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Arrhythmic risk profile in mitral valve prolapse: A systematic review and metanalysis of 1715 patients

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Abstract

Introduction: Mitral valve prolapse (MVP) is a common clinical condition in the general population. A subgroup of patients with MVP may experience ventricular arrhythmias and sudden cardiac death ("arrhythmic mitral valve prolapse" [AMVP]) but how to stratify arrhythmic risk is still unclear. Our meta-analysis aims to identify predictive factors for arrhythmic risk in patients with MVP.

Methods: We systematically searched Medline, Cochrane, Journals@Ovid, Scopus electronic databases for studies published up to December 28, 2022 and comparing AMVP and nonarrhythmic mitral valve prolapse (NAMVP) for what concerns history, electrocardiographic, echocardiographic and cardiac magnetic resonance features. The effect size was estimated using a random-effect model as odds ratio (OR) and mean difference (MD).

Results: A total of 10 studies enrolling 1715 patients were included. Late gadolinium enhancement (LGE) (OR: 16.67; $p = .005$), T-wave inversion (TWI) (OR: 2.63; $p < .0001$), bileaflet MVP (OR: 1.92; $p < .0001$) and mitral anulus disjunction (MAD) (OR: 2.60; $p < .0001$) were more represented among patients with AMVP than in NAMVP. Patients with AMVP were shown to have longer anterior mitral leaflet (AML) (MD: 2.63 mm; $p < .0001$), posterior mitral leaflet (MD: 2.96 mm; $p < .0001$), thicker AML (MD: 0.49 mm; $p < .0001$), longer MAD length (MD: 1.24 mm; $p < .0001$) and higher amount of LGE (MD: 1.41%; $p < .0001$) than NAMVP. AMVP showed increased mechanical

Abbreviations: AML, anterior mitral leaflet; AMVP, arrhythmic mitral valve prolapse; CMR, cardiac magnetic resonance; ECG, electrocardiogram; GLS, global longitudinal strain; LGE, late gadolinium enhancement; LVEF, left ventricle ejection fraction; MAD, mitral anulus disjunction; MR, mitral regurgitation; MVP, mitral valve prolapse; NAMVP, nonarrhythmic mitral valve prolapse; OR, odds ratio; PML, posterior mitral leaflet; SCD, sudden cardiac death; TWI, T-wave inversion; VA, ventricular arrhythmias.

Disclosures: None.

dispersion (MD: 8.04 ms; 95% confidence interval: 5.13–10.96; $p < .0001$) compared with NAMVP.

Conclusions: Our meta-analysis proved that LGE, TWI, bileaflet MVP, and MAD are predictive factors for arrhythmic risk in MVP patients.

KEYWORDS

arrhythmic mitral valve prolapse, arrhythmic risk, late gadolinium enhancement, meta-analysis, mitral annulus disjunction, sudden cardiac death, ventricular arrhythmias

1 | INTRODUCTION

Devereux et al.[1] provided a definition of mitral valve prolapse (MVP) as the displacement of one or both mitral leaflets >2 mm into the atrium during systole.[2] MVP is relatively common, with a prevalence of 2%–3% in the general population, and is generally considered a benign condition.[3,4] However, the outcomes of patients with MVP are highly heterogeneous and depend on associated conditions and consequences of the prolapse itself.[4] A subgroup of MVP patients may experience ventricular arrhythmias (VA), primarily originating from the papillary muscles, and sudden cardiac death (SCD), presenting with what is known as "malignant MVP" or "arrhythmic mitral valve prolapse" (AMVP).[3,5,6] Recently, the term AMVP has been proposed to define the coexistence of MVP and VA, which can be complex (sustained or nonsustained ventricular tachycardia, ventricular fibrillation, out-of-hospital cardiac arrest) or frequent.[7]

Several studies have aimed to identify features associated with AMVP that predict a higher risk of arrhythmias.[8–11] Some of the most commonly described features in AMVP patients include late gadolinium enhancement (LGE) detected by cardiac magnetic resonance (CMR), prolapse of both mitral leaflets, female sex, mitral annular disjunction (MAD), and repolarization abnormalities on electrocardiogram (ECG) (such as biphasic/inverted T waves in inferolateral leads).[2,6,8–11] However, there have been contradictory findings reported among these studies.[8–11] One critical factor contributing to this may be the limited number of studies with large populations, which hinders the accurate identification of risk features and a deeper understanding of the pathophysiological mechanisms underlying arrhythmogenesis in these patients. Consequently, AMVP remains a poorly understood entity, and little is known about its pathophysiology and the factors that can predict arrhythmic events. Therefore, we conducted a meta-analysis to assess the role of clinical history, ECG, echocardiographic, and CMR parameters in stratifying the arrhythmic risk in MVP patients.

2 | METHODS

2.1 | Data sources and searches

We systematically searched Medline, Cochrane, Journals@Ovid, Scopus electronic databases for studies published from inception to December 28, 2022 and comparing AMVP and nonarrhythmic mitral valve prolapse (NAMVP). Two investigators (L. P. and G. V.) independently performed searches including the following terms: ventricular arrhythmias, mitral valve prolapse and sudden cardiac death. Detailed information of our literature search strategy is available in the section Expanded Methods in Supporting Infomation.

This review was registered with the PROSPERO register of systematic reviews (ID: CRD42023395984).

2.2 | Study selection and data extraction

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for reporting systematic reviews and meta-analyses was used in this study.

All studies had to fulfill the following criteria to be included in the analysis: (1) have performed a direct comparison between AMVP and NAMVP, (2) included more than 30 patients, (3) included patients over 18 years, (4) reported one or more features analyzed. Arrhythmic MVP was defined when VAs at least Lown Grade II were present. Editorials, case series, case reports, reviews, expert opinion, and non-English studies were excluded. Two investigators (L. P. and G. V.) extracted data from each study using a standardized protocol and reporting forms and independently assessed the quality items. Disagreements were resolved by consensus. The quality of individual studies was assessed using the Newcastle–Ottawa Quality Assessment Scale for cohort studies.

