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ORIGINAL ARTICLE

Type of syncope and outcome in Brugada syndrome: A systematic review and meta-analysis

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Abstract

Introduction: Brugada syndrome is an inherited arrhythmic disease associated with major arrhythmic events (MAE). The importance of primary prevention of sudden cardiac death (SCD) in Brugada syndrome is well recognized; however, ventricular arrhythmia risk stratification remains challenging and controversial. We aimed to assess the association of type of syncope with MAE via systematic review and meta-analysis.

Methods: We comprehensively searched the databases of MEDLINE and EMBASE from inception to December 2021. Included studies were cohort (prospective or retrospective) studies that reported the types of syncope (cardiac, unexplained, vasovagal, and undifferentiated) and MAE. Data from each study were combined using the random-effects, generic inverse variance method of DerSimonian and Laird to calculate the odds ratio (OR) and 95% confidence intervals (CIs).

Results: Seventeen studies from 2005 to 2019 were included in this meta-analysis involving 4355 Brugada syndrome patients. Overall, syncope was significantly associated with an increased risk of MAE in Brugada syndrome (OR = 3.90, 95% CI: 2.22–6.85, $p < .001$, $I^2 = 76.0\%$). By syncope type, cardiac (OR = 4.48, 95% CI: 2.87–7.01, $p < .001$, $I^2 = 0.0\%$) and unexplained (OR = 4.71, 95% CI: 1.34–16.57, $p = .016$, $I^2 = 37.3\%$) syncope was significantly associated with increased risk of MAE in Brugada syndrome. Vasovagal (OR = 2.90, 95% CI: 0.09–98.45, $p = .554$, $I^2 = 70.9\%$) and undifferentiated syncope (OR = 2.01, 95% CI: 1.00–4.03, $p = .050$, $I^2 = 64.6\%$, respectively) were not.

Conclusion: Our study demonstrated that cardiac and unexplained syncope was associated with MAE risk in Brugada syndrome populations but not in vasovagal syncope and undifferentiated syncope. Unexplained syncope is associated with a similar increased risk of MAE compared to cardiac syncope.

KEYWORDS
Brugada syndrome, syncope

1 | INTRODUCTION

Brugada syndrome is characterized by a unique ECG pattern of a coved ST-segment elevation in leads V1–V3 and, by definition, excludes ischemia, electrical conduction disturbances/dysrhythmias, and structural heart diseases.[1] Given its pathophysiology, this condition results in syncope and cardiac arrest from polymorphic ventricular tachycardia (VT) with degeneration to ventricular fibrillation (VF).[2] Nevertheless, it remains unclear which subset of patients with the Brugada pattern will develop these major arrhythmic events (MAE)—especially those without prior documented arrhythmic episodes. While previous studies have identified risk factors associated with MAE in this population,[3,4] optimal risk stratification to determine which patients would most benefit from primary prevention is not well validated.

Given the association between syncope and increased risk of sudden cardiac death (SCD) in patients with Brugada syndrome, it remains unclear whether different types of syncope portend different risks of MAE and SCD. There is conflicting data from the previous publications.[5] Hence, we performed this systematic review and meta-analysis to define the association between types of syncope (cardiac, unexplained, vasovagal, and undifferentiated) among patients with Brugada syndrome and the risk of MAE.

2 | METHODS

2.1 | Search strategy

Two investigators (JK and CK) independently searched for published studies indexed in MEDLINE and EMBASE databases from inception to November 2021 using a search strategy described in online supplementary document 1 that included the terms "Brugada" and "syncope." Only English language publications were included. A manual search for additional pertinent studies and review articles using references from retrieved articles was also completed.

2.2 | Inclusion criteria

The eligibility criteria included the following:

1. Observational study (prospective or retrospective cohort or case–control) reporting incidents of MAE, including VF, sustained VT, appropriate shocks, sudden cardiac arrest, or SCD, in Brugada syndrome patients with syncope
2. Relative risk (RR), hazard ratio (HR), odds ratio (OR), incidence ratio, or standardized incidence ratio with 95% confidence intervals or sufficient raw data for the calculation were provided.
3. Brugada syndrome participants without syncope were used as controls.

