ORIGINAL RESEARCH

ECG Criteria to Differentiate Between Takotsubo (Stress) Cardiomyopathy and Myocardial Infarction

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***Background*—**ECG criteria differentiating Takotsubo cardiomyopathy (TTC) from mainly anterior myocardial infarction (MI) have been suggested; however, this was in small patient populations.

***Methods and Results*—**Twelve-lead admission ECGs of consecutive 200 TTC and 200 MI patients were compared in dichotomized groups based on the presence or absence of ST-elevation MI (STEMI versus STE-TTC and non-ST elevation MI versus non ST-elevation-TTC). When comparing STEMI and STE-TTC, ST-elevation in –aVR was characteristic of STE-TTC with a sensitivity/specificity of 43% and 95%, positive predictive value (PPV) 91%, and a negative predictive value (NPV) 62% ($P<0.001$); when ST-elevation in –aVR is accompanied by ST-elevation in inferior leads, sensitivity/specificity were 14% and 98% (PPV was 89% and NPV 52%) ($P=0.001$), and 12% and 100% when associated with ST-elevation in anteroseptal leads (PPV 100%, NPV 52%) ($P<0.001$). On the other hand, STEMI was characterized by ST-elevation in aVR (sensitivity/specificity of 31% and 95% $P<0.001$, PPV 85% and NPV 59%) and ST-depression in V2-V3-V4 (sensitivity/specificity of 24% and 100% $P<0.001$, PPV 100% and NPV 76%). When comparing non-ST elevation MI and non ST-elevation-TTC, T-inversion in leads I-aVL-V5-V6 had a sensitivity/specificity of 17% and 97% for non ST-elevation-TTC (PPV 83% and NPV 55%) ($P<0.001$), and ST-elevation in –aVR with T-inversion in any lead was also specific for non ST-elevation-TTC (sensitivity/specificity of 8% and 100%, PPV 100% and NPV 53%) ($P=0.006$). In non-ST elevation MI patients, the presence of ST-depression in V2-V3 was specific (sensitivity/specificity of 11% and 99%, PPV 91% and NPV 51%) ($P=0.01$).

***Conclusions*—**ECG on admission can differentiate between TTC and acute MI, with high specificity and positive predictive value.

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Takotsubo cardiomyopathy (TTC), also called stress-induced cardiomyopathy, is characterized by a transient, reversible, regional systolic and diastolic dysfunction usually involving the left ventricular apex and midventricle with hyperkinesia of the basal left ventricular segments.[1–6] The early clinical features are similar to those of acute coronary syndromes including chest pain, ECG changes, and modest elevation in cardiac troponin.[1,6–8] The differential diagnosis can be challenging, especially in the presence of ST-segment elevation on the admission ECG, where a rapid treatment decision including reperfusion therapy is crucial.

Electrocardiographic characteristics at the time of presentation have been proposed as a means to differentiate between TTC and acute coronary syndromes,[9–16] but data are still insufficient, partially due to limited sample size of most studies and heterogeneity of study designs. In addition, the

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Accompanying Tables S1 through S5 and Figures S1 through S4 are available at http://jaha.ahajournals.org/content/5/6/e003418/DC1/embed/inline-supplementary-material-1.pdf

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majority of ECG studies compared TTC to only anterior myocardial infarction (MI). In fact, admission ECG patterns of TTC patients are diverse, and the prevalence of ST-elevation is quite variable, ranging from 11% to 100%.[3,5,17,18]

The aim of the present study was to compare admission ECG between TTC and acute MI including ST elevation MI (STEMI) and non-ST elevation MI (NSTEMI) in our large cohort of patients in order to define specific ECG changes that differentiate between both entities.

Methods

Study Population

We retrospectively included 200 consecutive patients who met the revised TTC Mayo Clinic diagnostic criteria[7,19] from 7 cardiovascular centers of 4 countries (Austria, Germany, Poland, and Switzerland) (Data S1) participating in the International Takotsubo Registry (InterTAK$_{Registry}$; www.takotsubo-registry.com; ClinicalTrials.gov number NCT01947621) between 2002 and 2012, and 200 consecutive patients admitted for MI[20] from the Zurich Acute Coronary Syndromes Registry from February until August 2013. The registry adhered to the requirements of the respective local ethics committee and all patients gave informed consent. Inclusion criteria were hospital admission less than 12 hours after the onset of acute coronary syndromes symptoms, followed by emergency coronary angiography; no electrocardiographic findings such as bundle branch block, intraventricular conduction disturbance, or ventricular rhythm; TTC was defined as transient akinesia or dyskinesia of the left ventricular apical and midventricular segments with regional wall motion abnormalities extending to the epicardial coronary artery.

The admission ECGs at hospital presentation were reviewed in a blinded manner by 2 experienced cardiologists. ECGs from patients with TTC were compared to ECGs of patients with MI. Dichotomization of all patients into 2 groups was performed based on the presence or absence of ST-segment elevation (ST-elevation) on ECG: STEMI versus TTC with ST-elevation and NSTEMI versus TTC without ST-elevation. Subgroups were compared and specific differentiating ECG criteria were identified to differentiate between both diseases.

Electrocardiogram

A 12-lead ECG was recorded on admission at a paper speed of 25 mm/s and an amplification of 10 mm/mV. he isoelectric line was defined as the level of the preceding TP segment. ST-segment deviation was measured to the nearest 0.5 mm at the J point as recommended by the third universal definition of myocardial infarction.[20] An ST-elevation was considered present if it was ≥1.0 mm in any leads. A T wave inversion (T-inversion) was considered present if the depth was >1.0 mm in any lead. ST-segment depression (ST-depression) was defined as horizontal or downsloping ST-segment deviation ≥1.0 mm in any lead. ST-depression in aVR, also known as ST-elevation in –aVR, was considered an independent entity from STEMI and NSTEMI.

We analyzed the following electrocardiographic findings: the presence or absence of ST-elevation in limb and precordial lead (subgroup when ST-elevation ≥2.0 mm in V2 and V3) and/or the presence or absence of ST-depression and/or T-inversion. ST-elevation magnitude, when existing, was also measured to the nearest 0.5 mm in all leads. Furthermore, ECG localization was categorized as follows: inferior changes when the ECG pattern met the criteria mentioned above in ≥2 of 3 leads (II, III, and avF), anteroseptal when it applies in ≥2 of 3 leads (V1, V2, and V3), lateral in ≥2 of 4 leads (I, avL, V5, and V6), and anterior in ≥4 of 6 leads (V1, V2, V3, V4, V5, and V6).[20,21] Basic parameters (ventricular rate, PR interval, QRS duration, and QT interval) were measured in all cases of ECG and corrected QT intervals (QTc) were measured using Bazett's formula (QTc=QT/RR interval).

Statistical Analysis

Continuous data are expressed as mean±SD. Comparisons of continuous data were performed using the unpaired Student *t* test or the Mann–Whitney *U* test and paired Student *t* test for evolution comparison. Categorical data were analyzed using the Fisher's exact test or the χ^2 test as well as the McNemar test for evolution. Based on the results of the univariate analysis comparing simple ECG parameters to differentiate between TTC and acute MI, combinations of the most significant ECG parameters were performed and analyzed accordingly. Sensitivity and specificity for the most significant ECG combinations as well as positive and negative predictive values (PPV and NPV) were then computed. Afterwards, ECG criteria for the differentiation between TTC and MI proposed in previously published studies were collected and re-analysis of the same criteria with the same subgroups of patients from our data was performed. A binary logistic regression was performed on 2 steps in each subgroup, analyzing the significant baseline and clinical characteristics in univariate analysis at first, then adding to the model the specific differential ECG combinations. A $P<0.05$ was considered statistically significant. All analyses were performed using SPSS version 20.0 for Windows (SPSS, Inc., Chicago, IL).

Results

TTC Versus MI

Two hundred TTC patients were compared with 200 MI patients. Baseline clinical characteristics are summarized in

Table 1. While the median age was similar, the percentage of women was much higher in the TTC group (91% versus 27%, $P<0.001$). Furthermore, MI patients had significantly higher body mass index, a higher rate of diabetes mellitus, dyslipidemia, smoking history and, by definition, known coronary artery disease. Ejection fraction on admission was lower in TTC patients (43% versus 51%, $P<0.001$), as were peak levels of troponin, creatinine kinase, and C-reactive protein. In-hospital complications, cardiogenic shock, and all-cause mortality were similar in both groups.

Admission ECG features upon admission in TTC and MI are shown in Figure 1, Table 2, and Table S1. QTc was longer in TTC patients, but QTc prolongation was not significant (102 [51%] versus 84 [42%] for TTC and MI, respectively, $P=0.088$). Heart rate was higher, PQ interval longer, and QRS width smaller in TTC patients. Normal ECG was present in 14% in both groups. ST-elevation was present in 56% (n=111) in TTC and 53% (n=106) in MI, respectively, $P=0.69$.