2.3 | Data analyzed

Aim of this metanalysis was to identify features indicative of arrhythmic risk in patients with MVP at ECG, echocardiogram, CMR, and clinical history.

Extensive explanation and definition of each feature considered is available in the section Expanded Methods in Supporting Information.

ECG items were the presence of T-wave inversion (TWI) and corrected QT interval corrected by Bazett's formula (QTc) length. Single or bileaflet MVP, leaflet length (of both anterior and posterior leaflet), anterior leaflet thickness, prolapse with flail leaflet, global

longitudinal strain (GLS), mechanical dispersion and mitral regurgitation (MR) entity were the transthoracic echocardiogram (TTE) features evaluated. Left ventricle ejection fraction (LVEF), Mitral annulus diameter and Presence of MAD and MAD length were considered if assessed either by ETT or CMR. The presence of LGE at CMR was considered together with LGE amount (%). Sex differences and atrial fibrillation (AF) history were assessed.

2.4 | Statistical analysis

Descriptive statistics are presented as means and standard deviations (SD) for continuous variables or number of cases (*n*) and percentages (%) for dichotomous and categorical variables. The Mantel-Haenszel odds ratio (OR) model and mean difference (MD) were used to summarize the data between AMVP and NAMVP. Summary estimates and 95% confidence intervals (CIs) were reported for continuous variables as standardized MD. Freeman–Tukey double arcsine transformation was used to establish the variance of raw proportions. We used the Hartung–Knapp–Sidik–Jonkman method with the random effect model to combine the transformed proportions. The heterogeneity across studies was evaluated by using the χ^2, τ^2, and Higgins-I^2 statistics; random effects models of DerSimonian were used due to clinical heterogeneity across the patients included in our study. Publication bias was assessed using the funnel plot and Egger's test. Statistical analysis was performed using Review Manager (RevMan) (Computer program) Version 5.4.1 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020.

2.5 | Ethical approval

Ethical approval was not required because this study retrieved and synthesized data from already published studies.

3 | RESULTS

3.1 | Study selection

We screened 1345 articles, of which 68 full texts were retrieved and reviewed for possible inclusion. A total of 10 studies were identified[8,9,12–19] (Figure SA).

3.2 | Baseline characteristics

A total of 10 studies were included enrolling 1715 patients (AMVP: 492 patients; NAMVP: 1223 patients), 45% (95% CI: 40.7%, 55.9%) were males with an average age of 49 years (95% CI: 47.21, 50.86).[8,9,12–19] Baseline clinical characteristics of the included studies are reported in Table 1.

3.3 | Outcome

3.3.1 | ECG

TWI

Five studies enrolling 1393 patients compared TWI prevalence between AMVP and NAMVP.[9,13–16] AMVP was associated with TWI (OR: 2.63; 95% CI: 1.90–3.64; $p < .0001$) (Figure 1A). There was no heterogeneity observed among studies ($I^2 = 0\%$).

QTc interval

Six studies enrolling 1446 patients compared QTc interval between AMVP and NAMVP.[9,13–16,18] No statistically significant difference was found in the QTc interval (MD: 4.34 ms; 95% CI: −5.94 to 14.62; $p = .41$) (Figure 1B). There was high heterogeneity among studies ($I^2 = 77\%$).

AF

Four studies enrolling 1369 patients compared prevalence of AF between AMVP and NAMVP.[13–16] There was no statistically significant differences in AF prevalence between AMVP and NAMVP (OR: 1.01; 95% CI: 0.59–2.01; $p = .98$) (Figure 1C). There was moderate heterogeneity observed among studies ($I^2 = 47\%$).

3.3.2 | Mitral valve apparatus

MR

Five studies enrolling 1349 patients compared the history of AF between AMVP and NAMVP.[9,14–16,19] There was no statistically significant difference between AMVP and NAMVP in MR degree: Mild MR (OR: 0.98; 95% CI: 0.28–3.37; $p = .97$) and moderate-to-severe MR (OR: 1.24; 95% CI: 0.40–3.84; $p = .71$) (Figure 2A). There was high heterogeneity observed among studies ($I^2 = 85\%$; $I^2 = 81\%$). There was no statistically significant difference between the two groups ($p = .78$).

Bileaflet prolapse

Five studies enrolling 1393 patients compared prevalence of bileaflet prolapse between AMVP and NAMVP.[9,13–16] AMVP was associated with a higher prevalence of bileaflet prolapse (OR: 1.92; 95% CI: 1.48–2.5; $p < .0001$) (Figure 2B). There was no heterogeneity observed among studies ($I^2 = 0\%$).

Anterior mitral leaflet (AML) length

Three studies enrolling 699 patients compared AML length between AMVP and NAMVP.[9,12,14] AMVP had longer AML in comparison with NAMVP (MD: 2.63 mm; 95% CI: 1.99–3.27; $p < .0001$) (Figure 2C). There was no heterogeneity observed among studies ($I^2 = 0\%$).

Posterior mitral leaflet (PML) length

Three studies enrolling 699 patients compared PML length between AMVP and NAMVP.[9,12,14] AMVP had longer PML in comparison with NAMVP (MD: 2.96 mm; 95% CI: 2.38–3.54; $p < .0001$) (Figure 2D). There was no heterogeneity observed among studies ($I^2 = 0\%$).

TABLE 1 Study baseline characteristics of patients included in the analysis.

