Santo António, which may limit the generalizability of the findings to other populations, both nationally and internationally.

**Conclusion**

In conclusion, this study confirms that acute myocarditis disproportionately affects young males. While traditional cardiovascular risk factors are largely absent, tobacco use remains a notable exception. Furthermore, respiratory infections, particularly those of viral origin, are significant predisposing factors. The observed peak in hospitalizations during winter months underscores the influence of seasonal respiratory illnesses on myocarditis incidence.

The emergence of SARS-CoV-2 as a relevant risk factor is a critical finding, evidenced by a 42% increase in myocarditis cases following the pandemic's onset. Although patients with prior SARS-CoV-2 infection did not exhibit significant differences in demographic characteristics or medical history, their hospitalization periods were longer. Importantly, women with myocarditis

tend to present with more severe disease and complications, leading to worse outcomes compared to men.

These findings highlight the evolving landscape of myocarditis etiology and the need for continued vigilance in identifying and managing emerging risk factors, ultimately contributing to improved patient outcomes and public health strategies.

## Tables

**Table I –** Baseline characteristics of patients

| | Value |
|---|---|
| Age, years (N=161) | 33.0 (25.0 – 50.0) |
| Men, age, years (N=161) | 33.0 (25.0 - 45.0) |
| Woman, age, years (N=161) | 40.0 (28.0 - 65.50) |
| Male (N=161) | 120 (74.5%) |
| Total days of hospitalization (N=161) | 5.0 (3.0 – 8.0) |
| Origin (N=161) | |
| Emergency department | 0 |
| Cardiology department | 146 (90.7%) |
| Medicine department | 11 (6.8%) |
| Nephrology department | 2 (1.2%) |
| Hematology department | 2 (1.2%) |
| Medical history (N=161) | |
| Previous Heart Failure | 5 (3.1%) |
| Coronary Artery Disease | 8 (5.0%) |
| Valvular Heart Disease | 3 (1.9%) |
| Cancer | 6 (3.7%) |
| Cancer Therapies | |
| Tyrosine kinase inhibitor | 1 (0.6%) |
| Anthracycline + Anti-her2 | 1 (0.6%) |
| COPD | 10 (6.2%) |
| Autoimmune disease | 15 (9.3%) |
| Cerebrovascular disease | 4 (2.5%) |
| Peripheral vascular disease | 0 |
| Anemia | 10 (6.2%) |
| Hypertension | 26 (16.1%) |
| Diabetes | 13 (8.1%) |
| Obesity | 12 (7.5%) |
| Weight excess | 6 (3.7%) |
| Smoking | 53 (32.9%) |
| Alcohol abuse | 3 (1.9%) |
| Hyperthyroidism | 3 (1.9%) |
| Renal disease | 14 (8.7%) |
| Hepatic disease | 3 (1.9%) |
| Immunocompromised | 9 (5.6%) |
| Previous myocarditis (N=161) | 10 (6.2%) |
| Previous respiratory infection (N=161) | 64 (39.8%) |
| Previous gastroenteritis (N=161) | 26 (16.1%) |
| COVID infection last month (N=48) * | 6 (12.2%) |
| Vaccines | |
| COVID vaccination last month (N=38) ** | 5 (13.1%) |
| Days Post Vaccination | 4.0 (3.0 - 5.50) |
| Influenza vaccination last month (N=161) | 1 (0.6%) |
| Symptoms/Clinical presentation (N=161) | |
| Chest pain | 148 (91.9%) |