Study eligibility was independently determined by two investigators (NP and CK), and differences were resolved by mutual consensus. In case of overlap or duplication between populations among studies, the study with the largest sample size and clear definition of syncope from each representative population was selected, whereas the rest of the overlap or duplicated populations were excluded. If the identity of the declared participating institutions was unclear, the corresponding author of each study was contacted. Newcastle-Ottawa quality assessment scale (Table S1) was used to evaluate each study in three domains: recruitment and selection of the participants, similarity, and comparability between the groups, and ascertainment of the outcome of interest among studies.[6]

2.3 | Data extraction

Meta-analysis Of Observational Studies in Epidemiology (MOOSE) has been utilized (Table S2). A standardized data collection form was used to obtain the following information from each study: title of study, name of the first author, year of study, year of publication, country of origin, number of participants, demographic data of participants, the method used to identify cases and controls, the method used to diagnose outcomes of interest (MAE), syncope definition, the average duration of follow-up, confounders that were adjusted, adjusted effect estimates with 95% CI, and covariates that were adjusted for the multivariable analysis.

To ensure accuracy, all investigators independently performed this data extraction process. Any data discrepancy was resolved by referring back to the original articles.

2.4 | Definition of syncope type

In this study, we were interested in the correlation between each syncope type in Brugada syndrome patients and MAE. We classified the history of syncope used in the meta-analysis into four groups: cardiac syncope, unexplained syncope, vasovagal syncope, and undifferentiated definition syncope. The information that led to the classification of the four types of syncope from each study is provided in Table 1.

2.5 | Cardiac syncope

Cardiac syncope is defined as a transient loss of consciousness due to suspected cardiac arrhythmias (either tachyarrhythmias or bradyarrhythmias) or structural cardiac abnormalities obstructing blood flow.[7] The studies classified as cardiac syncope must define "cardiac syncope" or syncope with suspected arrhythmic origin.

2.6 | Unexplained syncope

Unexplained syncope, also known as syncope of unknown origin, is described when a cause of syncope cannot be determined despite

TABLE 1 Summary characteristics of individual included studies of patients with a Brugada syndrome.

Study/year	Study design	*N*	Country	Men (%)	Age (years)	Brugada ECG type	Symptomatic BrS (%)	Follow-up (months)	Outcomes
Deliniere et al., 2019	Retrospective cohort	115	France, Romania, Switzerland	91.3	45.1 ± 12.8	I	39.1	N/A	VF or SCD
Garcia-Iglesias et al., 2019	Prospective cohort	337	Spain	70.33	41 ± 14.4	I, II, III	32.6	55.8 ± 39.35	VT/VF or SCD or an appropriate ICD shock
Gray et al., 2017	Prospective cohort	54	Australia	81.4	44 ± 13	I	33.3	27.6 ± 30	Clinical (syncope, aborted sudden death) and/or sustained VT/VF
Kharazi et al., 2006	Case–control study	12	India	91.7	46.5 ± 11.8	I	83.3	27.8 ± 11.3	VF or SCD
Kyun Son et al., 2014	Retrospective cohort	69	South Korea	98.6	46.2 ± 13.5	I, II, III	79.7	59.0 ± 46.0	Appropriate ICD shock for VT or VF
Leong et al., 2018	Retrospective cohort	133	United Kingdom	68.4	44.5 ± 14.8	I	53	42.0 ± 26.0	VT/VF or SCD or an appropriate ICD shock
Letsas et al., 2019	Prospective cohort	111	Greece	77.5	45.3 ± 13.3	I, II, III	33.3	55.2 ± 42.0	VT/VF or SCD or an appropriate ICD shock
Makarawate et al., 2014	Prospective cohort	90	Thailand	97.8	46 ± 5.6	I	87.8	N/A	Appropriate ICD shock
Migliore et al., 2019	Prospective cohort	272	Italy	82	43 ± 12	I	30	85.0 ± 55.0	VT/VF or SCD or an appropriate ICD shock
Olde Nordkamp et al., 2014	Retrospective cohort	342	Netherlands	59.9	44 ± 14	I, II, III	41.2	57.5 ± 17.3	Aborted cardiac arrest
Priori et al., 2012	Prospective cohort	308	Italy	80.2	47 ± 12	I	N/A	36.0 ± 8.0	Appropriate ICD shock, SCD, VF
Probst et al., 2010	Prospective cohort	1029	France, Germany, Italy, Netherlands	72.4	45 ± 5.8	I, II, III	36.4	33.1 ± 11.7	VT/VF or SCD or an appropriate ICD shock
Rivard et al., 2016	Retrospective cohort	105	Canada	79.0	46.2 ± 13.3	I	44.8	59.6 ± 16.4	Appropriate ICD shock, SCD
Sieira et al., 2017	Prospective cohort	400	Belgium	58.3	41.1 ± 17.8	I, II	32.8	80.7 ± 57.2	Appropriate ICD shock, SCD
Subramanian et al., 2019	Retrospective cohort	103	India	86.4	44.5 ± 12.7	I	11.7	72.1 ± 29.2	VT/VF or SCD or an appropriate ICD shock
Takagi et al., 2013	Prospective cohort	460	Japan	93.9	52 ± 14	I	421.9	50.0 ± 32.0	SCD, VF
Yamagata et al., 2017	Prospective cohort	415	Japan	97.1	46 ± 14	I	45.1	98.5 ± 71.6	Appropriae ICD shock, ACA, SCD

