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Incremental diagnostic and prognostic value of the QRS-T angle, a 12-lead ECG marker quantifying heterogeneity of depolarization and repolarization, in patients with suspected non-ST-elevation myocardial infarction

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A B S T R A C T

Background: The value of the 12-lead ECG in the diagnosis of non-ST-elevation myocardial infarction (NSTEMI) is limited due to insufficient sensitivity and specificity of standard ECG criteria. The QRS-T angle reflects depolarization–repolarization heterogeneity and might assist in detecting patients with a NSTEMI (diagnosis) as well as predicting patients with an increased mortality risk (prognosis).
Methods: We prospectively enrolled 2705 consecutive patients with symptoms suggestive of NSTEMI. The QRS-T angle was automatically derived from the standard 10 s 12-lead ECG recorded at presentation to the ED. Patients were followed up for all-cause mortality for 2 years.
Results: NSTEMI was the final diagnosis in 15% ($n = 412$) of patients. QRS-T angles were significantly greater in patients with NSTEMI compared to those without ($p < 0.001$). The use of the QRS-T angle in addition to standard ECG criteria indicative of ischemia improved the diagnostic accuracy for NSTEMI as quantified by the area under the ROC curve from 0.68 to 0.72 ($p < 0.001$). An algorithm for the combined use of standard ECG criteria and the QRS-T angle improved the sensitivity of the ECG for NSTEMI from 45% to 78% and the specificity from 86% to 91% ($p < 0.001$ for both comparisons). The 2-year survival rates were 98%, 97% and 87% according to QRS-T angle tertiles ($p < 0.001$).
Conclusion: In patients with suspected NSTEMI, the QRS-T angle derived from the standard 12-lead ECG provides incremental diagnostic accuracy on top of standard ECG criteria indicative of ischemia, and independently predicts all-cause mortality during 2 years of follow-up.

1. Introduction

As highly effective treatments are available, the early and accurate detection of acute myocardial infarction (AMI) is crucial. The 12-lead electrocardiogram (ECG) is the central tool for the early detection of AMI (diagnosis), and complements clinical assessment and cardiac troponin (cTn) [1–3]. The rapid identification of patients with ST-segment elevation MI (STEMI) based on the ECG followed by immediate coronary revascularization has resulted in improved survival over the past decade [1].

In contrast, in patients without ST-segment elevations and suspected non-ST-elevation MI (NSTEMI), the ECG is usually not

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diagnostic [2,3]. The sensitivity of ECG criteria indicative of NSTEMI recommended in current guidelines, ST-depressions and T-wave inversions, is insufficient [2–4]. The specificity is limited because these ECG changes may be observed in other cardiac conditions such as acute pericarditis or cardiomyopathies, or in the presence of ECG confounders such as left ventricular hypertrophy (LVH) or bundle branch blocks, particularly left bundle branch block (LBBB) and others [2]. Additional ECG markers indicative of NSTEMI with better sensitivity and applicability also in patients with ECG confounders are an unmet clinical need.

The QRS-T angle measured between the QRS axis and the T-wave axis reflects heterogeneity between depolarization (QRS) and repolarization (T-wave). A small QRS-T angle reflects concordant T-waves and a large QRS-T angle discordant T-waves, however quantified in a continuous rather than a categorical variable. The QRS-T angle was found to predict all-cause mortality (prognosis) [5], cardiac death in the general population [6], cardiac-related admissions and death in patients with chronic heart failure [7] and adverse events after AMI [8]. One pilot study suggested that the QRS-T angle might assist in the diagnosis of AMI [9].

We performed a large observational multicenter cohort study to examine the diagnostic and prognostic value of the QRS-T angle in unselected patients presenting to the emergency department (ED) with symptoms suggestive of NSTEMI.

2. Methods

2.1. Study design and population

Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective international multicenter study designed to advance the early diagnosis of AMI (ClinicalTrials.gov registry, number NCT00470587) [4,10–12].

Unselected patients presenting to the ED with symptoms suggestive of AMI (such as acute chest discomfort and angina pectoris) with an onset or peak within the last 12 h and an age ≥18 years were recruited. Patients with terminal kidney failure requiring dialysis were excluded.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients. The authors designed the study, gathered, and analysed the data according to the STARD guidelines for studies of diagnostic accuracy [13] (see Supplemental Appendix), vouch for the data and analysis, wrote the paper, and decided to publish.

