Machine learning of microvolt-level 12-lead electrocardiogram can help distinguish takotsubo syndrome and acute anterior myocardial infarction

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BACKGROUND Qualitative differences in 12-lead electrocardiograms (ECG) at onset have been reported in patients with takotsubo syndrome (TTS) and acute anterior myocardial infarction (Ant-AMI). We aimed to distinguish these diseases by machine learning (ML) approach of microvolt-level quantitative measurements.

METHODS We enrolled 56 consecutive patients with sinus rhythm TTS (median age, 77 years; 16 men), and 1-to-1 random matching was performed based on age and sex of the patients. The ECG in the emergency room was evaluated using an automated system (ECAPs12c; Nihon-Koden). Statistical and ML predictive models for TTS were constructed using clinical features and ECG parameters.

RESULTS Statistically significant differences were observed in 25 parameters; the V1 ST level at the J point (V1 STJ) showed the lowest P value (P < .001). V1 STJ/C20 showed the highest accuracy for TTS (0.773). The highest area under the receiver operating characteristic curve (AUROC) was shown in the aVR ST level at 1/16th of the preceding R-R interval after the J point (aVR STmid: 0.727). Conversely, the light gradient boosting machine (model_LGBM) and extra tree classifier (model_ET) indicated higher accuracy (model_LGBM: 0.842, model_ET: 0.831) and AUROC (model_LGBM: 0.868, model_ET 0.896) than other statistical models. V1 STJ had high feature importance and Shapley additive explanation values in the 2 ML models.

CONCLUSION ML applied to automated microvolt-level ECG measurements showed the possibility of distinguishing between TTS and Ant-AMI, which may be a clinically useful ECG-based discriminator.

KEYWORDS Takotsubo syndrome; Acute anterior myocardial infarction; Machine learning; Electrocardiogram; SHAP method

Introduction

Takotsubo syndrome (TTS) and acute anterior myocardial infarction (Ant-AMI) at its onset show seemingly similar clinical features, and distinguishing between the 2 diseases without emergent cardiac catheterization is difficult. Although TTS, a diagnosis of exclusion, can be managed noninvasively with appropriate medical therapy, Ant-AMI is often managed invasively, with ST-elevation myocardial infarction (STEMI) cases requiring emergent revascularization. In cases of non-ST-elevation AMI (NSTEMI) without key clinical symptoms and signs of ST-elevation AMI (STEMI), noninvasive methods are desirable, especially in ambulances, clinics, and hospitals that cannot perform emergent cardiac catheterization. STEMI cases should be transferred to hospitals with cardiac catheterization laboratories immediately, but even in such hospitals, emergent catheterization is sometimes difficult to perform owing to various reasons: advanced age, dementia, frailty, poor physical status, and/or social problems. Twelve-lead electrocardiogram (ECG) is a fundamental examination that can be performed on arrival and has a time advantage compared to other examinations such as high-sensitivity troponin. Initial ECG on arrival can be useful to triage patients, but ECG between the 2 diseases at onset shows very similar patterns. The difference in ECG has been studied by several investigators. Difference in ST-T change has also been well studied, and several leads (eg, V1, aVR, inferior leads) were reported to have important roles in distinguishing between the diseases. Although these reports demonstrated good accuracy (0.95, Kosuge and Kimura, and 0.66-0.86, Jim and colleagues), external validity was not confirmed.

Machine learning (ML) applied to ECG has been developed in several cardiac diseases, and some investigators have reported methods for diagnosing myocardial infarction using a convolutional neural network on vector data of ECG. However, the accuracy (0.81, Makimoto and...
colleagues\(^4\) or area under the receiver operating characteristic curve (AUROC; 0.85–0.88, Cho and colleagues\(^5\)) was not higher than that of conventional ST-level examination. Moreover, there are no studies on the diagnosis of TTS using ML applied to ECG.

We aimed to build a predictive model for TTS by ML, not with ECG vector data but with table data of conventional 12-lead ECG parameters, and to elucidate the parameters of ECG with high feature importance in the ML models.