Abbreviations: CI, confidence interval; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; MAE, major arrhythmic events; N/A, not applicable; OR, odds ratio; SCA, sudden cardiac death; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

adequate evaluation.[7] The studies classified as unexplained syncope must define "unexplained syncope" or syncope when no cause was found.

2.7 | Vasovagal or non-cardiac syncope

Vasovagal syncope is a reflex syncope that frequently occurs in the upright position with a prodrome (e.g. diaphoresis, nausea, pallor) followed by fatigue.[7] The studies classified as vasovagal syncope must define syncope as noncardiac, "vasovagal," "neurally mediated," or "reflex" syncope in the studies.

2.8 | Undifferentiated syncope

Studies provided limited or no data on the characteristics to explain the potential causes of syncope (no definition of syncope was provided in the included studies). Patients from these studies were included in the undifferentiated syncope group for analysis.

2.9 | Statistical analysis

We performed a meta-analysis of the included studies using a random-effects model. Studies were excluded if they did not present an outcome in each intervention group or did not have enough information required for continuous data comparison. We pooled the point estimates of OR and RR from each study using the generic inverse-variance method of Der Simonian and Laird.[8] The heterogeneity of effect size estimates across these studies was quantified using the I^2 statistic. The I^2 statistic ranges in value from 0 to 100% ($I^2 < 25\%$, low heterogeneity; $I^2 = 25\%–50\%$, moderate heterogeneity; and $I^2 > 50\%$, substantial heterogeneity).[9] A sensitivity analysis was performed to assess the influence of the individual studies on the overall results by omitting one study at a time. Publication bias was assessed using a funnel plot and Egger's regression test[10] ($p < .05$ was considered significant) if at least 10 studies were included. All data analyses were performed using Stata SE Statistical Software: Release 14.1, College Station, TX: StataCorp LP, StataCorp 2015.

2.10 | Sensitivity analysis

We used a sequential exclusion strategy, as described by Patsopoulos and colleagues, to examine whether overall estimates were influenced by the substantial heterogeneity observed.[11] In accordance with Cochrane, evidence of publication bias was examined through funnel plots if there were more than ten available studies. Funnel plot asymmetry was further confirmed with Egger's test.

3 | RESULTS

3.1 | Description of included studies

Our search strategy yielded 1968 potentially relevant articles (1381 articles from EMBASE and 846 articles from MEDLINE). After excluding duplicate articles, 1587 articles underwent title and abstract review. Following the review, 1474 articles were excluded as they were not cohort, case–control, randomized controlled trials were not conducted in BrS patients, or the titles and abstracts were irrelevant. One hundred and twenty-five articles remained for a full-length review. An additional 113 studies were excluded as they did not report data regarding syncope.

Additionally, they did not provide sufficient data to calculate HR, risk ratio, or OR. Forty-four studies were excluded because of a duplicated population. Therefore, a total of 17 studies were included in this meta-analysis. Figure 1 outlines the search and literature review process.

Seventeen studies from 2006 to 2019 were included, with 4355 patients. There were six retrospective cohorts, ten prospective cohorts, and one case–control study from 16 countries. 3390 (77.8%) patients were male, 3340 (76.8%) patients were symptomatic (syncope, documented major arrhythmic event, or previous sudden cardiac arrest) at presentation, mean age of 45.1 ± 12.8 years, and follow-up time was 58.1 ± 45.3 months. Summaries of the included studies and the clinical characteristics are shown in Table 2. The clinical characteristics of syncope and the four types of syncope for the meta-analysis are shown in Table 1.

3.2 | Meta-analysis results

In the overall analysis, a history of syncope was significantly associated with an increased risk of MAE in patients with Brugada syndrome (pooled OR, 3.90; 95% CI, 2.22–6.85; $p < .001$, $I^2 = 76.0\%$). Results from each study were mixed, with ten studies[4,12–20] reporting the significant association between the history of syncope and risk of MAE, while the other eight studies[12,21–27] did not find the association to be statistically significant. Only two studies compared outcomes by syncope type[12,25] (Table 1). Olde Nordkamp et al. reported a significant association with cardiac syncope but not with vasovagal syncope.[12] The Forest plot is shown in Figure 2. Sensitivity analysis showed no significant changes in the results when omitted one study at a time (Supplement Figure S1).

