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ORIGINAL ARTICLE

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Total cosine R-to-T for predicting ventricular arrhythmic and mortality outcomes: A systematic review and meta-analysis

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Background: The total cosine R-to-T (TCRT), a vectorcardiographic marker reflecting the spatial difference between the depolarization and repolarization wavefronts, has been used to predict ventricular tachycardia/fibrillation (VT/VF) and sudden cardiac death (SCD) in different clinical settings. However, its prognostic value has been controversial.

Objective: This systematic review and meta-analysis evaluated the significance of TRCT in predicting arrhythmic and/or mortality endpoints.

Methods: PubMed and Embase databases were searched through December 31, 2016.

Results: Of the 890 studies identified initially, 13 observational studies were included in our meta-analysis. A total of 11,528 patients, mean age 47 years old, 72% male,

were followed for 43 ± 6 months. Data from five studies demonstrated lower TCRT values in myocardial infarction patients with adverse events (syncope, ventricular arrhythmias, or sudden cardiac death) compared to those without these events (mean difference = −0.36 ± 0.05, $p < .001$; $I^2 = 48\%$). By contrast, only two studies analyzed outcomes in heart failure, and pooled meta-analysis did not demonstrate significant difference in TCRT between event-positive and event-negative patients (mean difference = −0.01 ± 0.10, $p > .05$; $I^2 = 80\%$).

Conclusion: TCRT is lower in MI patients at high risk of adverse events when compared to those free from such events. It can provide additional risk stratification beyond the use of clinical parameters and traditional electrocardiogram markers. Its value in other diseases such as heart failure requires further studies.

KEYWORDS

risk stratification, sudden cardiac death, total cosine R-to-T, ventricular arrhythmias

1 | INTRODUCTION

The total cosine R-to-T (TCRT) is a descriptor of T-wave morphology derived from computed analysis of vectorcardiograms that are reconstructed from the standard 12-lead electrocardiography (ECG) (Acar, Yi, Hnatkova, & Malik, 1999; Ono, Saitoh, & Itakura, 2006; Perkiomaki, Hyytinen-Oinas, & Karsikas, 2006). It is defined as the average of the cosines of the angles between the QRS and T vectors, reflecting the spatial difference between the depolarization and repolarization wavefronts (Belloch et al., 2007). TCRT can be determined with the eigenvalue method, principal component analysis (PCA) (Ono et al., 2006; Vicente, Johannesen, & Mason, 2015). Previous studies have demonstrated success in using TCRT for the stratification of arrhythmic and mortality risks (Gang, Hnatkova, Mandal, Ghuran, & Malik, 2004; Hnatkova, Ryan, & Bathen, 2001; Huang, Lin, Yu, & Ho, 2009; Kentta, Karsikas, & Junttila, 2011; Porthan, Viitasalo, & Jula, 2009; Zabel et al., 2000; Zabel, Malik, & Hnatkova, 2002). However, other studies have failed to demonstrate significant prognostic value. One study showed predictive value in univariate but not multivariate analysis (Perkiomaki, Hyytinen-Oinas, & Karsikas, 2006), whereas another study did not quite achieve statistical significance due to a small sample size (Korhonen, Husa, & Konttila, 2009). Therefore, the aim of this systematic review and meta-analysis is to determine the value of TCRT in predicting arrhythmic or mortality outcomes.

2 | METHODS

2.1 | Search strategy, inclusion, and exclusion criteria

The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. MEDLINE and Embase were searched for studies that investigated the relationship between the total cosine R-to-T (TCRT) with arrhythmic or mortality endpoints using the following terms: ("TCRT" or "T-wave morphology" or "total cosine R-to-T" or "spatial QRS-T angle"). The search period was from 1999 through to 31st December 2016, with no language restrictions. The following inclusion criteria were applied: (i) the design was a case–control, prospective or retrospective cohort study in humans, (ii) TCRT values were related to endpoint events appropriate implantable cardioverter-defibrillator therapy (ICD), ventricular tachycardia/fibrillation (VT/VF), sudden cardiac death (SCD), cardiovascular death (CVD), or all-cause mortality were reported.