| | |
|---|---|
| Arrhythmia | 1 (0.6%) |
| Heart failure | 13 (8.1%) |
| Initial diagnosis (N=161) | |
| Myocarditis | 107 (66.5%) |
| STEMI | 20 (12.4%) |
| NSTEMI | 23 (14.3%) |
| Heart failure | 6 (3.7%) |
| Pericarditis | 1 (0.6%) |
| Pneumonia | 2 (1.2%) |
| Unknown | 2 (1.2%) |
| Etiology (N=161) | |
| Viral | 68 (42.2%) |
| Streptococcus tonsillitis | 14 (8.7%) |
| Other infectious | 4 (2.5%) |
| Other non-infectious | 2 (1.2%) |
| Presume autoimmune | 2 (1.2%) |
| Drugs | 4 (4.5%) |
| Unknown | 67 (41.6%) |
| ECG changes (N=161) | |
| ST elevation | 74 (46.0%) |
| T inversion | 32 (19.9%) |
| Peak TnT, ng/ml (N=161) | 0.59 (0.21 - 1.37) |
| Peak PCR, mg/L (N=153) | 63.83 (22.9 - 141.62) |
| NT-proBNP, pg/mL (N=88) | 533.4 (134.5 - 2457.5) |
| Electrolyte abnormalities (N=161) | 3 (1.9%) |
| Left Ventricle Ejection Fraction (N=161) | |
| Preserved | 118 (73.7%) |
| Mild depression | 24 (14.9%) |
| Moderate depression | 8 (5.0%) |
| Severe depression | 11 (6.8%) |
| Pericarditis (N=161) | 92 (57.1%) |
| Pericardial effusion (N=161) | |
| No | 128 (79.5%) |
| Yes | 33 (20.5%) |
| Mild | 30 (90.9%) |
| Moderate | 2 (6.06%) |
| Severe | 1 (3.03%) |
| Cardiogenic Shock (N=161) | 10 (6.2%) |
| Supraventricular Tachycardia (N=161) | 2 (1.2%) |
| Atrial Fibrilation (N=161) | 8 (5.0%) |
| Ventricular Tachycardia (N=161) | 5 (3.1%) |
| Ventricular Fibrilation (N=161) | 0 |
| Atrial Flutter (N=161) | 1 (0.6%) |
| Premature Ventricular Contractions (N=161) | 1 (0.6%) |
| Bundle branch block (N=161) | 4 (2.5%) |
| Atrioventricular block (N=161) | 2 (1.2%) |
| Sinus Node Dysfunction (N=161) | 0 |
| Pacemaker Placement (N=161) | 0 |

| | |
|---|---|
| ICD Placement (N=161) | 1 (0.6%) |
| Cardioversion (N=161) | 1 (0.6%) |
| Catheter Ablation (N=161) | 0 |
| Beta-blocker (N=161) | 78 (48.4%) |
| Antiarrythmics (N=161) | 7 (71.4%) |
| Amiodarone | 5 (71.4%) |
| Digoxin | 2 (28.6%) |
| Endomyocardial Biopsy | 3 (1.9%) |
| Negative | 1 (33.3%) |
| Lymphocytic myocarditis | 2 (66.7%) |
| Autoantibodies | 52 (32.3%) |
| Negative | 39 (75.0%) |
| ANA | 6 (11.5%) |
| RF | 2 (3.8%) |
| LC1 + PML | 1 (1.9%) |
| IgG anti-cardiolipin + IgG anti-B2-glycoprotein | 1 (1.9%) |
| ANCA + ASCA | 1 (1.9%) |
| ANA + IgG anti-prothrombin | 1 (1.9%) |
| IgM anti-cardiolipin | 1 (1.9%) |
| Serologies | 80 (49.7%) |
| Negative | 69 (86.3%) |
| Positive Non-Viral Serologies | 2 (2.5%) |
| Positive Viral Serologies | 9 (11.3%) |
| Anti-HBc | 1 (9.1%) |
| Anti-HBc + Anti-HCV | 1 (9.1%) |
| CMV | 2 (18.2%) |
| EBV | 2 (18.2%) |
| Paramyxovirus | 1 (9.1%) |
| Influenza | 2 (18.2%) |
| Leptospira | 1 (9.1%) |
| Toxoplasmose | 1 (9.1%) |
| Specific treatment | 12 (7.5%) |
| Immunossupression | 8 (66.7%) |
| Antivirals | 4 (33.3%) |
| Cardiac Magnetic Resonance | 116 (72.0%) |
| Date, days since admission | 15.0 (3.0-27.0) |
| Late Gadolinium Enhancement | 84 (72.4%) |
| Oedema | 60 (51.7%) |
| Early Gadolinium Enhancement | 12 (10.3%) |
| Segmental Wall Motion Abnormalities | 7 (6.0%) |
| Right Ventricular Abnormalities | 0 |
| Inhospital death | 3 (1.9%) |
| Cardiology Consult (N=158) | 132 (83.5%) |
| Consult discharge, months (N=158) | 13.5 (6.75-26.0) |

