

## The role of genetics in the prognosis of acute myocarditis: a systematic review and meta-analysis

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### Abstract

Myocarditis is a heterogeneous disease with varying clinical presentations, etiologies, and courses. Apart from environmental factors, genetic factors may also play a role in its pathophysiology. Through a systematic review and meta-analysis, we aimed to characterize the relationship between acute myocarditis (AM), underlying genetic background, and prognosis. We searched MEDLINE/PubMed and Web of Science for studies reporting clinical outcomes of patients presenting with AM and undergoing genetic testing. The prevalence of a positive genetic test result was 27.3%, with a higher proportion of males (61.3%). Patients with a positive genetic test often had a family history of cardiovascular events (53.3%) and late gadolinium enhancement on cardiac magnetic resonance (81.2%), suggesting that these clinical features may represent a population with a higher burden of genetic background and risk for worse outcomes. The risk of recurrence of AM among patients with a positive genetic test was four times greater than among non-carriers (relative risk = 4.02,  $p < 0.001$ ), and the most frequently observed variants among AM carriers were in the *TTN*, *DSP*, *PKP2*, *MYH7*, *BAG3*, *RMB20*, *DSG2*, *TNNT2*, and *SCN5A* genes. Overall, these findings underscore the need to improve the criteria used for genetic testing in the setting of AM episodes and to identify affected individuals who may benefit from increased surveillance and genetic testing.

**Key words:** acute myocarditis, myocarditis, genetic myocarditis, genetic burden, positive genetic test.

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### Introduction

Myocarditis, defined as an inflammatory disease of the myocardium, is a heterogeneous disease with various clinical presentations, aetiologies, and courses, often related to individual characteristics. Such heterogeneity in presentation, histological forms, and outcomes is a matter of permanent debate and investigation, and numerous studies suggest that, apart from environmental factors, it may also be related to genetic predisposition. Although the aetiology often remains undetermined, possible causes already described in literature include infectious diseases (viral infection has been widely reported as the most common cause of myocarditis in Europe and North America), systemic autoimmune disorders, drugs, toxins, allergens and hypersensitivity reactions. Familial clustering has been observed, reinforcing the hypothesis that patients might carry an inherited susceptibility to infection and inflammation [1,2].

Acute myocarditis (AM) can present with chest pain, electro-

cardiographic changes and elevation in biomarkers (troponins and/or natriuretic peptides), heart failure symptoms, cardiogenic shock, life-threatening arrhythmias and even sudden cardiac death (SCD). In patients with clinically suspected myocarditis, the history and clinical presentation may suggest a specific etiology, but a definitive cause is often difficult to identify [1-3]. Often, the diagnosis is presumptive based on temporal associations with relevant exposures and epidemiological context.

According to an expert consensus on myocardial and pericardial diseases from the European Society of Cardiology [3], a combination of clinical presentation and non-invasive diagnostic findings, including typical cardiac magnetic resonance (CMR) abnormalities, may be used to make a diagnosis of “clinically suspected myocarditis”. Although endomyocardial biopsy (EMB) remains the gold standard for the definitive diagnosis of myocarditis, this is an invasive procedure with a relatively low sensitivity and etiological diagnostic yield, mainly due to the focal nature of inflammation in most cases. EMB is useful to identify the specific mechanisms of myocarditis and the need for prompt specific therapy in



certain clinical scenarios, including severe heart failure or cardiogenic shock, ventricular arrhythmias or high-degree atrioventricular block, chronic inflammatory cardiomyopathy with persistent or relapsing symptoms and biomarkers of myocardial necrosis, myocarditis associated with auto-immune disorders, or suspected specific subsets with individualized treatment such as giant cell myocarditis. In patients without an indication for EMB, CMR is the non-invasive gold standard for the diagnosis [3]. CMR has informed clinical decisions in several cases and can avoid invasive procedures, such as coronary angiography and EMB. CMR findings consistent with myocarditis should be based on the updated Lake-Louise criteria [3,4].

After an acute episode of myocarditis, most patients experience full recovery; however, in some cases, progression to dilated cardiomyopathy (DCM) or development of arrhythmogenic cardiomyopathy (ACM) has been reported. These observations hypothesize that genetic defects in proteins of the cardiomyocyte could confer an increased susceptibility to myocardial inflammation induced by a pathogenic agent. Some of the most concerning outcomes related to AM are the development of SCD, life-threatening ventricular tachycardia (VT), the need for permanent implantable cardiac devices, recurrent myocarditis episodes, chronic heart failure, and cardiomyopathy.