ST-depression was more common in all ECG leads in MI patients except aVR. Indeed, ST-elevation in –aVR was more prevalent in TTC (31%; n=62) than in MI (3%; n=6; $P<0.001$). Similarly, T-inversion occurred more often in TTC (45%; n=90) than in MI (22%, n=43; $P<0.001$), especially in lateral and anterior leads. Of note, T-inversion in TTC patients also occurred more frequently in isolated form, with no concomitant ST-elevation or ST-depression (22%, n=43 versus 12%, n=24; $P=0.016$) and was more commonly present in 5 leads (30%, n=60) in TTC than in MI patients (7%, n=13; $P<0.001$).

When considering differences according to clinical presentation between physical and emotional triggers, no significant differences were noted between groups except for patients with 1 particular emotional trigger. Interestingly, we have found that patients presenting for TTC after panic/fear/anxiety had significantly more ST-elevation on admission ECG compared with other TTC patients (16/18, 89% versus 95/182, 52% with ST-elevation between groups, $P=0.002$).

TTC With ST-Elevation Versus STEMI

One hundred eleven TTC patients with ST-elevation were then compared to 106 STEMI patients. Baseline characteristics,

Table 1. Characteristics of the Total Study Population; Comparison Between MI and TTC

	Total TTC N=200	Total MI N=200	*P* Value
Baseline characteristics			
Age, y*	65.5±12.1	65.8±12.3	0.62
Female	182 (91)	53 (27)	<0.001
BMI, kg/m²*	24.5±4.4	28.4±6.0	<0.001
Cardiovascular risk factors and cardiovascular history			
Hypertension	109 (55)	125 (64)	0.10
Diabetes mellitus	18 (9)	37 (19)	0.006
Ever-smoker	71 (36)	114 (57)	<0.001
Current smoker	38 (19)	86 (43)	<0.001
Dyslipidemia	52 (26)	109 (56)	<0.001
Positive family history of cardiovascular disease	50 (25)	53 (28)	0.65
Known CAD	11 (6)	31 (16)	0.001
Clinical and laboratory parameters			
EF at admission (%)*	43±10 (N=193)	51±11 (N=151)	<0.001
Peak troponin level (ULN)*	21.0±27.7 (N=187)	36.4±63.5 (N=200)	0.002
Peak CK level (ULN)*	2.5±7.3 (N=164)	7.5±10.2 (N=200)	<0.001
Peak CRP level, mg/L*	35.4±54.5 (N=173)	67.5±109.9 (N=192)	0.001
In-hospital complications			
Cardiogenic shock	16 (8)	19 (10)	0.60
All-cause mortality	8 (4)	10 (5)	0.64

Depicted are counts, N incidence (%). BMI indicates body mass index; CAD, coronary artery disease; CK, creatine kinase; CRP, C-reactive protein; EF, ejection fraction; MI, myocardial infarction; TTC, Takotsubo cardiomyopathy; ULN, upper limit of normal.
*Mean±SD.

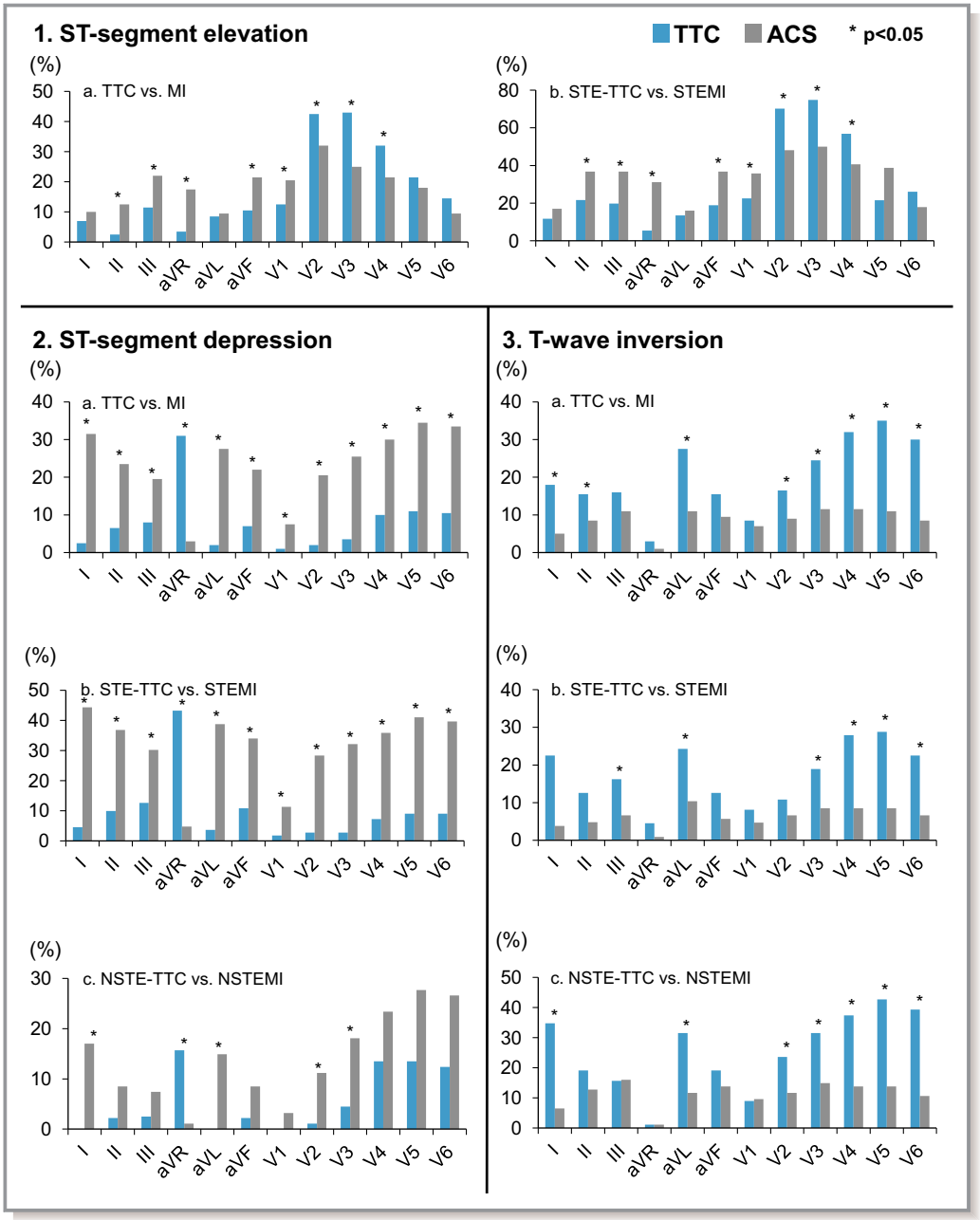

Figure 1. Comparison of 1—ST-elevation, 2—ST-depression, and 3—T-wave inversion in 12-lead ECG between Takotsubo cardiomyopathy and myocardial infarction in the setting of STEMI and NSTEMI presentation. ACS indicates acute coronary syndromes; MI, myocardial infarction; NSTEMI, non ST-elevation MI; STEMI, ST-elevation MI.

which were similar to that of the entire groups (Table 1), are listed in Table S2.

The characteristics of the admission ECGs in TTC and STEMI are shown in Figure 1, Table 3, and Table S3. QTc prolongation was similarly common in both groups and occurred in 46.8% (n=52) in TTC and in 49.1% (n=52) in STEMI, respectively (P=0.79). Heart rate was higher in TTC, but the prolongation of the PQ interval fell short of significance. On the other hand, QRS width was broader in STEMI patients. Among those, isolated ST-elevation with no concomitant ST-depression or T-inversion was more prevalent in the TTC group (30%, n=59) than in STEMI patients (12%, n=23; P<0.001), in which ST-elevation was particularly more prevalent in anteroseptal or anterior leads (38%, n=42 versus 22%, n=23; P=0.012 and 40%, n=44 versus 26%, n=27; P=0.03, respectively), whereas STEMI patients exhibited ST-

Table 2. Admission ECG Characteristics; Comparison Between MI and TTC

	Total TTC N=200	Total MI N=200	*P* Value
Sinus rhythm	194 (97)	188 (94)	0.23
Atrial fibrillation	5 (3)	11 (6)	0.20
Axis			
Normal	162 (81)	164 (82)	0.90
Left	33 (17)	27 (14)	0.48
QTc, ms*	457.3±36.5	439.9±37.2	<0.001
QT prolongation†	102 (51)	84 (42)	0.09
Heart rate, bpm*	83±20	76±19	<0.001
PQ, ms*	165.3±31.4	153.9±48.7	0.006
QRS, ms*	89.4±13.8	98.2±22.1	<0.001
RR, ms*	755±174	822±203	0.001
Normal ECG	28 (14)	28 (14)	1
Q wave	20 (10)	29 (15)	0.22
ST-elevation (STe)	111 (56)	106 (53)	0.69
STe with no concomitant ST depression or T wave inversion	59 (30)	23 (12)	<0.001
STe inferior‡	22 (11)	41 (21)	0.013
STe lateral§	15 (8)	9 (5)	0.29
STe anteroseptal‖	43 (22)	25 (13)	0.023
STe anterior¶	45 (23)	27 (14)	0.026
STe aVR	7 (4)	35 (18)	<0.001
ST-depression (STd)	31 (16)	106 (53)	<0.001
STd with no concomitant ST elevation or T wave inversion	8 (4)	25 (13)	0.003
STd inferior‡	15 (8)	39 (19)	<0.001
STd lateral§	19 (10)	43 (22)	0.001
STd anteroseptal‖	2 (1)	10 (5)	0.036
STd anterior¶	5 (3)	38 (19)	<0.001
STd in aVR (STe in -aVR)	62 (31)	6 (3)	<0.001
T wave inversion (Tinv)	90 (45)	43 (22)	<0.001
Sum of leads presenting Tinv*	2.20±0.16	2.29±2.46	0.71
Tinv present in ≥5 leads	60 (30)	13 (7)	<0.001
Tinv with no concomitant ST elevation or ST depression	43 (22)	24 (12)	0.016
Tinv inferior‡	31 (16)	18 (9)	0.066
Tinv lateral§	38 (19)	11 (6)	<0.001
Tinv anteroseptal‖	4 (2)	10 (5)	0.17
Tinv anterior¶	43 (22)	11 (6)	<0.001