Categorical variables are shown as counts (n) and percentages (%). Continuous variables are expressed as mean ± standard deviation for normally distributed data, and as median (interquartile range, IQR) for non-normally distributed data. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ASCA, anti–Saccharomyces cerevisiae antibody; CMR, cardiac magnetic resonance imaging; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; EBV, Epstein-Barr virus; ECG, electrocardiography; HER-2, human epidermal growth factor receptor 2; ICD, implantable cardioverter-defibrillator; LC1, liver cytosolic antigen type 1; LGE, late gadolinium enhancement; LVEF, left ventricular ejection

fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PML, promyelocytic leukaemia protein; NT-proBNP, pro-brain natriuretic peptide; RF, rheumatoid factor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STEMI, ST-segment elevation myocardial infarction; TnT, Troponin T.

* Were considered patients diagnosed after the first case of SARS-CoV-2 in Portugal, on March 1st, 2020

** Were considered patients diagnosed after the vaccination campaign for SARS-CoV-2 in Portugal, on December 27th, 2020.

**Table II –** Characteristics at follow-up (n=141)

| | Value |
|---|---|
| Reevaluation LVEF (N=141) | 112 (79.4%) |
| Date, months | 14.0 (7.0-34.0) |
| Preserved | 106 (94.6%) |
| Mild depression | 4 (3.6%) |
| Moderate depression | 2 (1.8%) |
| LVD persistence | 4 (2.8%) |
| Reevaluation CMR (N=141) | 18 (12.8%) |
| Date, months | 23.0 (14.0-39.0) |
| No changes | 1 (5.6%) |
| Complete resolution | 8 (44.4%) |
| Partial resolution | 9 (50.0%) |
| Death (N=141) | 9 (6.4%) |
| Date of death, months | 39.0 (19.5-63.0) |
| Recurrence of myocarditis (N=141) | 5 (3.5%) |
| Date of first recurrence, months | 11.0 (4.0-56.0) |
| Recurrence of pericarditis (N=141) | 7 (5.0%) |
| Dilated cardiomyopathy (N=141) | 1 (0.7%) |
| Heart failure (N=141) | 9 (6.4%) |
| Arrhythmias (N=141) | 3 (2.1%) |
| Follow-up, months (N=141) | 15.0 (7.0-36.0) |

Categorical variables are shown as counts (n) and percentages (%). Continuous variables are expressed as mean ± standard deviation for normally distributed data, and as median (interquartile range, IQR) for non-normally distributed data. CMR, cardiac magnetic resonance imaging; LV, left ventricular; LVEF, left ventricular ejection fraction.

**Table III -** Baseline Characteristics of Patients with and without SARS-CoV-2 infection prior to myocarditis, during Covid19 pandemic (March 2020-March 2023)