Genetic testing in patients presenting with AM, including which individuals may benefit from this diagnostic test, with the aim of improving management of patients and their families, is still debated in the literature. Monda *et al.* proposed an algorithm that helps physicians to consider genetic testing in the setting of AM [5]. Characteristics like family history of cardiomyopathies or SCD, echocardiographic or CMR findings suggestive of ACM, and presentation with heart failure with reduced ejection fraction and/or sustained VT are among the factors that may indicate the relevance of pursuing a genetic test, even to identify family members at risk and allow early detection and intervention [5,6].

In this systematic review, the authors aimed to understand the epidemiology, clinical presentation, outcomes, and prognosis of patients with AM and a predisposed genetic background characterized by the presence of a positive genetic test for a pathogenic/likely pathogenic variant related to myocarditis.

## Methods

### Search strategy

This study was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [7].

The literature search was done on November 14, 2023, in two electronic databases: MEDLINE (through PubMed) and Web of Science. Published research was collected using the following search terms “myocarditis”, “genetics”, “genetic test”, “pathogenic variant” and “mutation”. MeSH terms and keywords were combined accordingly on the respective databases previously mentioned (*Supplementary Tables 1 and 2*). Titles and abstracts of articles available in the English, Portuguese and Spanish languages were evaluated.

### Eligibility

Studies were included when the following general criteria were met: i) observational papers describing cohorts of pediatric and adult patients with a final diagnosis of AM; ii) reported data on

genetic testing; iii) studies published in English, Spanish, and Portuguese. Studies also needed to (iv) report at least one clinical outcome variable of interest, namely ejection fraction during follow-up, development of chronic heart failure, diagnosis of cardiomyopathy, recurrent myocarditis, life-threatening arrhythmias, or cardiovascular death.

Duplicate publications were identified and excluded. All non-human studies, editorials, reviews, and case reports were excluded.

### Study selection, data collection process, and study outcomes

Titles and abstracts of articles available were evaluated. The full texts of the publications first identified as potentially eligible were screened for original data. Each study was independently reviewed by two of the authors (MJT and AIP). Discordant decisions were managed by consensus. Details of the search process and article selection are represented in Figure 1. In this phase, information extracted from the studies included the title, authors, study type, case number, follow-up time, inclusion/exclusion criteria applied, information related to the genetic test, and the studied outcomes.

Each one of the screened studies was entirely read to extract all the relevant data and ensure its eligibility. In this review, the following patient data were considered: age, sex, personal history of myocarditis, family history of cardiovascular events, echocardiographic findings including left ventricular ejection fraction (LVEF), CMR LVEF, presence of late gadolinium enhancement (LGE), troponin elevation, and clinical outcomes including ventricular arrhythmias, recurrent myocarditis, heart failure, need for temporary hemodynamic support, cardiac transplantation or implantable cardioverter-defibrillator (ICD), full recovery and cardiovascular death.

Patients carrying pathogenic/likely pathogenic variants were considered as having a positive genetic test, while those lacking such variants were considered as having a negative test. Patients with a variant of unknown significance were excluded from this analysis.

Subsequently, a meta-analysis of the 5 studies with comparative data between patients with positive and negative genetic tests was conducted and included mainly the following data: acute heart failure; sustained VT or ventricular fibrillation (VF); SCD; need for heart transplant or temporary hemodynamic support; recovered LVEF; recurrent myocarditis; development of cardiomyopathy.

### Risk of bias assessment across studies

Risk of bias across studies was assessed by one author (MJT) using Robins-I criteria and graphic representation was obtained with Robvi's Tool. Domains regarding bias due to confounding, selection of participants, intervention, deviations from intended interventions, missing outcome data, measurement of outcomes, selection of the reported result and overall bias are summarized in Figure 2.

### Statistical analysis

The statistical analysis was performed using the software R, version 4.3.0 (package meta). Results were presented as relative risks (RR). We computed meta-analytical RR along with their corresponding 95% confidence intervals using the random-effects model. The restricted maximum likelihood method was applied. Heterogeneity across studies was assessed using the I<sup>2</sup> statistic and



the Q-Cochran test. Substantial heterogeneity was identified if  $I^2 > 50\%$  and Q-Cochrane  $p < 0.10$ .

