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REVIEW

Complex Ventricular Arrhythmias in Patients with Mitral Annular Disjunction: A Systematic Review and Meta-Analysis

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ABSTRACT

Purpose: Mitral annular disjunction (MAD) frequently co-occurs with mitral valve prolapse (MVP). It is unclear, however, whether MAD is associated with an additional risk of arrhythmogenic events in patients with MVP. We aimed to evaluate the incidence of complex ventricular arrhythmias (VA) and sudden cardiac death (SCD) in patients with MAD compared to those without MAD.

Methods: We systematically searched PubMed, Embase, and Web of Science for studies evaluating the incidence of complex VA and the composite outcome of complex VA and SCD among patients with versus without MAD. We performed a random-effects meta-analysis to pool odds ratios (OR) and hazard ratios (HR) with 95% confidence intervals.

Results: We included 16 studies comprising 6001 patients, of whom 23% had MAD; 41% were female; the mean age was 56.5 years. MVP was significantly present in both groups, with a higher prevalence in the MAD group in 1030 patients (74.5%) with MAD and in 1942 patients (47%) without MAD. The incidence of complex VA was significantly higher in patients with MAD (OR 3.88; 95% CI 1.69–8.93; $p = 0.001$), compared with patients without MAD. Patients with MAD also had a higher risk of the composite outcome of complex VA and SCD (HR 2.51; 95% CI 1.94–3.24; $p < 0.00001$) (OR 3.13; 95% CI 1.38–7.11; $p = 0.006$).

Conclusion: In this meta-analysis, the presence of MAD was significantly associated with the development of complex VA and the composite outcome of complex VA and SCD. The outcome of SCD was not evaluated as an isolated endpoint.

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CI, confidence interval; CMR, cardiac magnetic resonance; ECG, electrocardiogram; HR, Hazard ratios; MAD, mitral annular disjunction; MRI, magnetic resonance Imaging; MVP, mitral valve prolapse; NOS, Newcastle-Ottawa Scale; NSVT, non-sustained ventricular tachycardia; OR, odds ratios; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PROSPERO, International prospective register of systematic reviews; SCD, sudden cardiac death; VA, ventricular arrhythmias; VT, ventricular tachycardia.

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1 | Introduction

Mitral annular disjunction (MAD) is defined as a distinct separation between the left atrium/mitral valve annulus and the left ventricular myocardium and is frequently present in patients with arrhythmic MVP [1–3]. According to the updated criteria proposed by Faletra and colleagues [4], MAD can be classified into two types: pseudo-MAD, defined as an apparent systolic displacement resulting from the juxtaposition of a redundant mitral leaflet against the atrial wall without true anatomical separation; and true MAD, identified by disjunction that is evident in both systole and diastole, associated with an abnormal insertion of the leaflet into the atrial wall [4]. The detection and quantification of MAD are facilitated by careful high-resolution imaging using transthoracic and transesophageal echocardiography or cardiac magnetic resonance [5, 6].

While MAD was initially described more than three decades ago in conjunction with mitral valve prolapse (MVP), recent studies have unveiled associations with ventricular arrhythmias (VA), sudden cardiac death (SCD), and papillary muscle fibrosis, particularly in co-occurrence with MVP [7]. This likely happens due to left ventricular morphological and functional remodeling, which leads to these conditions [8]. Furthermore, the clinical importance of MAD independent of MVP is not yet fully understood, as existing studies often do not isolate MAD in the absence of MVP, thereby limiting our understanding of its standalone impact [9, 10].

Understanding whether the presence of MAD, either alone or in combination with MVP, influences the risk of complex VA and SCD would be helpful to refine clinical management strategies. Consequently, we planned to undertake a systematic review and meta-analysis to evaluate the incidence of complex VA and SCD in patients with and without MAD, to understand the importance of MAD in these patients.

2 | Material and Methods

This systematic review and meta-analysis were performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [11]. The prospective meta-analysis protocol was recorded on the International Prospective Register of Systematic Reviews on June 27, 2023 (PROSPERO) under the registration number CRD42023437324, with the last update in April 2024.

2.1 | Study Eligibility

We included studies in this meta-analysis that satisfied the following criteria: (1) studies that included patients who were submitted to either echocardiogram or cardiac magnetic resonance (CMR); (2) comparing the presence of MAD with the absence of MAD; and (3) reporting any of the outcomes of interest.