2.2. Routine clinical assessment

All patients underwent a clinical assessment that included medical history, physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood test, and chest radiography. Levels of high-sensitive cardiac Troponin T (hs-cTnT, Roche Diagnostics) were measured at presentation and serially thereafter as long as clinically indicated. For hs–cTnT, limit of blank and limit of detection have been determined to be 3 ng/L and 5 ng/L, an imprecision corresponding to 10% coefficient of variation was reported at 13 ng/L and the 99th-percentile of a healthy reference population at 14 ng/L [14]. Timing and treatment of patients was left to the discretion of the attending physician.

2.3. Adjudication of final diagnoses

Adjudication of the final diagnosis was performed in the core lab of the University Hospital Basel. Two independent cardiologists reviewed all available medical records including patient history, physical examination, results of laboratory testing (including serial hs-cTnT levels) [4,10–12,15–20], radiologic testing, ECG, echocardiography, cardiac exercise test, lesion severity and morphology in coronary angiography - pertaining to the patient from the time of ED presentation to 90-day follow up. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist.

AMI was defined and cTn levels interpreted as recommended in current guidelines [2,21–23]. In brief, AMI was diagnosed when there was evidence of myocardial necrosis with a significant rise and/or fall in a clinical setting consistent with myocardial ischemia [2,21]. Details on the adjudication in the derivation and validation cohort are given in the online Supplemental Appendix.

2.4. Recording of digital ECG's and automated calculation of the QRS-T angle, the ECG score and automated analysis of the ECG confounder type

Ten second resting 12-lead ECGs were acquired during standard clinical assessment of patients in the ED and using an AT-110 ECG device (Schiller AG, Baar, Switzerland) or a Page Writer TC30 ECG device (Philips Healthcare, Andover, MA, USA). The digital ECG raw data was recorded using a sampling rate of 500 Hz, a resolution of 5uV/bit and a diagnostic signal bandwidth of 0.05 Hz to 150 Hz (fulfilling the requirements by current international ECG device standards).

The frontal plane QRS axis and the T-wave axis were measured automatically from the 12-lead ECG raw data using the ETM V01.12.09.00 ECG analysis program (Schiller AG, Baar, Switzerland). The QRS-T angle was calculated as the absolute difference between the QRS axis and the T wave axis. If such a difference exceeded 180°, then the value was subtracted from 360° (Supplemental Fig. 1).

Automated analysis of the ECG confounder types was classified based on automated diagnostic statement codes (ETM V01.12.09.00, Schiller AG, Baar, Switzerland), QRS duration, and QRS-axis as previously reported by Strauss et al. [24] (see online Supplemental Appendix for details).

2.5. Manual analysis of standard 12-lead ECG's

All 12-lead resting ECG's were manually interpreted in the ECG core lab at the University Hospital Basel by internal-medicine specialists blinded to the clinical and biochemical patient details. ECG manifestations indicative of AMI in the absence of ST-elevations, i.e. ST-depressions, T-wave inversions and LBBB were defined as recommended in current guidelines [2].

2.6. Follow-up

After hospital discharge, patients were contacted after 3, 12 and 24 months by telephone calls or in written form. Information regarding death was furthermore obtained from the national registry on mortality, the hospital's diagnosis registry and the family physician's records.

2.7. Statistical analysis

Continuous variables are presented as mean (standard deviation) or median (interquartile range [IQR]); categorical variables as numbers and percentages. Differences in baseline characteristics between patients with and without AMI were assessed using the Mann-Whitney *U* test for continuous variables and the Pearson Chi Square test for categorical variables. Correlations among continuous variables were assessed with the use of the Spearman rank-correlation coefficient.

The independent diagnostic value of the QRS-T angle was assessed by calculation of the significance of the QRS-T coefficient in the internally validated multivariable logistic regression. A linear logistic regression model was fitted and validated to assess the performance of combinations of diagnostic predictors, for example ECG-Score and QRS-T angle. The diagnostic accuracy was estimated using optimism-adjusted C-Statistics. Comparison of C-Statistics was performed as recommended by DeLong [25] and Hanley [26]. The ECG-Score and the QRS-T angle were also binarized and incorporated into a simple algorithm (Fig. 2). The simple algorithm was compared to the binary ECG-Score. Optimal diagnostic cut-off values were selected based on the

Youden-index. To assess the diagnostic performance, sensitivity and specificity were calculated using standard formulas and compared using McNemar's test. Decision curve analysis was used to estimate clinical usefulness of the diagnostic models [27]. The net benefit estimates, true-positive minus false-positive weighted by the respective probability threshold, were computed using 5-fold cross validation.