Author	Journal (year)	Country	Study design	Patients enrolled	AMVP definition	Arrhythmic risk class	No. of patients	Age years	Male sex (*n*, %)	LVEF (%)
Bui et al.[8]	Heart (2017)	USA	Retrospective monocentric	32	Polymorphic PVCs, couplets, NSVT, VT, VF	AMVP	14	55 ± 13	10 (71)	63 (8)
						NAMVP	18	51 ± 10	11 (61)	61 (6)
Basso et al.[9]	Circulation (2015)	Italy	Retrospective monocentric	44	Complex VA (NSVT[a], VT, VF)	AMVP	30	41 (28–43)	8 (27)	64 (60–65)
						NAMVP	14	51 (24–64)	7 (50)	66 (64–69)
Ackay et al.[12]	Pace (2010)	Turkey	Retrospective monocentric	60	VT	AMVP	30	41.5 ± 15	9 (30)	65.6 ± 2.7
						NAMVP	30	43 ± 16	8 (27)	66.1 ± 4
Ermakov et al.[13]	Heart (2019)	USA	Retrospective monocentric	59	Complex ventricular ectopy[b], NSVT, VF, VF	AMVP	32	57 ± 13	15 (47)	63 ± 8
						NAMVP	27	53 ± 18	14 (52)	62 ± 5
Essayagh et al.[14]	JACC (2020)	USA	Retrospective monocentric	595	Arrhythmic burden >5%, NSVT, VT	AMVP	257	68 ± 15	157 (61)	62 ± 8
						NAMVP	338	63 ± 17	160 (47)	63 ± 6
van Wijngaarden et al.[15]	Heart (2020)	The Netherlands	Retrospective monocentric	610	Frequent PVC, NSVT, VT, VF	AMVP	67	62 (51–71)	35 (52)	65 ± 6
						NAMVP	543	66 (58–74)	356 (66)	66 ± 6
Lee et al.[16]	BMC Cardiovasc. Dis. (2021)	Korea	Retrospective multicenter	85	TVNS, VT, aborted arrhythmic SCD	AMVP	7	41 (33–49)	6 (85.7)	51 (49–67)
						NAMVP	78	55 (42–65)	40 (51.3)	60 (52–68)
Babuty et al.[17]	Pace (1994)	France	Retrospective monocentric	58	Polymorphic PVCs, couplets, NSVT, VT, VF	AMVP	10	52.5 ± 16.3	6 (60)	NR
						NAMVP	48	45.3 ± 18.1	23 (48)	NR
Sniezek-Maciejewska et al.[18]	Clin. Card. (1992)	Poland	Retrospective monocentric	53	Polymorphic PVCs, couplets, NSVT, VT, VF	AMVP	9	36 ± 5.40	NR	NR
						NAMVP	44	32 ± 8.53	NR	NR
Zuppiroli et al.[19]	Am. Heart J. (1994)	Italy	Retrospective monocentric	119	Polymorphic PVCs, couplets, NSVT, VT, VF	AMVP	36	47.1 ± 15.8	13 (36)	NR
						NAMVP	83	36.5 ± 17.2	42 (50)	NR

Abbreviations: AMVP, arrhythmic mitral valve prolapse; LVEF, left ventricle ejection fraction; NAMVP, nonarrhythmic mitral valve prolapse; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular complex; SCD, sudden cardiac death; VA, ventricular arrhythmias; VF, ventricular fibrillation; VT, ventricular tachycardia.

[a]>3 Consecutive ventricular beats.

[b]Ventricular bigeminy and couplets.