We excluded studies (1) without a control group; (2) patients with other arrhythmogenic heart diseases; (3) studies that do not report the data of interest with and without MAD separately; or (4) overlapping study populations. In the latter situation, we chose the study with the largest number of patients that included the outcomes of interest. There were no restrictions on the duration of follow-up.

2.2 | Search Strategy and Data Extraction

We systematically searched Medline, Embase, and Web of Science databases in March 2025 using the following medical terms: “MAD”, “mitral annulus disjunction”. The literature screening and studies selection process was conducted using Zotero software (version 6.0.23) for importing results from the databases into the program, removing duplicate articles, excluding articles based on the examination of the title and abstract, selecting articles for full-text reading, and subsequently excluding studies that did not meet the inclusion criteria previously determined. All stages of screening, eligibility assessment, and inclusion were performed independently by two authors (L.S.G. and P.C.N.). Disagreement was resolved through consensus with a third author (C.A.C.J.).

Data were extracted independently by two authors for the design of the study, year of publication, sample size, follow-up period, baseline patient characteristics, and echocardiographic parameters. Author consensus was reached to resolve disagreements after a thorough review of the full-text paper and the eligibility criteria.

2.3 | Endpoints of Interest

We had three outcomes of interest: complex VA, SCD, and the composite outcome of complex VA and SCD. Among the included studies reporting at least one of these outcomes of interest, we also pooled the frequency of secondary outcomes: atrial fibrillation (AF), syncope, chest pain, dyspnea, palpitations, and the presence of coronary arterial disease (CAD).

The authors referenced in our study classify complex VAs as ventricular fibrillation, both sustained and non-sustained ventricular tachycardia, the occurrence of more than three consecutive ectopic ventricular beats, polymorphic VAs, and the requirement for an implantable cardioverter-defibrillator. One study also included premature ventricular complexes in their classification, considering $\geq$5% as a complex VA [12]. A summary of the definitions of complex arrhythmias from each study can be found in Table S1. Similarly, the definitions of MAD used in each study were compiled in Table S4.

2.4 | Quality Assessment

Two researchers, working independently, employed the Newcastle-Ottawa Scale (NOS) [13] to perform a quality assessment of the included studies. Briefly, NOS grades studies based on the selection, comparability, and outcome domains. Within the selection category, each subcategory allows a study to be assigned a maximum of one star, totaling up to four stars. Likewise, in the comparability category, a study can receive a maximum of two stars, while in the outcome category, it can

earn up to three stars. Therefore, the maximum score a study can receive is 9, while the lowest is 0. Scores between 7 and 9 were considered low risk, between 4 and 6 were considered intermediate risk, and below 4 were considered high risk. Any disparities in assessing the risk of bias were resolved through discussion and consensus.

2.5 | Data Analysis

Statistical analysis was performed using Review Manager 5.4.1 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Binary outcomes were compared using odds ratios (OR) or hazard ratios (HR) with 95% confidence intervals. We used the Mantel–Haenszel random-effects model due to the observational nature of the studies. Heterogeneity was evaluated with the I^2 statistic and considered low ($I^2 \leq 25\%$), moderate ($26 \geq I^2 \leq 50\%$), and high ($I^2 > 50\%$). Further, statistical significance was established at a p-value < 0.05.

2.6 | Sensitivity Analysis

To address the high heterogeneity, we conducted a sensitivity analysis restricted to studies with a low risk of bias. Additionally, we performed a meta-regression analysis for complex VAs to assess potential interactions with the following characteristics: (1) age, (2) sex, (3) MAD length in millimeters, (4) technique modality—echocardiography versus CMR. We also conducted leave-one-out sensitivity analyses to ensure that the results were not driven by any single study. Finally, we carried out a subgroup analysis of studies based on different measurement techniques, echocardiography versus CMR.

3 | Results

3.1 | Study Selection and Pooled Population Characteristics

Our systematic search identified 1057 potential articles, as detailed in Figure 1. After removing duplicate records and studies that did not meet the exclusion criteria based on title/abstract review, 38 articles remained, which were thoroughly reviewed for inclusion and exclusion criteria. A total of 16 observational studies, with 6001 patients, were included.