Depicted are counts, N incidence (%). MI indicates myocardial infarction; TTC, Takotsubo cardiomyopathy.
*Mean±SD.
†QTc ≥440 ms and ≥460 ms for male and female sex, respectively.
‡More than 2 leads out of 3 in II-III-aVF.
§More than 2 leads out of 4 in (I-aVL-V5-V6).
‖More than 2 leads out of 3 in (V1-V2-V3).
¶More than 4 leads out of 6 in (V1-V2-V3-V4-V5-V6).

Table 3. Baseline ECG Characteristics; Comparison Between STE-TTC and STEMI

	STE-TTC N=111	STEMI N=106	*P* Value
Sinus rhythm	107 (96)	99 (93)	0.37
Atrial fibrillation	3 (3)	6 (6)	0.32
Axis			
Normal	82 (74)	83 (78)	0.53
Left	26 (23)	15 (14)	0.09
QTc, ms*	453±34	445±36	0.08
QT prolongation†	52 (47)	52 (49)	0.79
Heart rate, bpm*	87±22	81±20	0.031
PQ, ms*	165±31	158±48	0.22
QRS, ms*	88±17	102±24	<0.001
RR, ms*	720±154	776±13	0.023
Q wave	17 (15)	19 (18)	0.72
ST-elevation (STe)			
STe with no concomitant ST depression or T wave inversion	58 (52)	22 (21)	<0.001
STe inferior‡	22 (20)	40 (38)	0.004
STe lateral§	15 (14)	7 (7)	0.12
STe anteroseptal‖	42 (38)	23 (22)	0.012
STe anterior¶	44 (40)	27 (26)	0.03
STe aVR	6 (5)	33 (31)	<0.001
ST-depression (STd)	18 (16)	73 (69)	<0.001
STd inferior‡	13 (12)	33 (31)	<0.001
STd lateral§	11 (10)	27 (26)	0.004
STd anteroseptal‖	2 (2)	9 (9)	0.031
STd anterior¶	2 (2)	23 (22)	<0.001
STd in aVR (STe in -aVR)	48 (43)	5 (5)	<0.001
T wave inversion (Tinv)	40 (36)	18 (17)	0.002
Sum of leads presenting Tinv*	3.80±1.80	3.98±2.17	0.51
Tinv present in ≥5 leads	60 (30)	13 (7)	<0.001
Tinv inferior‡	14 (13)	6 (6)	0.10
Tinv lateral§	15 (14)	5 (5)	0.033
Tinv anteroseptal‖	1 (1)	3 (3)	0.36
Tinv anterior¶	20 (18)	5 (5)	0.003

Depicted are counts, N incidence (%). STEMI indicates ST-elevation myocardial infarction; STE-TTC, ST-elevation Takotsubo cardiomyopathy.
*Mean±SD.
†QTc ≥440 ms and ≥460 ms for male and female sex, respectively.
‡More than 2 leads out of 3 in II-III-aVF.
§More than 2 leads out of 4 in (I-aVL-V5-V6).
‖More than 2 leads out of 3 in (V1-V2-V3).
¶More than 4 leads out of 6 in (V1-V2-V3-V4-V5-V6).

elevation more commonly in aVR or in inferior leads (31%, n=33 versus 5%, n=6; *P*<0.001 and 38%, n=40 versus 20%, n=22; *P*=0.004, respectively).

ST-depression was more prevalent in STEMI compared to TTC ECGs (69%, n=73 versus 16%, n=18; *P*<0.001). This was the case in all leads, with the exception of aVR where ST-elevation in –aVR was more common in TTC (43%, n=48 versus 5%, n=5; *P*<0.001). On the other hand, T-inversion was more often observed in TTC in more than 5 leads (30%, n=60 versus 7%, n=13; *P*<0.001) and particularly in lateral and anterior leads.

Table 4 shows the diagnostic values of combined ECG findings for differentiating TTC from STEMI in the setting of a ST-elevation ECG. The presence of T-inversion in any lead on the admission ECG predicted TTC with a sensitivity and specificity of 36% and 83%, respectively (*P*=0.002) with a correspondent PPV of 63% and a NPV of 55%. ST-elevation in –aVR was characteristic for TTC with a sensitivity and specificity of 43% and 95%, respectively (*P*<0.001; PPV of 91% and NPV of 62%, respectively).

If ST-elevation in –aVR was combined with no ST-elevation in V1 along with no pathologic Q waves, the sensitivity and specificity rose to 32% and 97%, respectively (*P*<0.001; PPV of 92% and NPV of 58%). When ST-elevation in –aVR was accompanied by inferior ST-elevation, the sensitivity and specificity were 14% and 98%, respectively (*P*=0.001; PPV of 89% and NPV of 52%). An even better specificity (100%) with a lower sensitivity (12%) was reached, in the presence of ST-elevations in the anteroseptal leads together with ST-elevation in –aVR (*P*<0.001; PPV of 100% and NPV of 52%).

On the other hand, STEMI was characterized with ST-depression in any lead, and more specifically in inferior leads with a sensitivity and specificity of 31% and 88%, respectively (*P*<0.001; PPV of 72% and NPV of 57%). ST-elevation in aVR (sensitivity and specificity 31% and 95%, *P*<0.001; PPV of 85% and NPV of 59%), and ST-depression in V2, V3, and V4 (sensitivity and specificity 24% and 100%; *P*<0.001; with PPV of 100% and NPV of 76%) were the most specific ECG patterns directing the diagnosis towards a STEMI versus TTC (Table 4).

After multivariate analysis, the independent diagnostic parameters to differentiate TTC from STEMI in the setting of an ST-elevation ECG were sex, body mass index, peak troponin, peak creatine kinase levels, and ST-elevation in –aVR.

TTC Without ST-Elevation Versus NSTEMI

Eighty-nine TTC patients without ST-elevation were then compared to 94 NSTEMI patients. Baseline characteristics are listed in Table S4. NSTEMI patients more often had hypertension, a smoking history, and/or dyslipidemia, but a similar incidence of coronary artery disease as compared to TTC patients' subgroup.

Table 4. Diagnostic Values of Combined Electrocardiographic Findings for Differentiating TTC From STEMI and NSTEMI

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*P* Value
TTC vs STEMI in the setting of STe-ECG					
Specific criteria for TTC					
Tinv (any lead)	36	83	63	55	0.002
STe in –aVR	43	95	91	62	<0.001
STe in -aVR and No STe in V1	38	95	89	59	<0.001
STe in -aVR and no STe in V1 and no abnormal Q-waves	32	97	92	58	<0.001
STe in -aVR and STe in inferior*	14	98	89	52	0.001
STe in -aVR and STe in anterior†	19	98	91	54	<0.001
STe in -aVR and STe in anteroseptal‡	12	100	100	52	<0.001
Specific criteria for STEMI					
STd (any lead)	69	84	80	74	<0.001
STd in inferior*	31	88	72	57	<0.001
STe in aVR	31	95	85	59	<0.001
STd in I and aVL	34	96	90	64	<0.001
STe in aVR and STd in inferior*	13	96	74	54	0.03
STe in aVR and STd in anterior†	11	98	86	54	0.005
STd in V2, V3, and V4	24	100	100	76	<0.001
TTC vs NSTEMI in the setting of non STe-ECG					
Specific criteria for TTC					
Tinv in V5 and V6	39	90	80	61	<0.001
Tinv in ≥5 leads (any leads)	36	92	80	60	<0.001
Tinv in I and aVL	29	94	81	58	<0.001
Tinv in I, aVL, V5, and V6	17	97	83	55	0.002
STe in –aVR	16	99	93	55	<0.001
STe in -aVR and Tinv (any lead)	8	100	100	53	0.006
Specific criteria for NSTEMI					
STd (with no Tinv in any lead)	25	91	74	53	0.006
STd in anterior†	16	97	83	52	0.005
STd in V2 and V3	11	99	91	51	0.01

NPV indicates negative predictive value; NSTEMI, non ST-elevation myocardial infarction; PPV, positive predictive value; STd, ST-depression; STe, ST-elevation; STEMI, ST-elevation myocardial infarction; Tinv, T wave inversion; TTC, Takotsubo cardiomyopathy.
*More than 2 leads out of 3 in II-III-aVF.
†More than 4 leads out of 6 in (V1-V2-V3-V4-V5-V6).
‡More than 2 leads out of 3 in (V1-V2-V3).