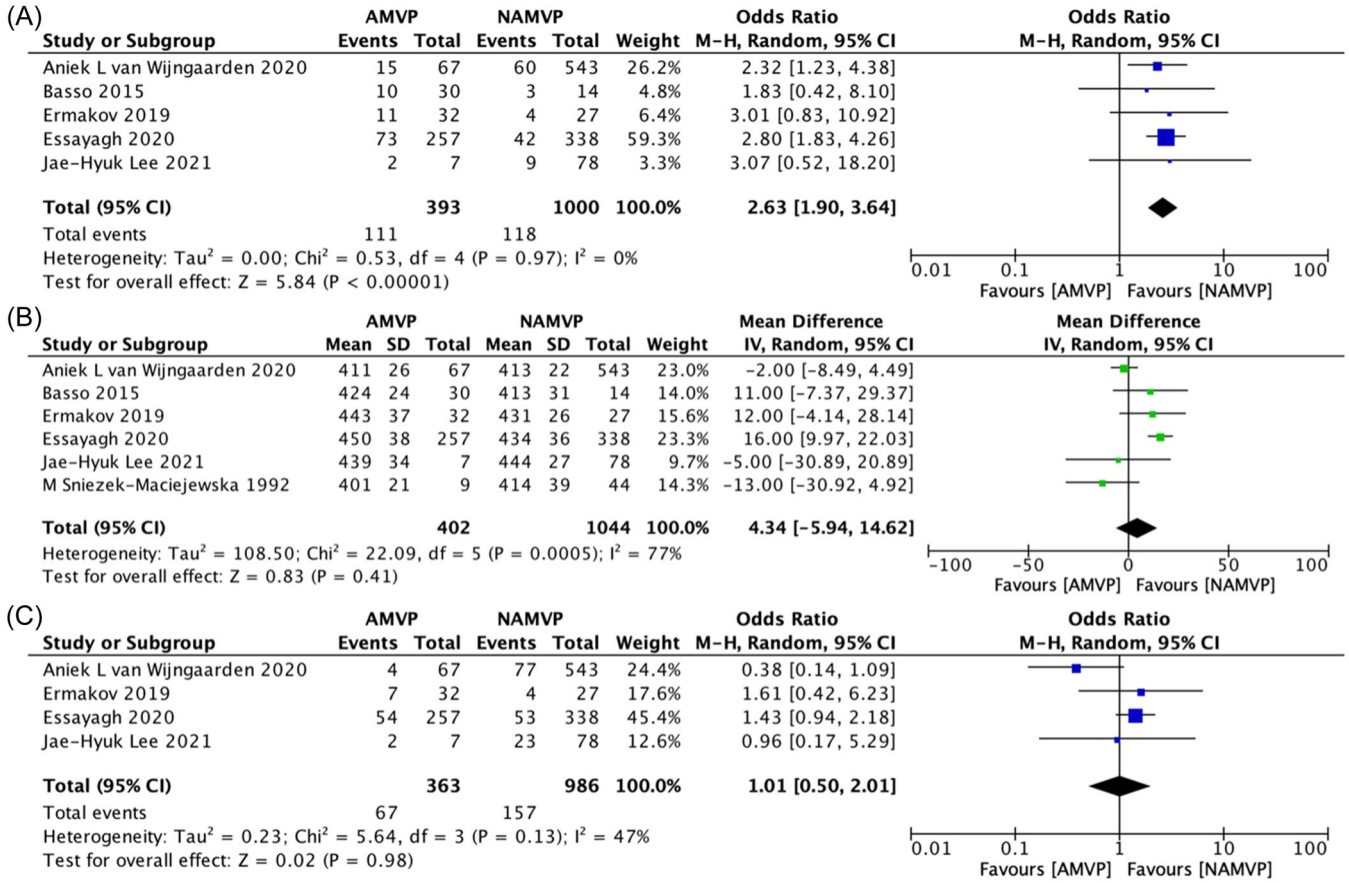


FIGURE 1 Forest plots comparing: ECG features between AMVP and NAMVP: (A) TWI, (B) QTc, (C) AF. AF, atrial fibrillation; AMVP, arrhythmic mitral valve prolapse; CI, confidence interval; NAMVP, nonarrhythmic mitral valve prolapse; QTc, QT interval corrected by Bazett's formula; TWI, T-wave inversion.

AML thickness

Four studies enrolling 833 patients compared AML thickness between AMVP and NAMVP.[12–14,19] AMVP had thicker AML in comparison with NAMVP (MD: 0.49 mm; 95% CI: 0.32–0.65; $p < .0001$) (Figure 2E). There was no heterogeneity observed among studies ($I^2 = 0\%$).

Flail-leaflet prolapse

Three studies enrolling 1290 patients compared prevalence of flail prolapse between AMVP and NAMVP.[14–16] AMVP was associated with a higher prevalence of flail-leaflet prolapse (OR: 1.62; 95% CI: 0.80–3.28; $p = .18$) (Figure 3A). There was moderate heterogeneity observed among studies ($I^2 = 61\%$).

Annulus diameter

Two studies enrolling 97 patients compared annulus diameter between AMVP and NAMVP.[12,15] No differences were found between the two groups (MD: 2.5 mm; 95% CI: −0.34 to 5.34; $p < .08$) (Figure 3B). There was high heterogeneity observed among studies ($I^2 = 93\%$).

Mitral anulus disjunction

Four studies enrolling 1349 patients compared the prevalence of MAD between AMVP and NAMVP.[13–16] Three studies assessed MAD by echocardiography while the study by Lee et al.[16] assessed MAD by CMR. AMVP was associated with a higher prevalence of MAD (OR: 2.6; 95% CI: 1.92–3.52; $p < .0001$) (Figure 3C). There was very low heterogeneity observed among studies ($I^2 = 5\%$).

Mitral anulus disjunction length

Two studies enrolling 1205 patients compared posterior MAD length assessed by echocardiography between AMVP and NAMVP.[14,15] AMVP had longer MAD compared to NAMVP (MD: 1.24 mm; 95% CI: 0.86–1.63; $p < .0001$) (Figure 3D). There was low heterogeneity observed between studies ($I^2 = 13\%$).

3.3.3 | Left ventricle assessment

LVEF (%)

Seven studies enrolling 1485 patients compared LVEF between AMVP and NAMVP.[8,9,12–16] There was no statistically significant difference between AMVP and NAMVP in LVEF, (MD: −0.11; 95% CI: −2.15 to 1.94); $p = .92$) (Figure 4A). There was high heterogeneity observed between studies ($I^2 = 80\%$).