The subgroup analysis of syncope type was performed. Types of syncope were categorized by the definition of syncope stated in each study (Table 1) into four categories: cardiac, unexplained, vasovagal, and undifferentiated syncope. Results for subgroup analysis of cardiac syncope, unexplained syncope, vasovagal, and undifferentiated syncope were available in eight,[4,12–16,19,21] five,[17,22–25] two,[12,25] and four[18,20,26,27] studies, respectively (Table 1).

The history of cardiac syncope (pooled OR, 4.48; 95% CI, 2.87–7.01; $p < .001$, $I^2 = 0.0\%$) and unexplained syncope (pooled OR,

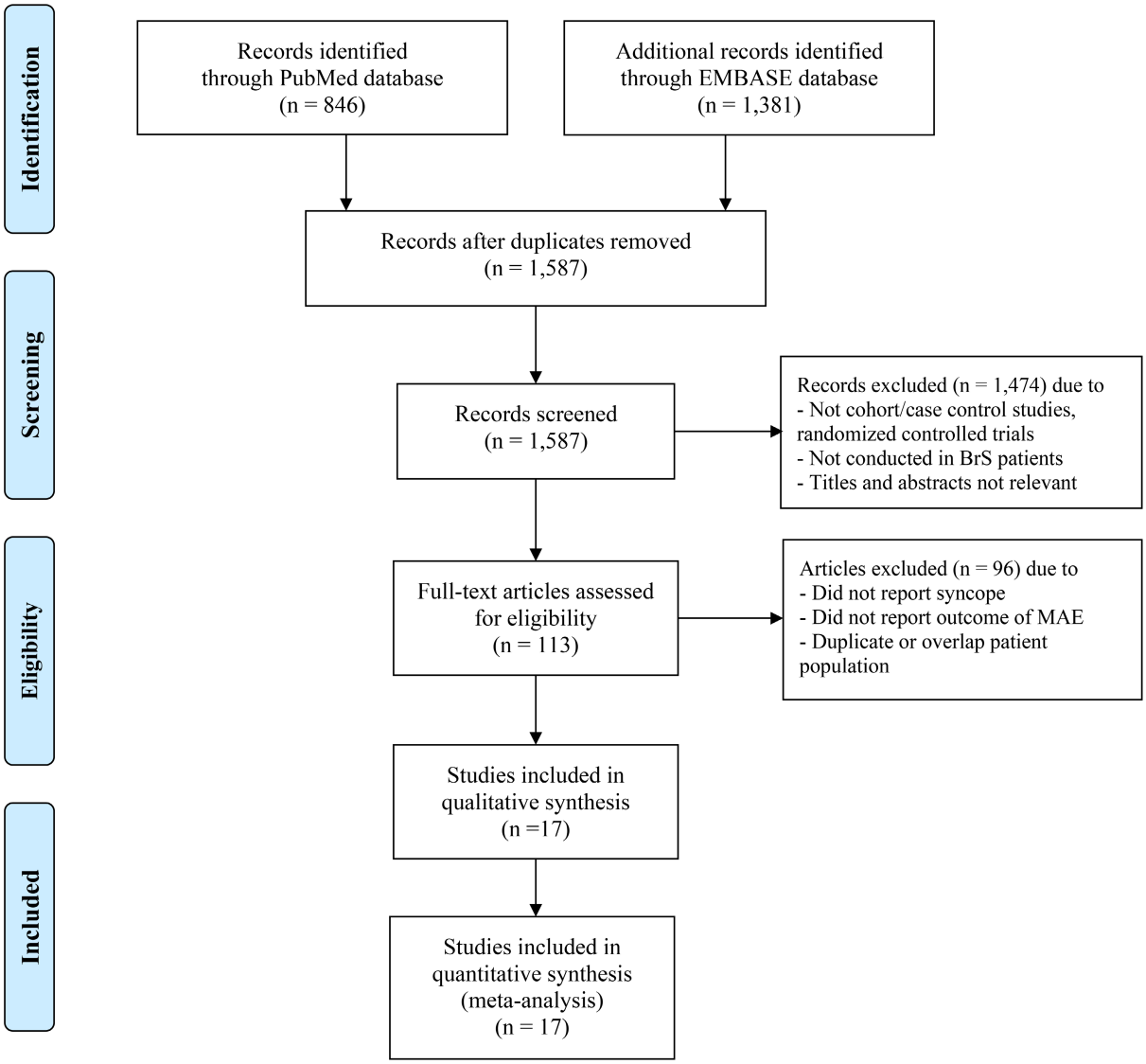

FIGURE 1 Search methodology and selection process.

