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Meta-analysis on risk stratification of malignant ventricular tachyarrhythmic events in arrhythmogenic right ventricular cardiomyopathy

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Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a cardiomyopathy characterized by predominant right ventricular fibro-fatty replacement, right ventricular dysfunction and ventricular arrhythmias. It is a rare but important cause of sudden cardiac death in children and young adults. A meta-analysis on risk stratification of major ventricular tachyarrhythmic events indicating the need for implantable cardioverter defibrillator therapy in ARVC was performed.
Methods: The pubmed database was searched from its inception to May 2015. Of the 433 citations identified, 12 were included in this meta-analysis. Data regarding major ventricular tachyarrhythmic events were retrieved in 817 subjects from the studies. For the variables, a combined odds ratio (OR) was calculated using a fixed-effects meta-analysis.
Results: Extensive right ventricular dysfunction (OR, 2.44), ventricular late potential (OR, 1.66), inducible ventricular tachyarrhythmia during electrophysiology study (OR, 3.67), non-sustained ventricular tachycardia (OR, 3.78), and history of fatal event/sustained VT (OR, 5.66) identified as significant risk factors (p<0.0001).
Conclusion: This meta-analysis shows that extensive right ventricular dysfunction, ventricular late potential, inducible ventricular tachyarrhythmia during electrophysiological study, non-sustained ventricular tachycardia, and history of sustained ventricular tachycardia/fibrillation are consistently reported risk factors of major ventricular tachyarrhythmic events indicating implantable cardioverter defibrillator therapy in patients with ARVC.

Keywords: Arrhythmogenic right ventricular cardiomyopathy; Defibrillator; Sudden death; Ventricular tachyarrhythmia; Meta-analysis

INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a progressive cardiomyopathy characterized by fibro-fatty replacement of the right ventricle, predominant right ventricular dilatation and dysfunction, and/or ventricular tachyarrhythmias. It is a rare but important cause of sudden cardiac death in children and young adults [1]. Furthermore, it has been reported to be an important cause of sports-related sudden cardiac arrest [1]. Although implantable cardioverter defibrillator (ICD) therapy is necessary in the secondary prevention after survived cardiac arrest, or sustained ventricular tachyarrhythmias in the patients [2,3], its role for the primary prevention in asymptomatic patients with ARVC with no history of sustained tachyarrhythmias or cardiac arrest remains unclear.

The aim of this meta-analysis was to identify patients with ARVC at a high risk of ventricular tachyarrhythmias, who might benefit from ICD therapy, via a systematic review of

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the literature and to analyze the predictive value of currently evaluated risk factors via a meta-analysis.

MATERIALS AND METHODS

1. Search strategy and study selection

We performed a computerized search of the literature in the PubMed database (from the time of inception to May 2015) to identify eligible studies focusing on the identification of patients with the ARVC at risk of ventricular tachyarrhythmia or sudden cardiac death, to whom the ICD therapy might be beneficial. We used a combination of the following keywords: "Arrhythmogenic Right Ventricular Dysplasia", "defibrillator", "ventricular tachycardia" and "sudden death". We subsequently reviewed the reference lists of all primary identified studies to find any relevant publications that were not named in the database search. Case reports and review articles were excluded. The search was limited to human studies and those in the English language. The titles and abstracts of all articles were reviewed and rejected after initial screening according to the following exclusion criteria: (1) studies on all cause of cardiac mortality, including heart failure and transplantation, (2) studies on atrial arrhythmias, ablation, and mapping, (3) studies with incomplete data, and (4) studies with overlapping data or apparent serial reporting of a particular patient cohort. There were no restrictions in the sample size or duration of follow-up. Two authors (Roh and Jang) independently screened the titles and abstracts of all the citations. Disagreements were resolved by discussing with Cho. Full-text articles were retrieved for a detailed review and then rescreened.

2. Data extraction

The following data were extracted: (1) year of publication, (2) study design, (3) patient demographics including sample size, age, sex, duration of follow up, family history, number of patients with ICD, and detailed information regarding candidate risk factors, and (4) relevant outcomes: occurrence of sustained ventricular tachyarrhythmias, appropriate device therapies, or arrhythmic death as determined by the individual study methods.