Cumulative survival rates during 2 years of follow-up according to QRS-T angle tertiles were plotted in Kaplan-Meier curves, and the log-rank test was used to assess differences in mortality between groups. The Independent prognostic value of the QRS-T angle was assessed by calculation of the significance of the QRS-T coefficient in the internally validated multivariable cox regression model. The prognostic accuracy was estimated using optimism-adjusted C-Indices. Decision curve analysis was used to estimate clinical usefulness of the prognostic models [27]. Comparison of correlated C-Indices was performed as recommended by Kang [28].

A models calibration is reported as intercept, the extent of systematically too low or to large predictions, and the slope [29]. All hypothesis testing was two-tailed and p-values <0.05 were considered statistically significant. All models were built and internally validated by bootstrapping using Frank Harrell rms package for R [30]. All statistical analyses were performed using R 3.3.1 [31] with package rms [30] and Survival 2.39.5 [32,33].

3. Results

3.1. Enrolment and characteristics of patients

From April 2006 to August 2015, a total of 4215 unselected patients were enrolled. Patients without a digital 12-lead ECG were excluded from analysis (n = 1288), as were patients with STEMI (n = 155), because no additional ECG markers are needed in those patients. Furthermore, patients with ventricular pacing (n = 56), patients in ventricular tachyarrhythmia (VT; n = 3), with WPW syndrome (n = 3) and patients with technical ECG artefacts (n = 5) were excluded, leaving 2705 patients for analysis (Supplemental Fig. 2).

Baseline characteristics of the 2705 patients with suspected NSTEMI are part of the appendix (Appendix Supplemental Table 1). The adjudicated final diagnosis was NSTEMI in 15% patients (n = 412). Among the patients with other causes of chest pain, unstable angina was the diagnosis in (12%) (n = 274), cardiac symptoms of origin other than CAD in 17% (n = 382), non-cardiac symptoms in 67% (n = 1537), and symptoms of unknown origin in 4% (n = 100).

3.2. Levels of the QRS-T angle

Overall, the median QRS-T angle was 27° (IQR [12, 55]). The distribution of several clinical baseline characteristics across QRS-T angle tertiles is shown in Table 1. Patients with greater QRS-T angles were older and had more cardiovascular risk factors as well as more often a history of coronary artery disease (CAD), AMI and myocardial revascularisation. Furthermore, patients with greater QRS-T angles had higher heart rates, a longer QRS duration and a longer QTc interval. QRS axis angles decreased in categories with greater QRS-T angles, while T-wave axis angles increased.

Presence and type of ECG confounders of cardiac de- and repolarization resulted in significant changes in the QRS-T angle. The ECG was free of confounders in 83% of patients. Overall isolated right bundle branch

Table 1
Baseline characteristics of patients in relation to QRS-T angle tertiles.

	Tertile 1	Tertile 2	Tertile 3	p value
	[0, 16°]	(17, 41°]	(42, 180°]	
	(n = 920)	(n = 886)	(n = 899)	
Age -yr	55 [44, 67]	58 [46, 71]	70 [56, 79]	<0.001
Male gender – no. (%)	634 (69)	607 (69)	613 (68)	0.946
Risk factors – no. (%)				
Hypertension	453 (49)	497 (56)	659 (73)	<0.001
Hypercholesterolemia	371 (40)	382 (43)	507 (56)	<0.001
Diabetes	90 (10)	119 (13)	197 (22)	<0.001
Current smoking	288 (31)	240 (27)	175 (19)	<0.001
History of smoking	323 (35)	301 (34)	386 (43)	<0.001
History – no. (%)				
Coronary artery disease	250 (27)	258 (29)	415 (46)	<0.001
Previous myocardial infarction	179 (19)	174 (20)	308 (34)	<0.001
Previous revascularization	217 (24)	226 (26)	350 (39)	<0.001
ECG findings - no. (%)				
Heart rate (bpm)	70 [61, 80]	71 [62, 81]	74 [65, 88]	<0.001
QRS duration (ms)	96 [88, 102]	96 [88, 102]	100 [90, 115]	<0.001
QTc time (ms)	423 [408, 440]	426 [410, 443]	442 [420, 464]	<0.001
ECG confounders				
No ECG confounder	838 (91)	807 (91)	594 (66)	<0.001
Intermediate ECG confounders	72 (8)	69 (8)	117 (13)	<0.001
Right bundle branch block (RBBB)	18 (2)	15 (2)	28 (3)	0.098
Left ventricular hypertrophy (LVH)	54 (6)	54 (6)	89 (10)	0.001
Remarkable ECG confounders	10 (1)	10 (1)	188 (21)	<0.001
Left anterior fascicular block (LAFB)	0 (0)	1 (0)	42 (5)	<0.001
Right bundle branch block and left anterior fascicular block LAFB (RBBB + LAFB)	1 (0)	2 (0)	39 (4)	<0.001
Nonspecific bundle branch block (NBBB)	4 (0)	6 (1)	50 (6)	<0.001
Left bundle branch block (LBBB)	5 (1)	1 (0)	57 (6)	<0.001
Standard ECG changes indicative of ischemia				
No ECG changes indicative of ischemia	849 (92)	804 (91)	570 (63)	<0.001
ST-depression	25 (3)	41 (5)	139 (16)	<0.001
T-inversion	48 (5)	48 (5)	210 (23)	<0.001
Left bundle branch block (LBBB)	5 (1)	1 (0)	57 (6)	<0.001
Biomarker				
hs-cTnT (ng/L)	6 [4, 11]	7 [4, 13]	14 [7, 36]	<0.001
Diagnosis - no. (%)				
NSTEMI	83 (9)	98 (11)	231 (26)	<0.001