4.71; 95% CI, 1.34–16.57; $p = .016$, $I^2 = 37.3\%$) were significantly associated with an increased risk of MAE in patients with Brugada syndrome. For vasovagal syncope (pooled OR, 2.90; 95% CI, 0.09–98.45; $p = .050$, $I^2 = 70.9\%$) and undifferentiated syncope (pooled OR, 2.01; 95% CI, 1.00–4.03; $p = .05$, $I^2 = 64.6\%$), there were positive trends toward the increased risk of MAE in patients, but the results were not statistically significant.

3.3 | Quality assessment of included studies

The quality of each study was evaluated by two independent authors (TY, WV). The Newcastle-Ottawa scale (0 to 9) was used to assess included studies on three domains: selection, comparability, and outcomes. Higher scores represent higher study quality. The score of each study ranged from 7 to 9, which reflected high quality (Supplement Table S1). Funnel plots of syncope and MAE are shown in Figure 3. Funnel plots were asymmetric. Egger's test showed significant publication bias ($p < .001$; Supplement Figure S2).

4 | DISCUSSION

In our systemic review and meta-analysis, we analyzed the association between types of syncope and MAE. Seventeen studies from 2006 to 2019 comprising 4355 Brugada syndrome patients were included in the meta-analysis. The major finding was the correlation between a history of cardiac and unexplained syncope with an increased risk of MAE in patients with Brugada syndrome. In contrast, a history of vasovagal syncope and undifferentiated syncope were not significantly associated with an increased risk of MAE in patients with Brugada syndrome.

The history of syncope is one of the most critical factors in predicting arrhythmic events, especially cardiac syncope. A

TABLE 2 Summary of the characteristics of individuals, including studies of patients with Brugada syndrome.

Study/year	Syncope definition	A phrase or sentence describing term of syncope in the study
Kharazi et al., 2006	Unexplained	Syncope of unknown origin
Deliniere et al., 2019	Unexplained	A syncope was defined as a sudden loss of consciousness with rapid recovery, when no cause was found
Leong et al., 2018	Unexplained	History of unexplained syncope
Makarawate et al., 2014	Unexplained	History of unexplained syncope
Priori et al., 2012	Cardiac	Syncope was defined as an abrupt loss of consciousness occurring at rest or a loss of consciousness during sleep with agonal respiration reported by bystanders
Rivard et al., 2016	Vasovagal syncope	History of vasovagal syncope
	Unexplained	History of unheralded syncope (syncope without prodrome)
Kyun Son et al., 2014	Undifferentiated	Syncope was defined as a transient loss of consciousness accompanied by a loss of postural tone
Garcia-Iglesias et al., 2019	Undifferentiated	Symptomatic patients were defined according to the presence of any type of syncope
Migliore et al., 2019	Undifferentiated	Syncope was defined as a nontraumatic transient loss of consciousness characterized by rapid onset, short duration, and spontaneous complete recovery
Yamagata et al., 2017	Undifferentiated	No data were collected on syncope as a cardiac event because it is difficult to differentiate neurally mediated syncope from truly arrhythmic syncope
Olde Nordkamp et al., 2014	Vasovagal	Certain or highly likely reflex syncope and orthostatic hypotension without ECG/Holter documentation of arrhythmia
Gray et al., 2017	Cardiac	Arrhythmic syncope
Letsas et al., 2019	Cardiac	The etiology of syncope was considered arrhythmic in the absence of prodromes and/or typical triggering factors for vasovagal syncope, followed by rapid recovery or severe trauma
Probst et al., 2010	Cardiac	Syncope (considered to be probably of arrhythmic origin)
Sieira et al., 2017	Cardiac	Syncope was considered if suspected to have an arrhythmic origin. Specific attention was paid to excluding vasovagal syncope
Subramanian et al., 2019	Cardiac	Syncope was defined as abrupt loss of consciousness, probably of arrhythmic origin
Takagi et al., 2013	Cardiac	A syncope group with at least 1 episode of syncope without documented VF and with exclusion of etiologies of syncope other than those of cardiac origin

meta-analysis by Gehi and colleagues in 2006—including 30 studies between 1990 to 2005 with 1545 Brugada syndrome patients—demonstrated that patients with a history of syncope had a 3.2-fold increased risk of cardiac events including SCD, syncope, and appropriate implantable cardioverter-defibrillator (ICD) therapy compared to patients without a history of syncope.[28] However, no study demonstrated the association between syncope by type and MAE in Brugada syndrome (cardiac, vasovagal, and unexplained syncope). Our meta-analysis, including studies between 2006 and 2019, found that cardiac and unexplained syncope are both associated with a similar 4-5-fold increased risk of MAE.