The quality assessment of these studies included in our meta-analysis was performed using the Newcastle–Ottawa Quality Assessment Scale (NOS). The point score system evaluated the categories of study participant selection, comparability of the results, and quality of the outcomes. The following characteristics were assessed: (i) representativeness of the exposed cohort; (ii) selection of the nonexposed cohort; (iii) ascertainment of exposure; (iv) demonstration that outcome of interest was not present at the start of study; (v) comparability of cohorts on the basis of the design or analysis; (vi) assessment of outcomes; (vii) follow-up period sufficiently long for outcomes to occur; and (viii) adequacy of follow-up of cohorts. This scale varied from zero to nine stars, which indicated that studies were graded as poor quality if they met <5 criteria, fair if they met five to seven criteria, and good if they met >8 criteria. The details of the NOS quality assessment are shown in Tables S1 and S2.

2.2 | Data extraction and statistical analysis

Data from the different studies were entered in pre-specified spreadsheet in Microsoft Excel. All publications identified were assessed for compliance with the inclusion criteria. In this meta-analysis, the extracted data elements consisted of the following: (i) publication details: last name of first author, publication year and locations; (ii) study design; (iii) follow-up duration; (iv) method of TCRT calculation; (v) endpoint(s); (vi) the quality score; and (vii) the characteristics

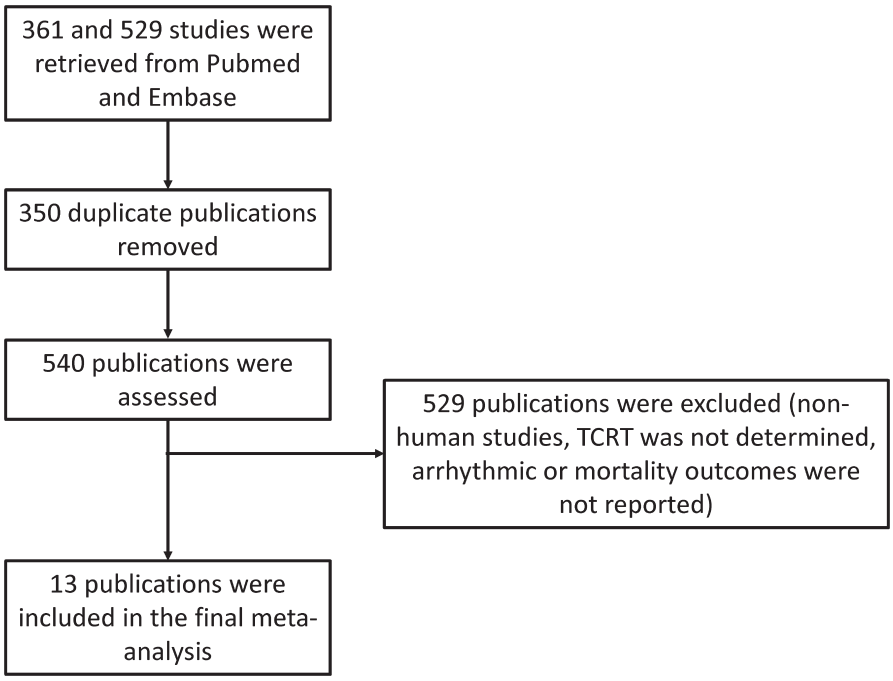

FIGURE 1 Flow diagram of the study selection process

of the population including sample size, gender, age, and number of subjects. Meta-analyses of observational studies are challenging due to differences in study designs and inherent biases. This systematic review was conducted in accordance to PRISMA statement (Moher, Liberati, Tetzlaff, & Altman, 2009) and registered with PROSPERO. Two reviewers (GT and MG) independently reviewed each included study and disagreements were resolved by adjudication with input from a third reviewer (TL).