ECG denotes electrocardiogram; hs-cTnT denotes high-sensitivity cardiac troponin; NSTEMI denotes non-ST-elevation myocardial infarction; numbers are presented as median (IQR) or numbers (%).

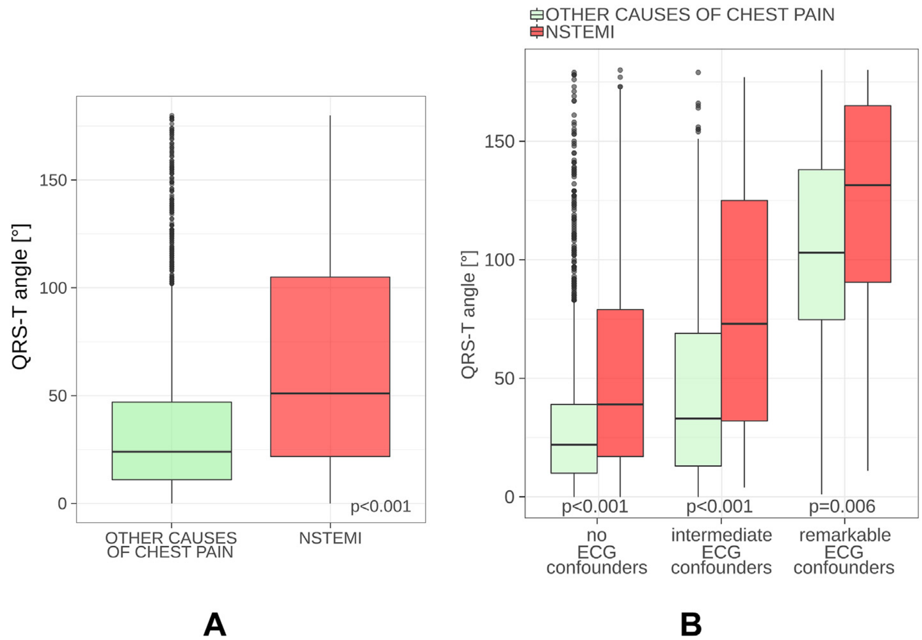

Fig. 1. Levels of the QRS-T angle in patients with NSTEMI and other causes of chest pain. Panel A shows QRS-T angle levels in patients with Non-ST-Elevation Myocardial infarction (NSTEMI) and those with other causes of chest pain. In the ECG's recorded at presentation to the emergency department. Panel B shows QRS-T angle levels of patients with and without NSTEMI for the group of patients with no ECG confounders (none), with intermediate ECG confounders (RBBB or LVH) and for those with remarkable ECG confounders (LAFB, RBBB + LAFB, LBBB or NBBB). Boxes represent IQR's, while whiskers display ranges (without outliers further than 1.5 IQR's from the respective end of the box).

block (RBBB) was present in 2%, combined right bundle branch and left bundle branch block (RBBB + LAFB) in 2%, isolated left anterior fascicular block (LAFB) in 2%, complete left bundle branch block (LBBB) in 2%, non-specific bundle branch block (NBBB) in 2% and left ventricular hypertrophy (LVH) in 7%.