**Methods**

**Study patients and ECG**

We enrolled 56 consecutive patients at Yokohama Minami Kyosai Hospital with sinus rhythm with apical ballooning–type TTS from 2013 to 2021. In all cases, cardiac catheterization was performed, and no coronary stenosis and left ventricular apical ballooning was confirmed in TTS cases. Stenosis/occlusion of the left anterior descending coronary artery was confirmed in the Ant-AMI cases. The diagnosis of TTS was based on Mayo’s criteria,\(^1\) and other diseases that mimicked AMI (acute myocarditis/pericarditis and vasospastic angina) were excluded by absence of inflammation or acetylcholine provocation test (several days after admission). The diagnosis of AMI (STEMI and NSTEMI) was based on the fourth universal definition of AMI.\(^6\) Among our AMI database, patients with same age and sex in each TTS case were extracted, and 1-to-1 random matching was performed. Finally, 112 patients (median age, 77 years [interquartile range, 67–84 years]; 32 men) were enrolled.

ECG on arrival (in the emergency room) in both groups was measured at the μV level using an automated system (ECAPs12c; Nihon-Koden, Tokyo, Japan).\(^7\) ECG variables, ST levels, T-wave amplitude, and other fundamental parameters were preselected, as explained in Figure 1, and those parameters were measured from 10-second waveforms. The ST levels of each lead were measured automatically at 3 points: (1) ST level at the J point (STJ), which was recorded at the end of the QRS complex, measured with respect to the baseline; (2) the middle of the ST level (STmid), which is the ST level at the point of 1/16th of the preceding R-R interval after the J point; and (3) the end of the ST level (STend), which is the ST level at the point 1/16\(^{\text{th}}\) of the preceding R-R interval after the J point. The T-wave amplitude was defined as the absolute distance from the apex of the T wave to the baseline. TTS = takotsubo syndrome.

**Figure 1**  Explanation of measurement on 1 beat of the electrocardiogram (ECG). All the parameters were measured automatically. Left figure shows schema of the measurement, and right figure a real ECG wave and real results. The ST level was measured at 3 points: (1) ST level at the J point (STJ), which was recorded at the end of the QRS complex as measured in μV with respect to the baseline; (2) the middle of the ST level (STmid), which is the ST level at the point of 1/16\(^{\text{th}}\) of the preceding R-R interval after the J point; and (3) the end of the ST level (STend), which is the ST level at the point 2/16\(^{\text{th}}\) of the preceding R-R interval after the J point. The T-wave amplitude was defined as the absolute distance from the apex of the T wave to the baseline. TTS = takotsubo syndrome.


J point; and (3) the end of the ST level (STend), at the point 2/16th of the preceding R-R interval after the J point. Qualitative ST elevation/depression was defined as at least 0.1 μV deviation at J point, judged on the automated measurement. The T-wave amplitude was defined as the absolute distance from the apex of the T wave to the baseline. The rate-corrected QT interval (QTc) was calculated using the modified Framingham (ECAPs12C) formula (QTc = QT/√RR).

The ethics committee of Yokohama Minami Kyosai Hospital approved the study protocol and written informed consent was obtained from all participants prior to the study.

### Statistical analysis for characteristics of patients

Numeric variables are displayed as the median value (interquartile range: 25%-75% value), and the Mann-Whitney test was used to compare the TTS and Ant-AMI groups. Fisher exact test was used to evaluate differences in categorical variables, and Holm’s multiple comparison was used as a post hoc test.