The endpoints of the study were the occurrences of ventricular arrhythmias (VT/VF), SCD, cardiovascular death, or all-cause mortality. The definition of these endpoints used in the different studies was analyzed. If more than one mortality endpoint was described, then SCD was preferentially used for analysis, followed by cardiovascular death and all-cause mortality. Mean differences in TCRT values between patients with adverse cardiac events (syncope, ventricular arrhythmias, or sudden cardiac death) compared to those without these events were extracted from each study and subsequently pooled in our meta-analysis. Heterogeneity across studies was determined using Cochran's Q value, which is the weighted sum of squared differences between individual study effects and the pooled effect across studies, and the I^2 statistic from the standard chi-square test, which describes the percentage of the variability in the effect estimates resulting from heterogeneity. $I^2 > 50\%$ was considered to reflect significant statistical heterogeneity. The fixed effect model was used if $I^2 < 50\%$, whereas the random-effects model using the inverse variance heterogeneity method was used when $I^2 > 50\%$. To locate the origin of the heterogeneity, sensitivity analysis excluding one study at a time, and subgroup analyses based on different disease conditions and different endpoints were performed. Funnel plots, Begg and Mazumdar rank correlation test, and Egger's test were used to assess for possible publication bias.

3 | RESULTS

A flow diagram detailing the above search terms with inclusion and exclusion criteria is depicted in Figure 1. A total of 361 and 529 entries were retrieved from PubMed and Embase, respectively. Comparing with the entries extracted from the PubMed search, 350 duplicate entries from the Embase were found and removed. This yielded 540 publications, of which 13 studies met our inclusion criteria (Batchvarov et al., 2003; Hnatkova et al., 2001; Huang et al., 2009; Kentta et al., 2011; Korhonen et al., 2009; Lin, Lin, & Chen, 2007; Lin, Lin, & Chen, 2009; Malik, Hnatkova, & Batchvarov, 2004; Perkiomaki et al., 2006; Porthan, Viitasalo, & Jula, 2009; Shi, Harding, & Larsen, 2016; Zabel et al., 2000, 2002).

In the final meta-analysis, 11,528 subjects (mean age: 47 years old, 72% male) with a follow-up duration of 43 ± 6 months were included. TCRT was studied in different clinical settings: myocardial infarction in six studies, heart failure in two studies, coronary artery disease in two studies, ICD implant subjects in one study, end-stage renal failure in one study, and the general population in one study. Table 1 shows the baseline characteristics of these studies and of the study populations. Six were prospective studies and 7 were retrospective studies.

Twelve of the 13 studies reported significant, inverse relationship between TCRT and increased risk of VT/VF or mortality. The pooled meta-analysis demonstrated that TCRT was significantly lower in patients with adverse events (syncope, ventricular arrhythmias, or sudden cardiac death) compared to those who did not suffer from these events across the range of clinical conditions studied ($I^2 = 99\%$) (standard mean difference = −0.34 ± 0.14, $p < .05$; Figure 2). The Cochrane's Q value was greater than the degrees of freedom (1,221 vs. 12), indicating that the true effect size was different between studies. Funnel plot plotting standard errors or precision against the logarithms of the odds ratio are shown in Figures S1 and S2, respectively.

TABLE 1 Characteristics of the 13 studies included in this meta-analysis

First author/ Year	Study design	Pathology	Sample size (*n*)	TCRT cutoff (ms)	Age	% Male	Endpoints	Follow-up (months)	Variables in multivariate model	Quality score	Ref
Shi 2016	P	ICD implant (ischemic heart disease and dilated cardiomyopathy)	150	−0.90	59	81	VT/VF	26	Male gender, secondary prevention, presence of premature ventricular beat, spatial QRS-T angle, T-wave morphology dispersion, relative T-wave residuum	8	(Shi et al., 2016)
Kentta 2011	P	Bicycle stress test in ischemic heart disease	1297	0.30	56	67	SCD	45	Age, sex, body mass index, LVEF, smoking, beta-blockers, diabetes, coronary heart disease, previous myocardial infarction, baseline heart rate, maximum heart rate, heart rate recovery at 1 min post-exercise, metabolic equivalent, ST-segment depression during baseline and maximum depression during the exercise test.	6	(Kentta et al., 2011)
Huang 2009	R	Heart failure	650	−0.47	63	72	CVD	32	Age, diabetes mellitus, hypertension, dyslipidemia, etiology of systolic heart failure, hemoglobin, serum creatinine, medication use (including β-blockers, angiotensin-converting enzyme inhibitor, angiotensin-II receptor blocker, spironolactone, or amiodarone), QRS duration, QT maximum and dispersion, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular mass	8	(Huang et al., 2009)
Lin 2009	R	Heart failure	27	−0.45	63	93	VT/VF	–	Age, gender, left ventricular ejection fraction, left ventricular hypertrophy	9	(Lin et al., 2009)
Porthan 2009	P	General population	5917	0.21	52	45	CVD	71	Age, current smoking status, body mass index, systolic BP, diastolic BP, total cholesterol/ high-density lipoprotein ratio, ECG LVH status, as well as history of hypertension, diabetes mellitus, coronary heart disease, and myocardial infarction), QT interval, principal component analysis ratio, T-wave morphology dispersion, T-wave residuum	6	(Porthan et al., 2009)
Korhonen 2009	P	Myocardial infarction	158	−0.02	61	10	Arrhythmic events	50	For BSPM: TLL (HR [CI] = 5.5 [2.0–14.6]), PCA3 (HR [CI] = 2.9 [1.0–8.0] as predictors of arrhythmic events. For 12-lead ECG, only TLL showed prediction (HR [CI] = 3.7 [1.4–9.9]). No parameter in BSPM or 12-lead ECG predicted total mortality.	6	(Korhonen et al., 2009)
Lin 2007	R	End-stage renal failure requiring hemodialysis	325	−0.30	64	14	CVD	26	Age, sex, BMI, hypertension, diabetes, prevalent CAD, smoking, albumin, LVEF, LVMI, LVH, left ventricular dilatation	5	(Lin et al., 2007)