3. Data synthesis and analysis

The analyses were performed using the Review Manager version 5.1.0 software (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). The results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs) for each study. Heterogeneity was assessed using the Cochran Q-test ($p<0.10$ was considered significant), and I2 statistics (I2>56% was considered as an indicator of significant heterogeneity) were calculated to estimate the proportion of variation attributable to heterogeneity across the studies. The studies that were homogenous for an outcome were analyzed using the Mantel-Haenszel fixed-effects model. In cases where evidence of heterogeneity was noted, a random-effects model was used. Publication bias was assessed using funnel plots. Statistical significance was defined as a two-sided p-value<0.05 for all tests except those for heterogeneity.

RESULTS

1. Identified studies

Four hundred thirty-three studies were identified in the primary literature search. After screening the titles and abstracts, 69 relevant studies were retrieved for detailed evaluation. Fifty-seven of them were further excluded. The results of the literature search and exclusion reasons are shown in Figure 1.

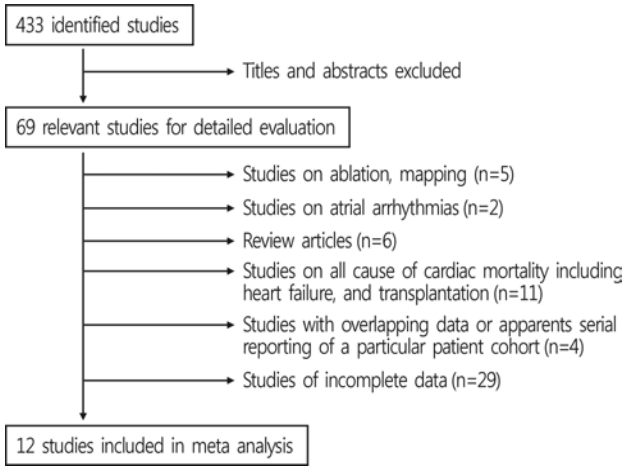


Fig. 1. Study selection flow diagram.

A total of 817 subjects with ARVC from 12 studies were finally included in our meta-analysis [4-15]. The characteristics of the individual studies are described in Table 1. The ages of the study patients varied from 2 to 78 years. The mean follow-up period of the study ranged from 19 to 80 months. The prevalence of appropriate ICD therapy or lethal arrhythmic events during follow up varied from 17% to 69%.

2. Identified candidate risk factors

A total of 19 candidate risk factors have been evaluated in one or more studies (Table 2). Nine of the 19 variables were available for the meta-analysis; extensive right ventricular dysfunction, left ventricular involvement, ventricular late potential on signal averaged electrocardiography (SAECG), T-wave inversion on the right precordial leads on electrocardiography, history of syncope, inducible ventricular tachyarrhythmias during electrophysiologic study, frequent ventricular premature beats on 24-hour Holter monitoring, nonsustained ventricular tachyarrhythmias, and history of sustained ventricular tachyarrhythmias (Fig. 2, Table 3).

Extensive right ventricular dysfunction was investigated in seven studies. Three of the sevenstudies were available for the subgroup analysis, which demonstrated that extensive right ventricular dysfunction in ARVC predicted an increased risk of future ventricular tachyarrhythmic events during the follow-up period (OR=2.44, 95% CI=1.02-5.82, z=2.01, p=0.04). Left ventricular involvement has also been evaluated in most of included studies (11/12 studies); we did not find any statistical correlation between left ventricular involvement and risk of future tachyarrythmic events in the subgroup analysis of five feasible studies (OR=1.80, 95% CI=1.00-3.24, z=1.96, p=0.05).