| | Patients diagnosed with SARS-CoV-2 (N=6) | Patients without the diagnosis of SARS-CoV-2 (N=42) | p-value |
|---|---|---|---|
| Age, years, median | 40.0 (29.5 – 76.5) | 27.5 (22.0 – 52.25) | 0.123 |
| Men | 5 (83.3%) | 31 (73.8%) | 1.0 |
| Total days of hospitalization, median | 7.5 (6.75 – 38.5) | 4.0 (2.0 – 7.0) | **0.01** |
| Medical history | | | |
| Previous Heart Failure | 0 | 0 | - |
| Coronary Artery Disease | 0 | 2 (4.8%) | 1.0 |
| Valvular Heart Disease | 0 | 1 (2.4%) | 1.0 |
| Cancer | 1 (16.7%) | 1 (2.4%) | 0.237 |
| Cancer Therapies | 0 | 0 | - |
| COPD | 0 | 1 (2.4%) | 1.0 |
| Autoimmune Disease | 0 | 6 (14.3%) | 1.0 |
| Cerebrovascular disease | 1 (16.7%) | 1 (2.4%) | 0.237 |
| Peripheral vascular disease | 0 | 0 | - |
| Anemia | 1 (16.7%) | 0 | 0.125 |
| Hypertension | 1 (16.7%) | 4 (9.5%) | 0.530 |
| Diabetes | 1 (16.7%) | 4 (9.5%) | 0.530 |
| Obesity | 1 (16.7%) | 1 (2.4%) | 0.237 |
| Weight excess | 0 | 5 (11.9%) | 1.0 |
| Smoking | 0 | 14 (33.3%) | 0.161 |
| Alcohol abuse | 0 | 0 | - |
| Hyperthyroidism | 0 | 1 (2.4%) | 0.237 |
| Renal disease | 1 (16.7%) | 2 (4.8%) | 0.336 |
| Hepatic disease | 1 (16.7%) | 0 | 0.125 |
| Immunocompromised | 0 | 2 (4.8%) | 1.0 |
| Previous myocarditis | 0 | 3 (7.1%) | 1.0 |
| Vaccines | | | |
| COVID vaccination last month (N=38) ** | 0 | 5 (13.8%) | 1.0 |
| Influenza vaccination last month | 0 | 1 (2.4%) | 1.0 |
| Initial diagnosis | | | |
| Myocarditis | 5 (83.3%) | 29 (69%) | 0.656 |
| STEMI | 1 (16.7%) | 4 (9.5%) | 0.530 |
| NSTEMI | 0 | 6 (14.3%) | 1.0 |
| Heart failure | 0 | 2 (4.8%) | 1.0 |
| Unknown | 0 | 1 (2.4%) | 0.237 |
| Symptoms/Clinical presentation | | | |
| Chest pain | 4 (66.7%) | 40 (95.2%) | 0.071 |
| Arrhythmia | 0 | 0 | - |
| Heart failure | 2 (33.3%) | 3 (7.1%) | 0.111 |
| ECG changes | | | |
| ST elevation | 4 (66.7%) | 20 (47.6%) | 0.666 |

| | | | |
|---|---|---|---|
| T inversion | 1 (16.7%) | 7 (16.7%) | 1.0 |
| Peak TnT, ng/ml | 1.29 (0.30 - 5.22) | 0.62 (0.21 - 1.55) | 0.275 |
| Peak PCR, mg/L | 149.83 (41.53 - 282.96) | 66.27 (26.1 - 141.85) | 0.265 |
| NT-proBNP, pg/mL | 1517.0 (142.25 - 24338.5) | 334.0 (277.0 - 1182.0) | 0.679 |
| Left Ventricle Ejection Fraction | | | |
| Preserved | 3 (50%) | 31 (73.8%) | 0.339 |
| Compromised | 3 (50%) | 11 (26.2%) | |
| Mild depression | 1 (16.7%) | 9 (21.4%) | |
| Moderate depression | 1 (16.7%) | 0 | |
| Severe depression | 1 (16.7%) | 2 (4.8%) | |
| Pericarditis | 3 (50%) | 19 (45.2%) | 1.0 |
| Pericardial effusion | | | |
| No | 4 (66.7%) | 32 (76.2%) | 0.631 |
| Yes | 2 (33.4%) | 10 (23.8%) | |
| Mild | 1 (16.7%) | 10 (23.8%) | |
| Moderate | 1 (16.7%) | 0 | |
| Severe | 0 | 0 | - |
| Cardiogenic Shock | 1 (16.7%) | 1 (2.4%) | 0.237 |
| Supraventricular Tachycardia | 0 | 1 (2.4%) | 0.237 |
| Atrial Fibrillation | 0 | 2 (4.8%) | 1.0 |
| Ventricular Tachycardia | 0 | 1 (2.4%) | 0.237 |
| Ventricular Fibrillation | 0 | 0 | - |
| Atrial Flutter | 0 | 0 | - |
| Premature Ventricular Contraction | 0 | 1 (2.4%) | 0.237 |
| Bundle branch block | 0 | 0 | - |
| Atrioventricular block | 0 | 1 (2.4%) | 0.237 |
| Sinus Node Dysfunction | 0 | 0 | - |
| Pacemaker Placement | 0 | 0 | - |
| ICD Placement | 0 | 0 | - |
| Cardioversion | 0 | 0 | - |
| Catheter Ablation | 0 | 0 | - |
| Beta-blocker | 4 (66.7%) | 26 (61.9%) | 1.0 |
| Antiarrhythmics | 0 | 0 | - |
| Endomyocardial Biopsy | 0 | 2 (4.8%) | 1.0 |
| Auto-antibodies | 2 (33.3%) | 11 (26.2%) | 1.0 |
| Negative | 2 (100%) | 9 (81.8%) | |
| Positive | 0 | 2 (18.2%) | |
| Serologies | 3 (50.0%) | 20 (47.6%) | |
| Negative | 2 (66.6%) | 20 (100%) | 0.249 |
| Positive Viral Serologies | 1 (33.3%) | 0 | |
| Specific treatment | 1 (16.7%) | 1 (2.4%) | 0.237 |
| Immunosuppression | 1 (100%) | 1 (100%) | |
| Antivirals | 0 | 0 | - |
| Cardiac Magnetic Resonance | 3 (50.0%) | 36 (85.7%) | 0.071 |
| Late Gadolinium Enhancement | 3 (100%) | 26 (72.2%) | 0.556 |
| Oedema | 2 (66.6%) | 24 (66.7%) | 1.0 |