The baseline characteristics of the included studies are depicted in Table 1. Of the 6001 patients, 1382 (23%) had MAD; 2457 (41%) were female; and the mean age was 56.5 years. Total follow-up ranged from 1 to 19.4 years. Furthermore, MVP was significantly present in both groups, with a higher prevalence in the MAD group in 1030 patients (74.5%) with MAD and 1942 patients (47%) without MAD. In Table 2, additional echocardiographic parameters are presented based on data from 11 studies, while the remaining 5 studies either did not report these parameters in sufficient detail or primarily focused on clinical outcomes rather than imaging-based assessments.

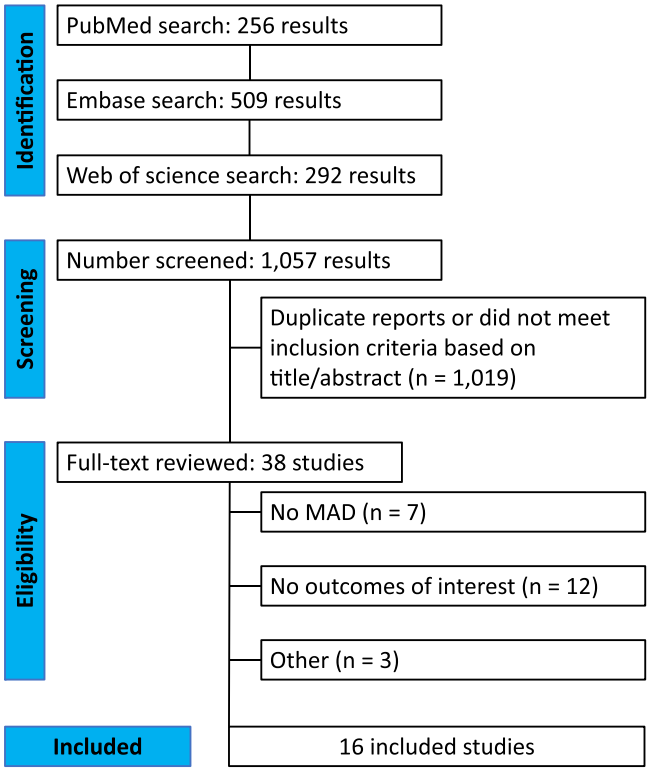


FIGURE 1 | PRISMA flowchart of study screening and selection.

3.2 | Pooled Analysis of All Studies

3.2.1 | Complex Ventricular Arrhythmias

The incidence of complex VA was significantly higher in patients with MAD, as compared with those without MAD (OR 3.88; 95% CI 1.69–8.93; $p = 0.001$, $I^2 = 93\%$; Figure 2). The meta-regression analysis for this outcome was not significant for age, sex, or MAD length. Significance was observed only for the imaging modality, with a positive association for echocardiography, thereby reinforcing the findings from the subgroup analysis comparing patients diagnosed by ECO and CMR (Figure S7).

3.2.2 | Complex Ventricular Arrhythmias or Sudden Cardiac Death

While none of the individual studies presented the individual outcome of SCD, the pooled analysis of the composite outcome of complex VA and SCD revealed a higher risk in patients with MAD (HR 2.51; 95% CI 1.94–3.24; $I^2 = 0\%$; $p < 0.00001$; Figure 3) and (OR 3.13; 95% CI 1.38–7.11; $I^2 = 42\%$; $p = 0.006$; Figure 4).

3.3 | Associated Symptoms

There were significant differences between the groups in palpitations (OR 1.46; 95% CI 1.08–1.96; $p = 0.01$; $I^2 = 21\%$; Figure S1), and syncope (OR 1.46; 95% CI 0.96–2.22; $p = 0.08$; $I^2 = 3\%$; Figure S2), therefore, no significant differences between the groups in terms of dyspnea (OR 0.86; 95% CI 0.66–1.11; $p = 0.25$; $I^2 = 0\%$; Figure S3), chest pain (OR 1.08; 95% CI 0.59–1.98; $p = 0.81$; $I^2 = 64\%$; Figure

TABLE 1 | Baseline characteristics of included studies.