## Results

### Study acquisition

A total of 2730 titles were identified through the search of MEDLINE/PubMed (1647 records) and Web of Science (1083 records). After removing the duplicates, a total of 2044 records were screened. Following the abstract and title screening, 30 articles potentially relevant to the topic were selected for full-text review. The full-text screening of these articles led to the exclusion of 19 studies due to their non-compliance with the inclusion criteria. Overall, 11 papers were considered for this review (Figure 1 for the PRISMA 2020 flow diagram and *Supplementary Table 3* for a summary table of the included studies).

Since authors utilized different methods of diagnosing AM,

*Supplementary Table 4* summarizes the diagnosis strategies used in each study, the genetic variants found, as well as the corresponding classification as pathogenic/likely pathogenic/unknown significance.

Overall risk of bias assessment detected low risk in eight studies, and some concerns in three studies (Figure 2).

### Clinical features of patients presenting with acute myocarditis and a positive genetic test

Overall, 11 studies reported 199 patients with AM carrying a pathogenic/likely pathogenic variant, from a total of 730 cases (patients with AM) [8-18]. The prevalence of positive genetic test results among the total cases analyzed was estimated at around 27.3%. Sex was reported in 199 cases with a positive genetic test, showing a higher proportion of males than females in this group (61.3% males and 38.7% females).

Within the subgroup of patients with available data, a previous personal history of AM was reported in 30.9% ( $n=30$  in 97