Statistical significance was set at P < .05. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

### Predictive model construction by statistical method

Fifty-six pairs of cases were randomly split into 80% and 20% (45 pairs vs 11 pairs), in which 45 pairs (90 cases) were set as the prediction data and 11 pairs (22 cases) as the test data. Statistical predictive models were constructed based on these 90 cases, as described below. Univariate logistic regression analysis for TTS was performed using the prediction data, and significant predictors were extracted. A multivariate logistic regression analysis was not performed because of the multicollinearity of many pairs of parameters. A receiver operating characteristic (ROC) curve analysis was performed, and the cutoff value was calculated based on the Youden index. The statistical predictive model consisted of an assessment of whether a parameter in each case was higher/lower than the cutoff value (named the cutoff value model). A confusion matrix was created, and the diagnostic performance (accuracy/sensitivity : recall/positive predictive value : precision) was evaluated. From the analysis of the predictive model, the propensity score (PS) of each predictor was calculated, and the PS formula for each predictor was constructed (the ROC curve model):

\[
PS \text{ formula} = 1 / (1 + \exp(-ax + \beta))
\]

where a = coefficient of predictor and \( \beta \) = intercept, calculated by logistic regression analysis. The model was applied to the test data and the AUROC was measured using ROC curve analysis.

### Predictive model construction and validation by ML

Among the ML methods for ECG data, we did not use conventional deep learning procedures using 1-dimensional data (vector data) because it was difficult to explain the feature importance in the model. To secure explainability, we adopted a novel method that used an ensemble learning procedure with conventional ECG parameters (eg, ST level, T-wave amplitude) as table data.

Eleven ML models were built using PyCaret, an open-source wrapper over several ML libraries in Python in a low-code environment. After screening of the 11 models,

### Table 1

Comparison of qualitative ST elevation/depression and T-wave inversion in takotsubo syndrome and acute anterior myocardial infarction

|                  | All cases (n = 112) |          |          | Prediction data (n = 90) |          |
|------------------|---------------------|----------|----------|-------------------------|----------|
|                  | TTS (n = 56) | AMI (n = 56) | P value | P value (post hoc) | TTS (n = 45) | AMI (n = 45) |
| Anterior STEMI   | 28 | 31 | .566 | 23 | 26 |
| \( V_1 \) ST elevation at J point | 3 | 18 | <.001 | 2 | 14 |
| \( V_1 \) ST depression at J point | 0 | 0 | .029 | 0 | 0 |
| \( V_1 \) T-wave inversion | 7 | 9 | .793 | 5 | 7 |
| \( V_2 \) ST elevation at J point | 27 | 33 | .462 | 22 | 28 |
| \( V_2 \) ST depression at J point | 1 | 2 | .032 | 0 | 1 |
| \( V_2 \) T-wave inversion | 8 | 5 | .557 | 6 | 4 |
| \( V_3 \) ST elevation at J point | 28 | 28 | .302 | 24 | 11 |
| \( V_3 \) ST depression at J point | 28 | 25 | .100 | 0 | 1 |
| \( V_3 \) T-wave inversion | 11 | 10 | 1.000 | 8 | 7 |
| \( V_4 \) ST elevation at J point | 23 | 17 | .029 | 18 | 14 |
| \( V_4 \) ST depression at J point | 2 | 11 | .032 | 1 | 7 |
| \( V_4 \) T-wave inversion | 15 | 16 | 1.000 | 11 | 13 |

ST elevation/depression was defined as at least 0.1 μV ST deviation at J point, and T-wave inversion as at least -0.1 μV amplitude judged on automated measurement. Diagnosis of ST-elevated acute anterior myocardial infarction was based on fourth universal definition of acute myocardial infarction—briefly, ST elevation at the J-point in 2 contiguous leads with the cut point measurement. Diagnosis of ST-elevated acute anterior myocardial infarction was based on these 90 cases, as described below. Univariate logistic regression analysis for TTS was performed using the prediction data, and significant predictors were extracted. A multivariate logistic regression analysis was not performed because of the multicollinearity of many pairs of parameters. A receiver operating characteristic (ROC) curve analysis was performed, and the cutoff value was calculated based on the Youden index. The statistical predictive model consisted of an assessment of whether a parameter in each case was higher/lower than the cutoff value (named the cutoff value model). A confusion matrix was created, and the diagnostic performance (accuracy/sensitivity : recall/positive predictive value : precision) was evaluated. From the analysis of the predictive model, the propensity score (PS) of each predictor was calculated, and the PS formula for each predictor was constructed (the ROC curve model):