Figure 1 and Table 5 show admission ECG characteristics of TTC without ST-elevation and patients with NSTEMI. Again, QTc prolongation was more prevalent in the TTC group (56%, n=50 versus 34%, n=32; *P*=0.005). Similarly to previously analyzed subgroups, heart rate was higher and PQ interval longer in TTC patients, whereas QRS width was comparable between the 2 subgroups.

ST-depression was overall more prevalent in NSTEMI patients (35%, n=33 versus 15%, n=13; *P*=0.002), particularly in anterior leads. Here again ST-elevation in –aVR was characteristic of TTC (16%, n=14 versus 1%, n=1; *P*<0.001). On the other hand, T-inversion was also more often present in TTC patients (56%, n=50 versus 27%, n=25; *P*<0.001) with ≈3 times as many leads involved, and T-inversion in more than 5 leads in 36% (n=32) of TTC as compared to 9% (n=8) in NSTEMI patients (*P*<0.001). Moreover, T-inversion in TTC was more isolated, with no concomitant ST-depression, and present particularly in anterior and lateral leads (Table 5 and Table S5).

Diagnostic values of combined ECG findings for differentiating TTC from NSTEMI in the setting of non ST-elevation ECG are shown in Table 4. T-inversion in more than 5 of any

Table 5. Baseline ECG Characteristics; Comparison Between NSTE-TTC and NSTEMI

	NSTE-TTC N=89	NSTEMI N=94	*P* Value
Sinus rhythm	87 (98)	89 (95)	0.45
Atrial fibrillation	2 (2)	5 (5)	0.45
Axis			
Normal	80 (90)	81 (86)	0.50
Left	7 (8)	12 (13)	0.34
QTc, ms*	463±38	434±38	<0.001
QT prolongation†	50 (56)	32 (34)	0.005
Heart rate, bpm*	78±18	71±17	0.004
PQ, ms*	165±32	148±49	0.008
QRS, ms*	90±15	94±19	0.14
RR, ms*	802±190	874±191	0.014
Normal ECG	28 (32)	28 (30)	0.87
ST-depression (STd)	13 (15)	33 (35)	0.002
STd with no concomitant ST elevation or T wave inversion	8 (9)	16 (17)	0.13
STd inferior‡	2 (2)	6 (6)	0.28
STd lateral‖	11 (12)	20 (21)	0.12
STd anteroseptal‖	0	1 (1)	1
STd anterior¶	3 (3)	15 (16)	0.005
STd in aVR (STe in -aVR)	14 (16)	1 (1)	<0.001
T wave inversion (Tinv)	50 (56)	25 (27)	<0.001
Sum of leads presenting Tinv*	3.04±3.11	1.37±2.11	<0.001
Tinv present in ≥5 leads	32 (36)	8 (9)	<0.001
Tinv with no concomitant ST depression	43 (49)	24 (26)	0.002
Tinv inferior‡	17 (19)	12 (13)	0.31
Tinv lateral§	23 (26)	6 (6)	<0.001
Tinv anteroseptal‖	3 (3)	7 (7)	0.33
Tinv anterior¶	23 (26)	6 (6)	<0.001

Depicted are counts, N incidence (%). NSTEMI indicates non ST-elevation myocardial infarction; NSTE-TTC, non ST-elevation Takotsubo cardiomyopathy.
*Mean±SD.
†QTc ≥440 ms and ≥460 ms for male and female sex, respectively.
‡More than 2 leads out of 3 in (II-III-aVF).
§More than 2 leads out of 4 in (I-aVL-V5-V6).
‖More than 2 leads out of 3 in (V1-V2-V3).
¶More than 4 leads out of 6 in (V1-V2-V3-V4-V5-V6).

leads had a sensitivity of 36% to diagnose TTC in this particular setting with a specificity of 92% ($P<0.001$, with PPV of 80% and NPV of 60%). When T-inversion was present in leads V5 and V6, or I and aVL the sensitivity and specificity became 39% and 90%, respectively (PPV of 80% and NPV of 61%) and 29% and 94%, respectively (PPV of 81% and NPV of 58%), respectively, $P<0.001$. When combining all these leads, T-inversion in V5-V6-I-aVL provided a sensitivity and specificity of 17% and 97% for diagnosing TTC rather than NSTEMI ($P=0.002$; PPV of 83% and NPV of 55%). Here again, ST-elevation in –aVR was specific for TTC with a sensitivity and specificity of 16% and 99% ($P<0.001$; PPV of 93% and NPV of 55%), rising to 8% and 100% when adding to it T-inversion in any lead ($P=0.006$; PPV of 100% and NPV of 53%). On the other hand, NSTEMI was characterized by isolated ST-depression with no concomitant T-inversion in any lead, with a sensitivity and specificity of 25% and 91% ($P=0.006$; with PPV of 74% and NPV of 53%). When ST-depression was present in anterior leads and particularly in V2 and V3, NSTEMI was likely present with a sensitivity and specificity of 16% and 97% ($P=0.005$; PPV of 83% and NPV of 52%) and 11% and 99% ($P=0.01$; PPV of 91% and NPV of 51%), respectively.

Receiver Operating Characteristic (ROC) curves showing the diagnostic accuracy of the different ECG parameters in identifying TTC are shown in Figures S1 through S4.

After multivariate analysis, the independent diagnostic parameters to differentiate TTC from NSTEMI in the setting of a non ST-elevation ECG were sex, body mass index, peak CK levels, and left ventricular ejection fraction.

Discussion

This is the largest study defining specific ECG criteria to differentiate between TTC and MI. Our aim was to generate simple and specific ECG criteria that are helpful in the differential diagnosis of TTC and acute MI in the emergency setting. Due to a different management, the acute recognition of TTC is clinically important, but usually a challenging task given the similarities in the clinical presentation, ECG, and biomarker characteristics of the 2 entities.[1,6–8] Eventually, emergency coronary angiography and ventriculography are required to confirm the underlying diagnosis of both conditions. The early differentiation between these 2 entities has a potential benefit regarding the timing of the coronary angiography and the antiplatelet/anticoagulation regimen to be used, especially in patients with multiple comorbidities such as those presenting after physical stressors such as subarachnoid hemorrhage or hemorrhagic stroke, known to be typical triggers for TTC.[1]

Twelve-lead surface ECG on admission is a simple diagnostic tool that is available in a primary emergency setting. Although several studies have proposed ECG characteristics to differentiate between TTC and acute MI,[9–15] data are still insufficient, partially due to limited sample size and the heterogeneity of study designs. Most of these studies compared TTC only to anterior MI. However, admission ECGs of TTC patients can vary, and the degree of ST-elevation,

Table 6. Review of Proposed Differentiating Electrocardiographic Criteria From Major Studies

Reference	Study Description	Onset of Pain	No. of Patients	Origin of ST-Segment	ECG Criteria for Identifying ACS/TTC	Sensitivity	Specificity	Testing of Proposed Criteria in Our Cohort*		*P* Value
								Sensitivity	Specificity	
Mugnai et al Journal of Electrocardiology 2015[15]	TTC vs AMI	<12 h	27 (STEMI) 27 (TTC)	J point	Lack of STe in lead V1, absence of abnormal Q waves and STd in aVR	40	95	25	98.1	<0.001
Parkkonen et al Journal of Electrocardiology 2014[14]	TTC vs AMI	<24 h	96 (AMI) 48 (apical TTC) 9 (midventricular TTC)	J point	Lack of STe in lead V1 and STe <2 mm in V2	63	93	57.5	100	<0.001
Jim et al Heart Vessels 2009[10]	TTC vs AMI	<12 h	27 (AMI) 8 (TTC)	80 ms from J point	STe in lead II >1 mm	62.5	92.6	12.5	84.6	0.644
Tamura et al Am J Cardiol 2011[12]	TTC vs AMI	<6 h	280 (AMI) 62 (TTC)	80 ms from J point	STe >1 mm in >1 V3-V5 and no STd >1 mm in V1	74.2	80.6	36.5	73.1	0.252
Guerra et al Am J Cardiol 2013[13]	TTC vs ACS	<12 h	45 (ACS) 45 (TTC)	J-point	∑STe V4-V6/∑STe V1-V3	Non discriminative		64.3	21.5	0.002
Kosuge et al JACC 2010[11]	TTC vs AMI	<6	342 (AMI) 33 (TTC)	80 ms from J-point	STd in aVR, and no STe in V1	91	95	28	96.2	<0.001
Ogura et al Circ J 2003[9]	TTC vs AMI		13 (AMI) 13 (TTC)	80 ms from J-point	Absence of reciprocal changes	100	69	92.5	44.2	<0.001
					∑STe V4-V6/∑STe V1-V3 ≥1	80	77	64.3	73.1	<0.001
					Combined criteria		100	61.3	86.5	<0.001

ACS indicates acute coronary syndromes; AMI, anterior myocardial infarction; STd, ST-segment depression; STe, ST-segment elevation; STEMI, ST-segment elevation myocardial infarction; TTC, Takotsubo cardiomyopathy.
*Onset of pain <12 h, origin of ST-segment J point.