(Continues)

TABLE 1 (Continued)

Perkiömäki 2006	P	Myocardial infarction	437	−0.76	61	77	CVD	43	Age, gender, and clinical characteristics, including ejection fraction, history of AMI, diabetes, AMI type, AMI location, New York Heart Association (NYHA) class, and statin, aspirin, warfarin, angiotensin-converting enzyme inhibitor/angiotensin-II receptor blocker, diuretic, and digitalis use	6	(Perkiomaki et al., 2006)
Malik 2004	R	Myocardial infarction	466	−0.37	58	9	SCD	60	LVEF, mean HR, HRVi, TS	6	(Malik et al., 2004)
Batchvarov 2003	R	Myocardial infarction	681	−0.88	57	82	CVD	33	(univariate)	7	(Batchvarov et al., 2003)
Zabel 2002	R	Veterans with cardiovascular disease	772	−0.17	61	10	All-cause mortality	10	Age, LVEF, BSA, LVH, relative TWR, absolute TWR, CR, TMD	5	(Zabel et al., 2002)
Hnatkova 2001	R	Myocardial infarction	319	−0.12	61	14	VT/VF	–	(univariate)	6	(Hnatkova et al., 2001)
Zabel 2000	P	Myocardial infarction	261	−0.16	58	11	SCD	32	Age, HR, LVEF, SDNN (*SD* of RR intervals on 24 hr holter), B-blockers, reperfusion therapy	6	(Zabel et al., 2000)

P, prospective; R, retrospective; ICD, implantable cardioverter-defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation; SCD, sudden cardiac death; CVD, cardiovascular death; ECG, electrocardiography.

Begg and Mazumdar rank correlation analysis demonstrated that Kendall's tau took a value of −0.32 with $p > .05$, suggesting no significant publication bias. Egger's test demonstrated no significant asymmetry (intercept 0.67, t value 0.13; $p > .05$). To identify the source of the heterogeneity, sensitivity analysis was performed by removing one study at a time to calculate the pooled mean difference (Figure 3). Removal of the Shi 2016 study led to a significant decrease in the mean difference to 0.23 ± 0.06 (Shi et al., 2016).

Subgroup analyses were performed for the different diseases. Data from six studies on myocardial infraction involving 2,322 subjects were included. The mean age was 52 years old with 82% male with a follow-up duration of 44 ± 5 months. All six studies consistently reported a positive association between decreased TCRT and increased risk of adverse events although the Korhonen 2009 and Zabel 2000 studies did not reach significance (Korhonen et al., 2009; Zabel et al., 2000). The pooled meta-analysis demonstrated that TCRT was significantly lower in event-positive compared to event-negative groups (mean difference = −0.36 ± 0.05, $p < .001$; Figure 4). The Cochrane's Q value was greater than the degrees of freedom (10 vs. 5), suggesting that true effect size was different in these studies. I^2 took a value of 48%, suggesting the presence of moderate heterogeneity. Funnel plot plotting standard errors or precision against the logarithms of the odds ratio are shown in Figs S3 and S4, respectively. Begg and Mazumdar rank correlation analysis demonstrated that Kendall's tau took a value of 0 with $p < .05$, suggesting significant publication bias. Egger's test demonstrated no significant asymmetry (intercept 0.25, t value 0.29; $p > .05$). To identify the source of the heterogeneity, sensitivity analysis was performed by removing one study at a time but this did not alter the pooled mean difference (Figure 5).