Study	Design	Patients, *n*	Follow-up (years)	Female, *n* (%)	Age[b], years	MVP, *n* (%)	ECO or CMR
Carmo 2010	Retrospective	38	NA	18 (47)	58 ± 15	38 (100)	ECO
Cesmat 2024	Retrospective	632	3.3	333 (53)	NA	632 (100)	ECO
Daniłowicz-Szymanowicz 2023	Retrospective	72	NA	51 (71)	40	72 (100)	ECO
Essayagh 2019	Retrospective	89	NA	63 (71)	64 ± 13	89 (100)	CMR
Essayagh 2020	Retrospective	595	6	278 (47)	65 ± 16	595 (100)	ECO
Essayagh 2021	Retrospective	595	10.3	278 (47)	61 ± 16	595 (100)	ECO
Figliozzi 2023	Retrospective	474	3.3	244 (51)	47 ± 16	474 (100)	CMR
Figliozzi 2024	Retrospective	441	1	174 (29)	NA	29 (7)	CMR
Gatti 2021	Case-control	52	NA	34 (65)	NA	52 (100)	CMR
Groeneveld 2022	Retrospective	144	7 (2–12)[a]	60 (42)	39 ± 14	5 (8)	CMR
Lee 2021	Retrospective	85	19.4	39 (46)	54 (41–65)[a]	85 (100)	CMR
Palmisano 2024	Retrospective	2611	NA	881 (34)	NA	188 (7)	CMR
Tijmes 2023	Retrospective	46	4.3 (1.5–8.4)	24 (52)	37.2 ± 14.3	9 (20)	CMR
Vaksmann 2023	Prospective	49	NA	33 (67)	12.8 ± 3.0	49 (100)	ECO
Wang 2021	Retrospective	42	1.6	19 (46)	54 ± 17	42 (100)	ECO
Wijngaarden 2020	Retrospective	610	NA	219 (36)	66 (57–73)[a]	610 (100)	ECO

Abbreviations: CMR, cardiac magnetic resonance; ECO, echocardiogram; MVP, mitral valve prolapse; NA, not available.
[a]IQR, interquartile range.
[b]Mean or median ± standard deviation.

S4), CAD (OR 0.79; 95% CI 0.35–1.79; $p = 0.58$; $I^2 = 51\%$; Figure S5), or AF (OR 0.73; 95% CI 0.47–1.14; $p = 0.17$; $I^2 = 40\%$; Figure S6).

3.4 | Quality Assessment

Table S2 summarizes the appraisal of individual studies using the NOS tool. Eight studies were classified as intermediate risk of bias due to reasons such as the sample not being representative of the general population [14]. Also, the origin of the unexposed population was not being identified, unspecified follow-up times to the two analyzed groups, and a lack of blinding among data assessors in these studies [14–22]. The remaining studies were categorized as having a low risk of bias.

4 | Discussion

In this meta-analysis of sixteen observational studies, we evaluated the incidence of complex VA and the composite outcome of complex VA and SCD among patients with versus without MAD. Patients with MAD had a significantly higher incidence of complex VA. Although individual studies did not report SCD as an individual outcome, a pooled analysis showed a higher risk of complex VA and SCD over time in patients with MAD. Furthermore, statistical significance was also observed for syncope and palpitations, and the subgroup analysis by imaging modality revealed a stronger association between MAD and complex VAs when the disjunction was diagnosed by echocardiography.

Anatomical variations suggesting the presence of MAD have been documented as early as 1876. However, it was only in 1886 that Hutchins and colleagues [10] formally described the term "disjunction" to characterize the separation observed between the left atrioventricular junction. Through an autopsy study of 900 adult hearts, they identified a strong association between a flaccid mitral valve and MAD, suggesting that the disjunction of the mitral annulus fibrosus may contribute to the pathological features of myxomatous valve disease [6].

MAD has been reported to coexist with MVP [9, 14, 15, 19], as evidenced by most of the studies included in our analysis. MVP affects approximately 2.4% of the general population [23, 24] and is the primary cause of mitral regurgitation in Western countries [24]. The increased frequency of VA in mitral valve myxomatous disease may be due to abnormal traction on the papillary muscles caused by the parachute-like closure of the mitral valve [25]. This anatomical alteration, along with myocardial fibrosis identified in cardiac MRI, has been proposed as a substrate for these arrhythmias [26]. While some reports suggest MVP has a benign course with rare complications and infrequent severe VAs [12, 27, 28], other studies associate MVP with NSVT, sustained VT, ventricular fibrillation, and SCD [5, 8, 26, 29-35].

The pathophysiology of VAs related to MAD is increasingly understood. MAD results in excessive mobility of mitral valve leaflets, placing augmented tension on the mitral apparatus [6]. This mechanical extension can cause myocardial damage and local fibrosis in the inferobasal wall and papillary muscles,

TABLE 2 | Echocardiographic or cardiac magnetic resonance parameters.