\[
PS \text{ formula} = 1 / (1 + \exp(-ax + \beta))
\]

where a = coefficient of predictor and \( \beta \) = intercept, calculated by logistic regression analysis. The model was applied to the test data and the AUROC was measured using ROC curve analysis.
Table 2  Comparison of takotsubo syndrome, acute anterior myocardial infarction, and univariate logistic regression analysis for takotsubo syndrome, on prediction data (n = 90)

| Comparison of TTS and Ant-AMI | OR | 95% CI | P value |
|-----------------------------|----|--------|---------|
| **Age (years)** | TTS (n = 45) | Ant-AMI (n = 45) | **Male** | NA | NA |
| **HTN** | 14 (31%) | 19 (42%) | 0.618 | 0.26-1.47 | .275 |
| **HL** | 9 (20%) | 29 (64%) | 0.138 | 0.05-0.36 | <.001* |
| **DM** | 2 (4%) | 14 (31%) | 0.103 | 0.02-0.49 | .004* |
| **CKD** | 14 (31%) | 8 (18%) | 2.090 | 0.78-5.63 | .145 |
| **BNP (pg/mL)** | 274 [67, 482] | 184 [59, 477] | 0.999 | 0.94-1.07 | .982 |
| **WBC (/mm³)** | 8200 [6700, 11325] | 9200 [7100, 11400] | 1.020 | 0.92-1.13 | .723 |
| **CRP (mg/dL)** | 1.38 [0.23, 6.58] | 0.23 [0.10, 0.76] | 1.100 | 1.00-1.21 | .053 |
| **HR (bpm)** | 95 [79, 131] | 84 [71, 94] | 1.030 | 1.01-1.05 | .002* |
| **P axis (degree)** | 57 [38, 73] | 55 [40, 62] | 0.999 | 0.94-1.07 | .982 |
| **PR (ms)** | 168 [154, 187] | 172 [156, 188] | 1.000 | 1.00-1.01 | .345 |
| **QRS axis (degree)** | 35 [-19, 74] | 22 [-2, 49] | 1.000 | 0.99-1.01 | .345 |
| **QRS width (ms)** | 90 [84, 100] | 92 [82, 102] | 0.976 | 0.76-1.21 | .849 |
| **QTc (ms)** | 429 [410, 449] | 430 [405, 442] | 1.030 | 0.92-1.15 | .611 |
| **I STJ** | 20 [-10, 75] | -20 [-10, 75] | 0.830 | 0.74-0.93 | <.001* |
| **II STJ** | 20 [-10, 75] | -20 [-10, 75] | 0.831 | 0.75-0.92 | <.001* |
| **III STJ** | 5 [-5, 5] | 5 [-5, 5] | 1.060 | 1.01-1.15 | .027* |
| **aVR STJ** | 13 [-15, 46] | -15 [-40, 35] | 0.976 | 0.94-1.00 | .205 |
| **aVL STJ** | 5 [-15, 30] | -5 [-40, 25] | 1.050 | 1.01-1.15 | .027* |
| **aVF STJ** | 70 [-30, 130] | -30 [-60, 45] | 1.040 | 0.99-1.10 | .164 |
| **V1 STJ** | 93 [31, 138] | 135 [75, 225] | 0.976 | 0.94-1.01 | .155 |
| **V2 STJ** | 15 [20, 35] | 10 [5, 20] | 1.060 | 0.98-1.15 | .344 |
| **V3 STJ** | 30 [15, 60] | 25 [-10, 60] | 1.030 | 0.97-1.08 | .366 |
| **V4 STJ** | 145 [90, 265] | 160 [63, 278] | 1.000 | 0.79-1.27 | .971 |
| **V5 STJ** | 5 [-5, 5] | 5 [-5, 5] | 1.030 | 0.99-1.07 | .154 |
| **V6 STJ** | 25 [5, 5] | 25 [5, 5] | 1.040 | 0.95-1.12 | .678 |
| **aVR STmid** | 13 [-15, 46] | -15 [-40, 35] | 1.050 | 0.99-1.09 | .155 |
| **aVL STmid** | 5 [-15, 30] | -5 [-40, 25] | 1.100 | 1.04-1.11 | .015* |
| **aVF STmid** | 10 [5, 20] | 10 [-10, 30] | 1.040 | 0.99-1.07 | .154 |
| **V1 STmid** | 30 [-10, 35] | 15 [-20, 50] | 1.040 | 0.99-1.11 | .011* |
| **V2 STmid** | 15 [20, 35] | 10 [-5, 25] | 1.040 | 0.99-1.07 | .154 |
| **V3 STmid** | 30 [15, 60] | 25 [-10, 60] | 1.040 | 0.95-1.12 | .678 |
| **V4 STmid** | 145 [90, 265] | 160 [63, 278] | 1.000 | 0.79-1.27 | .971 |
| **V5 STmid** | 5 [-5, 5] | 5 [-5, 5] | 1.030 | 0.97-1.08 | .366 |
| **V6 STmid** | 25 [5, 5] | 25 [5, 5] | 1.040 | 0.95-1.12 | .678 |
| **aVR STend** | 13 [-15, 46] | -15 [-40, 35] | 1.050 | 0.99-1.09 | .155 |
| **aVL STend** | 5 [-15, 30] | -5 [-40, 25] | 1.100 | 1.04-1.11 | .015* |
| **aVF STend** | 10 [5, 20] | 10 [-10, 30] | 1.040 | 0.99-1.07 | .154 |
| **V1 STend** | 30 [-10, 35] | 15 [-20, 50] | 1.040 | 0.99-1.11 | .011* |
| **V2 STend** | 15 [20, 35] | 10 [-5, 25] | 1.040 | 0.99-1.12 | .026* |
| **V3 STend** | 30 [15, 60] | 25 [-10, 60] | 1.040 | 0.99-1.07 | .154 |
| **V4 STend** | 145 [90, 265] | 160 [63, 278] | 1.000 | 0.79-1.27 | .971 |
| **V5 STend** | 5 [-5, 5] | 5 [-5, 5] | 1.030 | 0.97-1.08 | .366 |
| **V6 STend** | 25 [5, 5] | 25 [5, 5] | 1.040 | 0.95-1.12 | .678 |