Data from two studies on heart failure involving 795 subjects were included. The mean age was 63 years old with 75% male. The two studies demonstrated opposite results, in associating increased risk of adverse events with higher and lower TCRT values. The pooled meta-analysis demonstrated that TCRT was not significantly different between event-positive and event-negative groups (mean difference = −0.01 ± 0.10, $p > .05$; Figure 6). The Cochrane's Q value was greater than the degrees of freedom (5 vs. 1), suggesting that true effect size was different in these studies. I^2 took a value of 80%, suggesting the presence of substantial heterogeneity. To identify the source of the heterogeneity, sensitivity analysis was performed by removing one study at a time but this did not alter the pooled mean difference (Figure 7).

4 | DISCUSSION

Over the past decade, the relationship between the QRS complex and the T wave has been an area of intense research. Previous studies have demonstrated that the spatial QRS/T angle, which describes the angle between depolarization and repolarization, was an independent predictor of arrhythmic and mortality outcomes, as confirmed by a recent systematic review and meta-analysis (Zhang, Zhu, & Zhu, 2015). Total cosine R-to-T (TCRT) is the cosine of the angle between

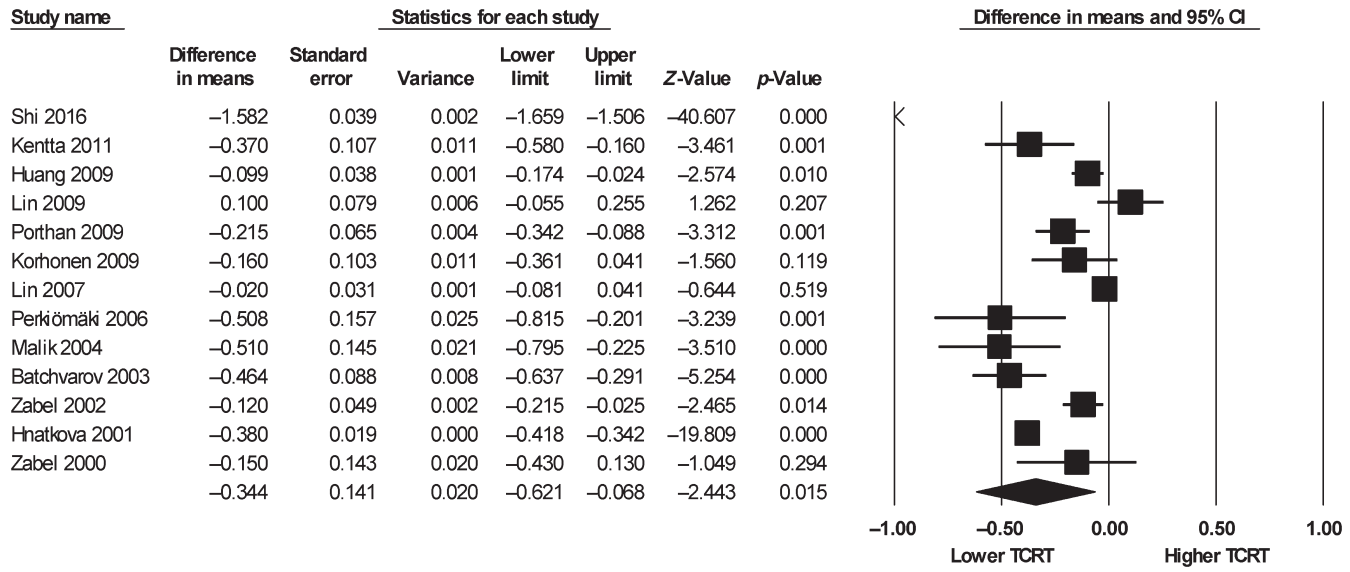

FIGURE 2 Forest plot demonstrating the mean differences of TCRT between event-positive and event-negative patients in the different disease populations