ST-depression, and T-inversion is considerably different (11–100%). Some patients may even present with a normal ECG.[3,5,17,18] This makes it more clinically relevant to define ECG findings specific to TTC compared to all MI patients, where the differential diagnosis is a question. In the current study, we compared not only admission ECGs between TTC and acute MI but we further dichotomized into TTC with ST-elevation versus STEMI and TTC without ST-elevation versus NSTEMI, and we defined specific ECG changes that differentiate between both entities. Moreover, we considered ST-segment deviation at the J point as recommended by the third universal definition of MI,[20] since this can affect the presence or absence of ST-elevation. We also classified ECG leads by localization-based ECG criteria (anterior, inferior, and lateral), which are easy to apply in the clinical setting. The patients with TTC in our study were predominantly postmenopausal women (91% with mean age of 65 years) and had lower rates of smoking history, dyslipidemia, and diabetes compared to MI patients, in accordance with previous publications.[8,22] Our results confirmed the heterogeneity of ECG at the time of presentation in both TTC and MI, with a comparable rate of ST-elevation, as well as a similar rate of normal ECGs, which supports the choice of our study design.

In our study cohort with TTC, normal QRS axis was the predominant feature, whereas there was a trend for left axis deviation in the ST-elevation subgroup, in accordance with previously reported findings.[23] This observation is likely due to severe apical ballooning and alterations in the cardiac

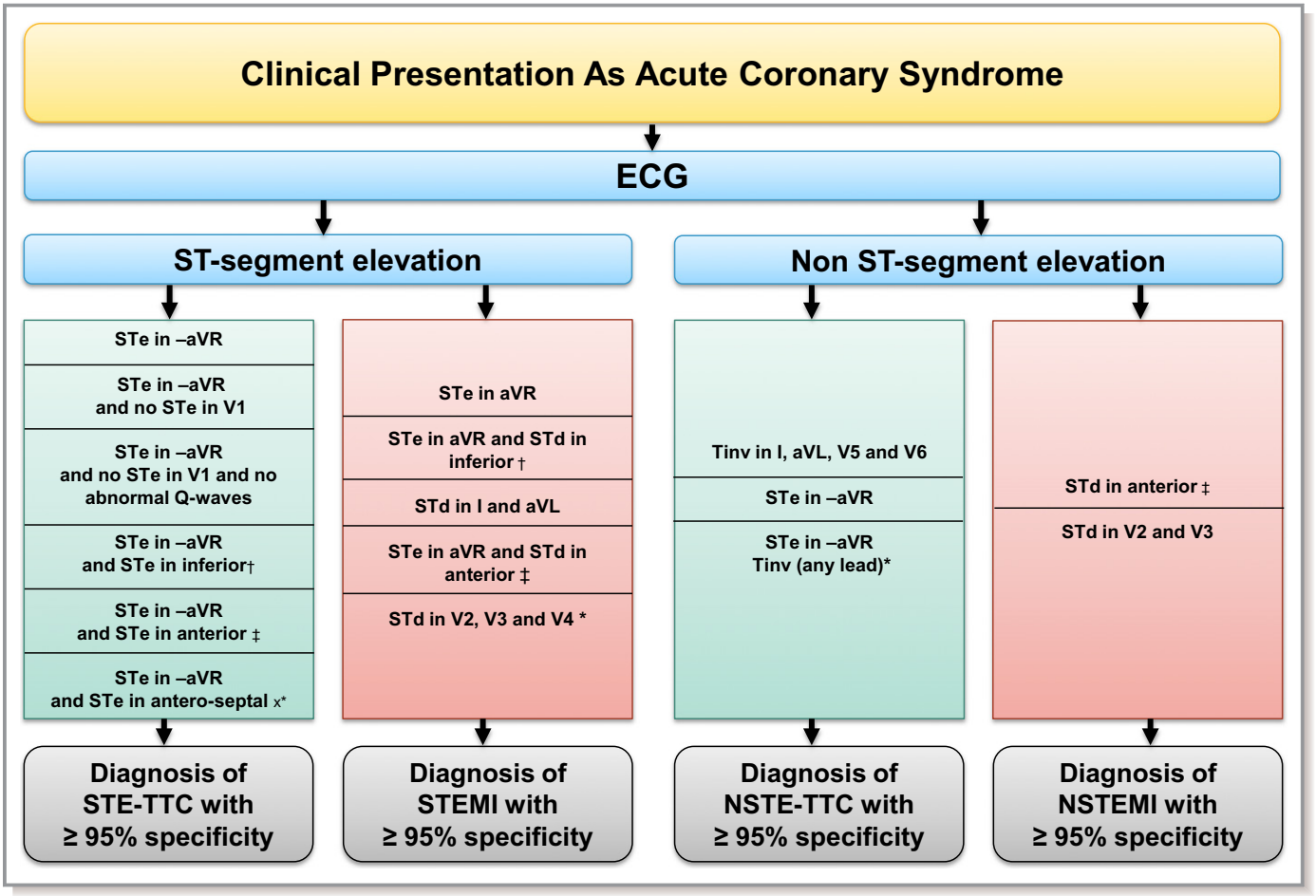

Figure 2. Algorithm favoring the diagnosis of Takotsubo based on highly specific admission ECG criteria in the setting of acute coronary syndrome (STEMI and NSTEMI). NSTEMI indicates non ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; STe, ST-segment elevation; STd, ST-segment depression; TTC, Takotsubo cardiomyopathy. *100% specificity and 100% positive predictive value; †More than 2 leads out of 3 in II-III-aVF; ‡More than 4 leads out of 6 in (V1-V2-V3-V4-V5-V6); ˣMore than 2 leads out of 3 in (V1-V2-V3).

conduction system.[23] QTc interval was described to be greater in patients with TTC, especially in the subacute phase,[17,24] probably reflecting a stunned myocardium. In our study, QTc prolongation was more prevalent in TTC patients, particularly in the subgroup without ST-elevation. Abnormal Q waves occurred in only 10% of TTC patients, which was not significantly different from MI patients (15%). The rate of abnormal Q waves in TTC was previously reported to be 6% to 85%.[18] Q waves often tend to regress afterwards along with R-wave reappearance, suggesting electrical stunning, even when Q-waves appear in the acute phase in TTC.

Although the ability of ECG to reliably differentiate TTC from MI was questioned in some studies,[5,14,17] our data showed that ECG criteria could in fact distinguish between the 2 entities. In our study, when ST-elevation was present in TTC patients, its distribution differed widely, which was consistent with previous studies.[11,12,14,15] In fact, in TTC, ST-elevation was diffusely prevalent, particularly in anteroseptal and anterior leads, and occurred more in commonly in –aVR. The lead –aVR (+30°), equivalent to the inverse lead of aVR, bridges the gap between lead I (0°) and lead II (+60°)[25] and faces the apical and inferolateral regions.[18] Moreover, the diffuse ST-elevation in TTC is thought to reflect the extensive distribution of wall-motion abnormalities centered around the apex, extending beyond the perfusion territory of any single coronary artery,[18] which gives the possibility to establish a differential diagnosis based on ECG criteria. In contrast, ST-elevation in V1 and inferior leads was less prevalent in TTC patients. The lead V1 points out to the right ventricular anterior region, as well as the right paraseptal region,[26] where TTC rarely extends,[27,28] whereas TTC possibly more commonly involves the posterolateral region.[27,29]

In our study, ST-depression in inferior leads was a rare finding in TTC patients. In the context of STEMI, the presence of ST-depression in inferior leads suggests left anterior descending coronary artery occlusion proximal to the first septal branch in opposite to mid or distal left anterior descending occlusion.[30] The absence of reciprocal changes in