Note: *P < 0.05; CI: confidential interval; OR: odd ratio
Table 2 shows a comparison of the TTS and Ant-AMI in the prediction data (n = 90). Hyperlipidemia and diabetes cases with TTS were significantly lower than those with Ant-AMI. Among ECG parameters, heart rate and several ST levels (lead II/aVR/aVF/V5/V2/V1) demonstrated significant differences. Univariate logistic regression analysis identified 25 significant predictors (asterisk [*] in Table 2). Multivariate logistic regression analysis was not performed because of the many significant correlations/confounding/multicollinearity among the variables.

The diagnostic performances of the statistical predictive models are presented in Table 3, and the ML models in Table 4. Among the statistical predictors, V1 STJ ≤18 μV showed the highest accuracy of 0.773 (in test data), and aVR STmid had the highest AUROC (0.727, in test data). The results of recursive feature elimination by cross-validation are demonstrated in Supplemental File 4. In model_LGBM, the best number of features was 16, 24, and 25; and in model_ET, 25. As a result, we adopted all 25 features to construct the ML models. Compared with the statistical predictive models, model_LGBM and model_ET had higher accuracy (0.842 and 0.831, respectively) and AUROC (0.868 and 0.896, respectively).

Figure 2 shows a comparison of ST levels. The STJ of TTS in lead II/aVF/V5/V6 was higher than that in Ant-AMI, and the STJ of TTS in lead aVR/V1/V2 was lower than that in Ant-AMI. The STmid and STend showed similar results to STJ, but V5 STmid, V5 STend, and I STend were not significant predictors. The representative ECG waveforms are shown in Figure 3. From Table 3, the representative ECG characteristics of TTS compared with Ant-AMI were as follows: no ST elevation of V1 STJ (≤+18 μV) and ST depression in aVRmid (≤-10 μV). The representative and visible ECG features of TTS were summarized as no ST elevation in V1 and ST depression in aVR.