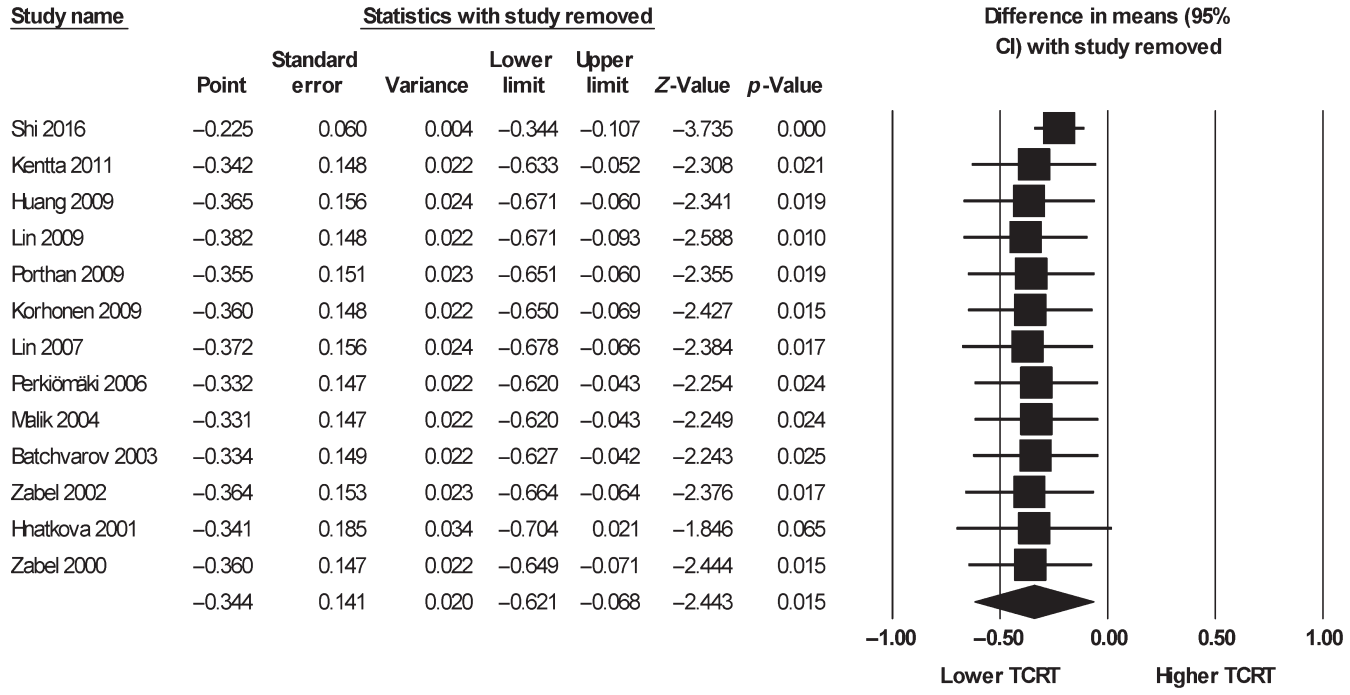

FIGURE 3 Forest plot demonstrating the results of sensitivity analysis by removing one study at a time

the vectors of the QRS and T-wave loops in three-dimensional space, reflecting the spatial difference between depolarization and repolarization wavefronts. It can have values between −1 and +1, which correspond to 180°–0°, respectively (Kentta et al., 2011). Smaller values reflect large differences in the direction of the two loops, which theoretically increases the likelihood of developing arrhythmias. In healthy individuals, TCRT is greater than 0.4 (Porthan et al., 2009). Vectorcardiographic (VCG) descriptors of ventricular electrophysiology, of which TCRT is an example, have several advantages over traditional ECG descriptors. These include ease of measurements, reduced susceptibility to observational biases, noise, problems of accurate definitions as well as better reproducibility.