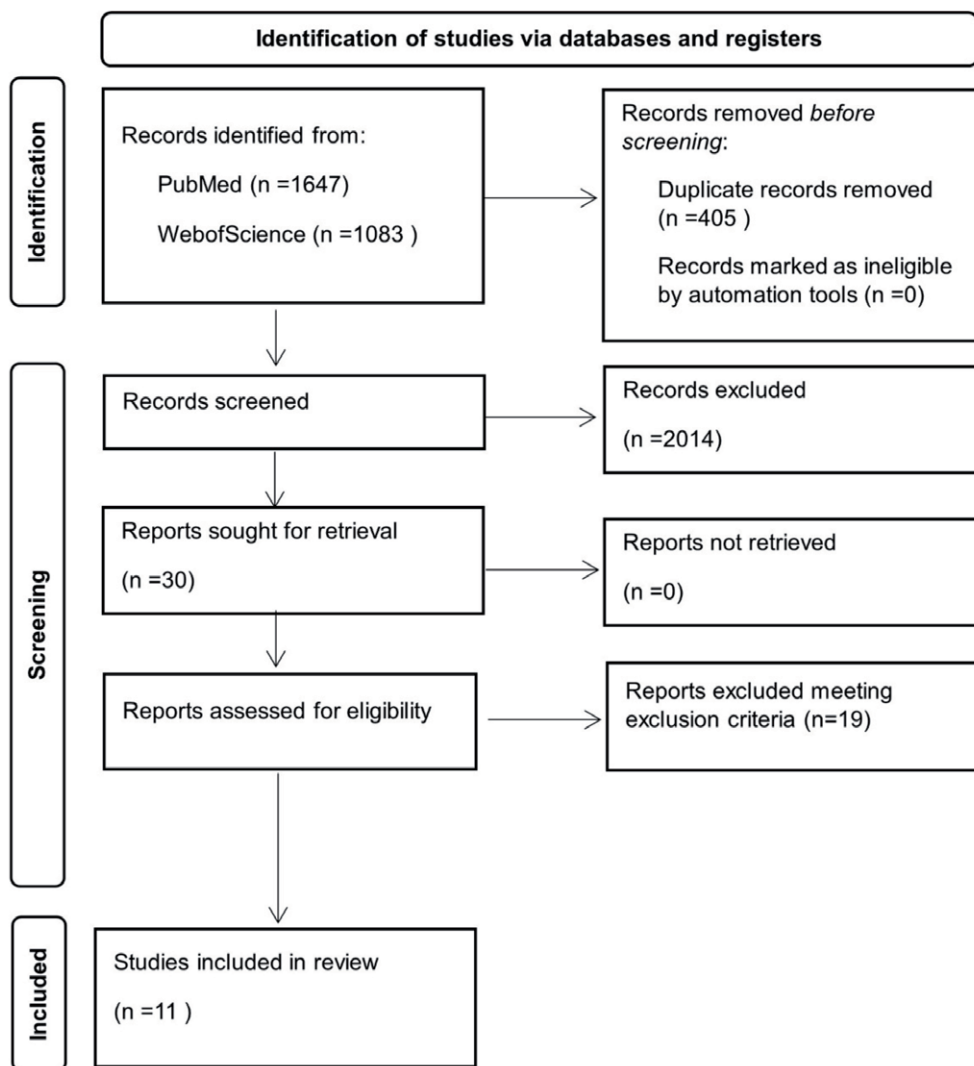


Figure 1. PRISMA flow diagram of literature research.



patients). In 120 patients, data on family history were available, and 53.3% (n=64) reported a family history of cardiovascular events, including myocarditis, SCD, heart transplantation, dilated/arrhythmogenic/non-specified cardiomyopathy in first or second-degree family members. The overall prevalence of LGE on CMR was 81.2% among those who presented with a positive test. The mean CMR/echocardiographic LVEF at presentation was 48.8% in patients with a positive genetic test (n=137), compared to 43.9% in those with a negative test result (n=44).

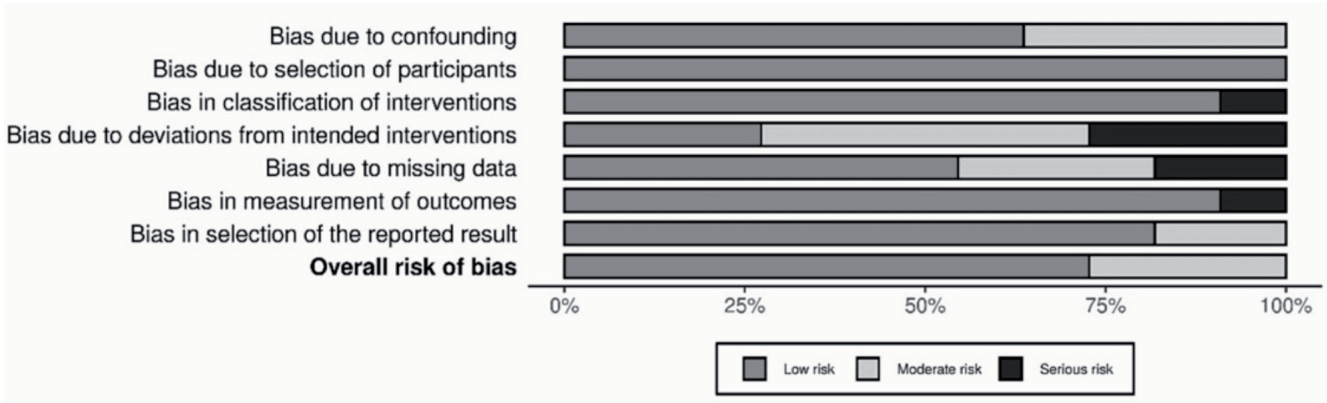
**Clinical prognosis of patients presenting with acute myocarditis and a positive genetic test**

Regarding patients with AM and a positive test result, 25 patients developed life-threatening arrhythmias [studies reporting this outcome included a total (T) of 421 patients] [9,13,14], 39 had recurrent myocarditis episodes (T=91) [8,9,15], 11 developed heart failure (T=364) [14,18], 20 required heart transplantation (T=85) [11,13,16,17], and 31 patients needed implantation of cardiac devices (T=348), including 2 ICDs [14,17]. A total of 16 patients also needed

Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Ader et al, 2020	-	+	+	X	X	+	-	-
Ammirati et al, 2022	-	+	+	X	+	+	+	+
Artico et al, 2020	-	+	X	X	X	X	-	-
Brown et al, 2019	+	+	+	-	+	+	+	+
Kontorovich, Patel et al, 2021	+	+	+	-	-	+	+	+
Kontorovich et al, 2021	+	+	+	-	+	+	+	+
Lota et al, 2022	+	+	+	-	-	+	+	+
Ollitrault et al, 2022	+	+	+	-	+	+	+	+
Seidel et al, 2021	+	+	+	+	+	+	+	+
Seidel et al, 2022	+	+	+	+	+	+	+	+
Tiron et al, 2022	-	+	+	+	-	+	+	-

Domains:  
D1: Bias due to confounding.  
D2: Bias due to selection of participants.  
D3: Bias in classification of interventions.  
D4: Bias due to deviations from intended interventions.  
D5: Bias due to missing data.  
D6: Bias in measurement of outcomes.  
D7: Bias in selection of the reported result.