The important features of the 2 ML models are shown in Supplemental File 5. In model_LGBM, the V1 STJ showed the highest feature importance. Conversely in model_ET, no V1 STJ but diabetes and hyperlipidemia showed high feature importance. The SHAP values of the models are shown in Figure 4, which showed similar pattern to Supplemental File 5. V1 STJ showed the highest feature importance.
Initially, a receiver operating characteristic (ROC) curve analysis was performed, area under ROC (AUROC) was measured, and cutoff value was calculated by Youden index. AUROC of hyperlipidemia (HL) and diabetes (DM) were not evaluated because they were bivariate categorical variables. The statistical predictive model consisted of 2 methods, an assessment of whether a parameter of each case had higher/lower value than the cutoff (named as cutoff value model), and propensity score (PS) of each predictor was calculated on the prediction data, and the PS formula for each predictor was constructed (named as ROC curve model), which was applied to the test data and AUROC was measured by ROC curve analysis. Confusion matrix was prepared from the model, and diagnostic performance was explained by accuracy (Acc) / sensitivity (Sens); named as recall / positive predictive value (PPV); named as precision (Prec.) / and F1 score (harmonic mean of recall and Prec.). Ten times random cross-validation was performed, and the average of results was displayed.

### Table 3  Diagnostic performance of statistical predictive models

| Prediction data (n = 90) | Test data (n = 22) |
|-------------------------|-------------------|
| **ROC curve model**     | **ROC curve model** |
| **Cutoff**               | **AUROC**         | **95% CI of AUROC** | **Acc** | **Recall (Sens)** | **Prec. (PPV)** | **F1** |
| HL                      | 0.278             | 0.020             | 0.237   | 0.217             | 0.217           | 0.213 |
| DM (n, %)               | 0.367             | 0.044             | 0.125   | 0.066             | 0.554           | 0.30-0.81 |
| HR (bpm)                | 0.711             | 0.711             | 0.702   | 0.717             | 0.649           | 0.39-0.91 |
| I STJ                   | 0.681             | 0.689             | 0.655   | 0.720             | 0.665           | 0.42-0.91 |
| II STJ                  | 0.672             | 0.644             | 0.610   | 0.692             | 0.674           | 0.58-0.77 |
| II STmid                | 0.701             | 0.678             | 0.660   | 0.695             | 0.661           | 0.42-0.90 |
| I STend                 | 0.667             | 0.644             | 0.860   | 0.709             | 0.624           | 0.38-0.87 |
| aVR STJ                 | 0.729             | 0.693             | 0.605   | 0.722             | 0.694           | 0.47-0.92 |
| aVR STend               | 0.732             | 0.678             | 0.711   | 0.667             | 0.727           | 0.51-0.95 |
| aVF STJ                 | 0.693             | 0.667             | 0.867   | 0.722             | 0.694           | 0.47-0.92 |
| aVF STmid               | 0.615             | 0.633             | 0.911   | 0.713             | 0.636           | 0.40-0.88 |
| aVF STend               | 0.614             | 0.633             | 0.911   | 0.713             | 0.636           | 0.40-0.88 |
| V1 STJ                  | 0.771             | 0.611             | 0.857   | 0.407             | 0.690           | 0.46-0.92 |
| V1 STmid                | 0.765             | 0.700             | 0.956   | 0.761             | 0.653           | 0.40-0.90 |
| V1 STend                | 0.699             | 0.667             | 0.778   | 0.700             | 0.628           | 0.37-0.89 |
| V1 T                    | 0.635             | 0.663             | 0.538   | 0.600             | 0.645           | 0.38-0.92 |
| V2 STJ                  | 0.629             | 0.652             | 0.750   | 0.680             | 0.616           | 0.37-0.87 |
| V2 STmid                | 0.658             | 0.656             | 0.756   | 0.687             | 0.665           | 0.56-0.77 |
| V2 STend                | 0.635             | 0.633             | 0.756   | 0.607             | 0.673           | 0.42-0.90 |
| V5 STJ                  | 0.724             | 0.733             | 0.822   | 0.698             | 0.755           | 0.645           |
| V5 STmid                | 0.768             | 0.733             | 0.800   | 0.706             | 0.669           | 0.43-0.91 |
| V5 STend                | 0.749             | 0.733             | 0.822   | 0.698             | 0.755           | 0.674           |
| V6 STmid                | 0.714             | 0.700             | 0.933   | 0.636             | 0.757           | 0.39-0.89 |
| V6 STend                | 0.708             | 0.688             | 0.790   | 0.729             | 0.736           | 0.39-0.89 |