| | | | |
|---|---|---|---|
| Early Gadolinium Enhancement | 0 | 5 (13.9%) | 1.0 |
| Segmental Wall Motion Abnormalities | 0 | 6 (16.7%) | 1.0 |
| Right Ventricular Abnormalities | 0 | 0 | - |
| Cardiology Consult | 4 (66.7%) | 36 (85.7%) | 0.258 |
| Inhospital Death | 0 | 1 (2.4%) | 0.237 |

Categorical variables are shown as counts (n) and percentages (%). Continuous variables are expressed as mean ± standard deviation for normally distributed data, and as median (interquartile range, IQR) for non-normally distributed data. CMR, cardiac magnetic resonance imaging; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECG, electrocardiography; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; NT-proBNP, pro-brain natriuretic peptide; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STEMI, ST-segment elevation myocardial infarction; TnT, Troponin T.
** Were considered patients diagnosed after the vaccination campaign for SARS-CoV-2 in Portugal, on December 27th, 2020.

**Supplementary table I –** Baseline characteristics of male and female patients

| | Male (N=120) | Female (N=41) | p-value |
|---|---|---|---|
| Age, years, median | 33.0 (25.0 – 45.0) | 40 (28.0 – 65.5) | **0.009** |
| Total days of hospitalization, median | 5.0 (3.0 – 7.0) | 6.0 (3.0 – 14.5) | 0.073 |
| Medical history | | | |
| Previous Heart Failure | 2 (1.7%) | 3 (7.3%) | 0.105 |
| Coronary Artery Disease | 6 (5.0%) | 2 (4.9%) | 1.0 |
| Valvular Heart Disease | 0 | 3 (7.3%) | **0.016** |
| Cancer | 3 (2.5%) | 3 (7.3%) | 0.173 |
| Cancer Therapies | 1 (33.3%) | 1 (33.3%) | - |
| COPD | 7 (5.8%) | 3 (7.3%) | 0.716 |
| Autoimmune Disease | 9 (7.5%) | 6 (14.6%) | 0.213 |
| Cerebrovascular disease | 2 (1.7%) | 2 (4.9%) | 0.268 |
| Peripheral vascular disease | 0 | 0 | - |
| Anemia | 3 (2.5%) | 7 (17.1%) | **0.003** |
| Hypertension | 13 (10.8%) | 13 (31.7%) | **0.003** |
| Diabetes | 7 (5.8%) | 6 (14.6%) | 0.096 |
| Obesity | 5 (4.2%) | 7 (17.1%) | **0.012** |
| Weight excess | 6 (5.0%) | 0 | 0.339 |
| Smoking | 44 (36.7%) | 9 (22.0%) | 0.123 |
| Alcohol abuse | 3 (2.5%) | 0 | 0.571 |
| Hyperthyroidism | 0 | 3 (7.3%) | **0.016** |
| Renal disease | 7 (5.8%) | 7 (17.1%) | **0.048** |
| Hepatic disease | 2 (1.7%) | 1 (2.4%) | 1.0 |
| Immunocompromised | 4 (3.3%) | 5 (12.2%) | **0.048** |
| Previous myocarditis | 9 (7.5%) | 1 (2.4%) | 0.454 |
| Previous respiratory infection | 46 (38.3%) | 18 (43.9%) | 0.581 |
| Previous gastroenteritis | 23 (19.2%) | 3 (7.3%) | 0.088 |
| COVID infection last month* | (N=36) 5 (13.89%) | (N=12) 1 (8.33%) | 1.0 |
| Vaccines | | | |
| COVID vaccination last month ** | (N=28) 3 (10.7%) | (N=10) 2 (20.0%) | 0.602 |
| Influenza vaccination last month | 1 (0.8%) | 0 | 1.0 |
| Initial diagnosis | | | |
| Myocarditis | 79 (65.8%) | 28 (68.3%) | 0.849 |
| STEMI | 17 (14.2%) | 3 (7.3%) | 0.410 |
| NSTEMI | 20 (16.7%) | 3 (7.3%) | 0.197 |
| Heart failure | 3 (2.5%) | 3 (7.3%) | 0.173 |
| Pneumonia | 0 | 2 (4.9%) | 0.064 |
| Pericarditis | 1 (0.8%) | 0 | 1.0 |
| Unknown | 0 | 2 ( 4.9%) | 0.064 |
| Etiology | | | |
| Viral | 51 (42.5%) | 17 (41.5%) | 1.0 |
| Other infectious | 2 (1.7%) | 2 (4.9%) | 0.268 |
| Other non-infectious | 2 (1.7%) | 0 | 1.0 |
| Streptococcus tonsillitis | 11 (9.2%) | 3 (7.3%) | 1.0 |
| Presume autoimmune | 1 (0.85%) | 1 (2.4%) | 0.446 |
| Unknown | 49 (40.8%) | 18 (43.9%) | 1.0 |