Judgement  
X Serious  
- Moderate  
+ Low



**Figure 2.** Risk of bias Assessment applying ROBINS-I criteria. Traffic-light and summary plots regarding risk of bias across studies with ROBINS-I criteria and Robvi’s tool.



extracorporeal hemodynamic support (T=58) [8,16], and 24 had a fatal outcome (T=587) [9,11-14,16] (the majority due to cardiovascular events).

In Brown *et al.* [11], and Seidel *et al.* [17], all patients with a positive genetic test presented with signs and symptoms of acute heart failure (who either had a heart transplantation or a fatal outcome). Additionally, Artico *et al.* reported 9 carriers with heart failure and left ventricular dysfunction at the time of AM diagnosis [10], and Ader *et al.* also reported 1 case of fulminant myocarditis culminating in heart transplantation, totalizing 29 patients with acute heart failure at diagnosis [8].

Clinical outcomes are described in more detail in the following subsections.

### In-hospital complications

In-hospital complications observed in patients with a positive genetic test included 2 cases of ventricular arrhythmias with fatal outcomes, 1 case that needed an ICD due to sustained VT, and 2 patients who needed extracorporeal hemodynamic support in the acute phase.

### Follow-up complications

Only 5 studies [9,10,14-16], including 151 patients with a positive genetic test, reported follow-up after hospitalization, with a median follow-up time of 39.3 months. Complications reported in these studies included the following: 13 patients developed major arrhythmias (5 cases of VT/VF; 8 cases of VT, aborted SCD, ICD implantation, or 2nd/3rd degree atrioventricular block), 39 patients had recurrent episodes of AM, 9 patients progressed to chronic heart failure, 14 cases needed extracorporeal hemodynamic support and 30 patients required implantation of cardiac devices (including ICD and unspecified devices). Additionally, 6 patients had heart transplantation, and 12 cases had a fatal outcome during follow-up.

The remaining complications reported in 3.3 and not further described in these subsections (10 cases of ventricular arrhythmias, 2 cases of chronic heart failure, 14 cases of heart transplantation, 12 deaths) were not described in detail in the respective studies and the timing of their occurrence is, therefore, unknown.

### Comparative data between patients with positive genetic test vs. negative test

Five studies [8-10,12,14] presented comparative data between patients with AM and a positive genetic test vs. patients with AM and a negative genetic test. These studies included data regarding outcomes such as the need for heart transplantation, extracorporeal hemodynamic support, recurrent myocarditis, improved LVEF, later diagnosis of cardiomyopathy, major heart failure, major arrhythmia, all-cause mortality, and SCD. This information was synthesized and presented in Figure 3; the forest plot includes a graphic representation of the variables included in the meta-analysis. The risk of individuals with a positive genetic test developing a certain outcome (variable of outcome) was compared with the risk of individuals with a negative test developing that same outcome (RR).

A statistically significant result was found regarding the development of recurrent episodes of AM (RR=4.02,  $p<0.001$ ), meaning that patients with a positive genetic test have 4 times higher risk of developing this outcome when compared with non-carriers. Heterogeneity was observed in some variables, indicating variability in effect sizes across studies, probably because of different study populations and inclusion criteria (Figure 3).

### Predominant genes found in patients with acute myocarditis

Although not all studies reported the exact number of patients carrying each variant, the most frequently found genetic variants across studies were *TTN*, *DSP*, *PKP2*, *MYH7*, *BAG3*, *RMB20*, *DSG2*, *TNNT2*, and *SCN5A* (*Supplementary Tables 4 and 5*), which suggests a possible gene panel to consider in clinical practice.

## Discussion

### Genetic variants associated with acute myocarditis and their pathophysiological role

Many gene mutations implicated in myocardial diseases and arrhythmic syndromes have been described and deeply studied over the years. The intrinsic connection between specific genetic mutations and some cardiac phenotypes is well known [2,8,9,19,20]; however, little is known about the potential correlation between AM and genetic background. To our knowledge, this is the first systematic review with meta-analysis that proposes to study the relationship between AM and pathogenic/likely pathogenic variants related to cardiomyopathies.