Initially, a receiver operating characteristic (ROC) curve analysis was performed, area under ROC (AUROC) was measured, and cutoff value was calculated by Youden index. AUROC of hyperlipidemia (HL) and diabetes (DM) were not evaluated because they were bivariate categorical variables. The statistical predictive model consisted of 2 methods, an assessment of whether a parameter of each case had higher/lower value than the cutoff (named as cutoff value model), and propensity score (PS) of each predictor was calculated on the prediction data, and the PS formula for each predictor was constructed (named as ROC curve model), which was applied to the test data and AUROC was measured by ROC curve analysis. Confusion matrix was prepared from the model, and diagnostic performance was explained by accuracy (Acc) / sensitivity (Sens); named as recall / positive predictive value (PPV); named as precision (Prec.) / and F1 score (harmonic mean of recall and Prec.). Ten times random cross-validation was performed, and the average of results was displayed.

### Table 4  Results of validation data of machine learning predictive models, which were built by PyCaret

| Light gradient boosting machine | Extra trees classifier | Ada boost classifier | Naive Bayes | Gradient boosting classifier | Random forest classifier | Linear discriminant analysis | Decision tree classifier | K neighbors classifier | Logistic regression | Quadratic discriminant analysis |
|--------------------------------|------------------------|----------------------|-------------|-------------------------------|--------------------------|-----------------------------|--------------------------|------------------------|---------------------|-----------------------------|
| Acc                            | 0.856                  | 0.881                | 0.872       | 0.821                         | 0.821                    | 0.786                       | 0.778                    | 0.776                  | 0.719               | 0.708                       |
| AUROC                          | 0.865                  | 0.881                | 0.872       | 0.850                         | 0.850                    | 0.844                       | 0.810                    | 0.827                  | 0.794               | 0.798                       |
| Recall (Sens)                  | 0.870                  | 0.830                | 0.875       | 0.805                         | 0.805                    | 0.804                       | 0.825                    | 0.800                  | 0.775               | 0.779                       |
| Prec. (PPV)                    | 0.867                  | 0.863                | 0.867       | 0.835                         | 0.835                    | 0.830                       | 0.778                    | 0.777                  | 0.775               | 0.772                       |
| F1                             | 0.860                  | 0.836                | 0.822       | 0.837                         | 0.831                    | 0.788                       | 0.783                    | 0.797                  | 0.717               | 0.734                       |

The diagnostic performance was explained by accuracy (Acc) / sensitivity (Sens); named as recall / positive predictive value (PPV); named as precision (Prec.) / and F1 score (harmonic mean of recall and Prec.). Ten times random cross-validation was performed, and the average of results was displayed.

### Discussion

We built predictive models for TTS and Ant-AMI using an automated ECG system with μV-level measurements. The ST levels in several leads were significant predictors, and we were able to provide clinically useful cutoff values for them, as shown in Table 3. Among them, V1 STJ ≤+18 μV showed the highest accuracy, and aVR STmid showed the highest AUROC in test data. Conversely, ML predictive models demonstrated higher accuracy and AUROC than statistical models. In the ML models, V1 STJ played an important role in model building.

#### ST level as a predictor of TTS

In addition to ST levels in V1, ST levels in I/II/aVR/aVF/V2/V6 were significant predictors of TTS.