As shown in Supplemental Fig. 3, the smallest QRS-T angles were observed in patients without ECG confounders. Intermediate elevations were found in patients with isolated RBBB or LVH. The greatest QRS-T angles were found in patients with remarkable ECG confounders including LAFB, RBBB + LAFB, NBBB or LBBB.

3.3. Diagnostic value of the QRS-T angle

The QRS-T angle was significantly greater in patients with NSTEMI as compared to patients with other causes of chest pain (51° (IQR [22, 105]) vs. 24° (IQR [11, 47], $p < 0.001$, Fig. 1A). Accordingly, the diagnostic accuracy of the QRS-T angle at presentation for the diagnosis of NSTEMI as quantified by the AUC in the overall cohort was 0.67 (95% confidence interval (CI) [0.64, 0.70]).

As shown in Fig. 1B, QRS-T angles were significantly higher in patients with NSTEMI as compared to patients with other causes of chest

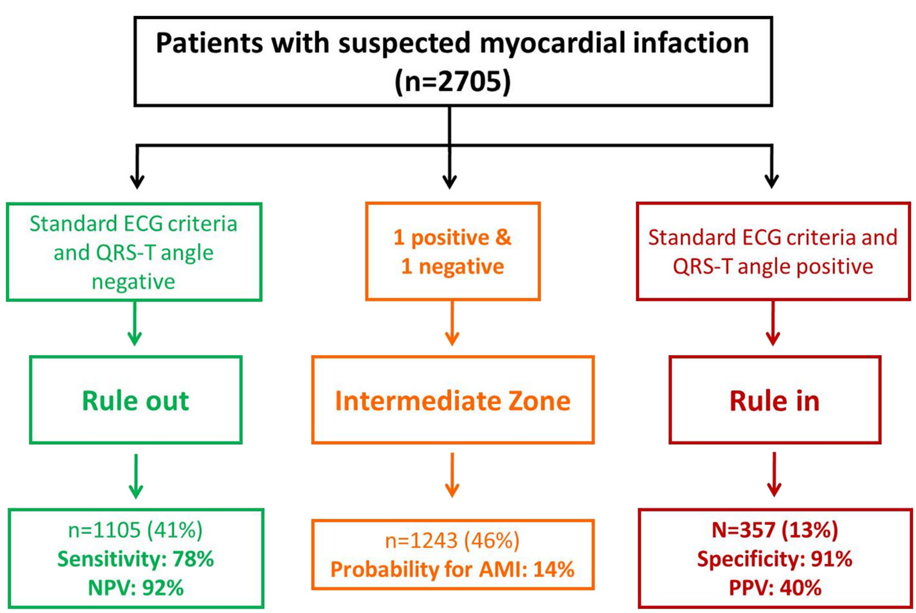

Fig. 2. Diagnostic performance of an algorithm for the combined use of standard ECG criteria and the QRS-T angle. Diagnostic performance of an algorithm for the combined use of standard ECG criteria indicative of ischemia and the QRS-T angle: patients negative for standard ECG criteria and negative for the QRS-T angle are triaged towards rule-out (left side in green). Patients with only one positive test result are in an intermediate zone (middle, orange). Patients with positive standard ECG criteria and positive QRS-T angle are triaged towards Rule-in (right side in red).