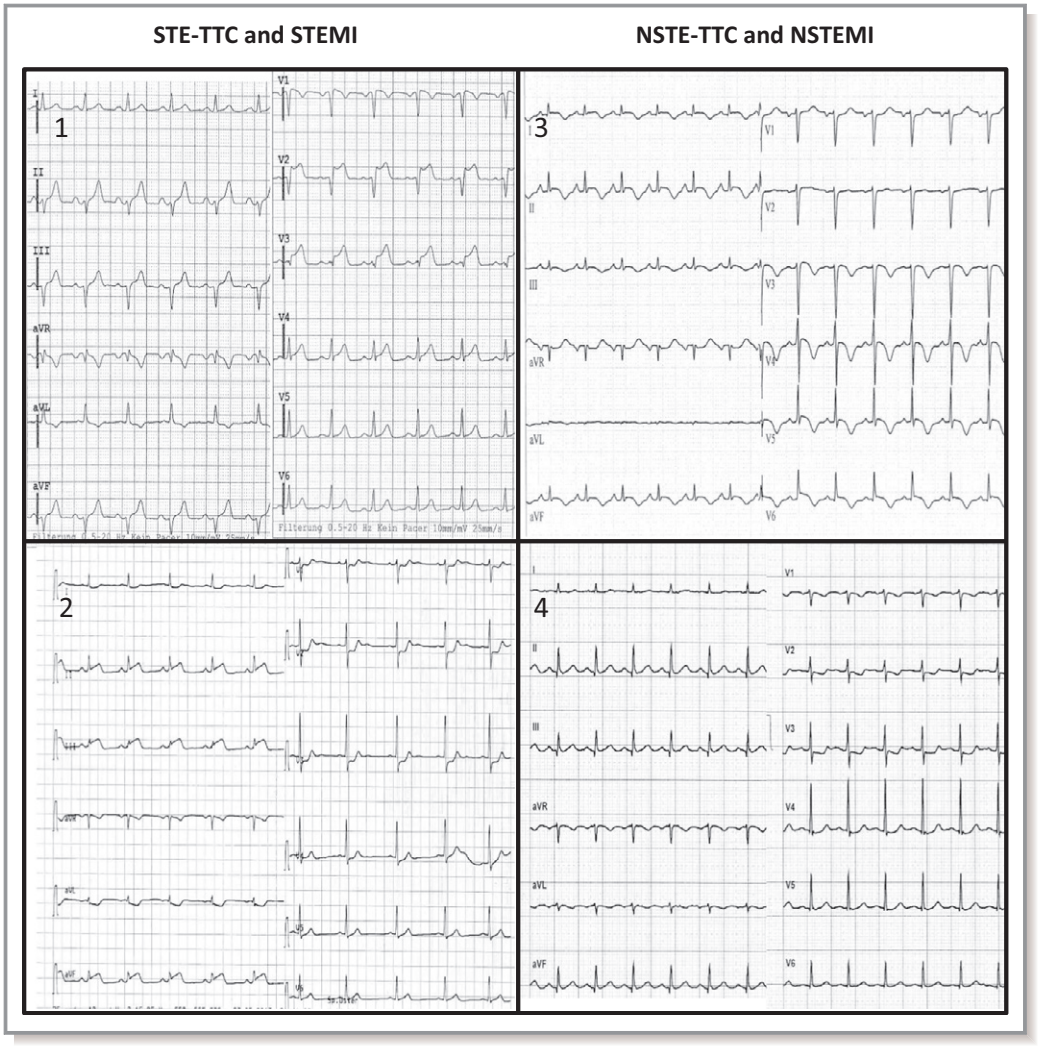

Figure 3. ECG examples for the most specific combination of criteria in each group of patients. *Group 1*: Takotsubo with ST-elevation (STE-TTC): STe in –aVR and STe in anteroseptal lead; *Group 2*: ST-elevation myocardial infarction (STEMI): STd in V2, V3 and V4 (among others); *Group 3*: Takotsubo without ST-elevation (NSTE-TTC): STe in –aVR and Tinv (any lead); *Group 4:* Non ST-elevation myocardial infarction (NSTEMI): STd in V2, V3.

inferior leads in TTC can be explained by the fact that the vector of injuries of opposing walls cancel each other out; simultaneous ischemia in both lateral and inferior walls tends to attenuate the ST-segment changes in their respective leads.[10] Another observation was the presence of more diffuse T-inversion in TTC patients, especially in anterior and lateral leads, which was consistent with previous studies.[13,16,31] These repolarization changes were also documented after reperfusion of prolonged myocardial ischemia and were referred to stunned as well as viable but sympathetically denervated myocardium.[32,33]

ECG criteria for the differential diagnosis of TTC proposed in previously published studies[9–15] are summarized in Table 6. The results of re-analysis of the same criteria with the same subgroups of patients from our data are also given in the table. This analysis showed similarities and confirmed many of the previously proposed criteria. However, when the results became inconsistent, this may be due to the effect of the sample size and the delay between onset of symptoms and ECG recordings. It is important to take into consideration that our ECG findings were obtained within 12 hours from the onset of symptoms and ST-segment changes were measured at the J point, as mentioned previously.

Moreover, in order to determine the most specific criteria differentiating TTC from MI, we dichotomized our study population into 2 subgroups of patients based on the presence or absence of ST-elevation on the admission ECG. The rationale was to reach higher sensitivity and specificity by selecting subgroups based on electrocardiographic changes, considering the variability of ECG patterns in TTC patients

discussed above and to be able afterwards to create a practical tool for cardiologists in the emergency setting to categorize their patients and look for specific ECG criteria that could help in the differential diagnosis.

Furthermore, we combined the most differentiating criteria and defined sensitivity and specificity as well as the correspondent NPV and PPV (Table 4, Figure 2). Interestingly, in the ST-elevation setting, ST-elevation in –aVR when combined with ST-elevation in anteroseptal leads was 100% specific for TTC versus STEMI with PPV of 100%, but NPV of 52% and low sensitivity of 12%. In contrast, ST-depression in V2, V3, and V4 was 100% specific for STEMI with 100% PPV, 72% NPV, and sensitivity of 24%. On the other hand, in the non ST-elevation setting, ST-elevation in –aVR combined with concomitant T-inversion in any lead was again 100% specific of TTC with 100% PPV, but 53% NPV and low sensitivity of 8%. The low sensitivity is due to the heterogeneity of ECG presentation, described above, as well as the fact that we compared all TTC patients to all acute MI patients including STEMI and NSTEMI, as seen in daily clinical practice.

The flow chart in Figure 2 is a guide for the clinician with admission ECG in hand in an acute setting. It shows highly specific ECG criteria, with a high PPV, helping in establishing the differential diagnosis. Figure 3 shows ECG examples for the most specific combination of criteria in each group of patients.

Limitations

Despite the large sample size and having the strengths of a multicenter registry, our study is limited by its retrospective design. Furthermore, we did not take into consideration the difference between typical and atypical forms of TTC, as our primary aim was to establish simple ECG criteria to differentiate TTC from acute MI in an acute setting.

In conclusion, ECG on admission proves to be helpful in differentiating between TTC and acute MI with high specificity and PPV.

Appendix

InterTAK Collaborators for this Study

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table of Contents

Supplemental Methods.

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Table S1	Baseline electrocardiographic changes in TTC and MI patients		
	TTC N=200	**MI N=200**	**P**
Q-wave			
Q-wave in lead I	1 (0.5)	2 (1)	1
Q-wave in lead II	4 (2)	14 (7)	0.027
Q-wave in lead III	7 (3.5)	19 (9.5)	0.024
Q-wave in lead aVR	-	-	-
Q-wave in lead aVL	2 (1)	1 (0.5)	1
Q-wave in lead aVF	6 (3)	17 (8.5)	0.019
Q-wave in lead V1	5 (2.5)	17 (8.5)	0.014
Q-wave in lead V2	11 (5.5)	20 (10)	0.034
Q-wave in lead V3	11 (5.5)	19 (9.5)	0.134
Q-wave in lead V4	7 (3.5)	11 (5.5)	0.347
Q-wave in lead V5	4 (2)	3 (1.5)	1
Q-wave in lead V6	4 (2)	2 (1)	0.685
ST elevation (STe)			
STe in lead I	14 (7)	20 (10)	0.37
STe in lead II	25 (12.5)	43 (21.5)	0.023
STe in lead III	23 (11.5)	44 (22)	0.004
STe in lead aVR	7 (3.5)	35 (17.5)	<0.001
STe in lead aVL	17 (8.5)	19 (9.5)	0.862
STe in lead aVF	21 (10.5)	43 (21.5)	0.004
STe in lead V1	25 (12.5)	41 (20.5)	0.032
STe in lead V2	85 (42.5)	64 (32)	0.038
STe in lead V3	86 (43)	50 (25)	<0.001
STe in lead V4	64 (32)	43 (21.5)	0.024
STe in lead V5	43 (21.5)	36 (18)	0.451
STe in lead V6	29 (14.5)	19 (9.5)	0.166
ST depression (STd)			
STd in lead I	5 (2.5)	63 (31.5)	<0.001
STd in lead II	13 (6.5)	47 (23.5)	<0.001
STd in lead III	16 (8)	39 (19.5)	0.001
STd in lead aVR	62 (31)	6 (3)	<0.001
STd in lead aVL	4 (2)	55 (27.5)	<0.001
STd in lead aVF	14 (7)	44 (22)	<0.001
STd in lead V1	2 (1)	15 (7.5)	0.001
STd in lead V2	4 (2)	41 (20.5)	<0.001
STd in lead V3	7 (3.5)	51 (25.5)	<0.001
STd in lead V4	20 (10)	60 (30)	<0.001
STd in lead V5	22 (11)	69 (34.5)	<0.001
STd in lead V6	21 (10.5)	67 (33.5)	<0.001
T wave inversion (Tinv)			
Tinv in lead I	56 (18)	10 (5)	<0.001

Tinv in lead II	31 (15.5)	17 (8.5)	0.045
Tinv in lead III	32 (16)	22 (11)	0.188
Tinv in lead aVR	6 (3)	2 (1)	0.284
Tinv in lead aVL	55 (27.5)	22 (11)	<0.001
Tinv in lead aVF	31 (15.5)	19 (9.5)	0.096
Tinv in lead V1	17 (8.5)	14 (7)	0.709
Tinv in lead V2	33 (16.5)	18 (9)	0.035
Tinv in lead V3	49 (24.5)	23 (11.5)	0.001
Tinv in lead V4	64 (32)	23 (11.5)	<0.001
Tinv in lead V5	70 (35)	22 (11)	<0.001
Tinv in lead V6	60 (30)	17 (8.5)	<0.001