In this systematic review, studies describing genetic mutations potentially correlated with increased susceptibility to AM and development of myocardial disease, including pathogenic/likely pathogenic variants already described in the literature, were compiled and summarized (*Supplementary Table 4*) [21]. Genes that codify structural myocardial proteins, such as *DES* (Desmin), *DSG2* (Desmoglein-2), *DSP* (Desmoplakin), *PKP2* (Plakophilin-2), *FLNC* (Filamin C), *LMNA* (Lamin A/C), *MYBPC3* (Myosin Binding Protein C), *TTN* (Titin), *TNNT2* (Troponin T2, cardiac type), *BAG3* (BAG Cochaperone 3), *JPH2* (Junctophilin 2) and *JUP* (Junction Plakoglobin), when altered, dysfunctional or deleted, contribute to greater susceptibility to myocardial injury. *RYR2* (Type 2 Ryanodine Receptor) and *SCN5A* (Sodium Voltage-gated Channel Alfa Subunit 5) are genes with a critical role in controlling, respectively, calcium and sodium voltage-gated channels, both crucial in cardiac excitation-contraction coupling; once altered, these mutations may predispose to arrhythmogenic disorders, like catecholaminergic polymorphic VT, long QT syndrome and Brugada syndrome, and even cardiomyopathies [22,23]. Genes like *DMD* (Dystrophin), *SGCG* (Sarcoglycan Gamma), *DYSF* (Dysferlin), *TRDN* (Triadin), and *CTF1* (Cardiotrophin 1) are responsible for codifying membrane proteins and receptors that provide cardiac structural support, stability of sarcolemma, coordination of the contraction-relaxation cycle, and adaptive responses to stress and injury, contributing to cardiac repair and remodeling [24,25]. *RBM20* (RNA Binding Motif Protein 20) is a gene involved in splicing other key genes involved in cardiac function, like *TTN*; *IDUA* (Alpha-L-Iduronidase) encodes an enzyme involved in the breakdown of glycosaminoglycans, and it is associated with pediatric mucopolysaccharidosis type I, a lysosomal storage disease that often culminates in cardiac dysfunction and death [26,27].

Different genotypes may be involved in similar cardiac phenotypes; the opposite is also true, with mutations in some specific genes causing distinct cardiac phenotypes, with some overlapping between ACM, DCM, and other cardiomyopathies [28,29]. Increasing evidence corroborates the interaction between environmental factors such as viral infections, pregnancy, and alcohol consumption, with a predisposed genetic background involving either non-structural or structural proteins of the myocardium [20]. This