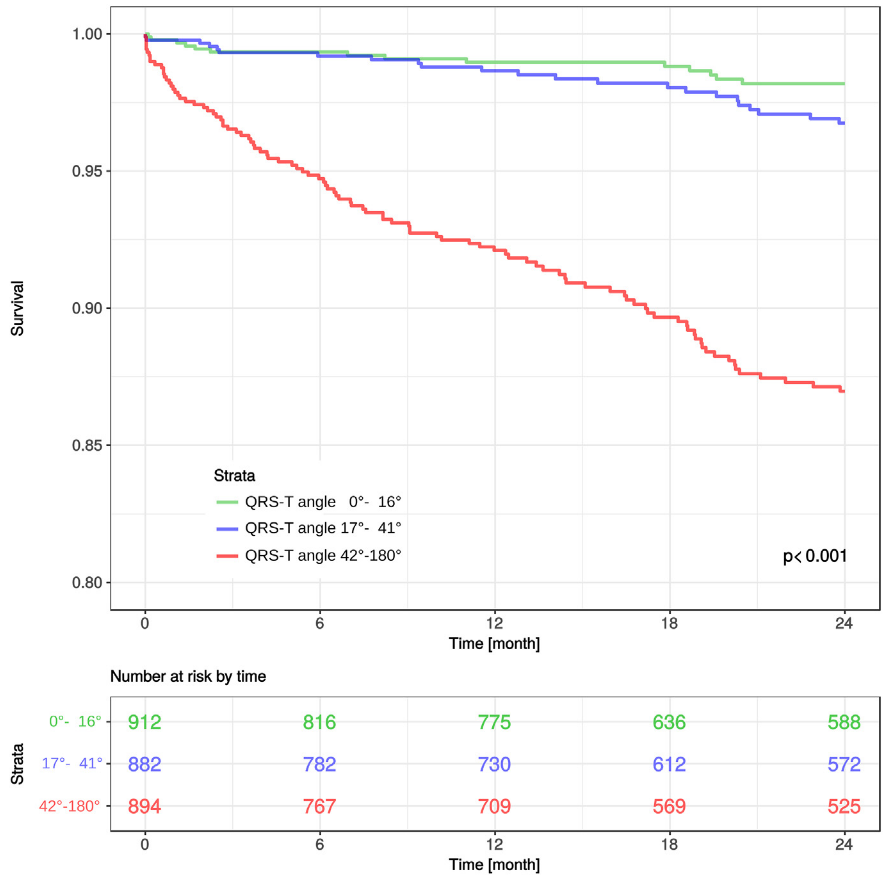

Fig. 3. Kaplan Meier curves for the cumulative survival according to Tertiles of the QRS-T angle. Kaplan Meier curves displaying survival during 2 years of follow-up according to tertiles of the QRS-T angle. Differences in survival were assessed using the log-rank test.

pain irrespective of the presence and type of ECG confounders (no confounders $p < 0.001$, intermediate confounders (RBBB or LVH) $p < 0.001$, remarkable confounders (LAFB, RBBB + LAFB, NBBB, LBBB) $p = 0.006$)). Accordingly, the AUC was similar for patients with no ECG confounders (AUC 0.65, 95% CI [0.61, 0.68], slope = 1.00, intercept = 0.00), intermediate ECG confounders (AUC 0.70, 95% CI [0.61, 0.80], slope = 1.09, intercept = 0.19) and remarkable ECG confounders (AUC 0.62, 95% CI [0.53, 0.71], slope = 1.26, intercept = 0.25) ($p > 0.2$ for all comparisons).

3.4. Incremental diagnostic value of the QRS-T angle in addition to standard ECG changes for the diagnosis of NSTEMI

Standard ECG changes indicative of AMI in the absence of ST-elevations, such as ST-depression, T-wave inversion and LBBB were found in 8%, 11% and 2%. Any of the three were present in 18%, significantly more often in patients with NSTEMI compared to those without (44% vs. 13%, $p < 0.001$). The presence of standard ECG changes indicative of ischemia reached a sensitivity of 45%, a specificity of 86%, a NPV of 87% and a PPV of 36% (Supplemental Table 2).

The rates of NSTEMI were 52% vs. 12% in patients with and without ST-depressions ($p < 0.001$), 33% vs. 13% in patients with and without T-wave inversions ($p < 0.001$) and 27% vs. 15% in patients with LBBB ($p = 0.01$). To quantify the weight observed for the individual standard ECG changes, an ECG score was calculated assigning 4 points for ST depressions, 3 points for T-wave inversions and 2 points for LBBB. The diagnostic accuracy of this ECG score for the diagnosis of NSTEMI as quantified by the area under the receiver operating characteristic curve (AUC) was 0.67 (95% CI 0.66–0.71, slope = 1.01, intercept = 0.01), which was similar compared to the QRS-T angle ($p = 0.32$).

The combination of the two markers significantly improved the diagnostic accuracy provided by the standard ECG marker score alone, with an AUC of 0.72 (95% CI 0.69–0.76, $p < 0.001$ for comparison, slope = 1.00, intercept = −0.01, Supplemental Fig. 4). This improvement was observed for both the subgroups of patients without and with ECG confounders (improvements in AUC from 0.67 to 0.72 and from 0.61 to 0.70, $p < 0.001$ for both comparisons). For a risk threshold probability of 0.1 the combination of ECG Score and QRS-T Angle predicts 17 more true positives per 1000 patients compared to the ECG Score alone (Supplemental Fig. 5). In multivariable binary logistic regression, the QRS-T angle provided independent diagnostic information on top of standard ECG parameters (Supplemental Table 3).