Study	LVEDd[b], mm		EF[b] (%)		MAD[b], mm	MADD[b], mm		MR II or III, *n*[b] (%)	
	MAD	NO MAD	MAD	NO MAD	MAD	MAD	NO MAD	MAD	NO MAD
Carmo 2010	56 ± 10	58 ± 8	66 ± 7	67 ± 7	7.4 ± 8.7	−4.6 ± 4.7	3.4 ± 1.1	19 (91)	14 (82)
Cesmat 2024	46 (41–50)[c]	46 (42–51)[c]	55 (55–60)[c]		NA	NA		32 (34)	148 (27.5)
Daniłowicz - Szymanowicz 2023	50	49	56	58	10	NA		NA	
Essayagh 2019[a]	NA	NA	67 ± 7	64 ± 7	8 ± 4	0.97 ± 3.45	−0.33 ± 3.16	41 (71)	14 (45)
Essayagh 2021	54 ± 7	51 ± 6	63 ± 7	62 ± 7	7.5 ± 2.8	NA		116 (62)	217 (53)
Figliozzi 2023[a]	NA	NA	59 (55–64)[c]	60 (56–65)[c]	5.8 (3.4–7.0)[c]	NA		NA	
Palmisano 2024[a]	NA		58 (53–65)[c]	58 (49–65)[c]	4 (3–6)[c]	NA		55 (38.7)	308 (12.5)
Tijmes 2023[a]	NA		58.2 ± 5.7	58.5 ± 7.4	4.4 ± 2.4	NA		NA	
Vaksmann 2023	1.44 ± 1.29	0.88 ± 1.58	NA		6 ± 1.3	NA		7 (28)	4 (17)
Wang 2021	NA	NA	59 ± 5	62 ± 6	9 ± 3	NA		NA	
Wijngaarden 2020	135 ± 42		66 ± 6		7.0 (6.0–9.0)[c]	NA		NA	

Abbreviations: EF, ejection fraction; LVEDd, left ventricular diastolic diameter; MAD, mitral annular disjunction; MADD, mitral annulus diameter difference; MR, mitral regurgitation (II: moderate; III: severe); NA, not available.

[a]Cardiac magnetic resonance parameters.

[b]Mean or median.

[c]IQR, interquartile range.