TCRT has been used for risk stratification owing to its ability to predict arrhythmic or mortality outcomes. Thus, decreases in TCRT have been associated with increased ventricular arrhythmogenicity (Batchvarov, Hnatkova, Poloniecki, Camm, & Malik, 2004), sudden cardiac death (Malik, Hnatkova, & Batchvarov, 2004), cardiovascular mortality (Huang et al., 2009), and all-cause mortality (Porthan et al.,

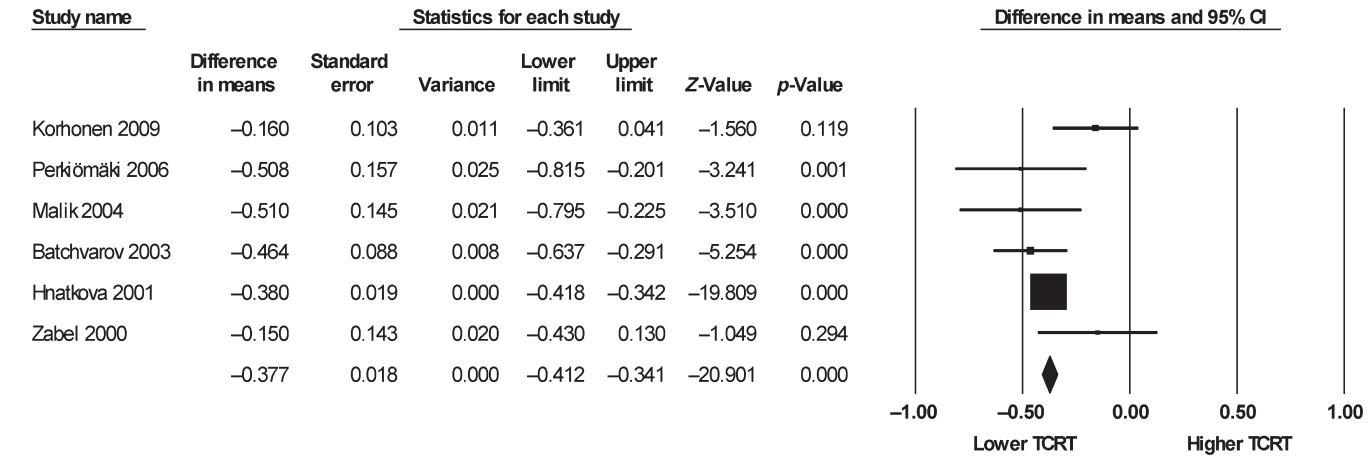

FIGURE 4 Forest plot demonstrating the mean differences of TCRT between event-positive and event-negative patients in myocardial infarction patients

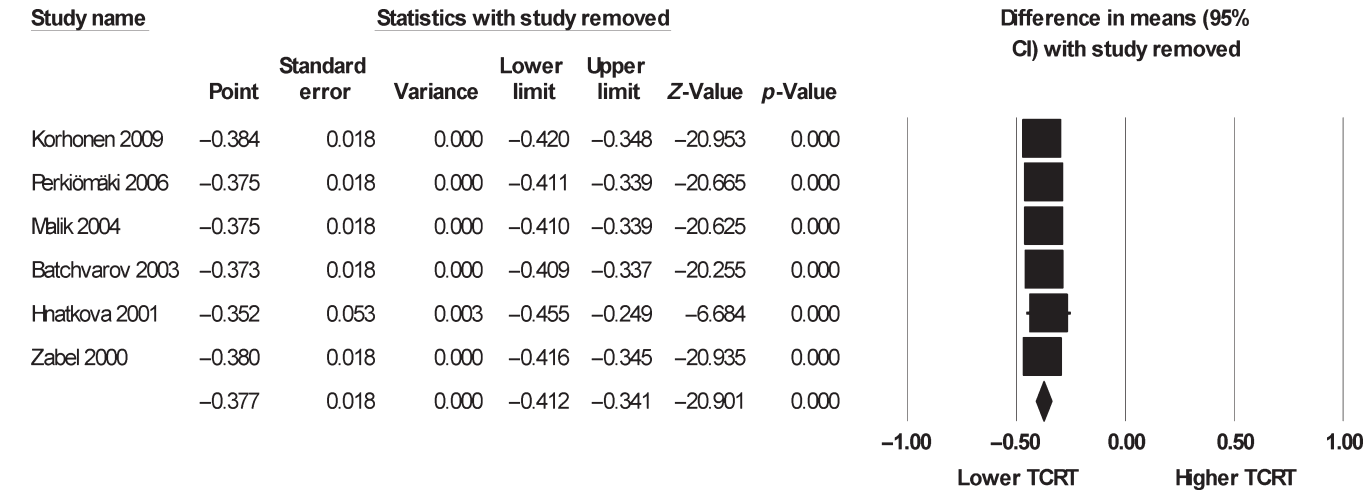

FIGURE 5 Forest plot demonstrating the results of sensitivity analysis by removing one study at a time for studies that examined outcomes in myocardial infarction patients