MI myocardial infarction, STd ST-segment depression MI myocardial infarction; STe ST-elevation, TTC Takotsubo cardiomyopathy, Tinv T-wave inversion; Depicted are counts, N incidence (%);

Table S2	Baseline Characteristics; Comparison between TTC with ST-elevation and STEMI		
	STE-TTC N = 111	**STEMI N = 106**	**P**
Baseline characteristics			
Age (years) *	67 ± 11	66 ± 13	0.28
Female	98 (88)	26 (25)	<0.001
BMI (kg/m²) *	24.3 ± 4	27.5 ± 5.2	<0.001
Cardiovascular risk factors and cardiovascular history			
Hypertension	65 (60)	65 (62)	0.89
Diabetes Mellitus	9 (8)	19 (18)	0.041
Current smoker	21 (19)	42 (40)	0.001
Ever-smoker	39 (35)	62 (59)	0.001
Dyslipidemia	26 (23)	52 (50)	<0.001
Positive family history of cardiovascular disease	26 (23)	30 (29)	0.36
Known CAD	7 (6)	21 (21)	0.004
Clinical and laboratory parameters			
EF (%) *	42 ± 9	49 ± 11	<0.001
Peak Troponin level (ULN) *	23.2 ± 28.2 (N=101)	54.9 ± 80.6 (N=106)	<0.001
Peak CK level (ULN) *	3.1 ± 9.4 (N=89)	11.0 ± 12.4 (N=106)	<0.001
Peak CRP level (mg/l) *	39.4 ± 56 (N=97)	78.6 ± 102.3 (N=105)	0.001
In-Hospital complications			
Cardiogenic shock	7 (6)	15 (14)	0.07
All-cause mortality	5 (5)	8 (8)	0.4

BMI denotes body mass index, CAD coronary artery disease, EF ejection fraction, STEMI ST-elevation myocardial infarction; STE-TTC Takotsubo cardiomyopathy with ST-elevation, ULN upper limit of normal; Depicted are counts, N incidence (%); * mean±SD;

Table S3 Baseline electrocardiographic changes in STE-TTC and STEMI patients

	STE-TTC N=111	STEMI N=106	P
Q-wave			
Q-wave in lead I	1 (0.9)	2 (1.9)	0.62
Q-wave in lead II	3 (2.7)	6 (5.7)	0.32
Q-wave in lead III	6 (5.4)	9 (8.5)	0.43
Q-wave in lead aVR	-	-	-
Q-wave in lead aVL	1 (0.9)	1 (0.9)	1
Q-wave in lead aVF	5 (4.5)	8 (7.5)	0.40
Q-wave in lead V1	4 (3.6)	14 (13.2)	0.013
Q-wave in lead V2	9 (8.1)	17 (16.2)	0.09
Q-wave in lead V3	9 (8.1)	17 (16.2)	0.09
Q-wave in lead V4	7 (6.3)	11 (10.4)	0.33
Q-wave in lead V5	4 (3.6)	3 (2.8)	1
Q-wave in lead V6	4 (3.6)	2 (1.9)	0.68
ST elevation (STe)			
STe in lead I	13 (11.7)	18 (17)	0.33
STe in lead II	24 (21.6)	39 (36.8)	0.017
STe in lead III	22 (19.8)	39 (36.8)	0.007
STe in lead aVR	6 (5.4)	33 (31.1)	<0.001
STe in lead aVL	15 (13.5)	17 (16)	0.7
STe in lead aVF	21 (18.9)	39 (36.8)	0.004
STe in lead V1	25 (22.5)	38 (35.8)	0.036
STe in lead V2	78 (70.2)	51 (48.1)	0.001
STe in lead V3	83 (74.8)	50 (47.2)	<0.001
STe in lead V4	63 (56.8)	43 (40.6)	0.021
STe in lead V5	43 (38.7)	36 (34)	0.48
STe in lead V6	29 (26.1)	19 (17.9)	0.19
ST depression (STd)			
STd in lead I	5 (4.5)	47 (44.3)	<0.001
STd in lead II	11 (9.9)	39 (36.8)	<0.001
STd in lead III	14 (12.6)	32 (30.2)	0.002
STd in lead aVR	48 (43.2)	5 (4.7)	<0.001
STd in lead aVL	4 (3.6)	41 (38.7)	<0.001
STd in lead aVF	12 (10.8)	36 (34)	<0.001
STd in lead V1	2 (1.8)	12 (11.3)	0.005
STd in lead V2	3 (2.7)	30 (28.3)	<0.001
STd in lead V3	3 (2.7)	34 (32.1)	<0.001
STd in lead V4	8 (7.2)	38 (35.8)	<0.001
STd in lead V5	10 (9.0)	43 (41.0)	<0.001

STd in lead V6	10 (9.0)	42 (39.6)	<0.001
T wave inversion (Tinv)			
Tinv in lead I	25 (22.5)	4 (3.8)	<0.001
Tinv in lead II	14 (12.6)	5 (4.8)	0.054
Tinv in lead III	18 (16.2)	7 (6.6)	0.033
Tinv in lead aVR	5 (4.5)	1 (0.9)	0.21
Tinv in lead aVL	27 (24.3)	11 (10.4)	0.007
Tinv in lead aVF	14 (12.6)	6 (5.7)	0.10
Tinv in lead V1	9 (8.1)	5 (4.7)	0.41
Tinv in lead V2	12 (10.8)	7 (6.6)	0.34
Tinv in lead V3	21 (18.9)	9 (8.5)	0.031
Tinv in lead V4	31 (27.9)	9 (8.5)	<0.001
Tinv in lead V5	32 (28.8)	9 (8.5)	<0.001
Tinv in lead V6	25 (22.5)	7 (6.6)	<0.001

STd ST-segment depression STEMI ST-elevation myocardial infarction; STE-TTC Takotsubo cardiomyopathy with ST-elevation, Tinv T-wave inversion; Depicted are counts, N incidence (%);

Table S4	Baseline Characteristics; Comparison between TTC without ST-elevation and NSTEMI		
	NSTE-TTC N = 89	**NSTEMI N = 94**	**P**
Baseline characteristics			
Age (years) *	63 ± 13	64 ± 12	0.61
Female	84 (94)	27 (29)	<0.001
BMI (kg/m²) *	24.6 ± 4.8	29.2 ± 6.5	<0.001
Cardiovascular risk factors and cardiovascular history			
Hypertension	44 (49)	60 (66)	0.034
Diabetes Mellitus	9 (10)	18 (20)	0.09
Current smoker	17 (19)	44 (47)	<0.001
Ever-smoker	32 (36)	52 (55)	0.012
Dyslipidemia	26 (29)	57 (63)	<0.001
Positive family history of cardiovascular disease	24 (27)	23 (26)	0.87
Known CAD	4 (5)	10 (11)	0.16
Clinical and laboratory parameters			
EF (%) *	44 ± 11	54 ± 11	<0.001
Peak Troponin level (ULN) *	18.4 ± 27.1 (N=86)	15.7 ± 21.9 (N=94)	0.46
Peak CK level (ULN) *	1.8 ± 3.6 (N=75)	3.5 ± 4.0 (N=94)	0.007
Peak CRP level (mg/l) *	29.6 ± 52.2 (N=76)	54.0 ± 117.6 (N=87)	0.10
In-Hospital complications			
Cardiogenic shock	9 (10)	4 (4)	0.16
All-cause mortality	3 (3)	2 (2)	0.68

BMI denotes body mass index, CAD coronary artery disease, EF ejection fraction, NSTEMI Non ST-elevation myocardial infarction; NSTE-TTC Takotsubo cardiomyopathy without ST-elevation, ULN upper limit of normal; Depicted are counts, N incidence (%); * mean±SD;

Table S5 Baseline electrocardiographic changes in TTC without ST-elevation and NSTEMI patients

	NSTE-TTC N=89	NSTEMI N=94	P
ST depression (STd)			
STd in lead I	0	16 (17)	<0.001
STd in lead II	2 (2.2)	8 (8.5)	0.10
STd in lead III	2 (2.2)	7 (7.4)	0.17
STd in lead aVR	14 (15.7)	1 (1.1)	<0.001
STd in lead aVL	0	14 (14.9)	<0.001
STd in lead aVF	2 (2.2)	8 (8.5)	0.10
STd in lead V1	0	3 (3.2)	0.25
STd in lead V2	1 (1.1)	11 (11.2)	0.005
STd in lead V3	4 (4.5)	17 (18.1)	0.005
STd in lead V4	12 (13.5)	22 (23.4)	0.09
STd in lead V5	12 (13.5)	26 (27.7)	0.028
STd in lead V6	11 (12.4)	25 (26.6)	0.017
T wave inversion (Tinv)			
Tinv in lead I	31 (34.8)	6 (6.5)	<0.001
Tinv in lead II	17 (19.1)	12 (12.8)	0.31
Tinv in lead III	14 (15.7)	15 (16)	1
Tinv in lead aVR	1 (1.1)	1 (1.1)	1
Tinv in lead aVL	28 (31.5)	11 (11.7)	0.001
Tinv in lead aVF	17 (19.1)	13 (13.8)	0.43
Tinv in lead V1	8 (9)	9 (9.6)	1
Tinv in lead V2	21 (23.6)	11 (11.7)	0.050
Tinv in lead V3	28 (31.5)	14 (14.9)	0.009
Tinv in lead V4	33 (37.1)	14 (13.8)	0.001
Tinv in lead V5	38 (42.7)	13 (13.8)	<0.001
Tinv in lead V6	35 (39.3)	10 (10.6)	<0.001