| | | | |
|---|---|---|---|
| Symptoms/Clinical presentation | | | |
| Chest pain | 113 (94.2%) | 35 (85.4%) | 0.096 |
| Arrhythmia | 0 | 1 (2.4%) | 0.255 |
| Heart failure | 6 (5.0%) | 7 (17.1%) | **0.022** |
| ECG changes | | | |
| ST elevation | 61 (50.8%) | 13 (31.7%) | **0.045** |
| T inversion | 24 (20.0%) | 8 (19.5%) | 1.0 |
| Peak TnT, ng/ml | 0.690 (0.262 - 1.553) | 0.282 (0.099 - 0.650) | **0.030** |
| Peak PCR, mg/L | (N=114) 56.32 (19.278 - 211.790) | (N=39) 114.240 (33.900 - 147.610) | **0.048** |
| NT-proBNP, pg/mL | (N=57) 340.0 (119.5 - 1242.5) | (N=31) 1024.0 (303.0 - 4548.0) | **0.024** |
| Left Ventricle Ejection Fraction | | | |
| Preserved | 95 (79.2%) | 23 (56.1%) | **0.007** |
| Compromised | 25 (20.8%) | 18 (43.9%) | |
| Mild depression | 17 (68.0%) | 7 (38.89%) | |
| Moderate depression | 2 (8.0%) | 6 (33.33%) | |
| Severe depression | 6 (24.0%) | 5 (27.78%) | |
| Pericarditis | 64 (50.8%) | 31 (75.6%) | **0.006** |
| Pericardial effusion | | | |
| No | 104 (86.7%) | 24 (58.5%) | **<0.01** |
| Yes | 16 (13.3%) | 17 (41.5%) | |
| Mild | 16 (100.0%) | 14 (82.35%) | |
| Moderate | 0 | 2 (11.76%) | |
| Severe | 0 | 1 (5.88%) | |
| Cardiogenic Shock | 3 (2.5%) | 7 (17.1%) | **0.003** |
| Supraventricular Tachycardia | 1 (0.8%) | 1 (2.4%) | 0.446 |
| Atrial Fibrillation | 2 (1.7%) | 6 (14.6%) | **0.004** |
| Ventricular Tachycardia | 5 (4.2%) | 0 | 0.330 |
| Ventricular Fibrillation | 0 | 0 | - |
| Atrial Flutter | 1 (0.8%) | 0 | 1.0 |
| Premature Ventricular Contraction | 1 (0.8%) | 0 | 1.0 |
| Bundle branch block | 4 (3.3%) | 0 | 0.573 |
| Atrioventricular block | 0 | 2 (4.9%) | 0.064 |
| Sinus Node Dysfunction | 0 | 0 | - |
| Pacemaker Placement | 0 | 0 | - |
| ICD Placement | 1 (0.8%) | 0 | 1.0 |
| Cardioversion | 1 (0.8%) | 0 | 1.0 |
| Catheter Ablation | 0 | 0 | - |
| Beta-blocker | 60 (50.0%) | 18 (43.9%) | 0.588 |
| Antiarrhythmics | 4 (3.3%) | 3 (7.3%) | 0.538 |
| Endomyocardial Biopsy | 2 (1.7%) | 1 (2.4%) | 1.0 |
| Auto-antibodies | 32 (26.7%) | 20 (48.8%) | |
| Negative | 27 (84.4%) | 12 (60%) | 0.097 |
| Positive | 5 (15.6%) | 8 (40%) | |
| Serologies | 59 (49.2%) | 21 (51.2%) | |
| Negative | 51 (86.4%) | 18 (85.7%) | 1.0 |
| Positive | 8 (15.6%) | 3 (14.3%) | |
| Specific treatment | 7 (5.8%) | 5 (12.2%) | 0.184 |