Given the observed influence of ECG confounders on QRS-T angle values, the optimal cut-off levels for dichotomization of the QRS-T angle as a diagnostic test for AMI were derived for each of the 3 groups of ECG confounders. The resulting optimal cut-off levels were 20° in patients with no ECG confounders, 50° for patients with intermediate ECG confounders and 100° for patients with remarkable ECG confounders. The use of the QRS-T angle as a binary test stratified for these cut-off levels resulted in a sensitivity of 69%, a specificity of 48%, a NPV of 90% and a PPV of 19% (Supplemental Table 2). The diagnostic performance of a simple algorithm for the combined use of standard ECG criteria indicative of ischemia (ST depression, T-wave inversion or LBBB) and the QRS-T angle is shown in Fig. 2. Compared to standard ECG criteria alone, the combined use of standard ECG criteria and the QRS-T angle improved the sensitivity for "rule-out" from 45% to 78% ($p < 0.001$) as well as the specificity for "rule-in" from 86% to 91% ($p < 0.001$).

3.5. Prognostic value of the QRS-T angle for the prediction of mortality during follow-up

During a median follow-up time of 25 (ICR [13,28]) months, there were 179 deaths in the whole cohort. Median QRS-T angle levels in deceased patients were significantly higher as compared to those in survivors (77° (IQR [34, 126]) vs. 25° (IQR [11, 49]), $p < 0.001$). Cumulative 24-months mortality rates were 98%, 97% and 87% according to QRS-T angles tertiles ($p < 0.001$, Fig. 3).

The prognostic value of the QRS-T angle for the prediction of death measured by C-index is 0.76 (95% CI 0.71–0.79) (slope = 1.00, intercept = 0.01), which was inferior compared to hs-cTnT (0.80, 95% CI 0.77–0.83, $p = 0.04$ for comparison) (slope = 1.05, intercept = 0.14).

In univariate Cox proportional hazard analysis, the QRS-T Angle predicted mortality with a Hazard Ratio of 1.32 (95%CI [1.26, 1.40], $p < 0.001$) per increase of 10°. In multivariable Cox proportional hazard analysis, the QRS-T Angle was independent of important clinical factors including age and hs-cTnT as well as independent of important ECG parameters including presence of ECG confounders, ECG signs indicative of ischemia, QRS duration and the QTc interval (Supplemental Table 4).

4. Discussion

This large observational study assessed the diagnostic and prognostic value of the QRS-T angle, a simple and easily available 12-lead ECG marker quantifying heterogeneity of depolarization and repolarization, in patients with suspected non-ST-elevation myocardial infarction. We report four major findings:

First, higher levels of the QRS-T angle were observed in patients that were older, had more cardiovascular risk factors and in those with known CAD or prior AMI. Furthermore, levels of the QRS-T angle were higher in the presence of ECG confounders such as bundle branch blocks or LVH. Second, the QRS-T angle was significantly higher in patients with NSTEMI as compared to patients with other causes of chest pain, irrespective of the presence of absence of ECG confounders. Accordingly, the diagnostic accuracy of the QRS-T angle for the diagnosis of AMI was 0.67 overall, and similar for patients with no ECG confounders (AUC 0.65), intermediate ECG confounders (AUC 0.70) and remarkable ECG confounders (AUC 0.62, $p > 0.2$ for all comparisons). Third, the use of the QRS-T angle in addition to standard ECG criteria indicative of ischemia improved the diagnostic accuracy for NSTEMI as quantified by the area under the ROC curve from 0.68 to 0.72 ($p < 0.001$). An algorithm for the combined use of standard ECG criteria and the QRS-T angle improved the sensitivity of the ECG for NSTEMI from 45% to 78% and the specificity from 86% to 91% ($p < 0.001$ for both comparisons). Fourth, the QRS-T angle was an independent and powerful predictor of all-cause mortality during follow-up with cumulative 2-year survival rates of 98%, 97% and 87% according to QRS-T angle tertiles ($p < 0.001$).

Our findings have clinical implications. The ECG is the cornerstone of the diagnosis of STEMI patients. In NSTEMI patients however, the standard ECG markers of ischemia being ST-segment depression, T-wave inversion and LBBB [2] have an acceptable specificity (86% in our study), but suffer from a low sensitivity (45% in our study). Unlike the recent progress with more sensitive cTn assays [4,9,12,14,16–20], progress in the acquisition, analysis and interpretation of the 12-lead ECG for an improved diagnosis of NSTEMI has been very limited. Accordingly, ECG markers with improved sensitivity for NSTEMI, that are simple, readily available and interpretable by a wide range of healthcare professionals, are a major unmet clinical need.