NSTEMI Non ST-elevation myocardial infarction; NSTE-TTC Takotsubo cardiomyopathy without ST-elevation, STd ST-segment depression; Depicted are counts, Tinv T-wave inversion; N incidence (%);

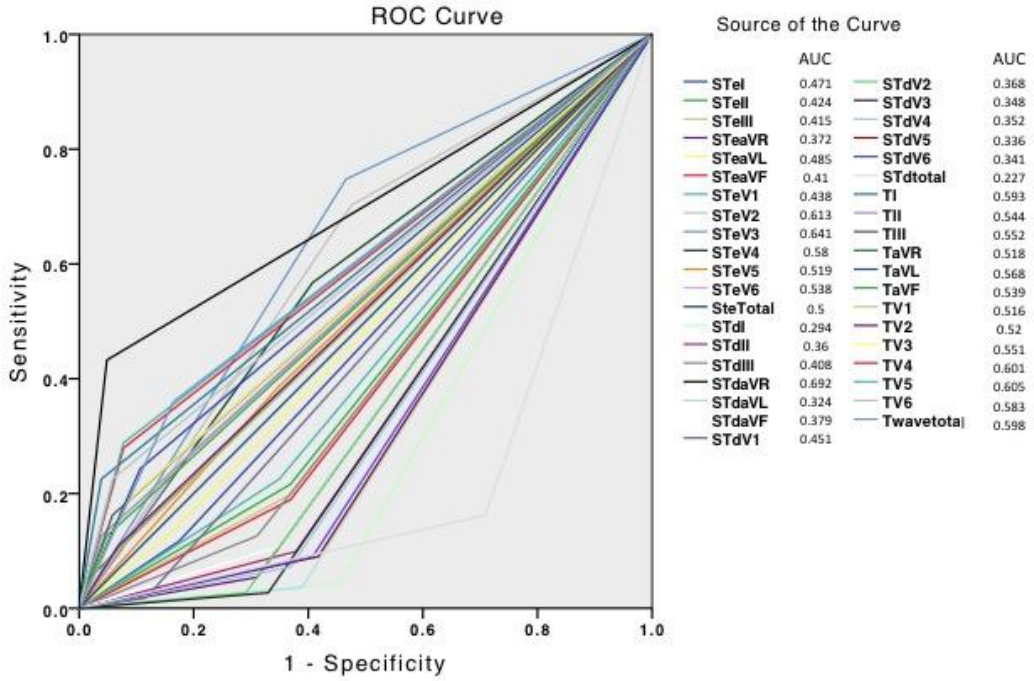

Figure S1. Receiver operating characteristic (ROC) curves showing the diagnostic accuracy of different ECG parameters to identify TTC in the setting of an ST-elevation ECG

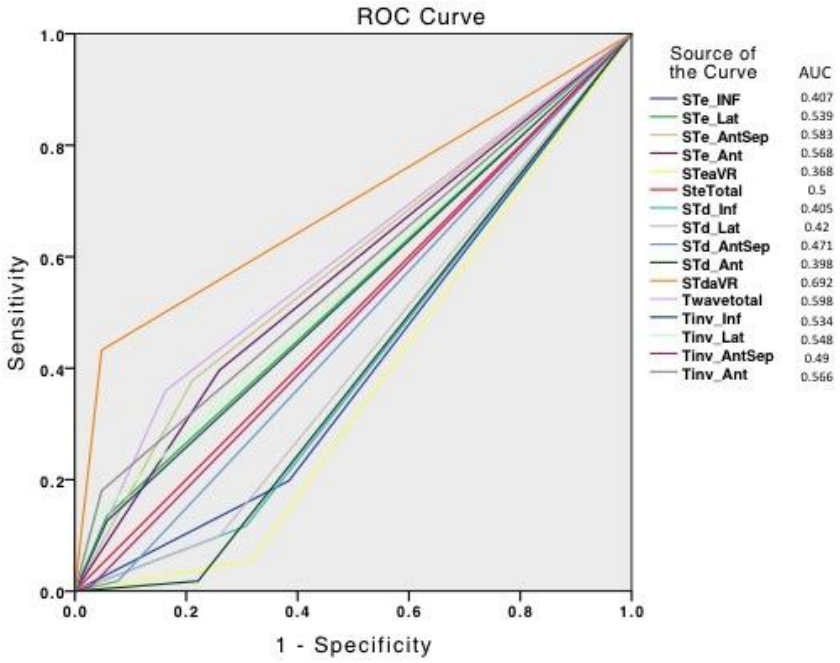

Figure S2. Receiver operating characteristic (ROC) curves showing the diagnostic accuracy of different ECG localization parameters to identify TTC in the setting of an ST-elevation ECG

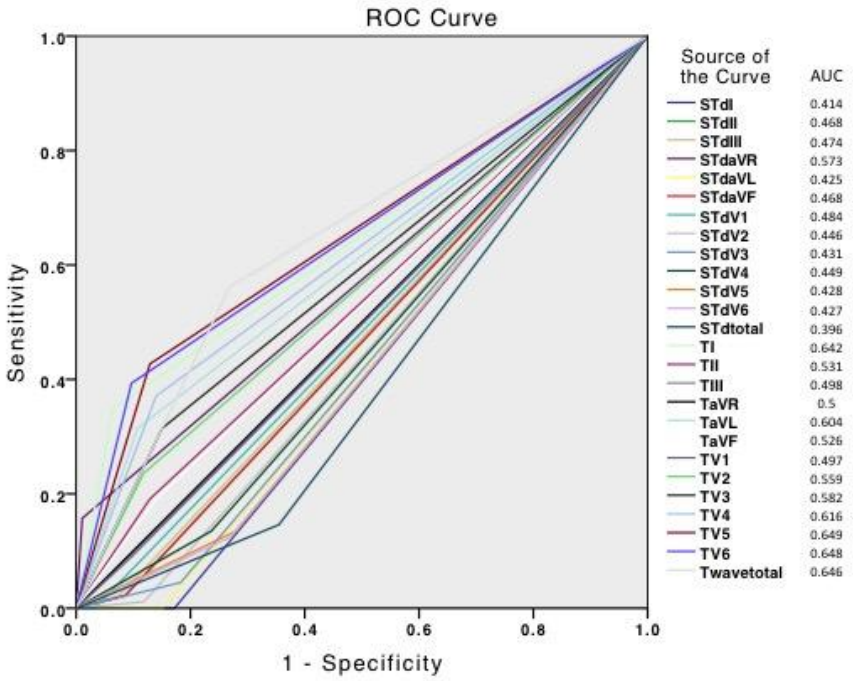

Figure S3. Receiver operating characteristic (ROC) curves showing the diagnostic accuracy of different ECG parameters to identify TTC in the setting of a non ST-elevation ECG.

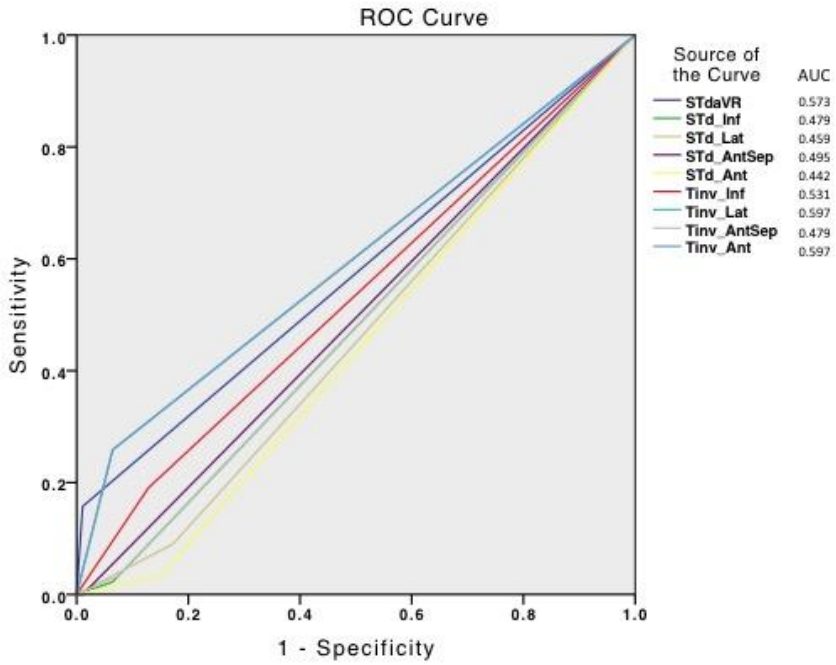

Figure S4. Receiver operating characteristic (ROC) curves showing the diagnostic accuracy of different ECG localization parameters to identify TTC in the setting of a non ST-elevation ECG.