| | | | |
|---|---|---|---|
| Immunossupression | 6 (85.7%) | 2 (40%) | 0.222 |
| Antivirals | 1 (14.3%) | 3 (60%) | 0.222 |
| Cardiac Magnetic Resonance | 93 (77.5%) | 23 (56.1%) | **0.015** |
| Late Gadolinium Enhancement | 75 (80.7%) | 9 (39.1%) | **<0.01** |
| Oedema | 54 (58.1%) | 6 (66.7%) | **0.009** |
| Early Gadolinium Enhancement | 11 (11.8%) | 1 (11.1%) | 0.485 |
| Segmental Wall Motion Abnormalities | 5 (5.4%) | 2 (22.2%) | 0.624 |
| Right Ventricular Abnormalities | 0 | 0 | - |
| Cardiology Consult | 102 (85.0%) | (N=38) 30 (70.2%) | 0.102 |
| Inhospital Death | 0 | 3 (7.3%) | **0.016** |

Categorical variables are shown as counts (n) and percentages (%). Continuous variables are expressed as mean ± standard deviation for normally distributed data, and as median (interquartile range, IQR) for non-normally distributed data. CMR, cardiac magnetic resonance imaging; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECG, electrocardiography; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; NT-proBNP, pro-brain natriuretic peptide; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STEMI, ST-segment elevation myocardial infarction; TnT, Troponin T.
* Were considered patients diagnosed after the first case of SARS-CoV-2 in Portugal, on March 1st, 2020.
** Were considered patients diagnosed after the vaccination campaign for SARS-CoV-2 in Portugal, on December 27th, 2020.