At the time of diagnosis, approximately 30% of patients with Brugada syndrome either present with syncope or have had a prior syncopal episode. Two previous studies correlated clinical features of syncope (in Brugada syndrome patients) with various etiologies, finding a cardiac cause in 40%, a noncardiac cause, likely vasovagal, in 30%, and an unexplained cause in approximately 30%.[12,29] These data further highlight the importance of differentiating cardiac syncope from other noncardiac causes of syncope because many of the younger patients with Brugada syndrome have noncardiac syncope. Types of syncope had a substantial difference in the subsequent risk of MAE.

Previous reviews suggested that vasovagal syncope is frequently observed in Brugada syndrome patients confirmed with a tilt-table test[30] and that history-taking with comprehensive risk stratification is essential.[5,31] However, the previous reviews did not include every study, exclude studies with duplicated populations, nor perform pooled analysis by meta-analysis. Our systematic review and meta-analysis performed a more comprehensive search, systematic review, and meta-analysis that included all studies reported in the previous review with an additional thirteen studies[13–15,17,18,20–27] and excluded the duplicated population studies or studies without non-syncope as a control group (supplemental document).

Both cardiac syncope and unexplained syncope are part of the new diagnostic score system. The Shanghai Score was recently proposed by an expert consensus[32] and was validated as new diagnostic criteria for Brugada syndrome.[33] Shanghai score system allots two points for cardiac syncope but only one for unexplained syncope by expert consensus; however, no study was conducted to assess the