Eight studies assessed whether ventricular late potential is a predictor of ventricular arrhythmias; existence of ventricular late potential might be a weak, but significant predictive factor of ventricular arrhythmias according to the subgroup analysis of five studies (OR=1.66, 95% CI=1.03-2.68, z=2.08, p=0.04). T-wave inversion on the right precordial leads was investigated in five studies, and four studies were available for the subgroup analysis. There was no significant association between T-wave inversion on the right precordial leads and major ventricular tachyarrhythmic events (OR=1.79, 95% CI=0.97-3.31, z=1.86, p=0.06).

Data regarding the history of syncope for the risk of ventricular tachyarrhythmias were retrieved from eight articles. A history of syncope was not a significant predictor of life-threatening ventricular arrhythmias according to this subgroup analysis (OR=1.41, 95% CI=0.65-3.05, z=0.86, p=0.39).

Inducible ventricular tachyarrhythmias during electrophysiologic study were investigated in seven articles; five of them were available for the subgroup analysis. These studies showed higher risks of future ventricular tachyarrhythmic events in patients (OR=3.67, 95% CI=1.58-8.49, z=3.03, p=0.0002). Frequent ventricular premature beats on 24-hour Holter monitoring were evaluated as predictors of ventricular tachya-

Table 1. Main characteristics of the selected studies

	Corrado 2003 [4]	Wichter 2004 [5]	Piccini 2005 [6]	Pezawas 2006 [7]	Corrado 2010 [8]	Bhonsale 2011 [9]	Schuler 2012 [10]	Battipaglia 2012 [11]	Santangeli 2012 [12]	Canpolat 2013 [13]	Link 2014 [14]	Ruiz-Salas 2014 [15]
Cohort	Italy, USA	Germany	USA	Austria	Italy, UK, Germany, USA	USA	Switzerland	Italy	Italy, USA	Turkey	USA	Spain
n	132	60	67	34	106	84	26	30	32	78	137	31
Age (yr)	40±15 (15-72)	43±16 (14-70)	36±14 (2-78)	49±12 (14-68)	35.6±18 (16-65)	31.9±11 (11-59)	median 40	45.4±18	48±15	31.2±11	40±14	47.3±17
% Male	70	81	52	61	67	64	80	56	NA	65.4	68.6	77.4
% FHx. of RVD/SD	3	15	22	NA	46	17	15.3	26	NA	26.9	NA	16.13
Follow up (mo)	39±25	80±43	52±34	78±28	58±35	56±40	median 120	19±7	25±7	38±14	39±20	73±64
% of ICD implantation (n)	100 (132)	100 (60)	100 (67)	47 (16)	100 (106)	100 (84)	100 (26)	50 (15)	100 (32)	59 (46)	78 (108)	100 (31)
% of prophylactic ICD in total ICD (n)	28 (37)	7 (4)	41 (28)	0	100 (106)	100 (84)	3 (1)	100 (15)	100 (32)	45.6 (21)	NA	19 (6)
% of appropriate ICD Tx or lethal events (n)	48 (64)	69 (41)	66 (59)	34 (12)	40 (42)	48 (40)	46 (12)	17 (5)	38 (12)	50 (39)	44 (48)	61 (19)

Values are presented as mean±deviation or number (%).
ARVD/SD, arrhythmogenic right ventricular dysplasia/sudden death; ICD, implantable cardioverter-defibrillator.

rrhythmias in seven studies. Meta-analysis was available in five studies. Combining the five studies available for the meta-analysis yielded an OR of 1.24 (95% CI=0.75-2.07), indicating no significant association with an increased risk of ventricular tachyarrhythmias (z=0.84, p=0.40). Non-sustained ventricular tachyarrhythmia was investigated in six studies, with four studies available for the meta-analysis. Non-sustained ventricular tachyarrhythmia was identified as a significant predictor of ventricular tachyarrhythmias and appropriate ICD therapy (OR=3.78, 95% CI=2.08-6.85, z=4.38, p<0.0001).