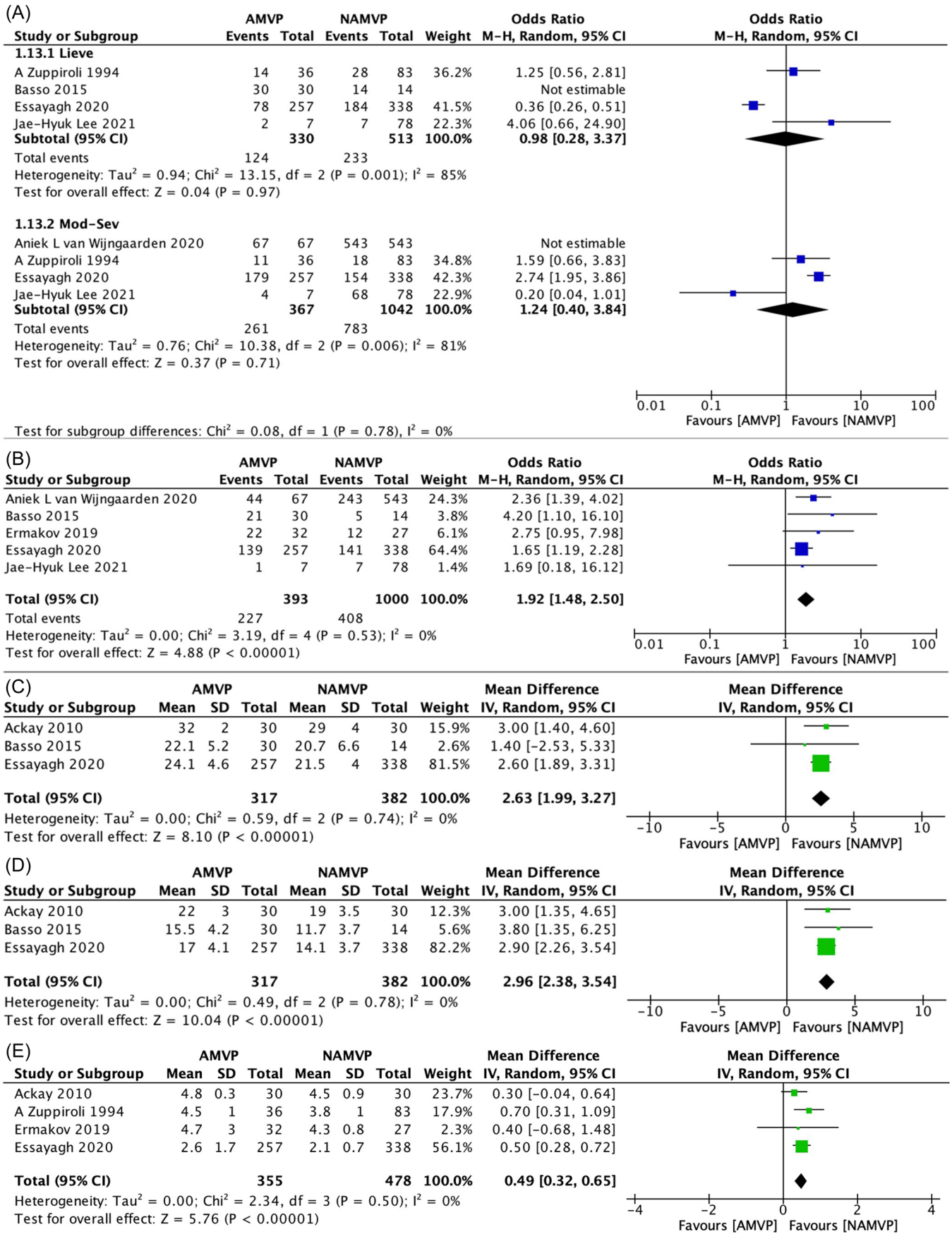


FIGURE 2 Forest plots comparing: mitral valve apparatus features between AMVP and NAMVP: (A) MR, (B) bileaflet prolapse, (C) AML length, (D) PML length, (E) AML thickness. AML, anterior mitral leaflet; AMVP, arrhythmic mitral valve prolapse; CI, confidence interval; MR, mitral regurgitation; NAMVP, nonarrhythmic mitral valve prolapse; PML, posterior mitral leaflet.

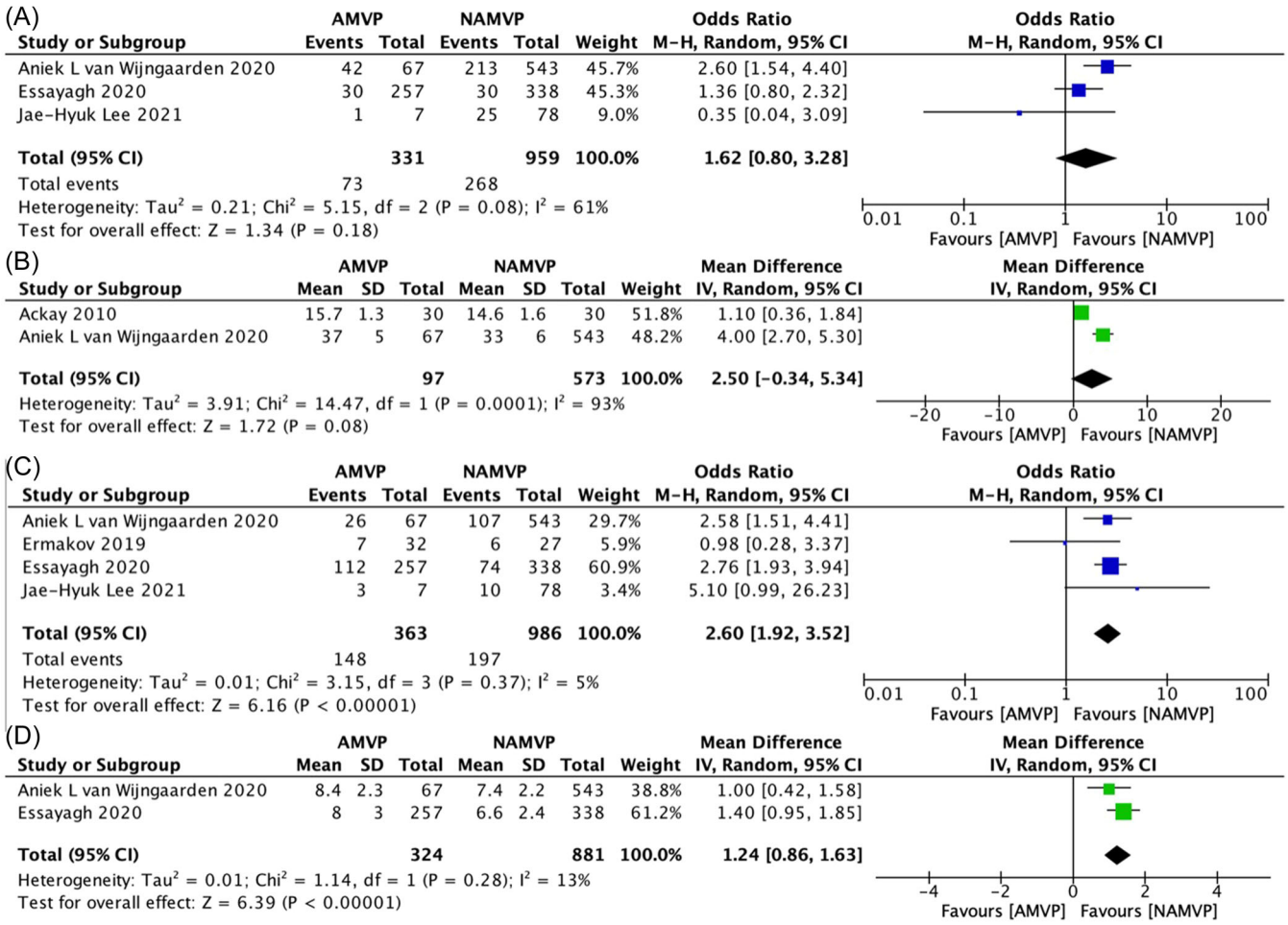


FIGURE 3 Forest plots comparing: mitral valve apparatus features between AMVP and NAMVP: (A) prolapse with flail leaflet, (B) mitral annulus diameter, (C) MAD, and (D) MAD length. AMVP, arrhythmic mitral valve prolapse; CI, confidence interval; MAD, mitral annulus disjunction; NAMVP, nonarrhythmic mitral valve prolapse.