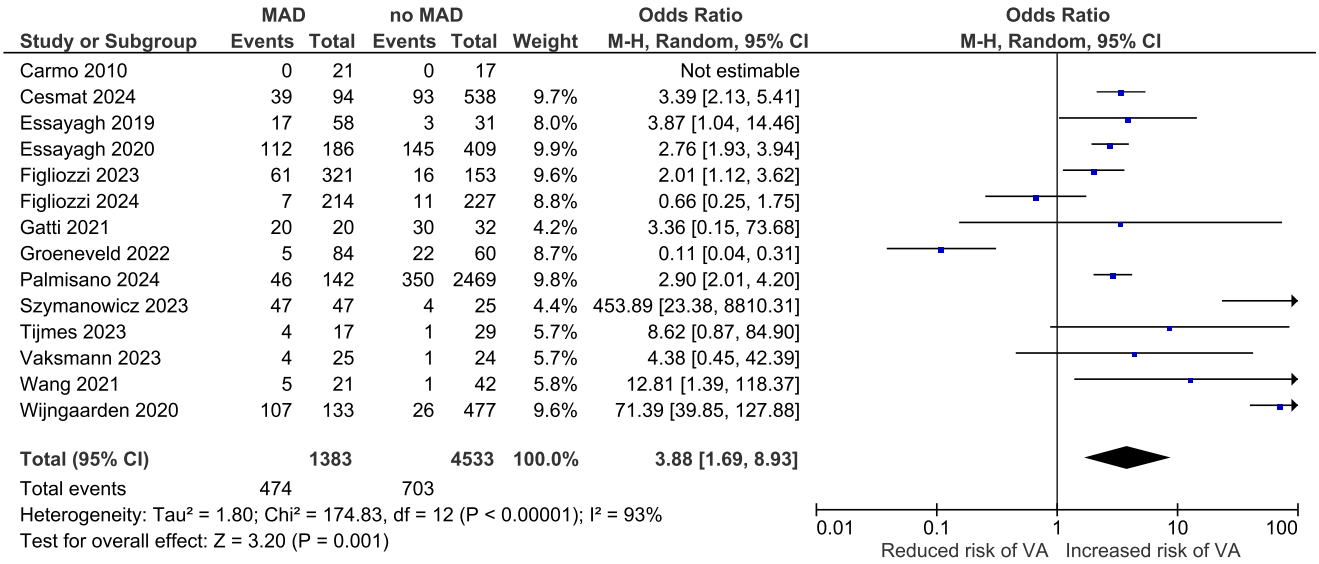


FIGURE 2 | The incidence of complex ventricular arrhythmias was significantly higher in the patients with MAD ($p = 0.001$).

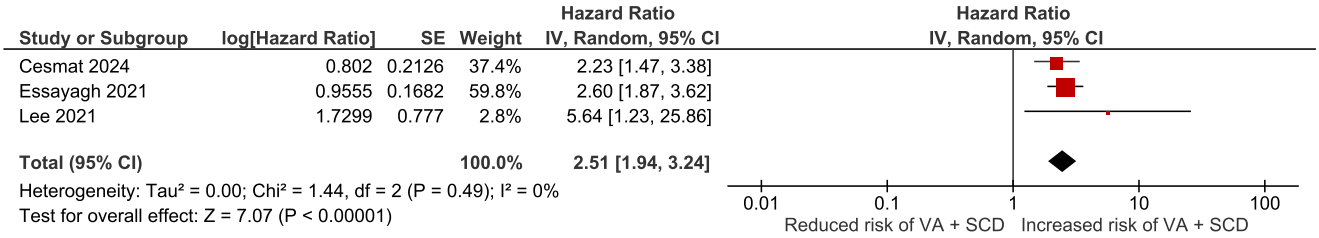


FIGURE 3 | The incidence of complex ventricular arrhythmias and sudden cardiac death was significantly higher in the patients with MAD ($p < 0.00001$).

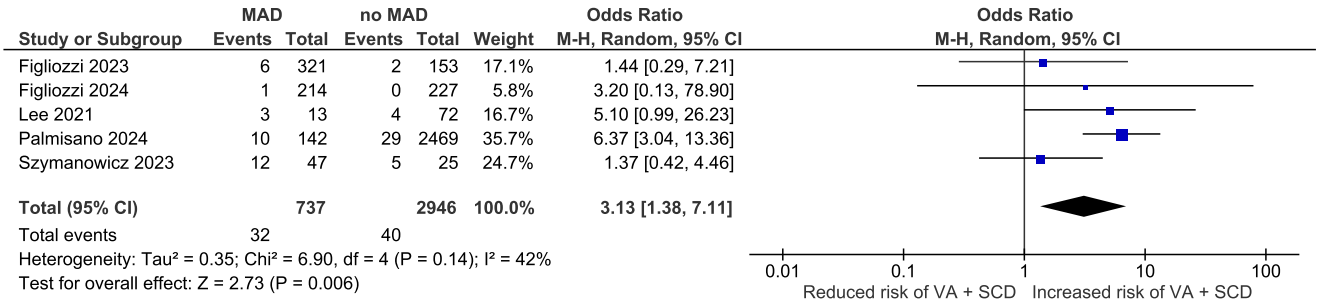


FIGURE 4 | The incidence of complex ventricular arrhythmias and sudden cardiac death was significantly higher in the patients with MAD ($p = 0.006$).

forming a substrate for VAs [29, 36, 37]. Hypercontractility in segments neighboring MAD may also contribute to the emergence of myocardial fibrosis, setting the stage for VAs [27, 37]. This hypermobility is observable in the global longitudinal strain through echocardiography [38], wherein abnormally negative values of longitudinal deformation in the basal segments [14]. Similarly, CMR has revealed unusual patterns of circumferential and radial deformation in basal segments [17]. These findings suggest that myocardial strain metrics could be promising indicators of regional left ventricular dysfunction and an elevated risk of complex VA in patients with MAD.

Notably, the measured length of displacement in MAD, capable of being quantified by various methods, is not interchangeable and warrants careful interpretation [1, 8, 39] due to the morphological complexity and location variability of MAD and to the comparative limitations of echocardiography vis-à-vis CMR in diagnosing this condition [40]. CMR is also instrumental in accurately identifying myocardial fibrosis, common in this pathology [41–43]. Moreover, some studies link the extent of MAD displacement to the presence of VAs [15, 44], although the measurement standards remain undetermined. Ventricular fibrosis, identifiable on CMR, is linked to both MAD [5, 34, 45] and MVP [8, 45-47].