Table 2. Identified candidate risk factors

	Corrado, 2003 [4]	Wichter, 2004 [5]	Piccini, 2005 [6]	Pezawas, 2006 [7]	Corrado, 2010 [8]	Bhonsale, 2011 [9]	Schuler, 2012 [10]	Battipaglia, 2012 [11]	Santangeli, 2012 [12]	Canpolat, 2013 [13]	Link, 2014 [14]	RuizSalas, 2014 [13]	Studied (#)	Significant (#)
Proband status						s							1	1
Pathologic mutation													1	0
FHx of ARVD or SD													10	0
Male gender												s	9	1
Age	s												10	1
Extensive RV dysfunction		s	s	s						s			7	4
LV involvement	s			s						s			11	3
Symptoms of heart failure							s						1	1
Abnormal EAM finding									s				1	1
Ventricular late potentials on SAECG				s									8	1
Epsilon wave													1	0
Fragmented QRS										s			1	1
T-inversion in V1-V3			s								s		5	2
Hx of syncope					s			s		s			9	3
Induced VT on EPS			s			s							7	2
Holter: frequent PVCs						s				s			7	2
Nonsustained VT			s			s				s			6	3
Hx of sustained VT/VF, aborted CA	s		s								s	s	4	4
Abnormal heart rate variability on holter								s					1	1

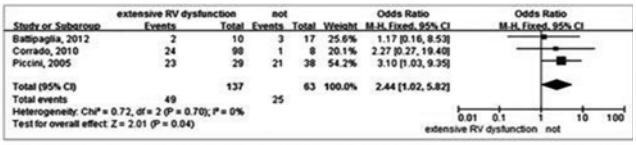
ARVD, arrhythmogenic right ventricular dysplasia; SD, sudden death; RV, right ventricle; LV, left ventricle; EAM, electroanatomic mapping; SAECG, signal averaged Electrocardiography; VT, ventricular tachycardia; EPS, electrophysiologic study; PVC, premature ventricular complex; VF, ventricular fibrillation; CA, cardiac arrest.
Shaded indicates that sufficient analysis results were provided in the paper to be included in meta-analysis; s, significant association with risk.

Table 3. Combined risk of candidate risk factors

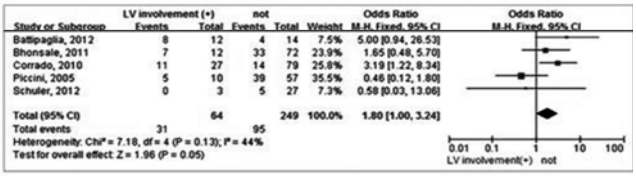
Candicate risk factor	n	OR	CI	p-value
Extensive RV dysfunction	200	2.44	1.02-5.82	0.04
LV involvement	313	1.8	1.00-3.24	0.05
Ventricular late potential	364	1.66	1.03-2.68	0.04
T-wave inversion on V1-3	285	1.76	0.97-3.31	0.06
Hx of syncope	585	1.41	0.65-3.05	0.39
Inducible VT/VF during EPS	344	3.67	1.58-8.49	0.002
Frequent PVCs on holter	300	1.24	0.75-2.07	0.4
Nonsustained VT	248	3.78	2.08-6.85	<0.00001
Fatal event/sustained VT	452	5.66	3.36-9.53	<0.00001

OR, odds ratio; CI, confidence interval; RV, right ventricle; LV, left ventricle; Hx, history; VT, ventricular tachycardia; VF, ventricular fibrillation; EPS, electrophysiologic study; PVC, premature ventricular complex.

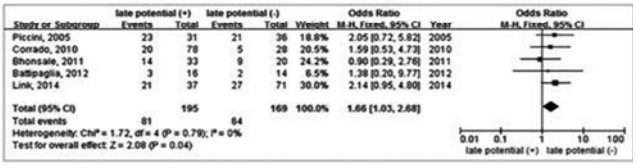
a. Extensive right ventricular dysfunction