Global longitudinal strain

Two studies enrolling 669 patients compared Left Ventricle systolic Longitudinal deformation assessed by GLS at TTE between AMVP and NAMVP.[13,15] AMVP had reduced GLS compared to NAMVP (MD: 4.19%; 95% CI: −1.98 to 10.36; $p < .18$) (Figure 4B). There was high heterogeneity observed between studies ($I^2 = 97\%$).

Mechanical dispersion

Two studies enrolling 669 patients compared mechanical dispersion by TTE between AMVP and NAMVP.[13,15] AMVP had a higher mechanical dispersion compared to NAMVP (MD: 10.58 ms; 95% CI: 1.94–19.21; $p < .02$) (Figure 4C). There was high heterogeneity observed between studies ($I^2 = 73\%$).

LGE

Three studies enrolling 161 patients compared prevalence of LGE between AMVP and NAMVP.[8,9,16] LGE was most frequently localized on the papillary muscles (63.1%; 95% CI: 18.5–100) and on the basal segment of the inferior wall (50.9%; 95% CI: 3.7–98.2). AMVP was associated with a higher prevalence of LGE (OR: 16.67; 95% CI: 2.30–120.65; $p = .005$) (Figure 4D). There was moderate heterogeneity observed between studies ($I^2 = 71\%$).

LGE (%)

Two studies enrolling 129 patients compared prevalence of LGE between AMVP and NAMVP.[9,16] AMVP had a higher LGE amount (%) compared to NAMVP (MD: 1.41%; 95% CI: 1.05–1.76; $p < .0001$) (Figure 4E). There was no heterogeneity observed between studies ($I^2 = 0\%$).

3.3.4 | Clinical features

Female sex

Ten studies enrolling 1715 patients compared the prevalence of female sex between AMVP and NAMVP.[8,9,12–19] No statistically significant differences between the two groups were observed for what concerns female sex (OR: 1.05; 95% CI: 0.63–1.73, $p = .85$) (Figure 5). There was moderate heterogeneity observed among studies ($I^2 = 66\%$).