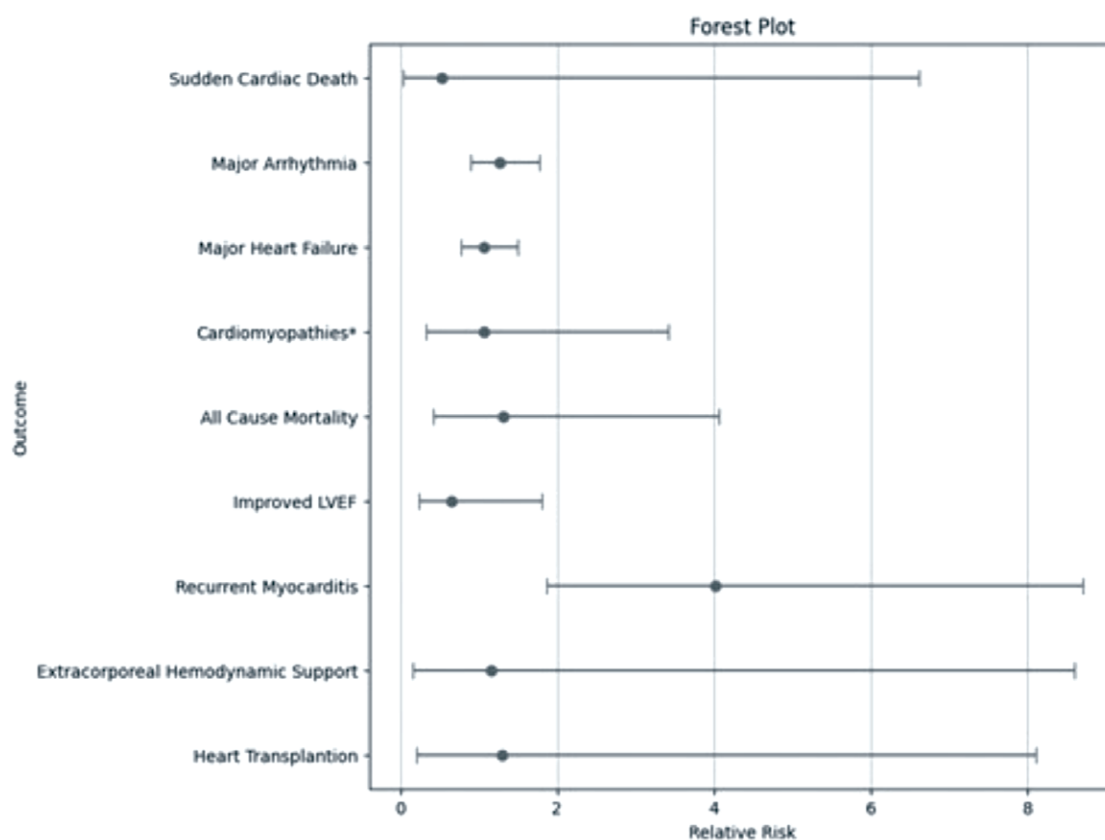
interaction between environmental and genetic factors can determine AM with different clinical presentations, prognosis, and life-long development of cardiomyopathies like DCM or ACM in genetically predisposed individuals [2,21,30].

### Frequent unfavorable outcomes in patients with a positive genetic test

Based on data from these 11 studies, the prevalence of pathogenic/likely pathogenic variants among patients with AM seems to be around 27.3%, which suggests that genetic factors may play a significant role in a subset of AM cases, since almost 3 in every 10 patients with AM analyzed had a predisposing genetic mutation. There was a higher proportion of males with myocarditis and a positive genetic test than females, which suggests that genetic variants associated with AM may also be sex related. Additionally, a significant proportion (30.9%) of patients with AM and a positive genetic test had a previous history of AM, which highlights a possible predisposition for recurrent episodes and higher morbidity in these individuals with a genetic background. Previous family history of cardiovascular events, including AM, SCD, heart transplantation, dilated/arrhythmogenic/non-specified cardiomyopathy, was reported in more than half of patients with a positive genetic test, which reinforces the role of familial screening and genetic testing, as a family history may provide valuable insights into the underlying genetic predisposition.

Patients with AM and a positive genetic test show a high incidence of in-hospital and after-discharge complications. The presence of a positive genetic test was also frequently observed in patients with unfavorable outcomes, such as the development of ventricular arrhythmias, recurrent AM episodes, later diagnosis of chronic heart failure, need for implantable cardiac devices, heart transplantation, requirement for extracorporeal hemodynamic support due to the severity of clinical presentation, and cardiovascular/presumed cardiovascular death. The overall prevalence of LGE on CMR in patients with AM was 81.2% among those who presented with a positive test. Extrapolations about this data are limited by the absence of quantification of the extent of LGE. In terms of CMR/echocardiographic LVEF, the values exhibited remarkable similarity between both groups.

Overall, these findings emphasize the importance of identifying affected individuals who may benefit from genetic testing since patients with a positive genetic test may represent a subset of patients with a higher risk of complications and need for specific interventions. Identifying at-risk individuals may help implement strategies in the early stages of disease that can modify the disease course, improve outcomes, and reduce the burden of cardiac events. Such strategies may include primary prevention interventions, closer surveillance of affected individuals, and cascade screening of family members at risk. Notably, individuals affected with AM, often pediatric patients, young or middle-aged adults, face significant morbidity, with profound implications on their quality of life.



**Figure 3.** Comparison between the risk of developing a certain outcome in cases with a positive genetic test vs. cases with a negative genetic test.



## Comparative outcomes between cases with a positive and a negative test

The observed outcomes in 5 studies with comparative data between cases with a positive genetic test and cases with a negative genetic test were meta-analyzed (Figure 3). Overall, patients with a positive genetic test were found to have a 4 times higher risk of developing recurrent episodes of AM when compared to patients with a negative genetic test, which has important implications for clinical practice. Since patients with myocarditis and a pathogenic/likely pathogenic genetic variant have been found to have more episodes of recurrent myocarditis during follow-up compared with those without, identification of a genetic variant should prompt stricter surveillance of these patients. Also, clinicians should consider referral for genetic testing in patients with recurrent episodes of AM.