In one study, palpitations were the most frequently reported symptom among patients with MAD, occurring in 71% of cases [5]. Similarly, in our study, palpitations also showed a significant prevalence, reinforcing the need for close monitoring due to the substantial arrhythmic potential associated with this condition.

Syncope in patients with MAD associated with VAs has been investigated in the context of arrhythmogenic MPV syndrome, with one study reporting its occurrence in 48% of cases [48]. In our study, the presence of syncope emerged as a significant factor associated with MAD. Current literature emphasizes that careful evaluation and close monitoring of these patients are essential for appropriate management and risk stratification [5].

In patients with mitral MAD and/or mitral MVP presenting with palpitations or syncope, the 2024 expert consensus recommends a structured arrhythmic evaluation including 12-lead ECG, ambulatory rhythm monitoring, transthoracic echocardiography, and CMR to assess for arrhythmic MVP phenotype features such as bileaflet prolapse, myocardial fibrosis, and excessive leaflet mobility. For asymptomatic individuals with incidental MAD or MVP, longitudinal follow-up should be guided by risk stratifiers such as ectopic burden, family history of SCD, and imaging findings. Periodic clinical and ECG assessments are advised, with CMR reserved for cases with concerning features, to support tailored surveillance and early identification of high-risk individuals [5].

The investigation of MAD can be performed using various imaging techniques, each with its advantages and limitations. Two-dimensional (2D) echocardiography is widely used as the first-line modality in the assessment of the mitral valve due to its broad availability and ability to provide both anatomical and hemodynamic information [49, 50]. It has demonstrated high accuracy and reproducibility, with strong inter- and intraobserver agreement [51]. However, it may be limited in detecting small-length MAD and in accurately assessing the full extent of the disjunction [49, 50]. Three-dimensional (3D) echocardiography enhances anatomical characterization [52]. CMR is considered a robust technique for evaluating MAD owing to its high spatial resolution that allows the detection of disjunctions as small as 1 mm, as well as its capacity to identify tissue changes such as myocardial fibrosis [49]. However, CMR is generally less accessible and more expensive compared to echocardiography, and it requires longer acquisition times. In terms of concordance between imaging modalities, the literature indicates that CMR may detect MAD more frequently than ECO, and the agreement between techniques can vary depending on the diagnostic criteria applied [49, 53]. The integration of multiple imaging modalities may be necessary for a comprehensive evaluation of MAD and symptoms suggestive of arrhythmias [49].

Our subgroup analysis, which stratified imaging modalities into echocardiography and CMR, suggests that echocardiography tends to MAD primarily when it is more extensive, whereas CMR—due to its higher spatial resolution—is capable of detecting both small lesions (from 1 mm) and larger ones [49]. Consequently, echocardiography demonstrated a stronger correlation with the occurrence of complex VAs compared to CMR. Nonetheless, in the pooled analysis, both imaging modalities showed a statistically significant association with these outcomes.

This finding is supported by current literature, which highlights the extent of MAD as a relevant factor in risk stratification for VAs. A recent study (2025) demonstrated that the presence of NSVT was more prevalent in patients with MAD measuring ≥6 mm [54], whereas a classic study (2010) identified MAD >8.5 mm as a strong predictor of NSVT [15].

Recent studies also emphasize that the location of MAD is clinically relevant, with MAD in the inferolateral region being associated with an increased risk of complex VAs [55, 18]. Evidence suggests that the presence of ventricular fibrosis—particularly in the papillary muscles and inferobasal wall—represents an underlying mechanism for electrical instability, especially in patients with coexisting MAD and MVP [56]. Therefore, MAD in the inferolateral region appears to be a critical finding and may warrant special attention in the assessment and management of these patients.

While most of the available data focuses on adults, emerging evidence suggests that children with MAD may also be at risk for VAs, as demonstrated by the presence of myocardial fibrosis and/or abnormal findings on tissue Doppler imaging [22, 57]. Prospective studies are needed to better understand the natural history of MAD in pediatric populations and its impact on the development of VAs over time.