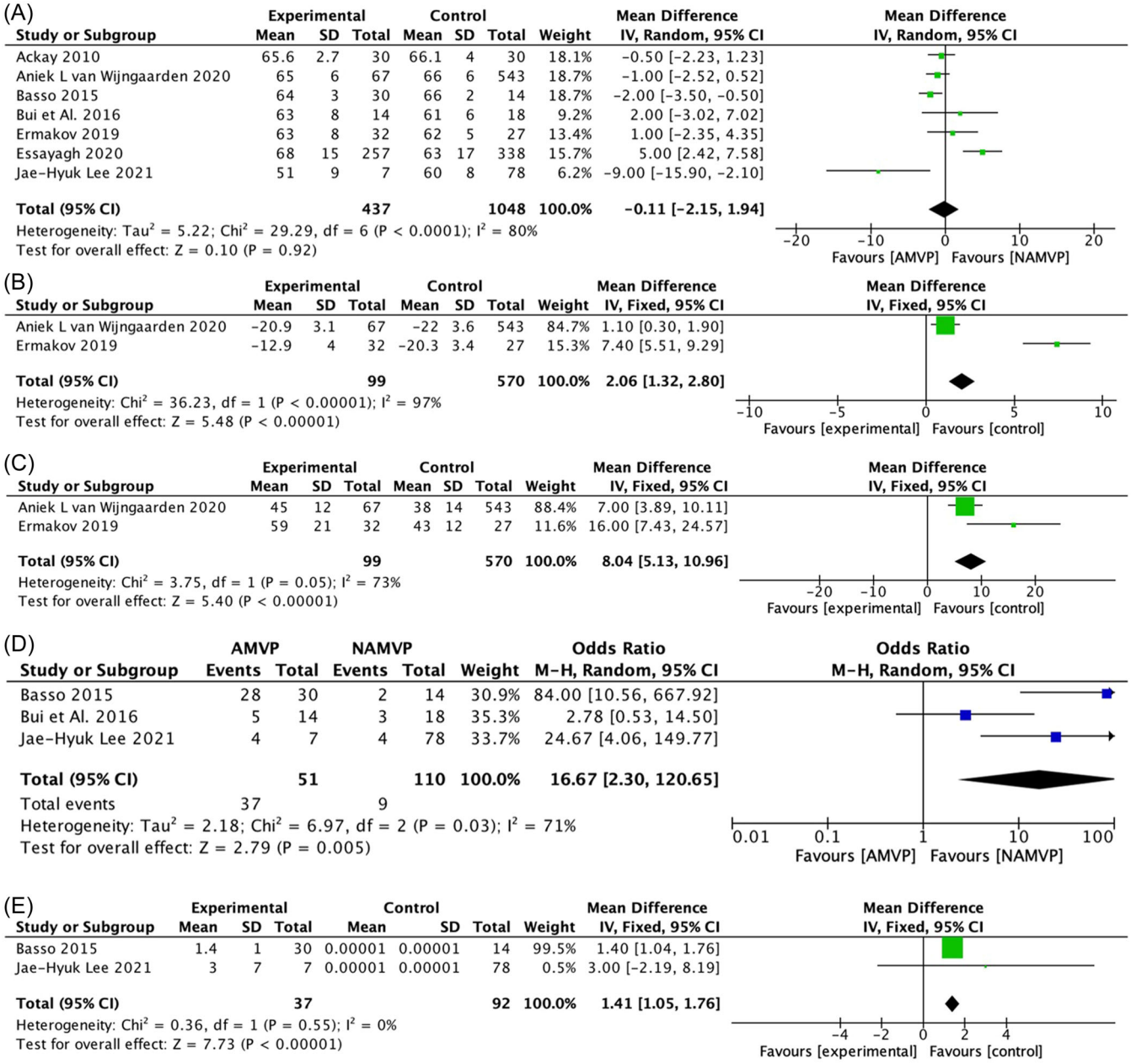


FIGURE 4 Forest plots comparing: left ventricle assessment features between AMVP and NAMVP: (A) LVEF, (B) GLS, (C) mechanical dispersion, (D) presence of LGE and (E) LGE % amount. AMVP, arrhythmic mitral valve prolapse; CI, confidence interval; GLS, global longitudinal strain; LGE, Late gadolinium enhancement; LVEF, left ventricle ejection fraction; NAMVP, nonarrhythmic mitral valve prolapse.

3.4 | Publication bias

A graph and summary of the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies for each individual study is reported in Figure SB. The funnel plot for visual inspection of the bias showed no bias (Figure SC), which was confirmed by Egger's test ($p = .53$).

4 | DISCUSSION

Previous studies have assessed risk factors for arrhythmias in MVP. However, to the best of our knowledge, our study is the first to weigh each risk factor for arrhythmogenicity in MVP. According to our results, not all features indicative of arrhythmogenicity are equally significant in defining the risk of developing VA. Therefore, each factor should be carefully considered to ensure a balanced assessment of arrhythmic risk and guide the selection of appropriate therapeutic strategies.

We demonstrated that the presence of LGE by CMR, TWI, MAD, and bileaflet prolapse are associated with an increased likelihood of developing VA in MVP patients. In particular, the presence of LGE increases the likelihood of VA by more than 16 times (OR: 16.67).[20–23] LGE is suggestive of fibrosis, which may result from myocardial stretch due to prolapsing leaflets and abnormal extracellular matrix deposition. Previous studies by Miller et al.[24] using hybrid imaging with CMR and positron emission tomography have shown that fibrosis in AMVP is preceded by inflammation. Based on this, it could be hypothesized that

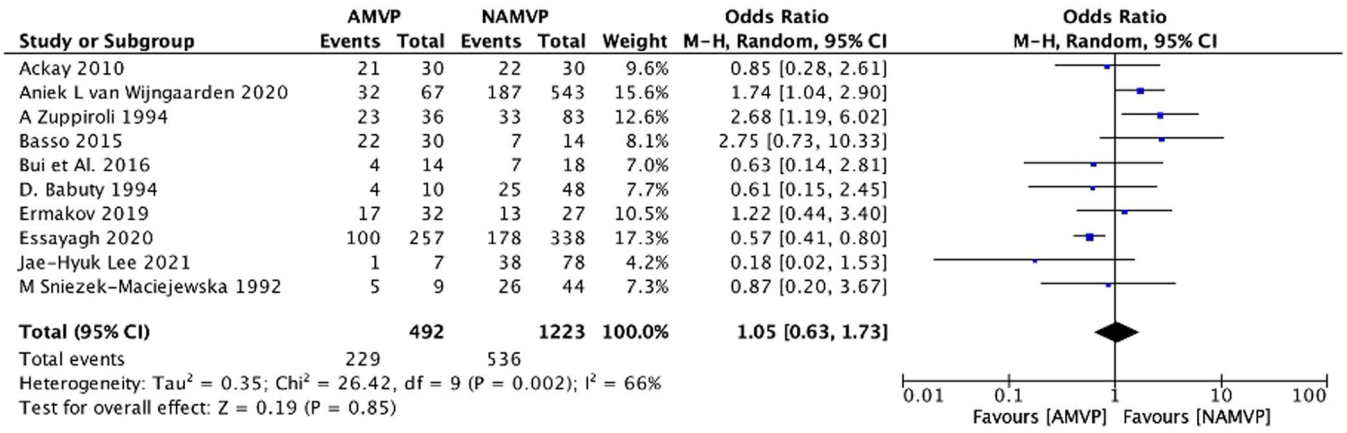
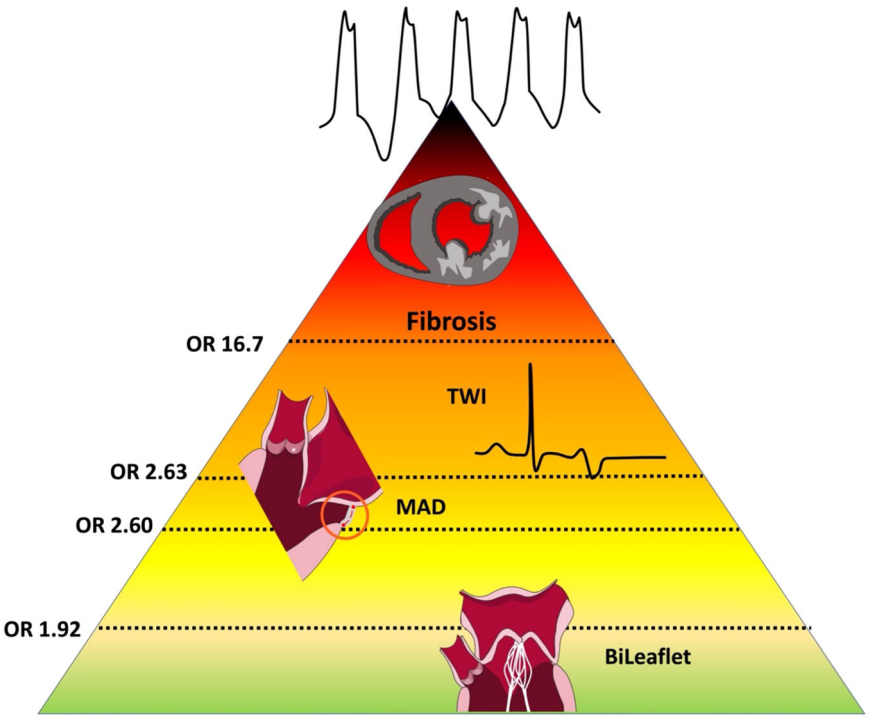