The lack of statistical power, likely due to the presence of a small sample size, may have prevented achieving additional statistically significant findings. However, it is crucial to acknowledge that the prevalence of patients with a positive genetic test and the incidence of complications in this group were substantial, and, despite the absence of more statistically significant results, the insights collected from this study may remain relevant in clinical practice.

## When to consider genetic testing in patients with acute myocarditis?

According to Monda *et al.* [5], we should consider genetic testing in patients presenting with a first episode of AM and the following additional findings: family history of cardiomyopathies or SCD, echocardiographic or CMR suggestive of arrhythmogenic cardiomyopathies or heart failure with reduced ejection fraction and/or sustained VT. In this systematic review, we also found a high burden of these characteristics in carriers of pathogenic/likely pathogenic variants, especially in the presence of previous family history of cardiovascular events, reinforcing these indications [5]. Additionally, we also noticed a higher number of carriers among patients with recurrent episodes of AM, suggesting the importance of integrating genetic testing into the management of these patients.

These findings are corroborated in a recently published review by Monda *et al.* [31], in which the authors describe a significant prevalence of pathogenic/likely pathogenic variants in cardiomyopathy-associated genes in patients with AM (4.2% in uncomplicated myocarditis and 21.9% in complicated myocarditis). The authors concluded that genetic variants are present in a large proportion of patients presenting with AM; the prevalence and genes involved vary according to age and clinical presentation [31]. Multicenter prospective studies with comprehensive data regarding clinical outcomes would be useful to test and confirm these findings and provide a deeper understanding of the relationship between genetic test results and patient prognosis, in order to help improve the criteria used for genetic testing in the setting of AM episodes.

## Study limitations

This systematic review presents some study limitations that warrant consideration when interpreting its results. Firstly, the reliance on data sourced exclusively from two databases may restrict the extent and representativeness of the evidence found. Secondly, the available studies were observational and case series, with methodological issues inherent to this type of studies, restricting the generalizability of the results. Furthermore, variability in the clinical diagnosis of AM across studies may introduce heterogeneity and mis-

classification bias. Additionally, it would have been interesting to stratify results by age and countries to clarify age-related variations and ethnicity's impact on outcomes; however, this analysis was limited by the lack of age stratification and ethnicity data in the majority of included studies, and since most studies originate from Europe and the United States. Finally, the review was constrained by limitations associated with small sample size, heterogeneity of the genetic variants, and missing data across studies, which likely influenced the statistical significance of the reported results. Also, these results cannot be overgeneralized without reflecting on the associated costs and implications of identifying genetic variants. More robust evidence from large-scale studies is required.

## Conclusions

To our knowledge, this is the first systematic review with meta-analysis that proposes to study the relationship between AM, genetic background, and prognosis. The prevalence of a positive genetic test for pathogenic/likely pathogenic variants associated with myocardial disease was considerable in patients with AM, and these variants were frequently observed in patients with unfavorable outcomes. Also, patients with a positive genetic test showed a greater risk of developing recurrent episodes of AM. Overall, these findings emphasize the importance of identifying affected individuals who may benefit from genetic testing, especially those with recurrent episodes of AM and relevant family history. Identifying at-risk individuals may help implement strategies in the early stages of disease that can modify the disease course, improve outcomes, and reduce the burden of cardiac events. More robust evidence from large-scale studies is required.

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*Online supplementary material:*

*Supplementary Table 1 PubMed search strategy.*

*Supplementary Table 2. Web of Science search strategy.*

*Supplementary Table 3. Characteristics of the eleven studies included in the literature review.*

*Supplementary Table 4. Diagnostic criteria of myocarditis applied in each study, genetic variants found and their corresponding classification.*

*Supplementary Table 5. Classification of genetic variants: OMIM codification, inheritance and number of carriers reported.*

Received: 18 October 2024; Accepted: 10 December 2024; Early view: 25 February 2025.

Contributions: all the authors have contributed significantly to the work. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: not applicable.

Informed consent: not applicable.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

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