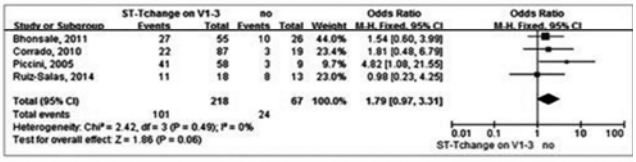
b. LV involvement



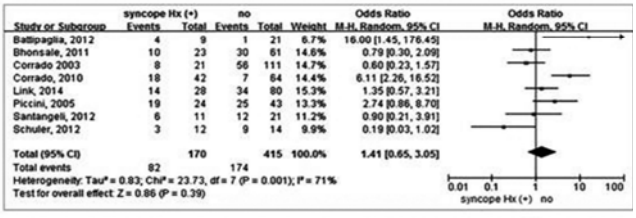
c. Ventricular late potential (+)



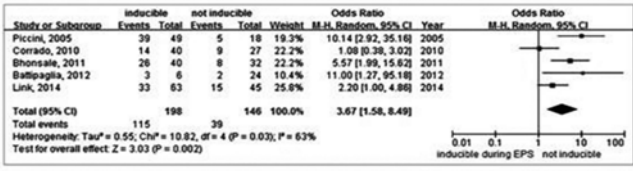
d. T - inversion on lead V1-3



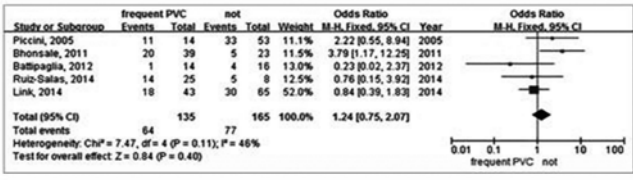
e. History of syncope



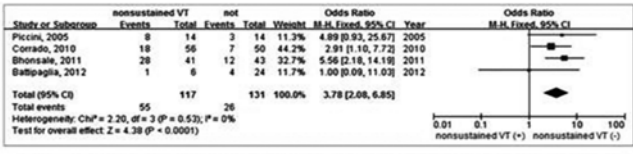
f. Inducible VT/VF during EPS



g. Frequent PVCs on Holter



h. Nonsustained VT



i. Fatal event / sustained VT

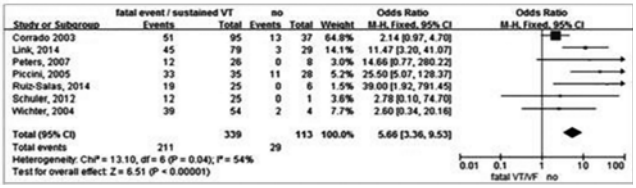


Fig. 2. Forest plots showing. RV, right ventricular; LV, left ventricular; VT, ventricular tachycardia; VF, ventricular fibrillation; PVCs, premature ventricular complexes.

DISCUSSION

Although ICD therapy is widely accepted in the termination of life-threatening tachyarrhythmias in ARVC, its role for the primary prevention of ventricular tachyarrhythmias and sudden cardiac death in asymptomatic ARVC patients remains controversial, as not all patients with ARVC are at risk for such events [16]. Further, frequent device-related complications and inappropriate interventions mostly in young patients who are expected to live for many years with the device make the decision-making process more complicated. Some of the most studied risk factors for ventricular tachyarrhythmias/ICD therapy include extensive right ventricular dysfunction, coexisting left ventricular involvement, unexplained syncope, induction of ventricular tachyarrhythmias during electrophysiological testing, non-sustained ventricular tachyarrhythmias on noninvasive monitoring, male sex, familial history of sudden death, and young age at presentation [4,7-11,17,18]. In our meta-analysis, the pooled data have confirmed that severe right ventricular involvement, inducible ventricular tachyarrhythmias during electrophysiologic study, and nonsustained ventricular tachyarrhythmias on 24-hour Holter monitoring and/or exercise testing are significant predictors of ventricular tachyarrhythmias and ICD therapy in asymptomatic patients with ARVC.