FIGURE 5 Forest plots comparing: female sex distribution between AMVP and NAMVP: AMVP, arrhythmic mitral valve prolapse; CI, confidence interval; NAMVP, nonarrhythmic mitral valve prolapse.

chronic stretch stress on papillary muscles leads to inflammation, fibroblast proliferation, and subsequent fibrosis deposition, contributing to the development of a proarrhythmic substrate. This mechanism may also explain our finding of increased mechanical dispersion in AMVP patients compared to NAMVP patients, which is consistent with the results reported by Vairo et al.[25]

A recent study by Scheirlynck et al.[20] provided evidence of the relationship between myocardial stretch and VA in AMVP patients. They demonstrated that MVP patients with arrhythmias have higher levels of soluble suppression of tumorigenicity 2, a marker released from stretched myocardium, compared to MVP patients without arrhythmias.[20] TWI in inferior and lateral leads may be an electrical manifestation of myocardial distress secondary to stretch stress, rather than the expression of a structural abnormality. This hypothesis is supported by findings from Alqarawi et al.,[26] who reported the normalization of TWI after mitral valve repair. Chivulescu et al.[27] also found an increased risk of complex VA in MVP patients with a more extensive TWI, showing the correlation between TWI, the percentage of extracellular volume by T1 mapping at CMR, and VAs.[28] Consistent with these findings, our results indicate that LGE and TWI are the most indicative features of an increased arrhythmic risk (OR: 16.67 and 2.63, respectively) (**Central Figure**).



CENTRAL FIGURE Arrhythmic risk stratification in mitral valve prolapse patients. Color map: Green: low OR of ventricular arrhythmias; light yellow to orange: medium OR of ventricular arrhythmias; red: high OR of ventricular arrhythmias. The figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

Although with slightly lower risks, other factors associated with arrhythmic risk in MVP include MAD, bileaflet prolapse, a higher amount of LGE, longer mitral leaflets, thicker AML, and longer MAD. Importantly, all these factors are also indicative of phenotype severity in Barlow disease.[28] These findings suggest a relationship between the severity of "myxomatous" degeneration (including leaflet degeneration, MAD, and fibrosis) and arrhythmogenesis in AMVP, as previously proposed in other studies.[29] Moreover, Chivulescu et al.[27] associated MAD length with VA, while levels of circulating transforming growth factor-beta (TGF-β) were found to correlate with circumferential MAD and fibrosis in another study.[20] It is well known how TGF-β promotes myxomatous degeneration of the mitral valve through its interaction with Filamins.[22,23] This aspect becomes more relevant in light of the recently emerged association between AMVP and mutated filamin C (FNLC), a cardiac-expressing filamin that is mutated in cases of arrhythmogenic dilated cardiomyopathy phenotype, suggesting a possible underlying mutated genotype in these patients.[30,31]

Furthermore, the traction exerted on papillary muscles by longer and thicker leaflets could be stronger and more likely to trigger ventricular extrasystoles, especially in the presence of a favorable substrate created by inflammation and fibrosis.[24]

On the other hand, left ventricular ejection fraction, corrected QT interval, female sex, history of AF, mitral annulus diameter, and MR severity did not differ significantly between AMVP and NAMVP patients. The high heterogeneity observed in QTc measurements may have affected the results, as there are conflicting findings in the literature regarding the role of QTc length as a stratification factor for arrhythmic risk in MVP patients.[7] Interestingly, female sex, previously believed to be a risk factor for AMVP, was equally distributed between AMVP and NAMVP groups.[22] The retrospective analysis of MVP patients who experienced SCD by Han et al.[32] and Delling et al.[33] also support our findings, as they showed no higher arrhythmic risk associated with female sex. Changes in mitral annulus diameter, significant MR, AF, and reduced LVEF usually manifest at a later age when the arrhythmic pattern is already established or as a consequence of other comorbidities and diseases. Rather than being markers of arrhythmogenicity, these factors should be considered as results of the progressive degeneration of the mitral valve apparatus due to MVP itself and subsequent left atrial dilation.

In conclusion, our study identifies five features associated with AMVP: LGE by CMR, TWI, MAD, and bileaflet prolapse. Each of these features should be weighed according to its relative risk to make a balanced assessment of arrhythmic risk in these patients **(Central Figure)**. Considering these findings, our study represents a first step towards a multiparametric quantitative risk assessment that can guide risk-targeted follow-up strategies and arrhythmia prevention therapies without overtreatment of lower-risk individuals.

5 | CONCLUSION

Our meta-analysis demonstrated that the presence of LGE by CMR, TWI, MAD, and bileaflet prolapse, along with longer mitral leaflets, thicker AML, and longer MAD, are associated with VAs in MVP.

However, it was observed that these features do not equally represent the risk of arrhythmias. Therefore, each of these factors should be carefully considered to ensure a balanced evaluation of the patient and, consequently, the selection of appropriate follow-up strategy and therapy.

5.1 | Limitations

This study has certain limitations. First, being a meta-analysis, it relies on available data from the literature, which limits the investigation of certain interesting features (such as the PickelHaube sign or extracellular volume by T1 mapping) that have been described in the literature but in different contexts unrelated to the comparison between AMVP and NAMVP patients. Furthermore, our meta-analysis is limited by the observational nature of the studies. Finally, some large cohort studies reporting on the risk of arrhythmia based on certain predictors were not included since they did not report specifically as a comparison between arrhythmic and nonarrhythmic patients.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Pubmed at https://pubmed.ncbi.nlm.nih.gov.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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