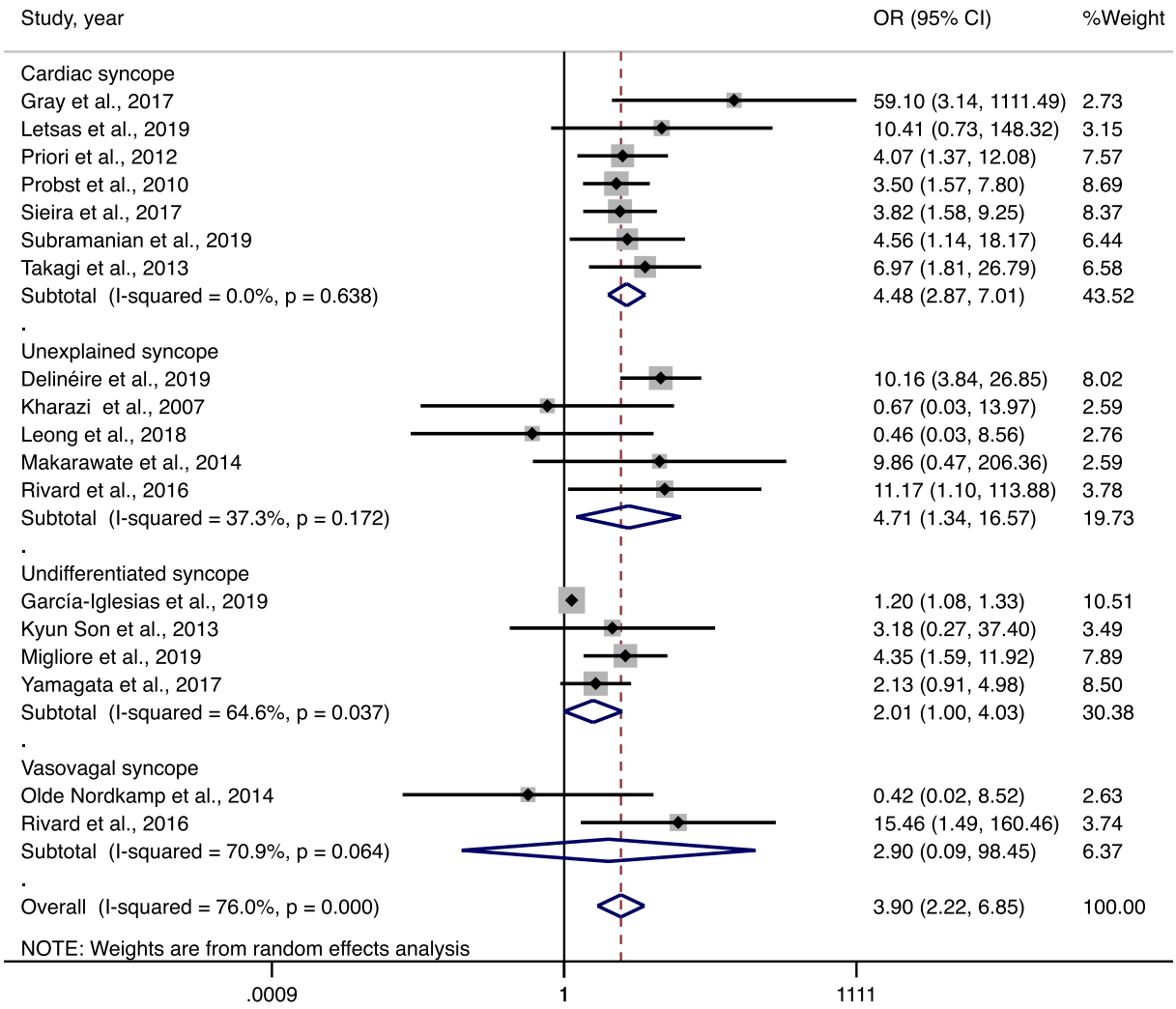

FIGURE 2 The forest plot demonstrates the association of syncope and MAE in patients with Brugada syndrome.

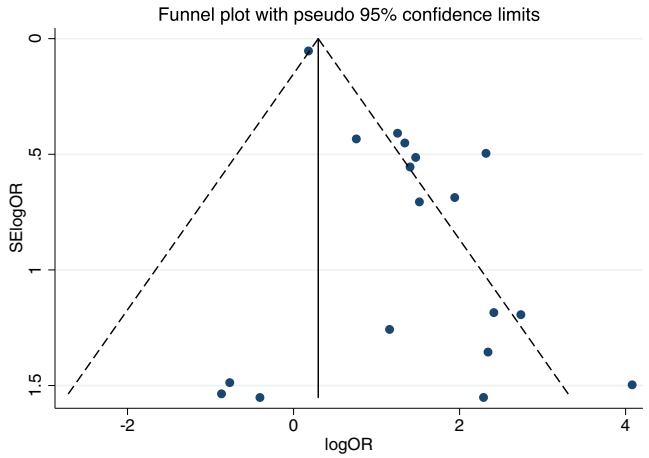

FIGURE 3 Funnel plot of syncope and MAE in patients with Brugada syndrome.

difference between cardiac and unexplained syncope. Moreover, a 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society Guideline recommends ICD implantation in Brugada patients with cardiac syncope, but unexplained syncope was not stated.[34] Our meta-analysis is the first study showing that MAE is significantly associated with unexplained syncope with a similar increased risk of MAE compared to cardiac syncope (OR = 4.71 and OR = 4.48, respectively). Our results sugestes that ventricular arrhythmias are likely to be the pathophysiology of unexplained syncope in Brugada syndrome.

All studies included in our meta-analysis that defined their syncope as cardiac syncope had the same trends toward increased risk of MAE without heterogeneity between studies (I^2 =0.0). However, there was moderate heterogeneity between studies among the unexplained syncope group (I^2 =37.3). Studies with unexplained syncope patients stated either a cause of syncope could not be found or there was no prodrome to syncope (Table 1). These inclusion criteria likely selected cohorts with a higher probability of cardiac syncope and less vasovagal syncope.

One observational study, including 23 patients who had a history of suspected cardiac syncope and ICD implantation, showed a MAE rate of 5.5% per year during follow-up. A MAE rate of 3.1% was reported in another study of 88 patients with undifferentiated causes

of syncope.[29,35] This lower rate of MAE in the undifferentiated syncope than in the group with cardiac syncope is not surprising as the undifferentiated group likely included patients with noncardiac syncope. These findings are consistent with the results from our meta-analysis with larger sample size. The MAE rate is lower in the undifferentiated group. The OR did not reach statistical significance. We suspected that the high heterogeneity in undifferentiated syncope could be explained by variable proportions of cardiac or noncardiac causes of syncope.

The vasovagal syncope group had positive OR trends toward increased risk of MAE but was not statically significant. With only two studies included in the analysis, there was substantial heterogeneity among the studies. A thorough history is critical in syncope evaluation.[7] The rigor of taking history and interpreting the clinical presentation from the history could have varied among the studies and in the medical training of the healthcare provider. Combined with the lack of standardization of clinical testing, some patients with cardiac causes of syncope could have been included in the vasovagal group. A publication bias was observed in the overall funnel plot (Figure 2) and confirmed with significant Egger's test.