Previous studies have suggested a potential value for markers of depolarization, such as high-frequency components within the QRS complex [34,35] or for changes in QRS slopes, angles, vectors or the T-wave complexity ratio [36–38]. We could recently demonstrate that the V-index, a novel 12-lead ECG marker quantifying the spatial heterogeneity of ventricular repolarization, was significantly higher in NSTEMI patients compared to patients with chest pain of other causes, which resulted in an AUC of 0.66 [39]. The diagnostic accuracy of the QRS-T angle in the current study was similar (AUC 0.67), but the QRS-T angle has two important advantages over other markers such as the V-Index: First, QRS-axis and T-wave axis are automatically calculated by all standard 12-lead ECG machines from the standard 10 second ECG recordings and the QRS-T angle can then easily be calculated. Calculation of the QRS-T angle does not need neither a prolonged ECG recording duration (for example 5 min such as with the V-index) nor sophisticated software algorithms. Second, while most automated ECG markers can only be applied in the absence of ECG confounders such as bundle branch blocks or LVH, levels of the QRS-T angle were significantly elevated in NSTEMI without and with ECG confounders and accordingly can be used also in patients with ECG confounders.

It is important to highlight that the QRS-T angle should always be used in conjunction with standard ECG markers of ischemia rather than replacing them. Doing so, the combination of the two markers in a simple algorithm significantly improved the sensitivity of the ECG for NSTEMI from 45% to 78% and the specificity from 86% to 91%. Despite this remarkable improvement, the diagnostic performance is still clearly inferior compared to diagnostic algorithms based on high-sensitive troponins [10,40].

Hence, the search for other, more promising ECG markers of NSTEMI must go on. In addition to approaches focusing on markers derived from pathophysiological reasoning [34–39], an alternative approach could use advanced signal processing techniques (such as Fourier transformation, wavelet decomposition or principal component analysis) for extraction of large feature sets from the digital ECG followed by the application of machine learning algorithms for optimal classification of the NSTEMI ECGs [41,42].

In addition to the incremental diagnostic value, the QRS-T angle was also found to independently predict death during follow-up. This can likely be explained by the fact that a wider QRS-T angle reflects a mismatch between ventricular de- and repolarization, which can be the source for potentially lethal ventricular arrhythmias. Our findings extend and corroborate previous studies that found the QRS-T angle to predict cardiac death in the general population [6], cardiac-related admissions and death in patients with chronic heart failure [7] and adverse events after AMI [8]. Given that the QRS-T angle can be calculated easily in an automated fashion, it recently has been used to successfully screen entire health system ECG databases to identify patients at increased risk of death [24]. Our results agree with studies on the association of wide spatial QRS-T angle with all-cause mortality. Wide spatial QRS-T angle were, like wide QRS-T angles, strongly associated with higher incidence of all-cause mortality [5].

5. Limitations

Potential limitations of the present study merit consideration. First, our study was conducted in ED patients with symptoms suggestive of AMI. Further studies are needed to assess the value of the QRS-T angle in other patient populations, particularly for risk stratification of SCD in patients with heart failure. Second, we did not record serial ECG's in our patients, which could have increased the diagnostic value of the ECG due to the detection of dynamic ECG changes. Third, we have assessed the value of the QRS-T angle in patients at rest in the ED. Whether or not the marker would be helpful to detect myocardial ischemia in patients undergoing ECG stress testing cannot be answered from our data. There are multiple measures to quantify the heterogeneity of the cardiac depolarization and repolarization phase. The frontal projection of the QRS-T angle, as well as the spatial QRS-T angle, are scalar quantities and are therefore unable to take into account all aspects of QRS and T vectors. However, whether the frontal QRS-T angle or the spatial QRS-T angle is more suitable for the prediction of Coronary Heart Disease and all-cause mortality is still an ongoing research topic [43].

6. Conclusions

In conclusion, the QRS-T angle, a 12-lead ECG marker quantifying heterogeneity of depolarization and repolarization, provides incremental diagnostic accuracy for the diagnosis of NSTEMI on top of standard

ECG criteria, and independently predicts all-cause mortality during 2 years of follow-up.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.040.

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