Although some studies suggest that MAD may have a benign clinical course, evidence indicates that it can be detected in structurally normal hearts when high-resolution imaging techniques such as CMR and high-resolution computerized tomography are used [58, 59]. Additionally, some data do not indicate clinical relevance, as MAD does not appear to impact mortality [7]. However, recent studies have highlighted phenotypic differences in MAD, leading to its reclassification as either “true” or “pseudo” MAD based on its observation during the cardiac cycle—whether visible in both systole and diastole or only in systole, respectively [60, 61]. These findings support the hypothesis that the anatomical characteristics of MAD influence its clinical significance. Specifically, pseudo-MAD, particularly when exhibiting greater displacement lengths, association with myxomatous valve disease, and significant mitral regurgitation, has been linked to an increased risk of malignant VAs and sudden cardiac death [3, 51], warranting careful clinical consideration when identified.

This body of studies highlights the complex and still controversial association between MAD and complex VAs. Initially, MAD was linked to MVP as a factor that potentiates the risk of arrhythmic events [38, 62]. Subsequently, emerging evidence suggested that isolated MAD could also be arrhythmogenic [5]. With the advancement of imaging techniques, particularly CMR, MAD has been identified even in structurally normal hearts [58], enabling the anatomical differentiation between pseudo-MAD—characterized by disjunction visible only during systole—and true-MAD, in which the disjunction is present in both systole and diastole [4]. However, to date, no study has directly evaluated the association between these anatomical subtypes and outcomes of complex VAs. A single study published in December 2024, which defined MAD as a displacement of ≥1 mm visible in both systole and diastole (true-MAD) on CMR, found a higher prevalence of arrhythmias in patients with MAD compared to those without;

the study also demonstrated that MAD in combination with MVP was associated with an increased prevalence of arrhythmias and that a MAD length of ≥5 mm was an independent predictor of arrhythmia [63]. Nevertheless, the risk stratification between pseudo-MAD and true-MAD remains unresolved, underscoring the need for further investigation. The literature suggests that MAD induces abnormal systolic curling motion resulting from atypical traction on the mitral leaflet, which may promote myocardial fibrosis [45]. This process can be detected through advanced imaging techniques such as T1 mapping and extracellular volume quantification [64]. The presence of late gadolinium enhancement, a marker of myocardial fibrosis, has been associated with adverse clinical outcomes in patients with MAD [6, 64]. Thus, myocardial fibrosis appears to be the most relevant pathophysiological link between MAD and arrhythmic events, serving as a key risk marker for complex VAs and SCD.

Our study has limitations. First, the diagnosis of MAD was made using various imaging techniques, such as echocardiography and magnetic resonance imaging, which could contribute to variability in detection. Second, given the lack of standardized measurement protocols for MAD, anatomical measurements were conducted in different sections by each author, affecting consistent distance quantification from the hinge point of the mitral valve. Larger studies are needed to define whether there is a correlation between severity and distance from MAD and assess the clinical significance of fibrosis. Three, there was slight variability in the definition of complex VAs across studies. And finally, due to the absence of magnetic resonance imaging data, we were unable to determine the relationship between myocardial fibrosis in the context of MAD, which was the main driver of the increased risk of complex VAs.

Another relevant limitation of our meta-analysis is the high prevalence of MVP among patients with MAD, observed in approximately 74.5% of individuals in the MAD group and 47% in the non-MAD group. This substantial overlap may represent a confounding factor, as it limits the ability to isolate the independent effect of MAD on ventricular arrhythmic outcomes. The arrhythmogenic potential of MVP itself could contribute to the observed findings, making it difficult to determine to what extent the increased arrhythmic risk is attributable solely to MAD or to the coexistence of both conditions. However, the presence of MVP in both groups, despite differing proportions, provides a degree of balance between the cohorts, which partially mitigates this bias. Future studies may shed light on the true significance of this anatomical variation, not only by assessing the presence or absence of MAD but also by determining whether its length correlates with the presence of localized myocardial fibrosis, potentially serving as a risk factor for complex VAs.

5 | Conclusion

The results of this meta-analysis, including over 6001 patients, suggest that MAD correlates with complex VA and the composite outcome of complex VA and sudden cardiac death. Additional studies are warranted to examine therapeutic strategies to mitigate arrhythmogenic risk in this patient population.

Conflicts of Interest

The authors have nothing relevant to disclose regarding financial or non-financial interests. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting file 1: echo70211-sup-0001-SuppMat.docx