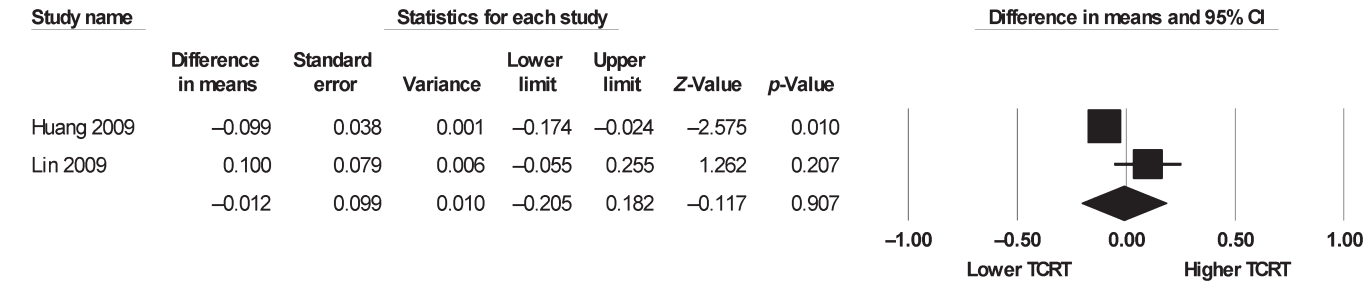

FIGURE 6 Forest plot demonstrating the mean differences of TCRT between event-positive and event-negative patients in heart failure patients

2009). However, data from a number of studies have failed to demonstrate its prognostic value (Korhonen et al., 2009; Lin et al., 2007; Perkiomaki et al., 2006). Our meta-analysis found that a decrease in the TCRT was a significant predictor of ventricular arrhythmias and mortality. For subgroup analyses, TCRT demonstrated predictive value for risk stratification in myocardial infarction, but not in heart failure.

5 | LIMITATIONS

There are some limitations of this systematic review and meta-analysis. First, some studies included in our studies are retrospective studies, which may have more recall bias. Second, while our pooled mean difference for TCRT was significant for myocardial infraction

Study name	Statistics with study removed						
	Point	Standard error	Variance	Lower limit	Upper limit	*Z*-Value	*p*-Value
Huang 2009	0.100	0.079	0.006	–0.055	0.255	1.262	0.207
Lin 2009	–0.099	0.038	0.001	–0.174	–0.024	–2.575	0.010
	–0.012	0.099	0.010	–0.205	0.182	–0.117	0.907

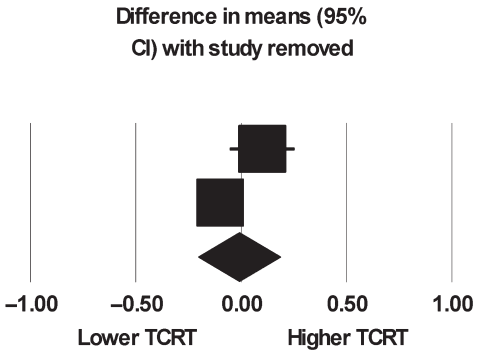

FIGURE 7 Forest plot demonstrating the results of sensitivity analysis by removing one study at a time for studies that examined outcomes in heart failure patients

who suffered from adverse cardiac events compared to those who did not, TCRT was not significantly different between event-positive and event-negative groups in heart failure. This is likely due to the small number of studies and small sample size.

6 | CONCLUSION

TCRT can distinguish patients at high risk of ventricular arrhythmias and sudden cardiac death from those at a low risk particularly in the context of myocardial infarction. It can provide additional risk stratification beyond the use of clinical and traditional ECG parameters.

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CONFLICT OF INTEREST

None declared.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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