Pathologically, ARVC is characterized by a fibro-fatty replacement primarily affecting the right ventricular myocardium [19-21], which is responsible for regional wall motion abnormalities and/or global right ventricular dysfunction [20,22]. Extensive right ventricular dysfunction detected on echocardiography or magnetic resonance imaging could be a meaningful risk factor of ventricular tachyarrhythmias, usually originating from the right ventricle. Late potentials detected on SAECG represent delayed depolarization of the ventricular myocardium; thus they can be considered another marker of right ventricular problems [23,24]. In our meta-analysis, a significant association was observed between late potentials and occurrence of tachyarrhythmias in the patients with ARVC. The presence of T-wave inversion in V1-V3 or premature ventricular complexes of the left bundle branch block morphology on 12-lead electrocardiography could also be the first alarming signs of right ventricular change [25]; however, their values in identifying patients at risk of ventricular tachyarrhythmias/ICD therapy were not significant in our subgroup analysis.

Conflicting data exist on the prognostic significance of programmed ventricular stimulation during electrophysiological study in patients with ARVC [4,9,26]. Our subgroup analysis with five eligible studies concluded that inducibility during electrophysiological study can be a significant predictor of ventricular tachyarrhythmias in patients with ARVC. Nonetheless, it should be borne in mind that there surely exists a limitation of electrophysiological studies in arrhythmic risk stratification in general, and that current guidelines do not support the routine use of programmed ventricular stimulations for risk stratification in ARVC [16,27].

Many individual studies have suggested that asymptomatic patients with nonsustained ventricular tachyarrhythmias show a somewhat high (3-6%/year) appropriate ICD discharge rate and significant (2%/year) ventricular fibrillation rate [8,9]. In line with the findings from individual studies, nonsustained ventricular tachyarrhythmias on 24-hour Holter monitoring were identified as a useful independent predictor of ventricular tachyarrhythmias in our subgroup analysis. However, frequent ventricular ectopy on 24-hour Holter monitoring in asymptomatic patients did not predict the occurrence of ventricular tachyarrhythmias, despite a previous suggestion that an increased ventricular ectopy burden may be associated with electrical instability leading to malignant ventricular tachyarrhythmias over time [9].

Syncope is one of the most typical clinical presentations in adolescents or young individuals with ARVC [27]. A history of syncope as a predictive factor for ventricular tachyarrhythmias in ARVC has been evaluated by many groups [9,28-30]; however, a clear conclusion has not been reached yet. The significance of syncope as a risk factor of lethal tachyarrhythmias in patients with ARVC was first reported by Marcus et al. [30]. Although a previous study has even suggested that patients with prior syncope have a four-fold increased risk for subsequent ventricular tachyarrhythmias [8], the result of our subgroup analysis suggests that prior syncope cannot predict subsequent ventricular tachyarrhythmias. Syncope itself may be a nonspecific clinical feature, may not be of an arrhythmic origin, and may be linked to a neurocardiogenic mechanism. An inclusion of nonarrhythmic syncope would possibly make the differential diagnosis difficult and its prognostic value elusive. Nevertheless, a previous study by Bhonsale et al. observed that significantly more patients

with recent (less than 6 months) unexplained syncope received ICD therapy than those with remote syncope [9], which can be considered in clinical situations.

There has been one study that evaluated and speculated that the proband status might be a factor for risk prediction of ventricular tachyarrhythmias in ARVC; 36 probands (90%) had appropriate ICD therapies compared with only four family members (9%) who received ICD therapy [9]. More extensive analyses may be needed on this issue.

In summary, ICD therapy is mandatory for patients with ARVC with previous cardiac arrest or sustained ventricular tachyarrhythmias. For the primary prophylaxis of sudden cardiac events, this meta-analysis demonstrated that extensive right ventricular dysfunction, ventricular late potential on SAECG, inducible ventricular tachyarrhythmias during electrophysiologic study, and non-sustained ventricular tachyarrhythmias are meaningful risk factors of sudden death in patients with ARVC. However, the following are the limitations of our analysis: (1) most of the studies included were relatively small retrospective observational studies, and (2) an inevitable potential duplicate patient inclusion may exist. As such, we cannot recommend the application of our result automatically in the consideration of primary ICD implantation; deciding primary ICD implantation should remain as an individual decision based on whether any of the above risk factors are present.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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