## Figures

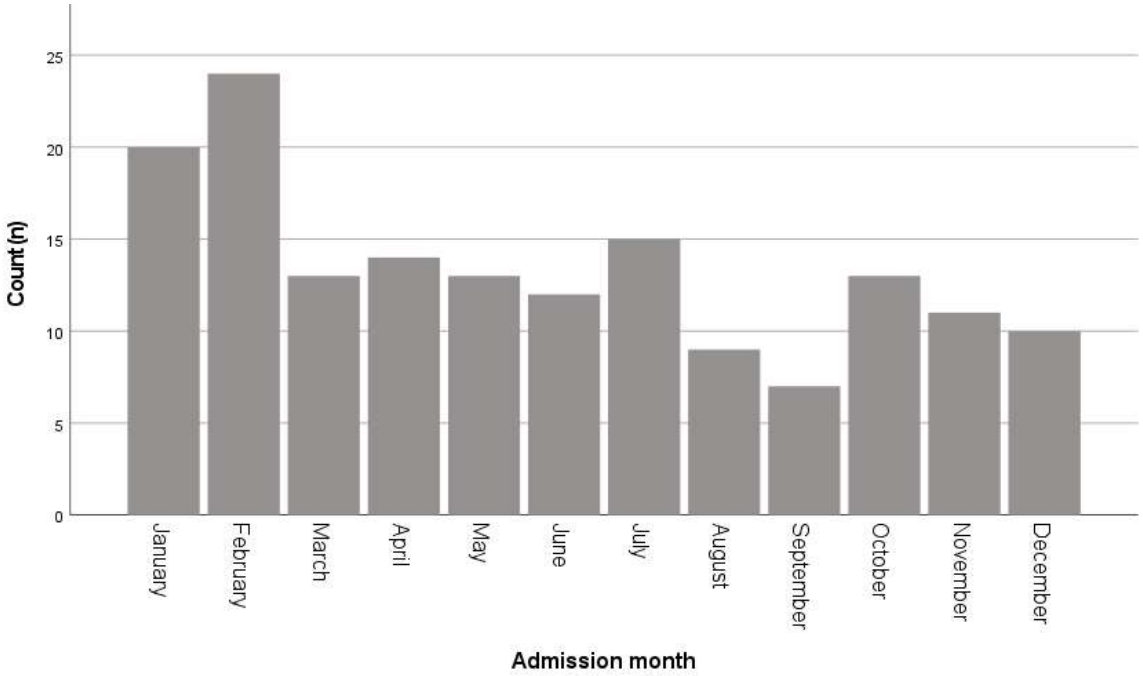


**Figure 1 -** Distribution of hospitalizations throughout the months of the year (the month presented corresponds to the admission month)

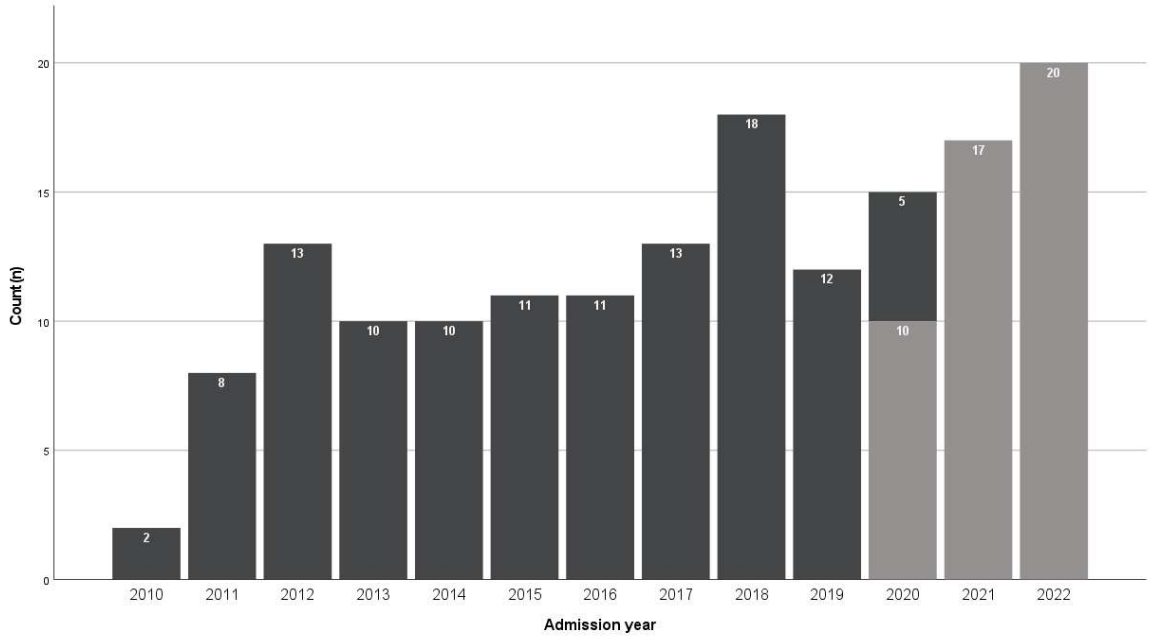


**Figure 2 -** Annual distribution of hospitalization cases before and after the onset of SARS-CoV-2

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