Several studies in our meta-analysis performed programmed electrical stimulation to risk-stratify Brugada syndrome patients. The usefulness of programmed electrical stimulation in a setting of syncope in Brugada syndrome patients remained to be better defined.[4,19,29] In a meta-analysis investigating the prognostic value of programmed electrical stimulation in patients with Brugada syndrome, the VT/VF inducibility, irrespective of protocol used, might be helpful to predict subsequent MAE in patients presenting with syncope.[36] However, another small prospective study demonstrated no difference between VT/VF inducibility and syncope types, including cardiac syncope, vasovagal syncope, and unexplained syncope.[29] The systematic review for the 2017 guideline on the management of ventricular arrhythmias and prevention of SCD showed that the inducibility of VT/VF in asymptomatic patients with Brugada syndrome does not predict higher VA or ICD shocks.[37] The result from the systematic review led to a IIb recommendation for programmed stimulation for risk stratification in asymptomatic Brugada patients.[34] The usefulness of programmed stimulation in Brugada patients with syncope is unknown. This could have been another confounder for the equivocal result in the undifferentiated syncope group in our systematic review and meta-analysis.

In a large observational study, Probst et al. showed that patients with a history of suspected cardiac syncope had a lower incidence of developing appropriate ICD shocks during follow-up after ICD implantation, with a 1.9% annual cardiac event rate compared to 7.7% in patients with implanted ICD due to aborted SCD. This difference in annual rates of appropriate ICD discharge for "primary" vs. "secondary" SCD prevention is similar to other familial conditions such as LQTs[38] and hypertrophic cardiomyopathy.[39] Syncope, presumed due to a cardiac cause, remains a factor in the risk stratification for SCD. In 2017, the American College of Cardiology/American Heart Association/Heart Rhythm Society stated that ICD implantation is recommended in Brugada syndrome with spontaneous Type-1 Brugada pattern with a history of cardiac arrest, sustained ventricular arrhythmia, or history of syncope suspected due to ventricular arrhythmia.[34] Findings from our study further highlight the importance of differentiating cardiac from noncardiac causes of syncope.

Syncope is a symptom that can be caused by cardiac and noncardiac conditions. Most patients are asymptomatic when seeking medical evaluation after the index event. Concerns that well-appearing patients may be at significant risk of cardiac arrhythmias or sudden death are particularly relevant in younger patients with familial arrhythmic conditions, including Brugada syndrome. The presumptive diagnosis of cardiac, unexplained, or vasovagal syncope is primarily derived from a thorough history and initial evaluation.[7] The subjectivity of self-reported history, the variability of gathering and interpreting the history, and the lack of standardization of diagnostic testing remain challenging in syncope evaluation. The definition of syncope from each included study in our meta-analysis, summarized in Table 1, is based on the information provided by the investigators of each original study. Some cardiac syncope patients were likely included in the unexplained, vasovagal, and undifferentiated groups. The balance of ICD-mediated benefit vs. ICD-related short- and long-term complications is a derivative of the effectiveness of risk predictors for primary sudden cardiac prevention. A continuing effort to develop algorithms differentiating cardiac vs. noncardiac syncope is imperative in managing Brugada patients with syncope.

5 | LIMITATIONS

There are several limitations to our study. First, all studies in our meta-analysis were observational. Second, there were differences between studies in the thoroughness of history taking, the definition of syncope, the extent of syncope investigation, and established criteria in achieving the diagnosis. Because no definition of syncope was provided in several studies (undifferentiated syncope), the cause of syncope in this subgroup may be overlapped. These were confounders. Well-designed and randomized controlled studies would be ideal, although unlikely, due to the overall small patient population and low MAE rates. Third, specific MAE outcomes reported in the studies varied in their definitions and follow-up durations. Random-effect modeling was used to compensate for these variabilities. Fourth, the included studies were conducted primarily on Caucasian populations from selected databases.

6 | CONCLUSION

Our systemic review and meta-analysis emphasize that cardiac and unexplained syncope is associated with an increased risk of MAE in patients with Brugada syndrome. However, vasovagal and

undifferentiated syncope were not. Our meta-analysis result is the first study showing that unexplained syncope is significantly associated with an increased risk of MAE, similar to cardiac syncope. The observation from our meta-analysis supports the practice guideline that recommends that ICDs should be considered in Brugada patients presenting with syncope with suspected arrhythmic causes. Our meta-analysis also advocates further investigations on unexplained syncope as a risk of MAE in this unique patient population with Brugada syndrome.

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None.

CONFLICT OF INTEREST STATEMENT

None to declare.

FUDING INFORMATION

None.

ETHICAL APPROVAL STATEMENT

Ethical approval is not required for a systematic review study.

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