The significance of lead V2 can be explained by the importance of the nearest lead, V1, which is well known. Kosuge...
Figure 2  Comparison of ST levels of takotsubo syndrome (TTS) and acute anterior myocardial infarction (Ant-AMI) in prediction data (90 cases). Left figure shows ST level at the J point (STJ), middle figure shows the middle of the ST level (STmid), and right figure shows the end of the ST level (STend). After Mann–Whitney U test, a box-and-whisker plot was drawn in each lead. The box indicates interquartile range and median value, and the whisker corresponds to maximum and minimum value. The red and blue triangles show significant upper and lower values, respectively.

Figure 3  Representative 12-lead electrocardiograms. Left figure demonstrates a takotsubo syndrome (TTS) case, in which ST repression is observed in aVR and V1. Right figure displays an ST-elevation acute anterior myocardial infarction (Ant-AMI) case, in which ST elevation is found in aVR and V1–V3. The patient’s coronary arteriography showed occlusion of the left anterior descending branch (segment 6).
and colleagues explained that V1 is located in both the right ventricular anterior region and the right paraseptal region; however, abnormalities of wall contraction in TTS rarely extend to the right ventricle region, compared with AMI. Therefore, the significance of other leads can be explained as follows:

**Lead aVR**
Several investigators found more ST depression in TTS than in Ant-AMI. Ant-AMI causes greater injury than TTS. In the present study, the CK-MB level in Ant-AMI was higher than that in TTS. Lead aVR is known as a “cavity lead” and allows for visualization of the left ventricle (LV); therefore, the aVR lead can help determine the total damage of the LV.

**Lead II/aVF**
ST elevation was found in inferior leads in 33%-50% of TTS cases in large series. Jim and colleagues emphasized the importance of ST elevation in the inferior leads as a new criterion for TTS diagnosis. They described that the inferior myocardium is universally affected in typical TTS, theoretically expressed as inferior ST-segment elevation. Compared with TTS, Ant-AMI tends to show large LV damage, in which the vector of injuries of opposing walls cancel each other out, and simultaneous ischemia in both the lateral and inferior walls reduces the ST-segment changes in their respective leads.

**Lead V6/I**
Inoue and colleagues reported more prevalent V6 ST elevation in TTS than in Ant-AMI. Ogura and colleagues reported that the ratio of ST elevation of V1–V6 / ST elevation of V1–V3 was a significant predictor of TTS. Regarding lead I of TTS, there were no reports. However, these differences can easily be understood from the perspective of RV involvement. Chia and colleagues reported ST depression of the lateral lead as a sign of right ventricular ischemia. Both lead V1 ST elevation and lead I/V6 ST depression can show RV involvement of Ant-AMI.

**Machine learning of ECG to distinguish between TTS and Ant-AMI**
Although the accuracy was not very high for each of the 25 significant predictors, their aggregation created excellent predictive ML models with the algorithms Model_ET and Model_LGBM, which are ensemble learning models and use decision trees. The method of model_ET to divide trees is based not on the best fit method but on a random choice of the Gini coefficient or entropy; consequently, model_ET can show high performance, especially in the presence of noisy features. Therefore, model_ET has an advantage if the importance of each variable is not very high. In the present study, the accuracy of 22 significant predictors was limited, and model_ET was suitable for building a predictive model.
Model_LGBM is frequently used and is known to exhibit higher diagnostic performance, especially on table data, compared to other ensemble ML methods. Following are the advantages of model_LGBM: (1) Model_LGBM uses the boosting method, which is a series data composition, instead of bagging (bootstrap aggregating; used in random forest method). Consequently, the learning speed is faster than that of the parallel data composition of bagging. (2) Decision trees of model_LGBM are a leaf-wise tree growth method, which is much faster than the level-wise tree growth method (used, eg, in XG boosting). (3) Fine-tuning of hyper-parameters can be performed more easily in model_LGBM than in other ML models, which improves the accuracy of the model. Therefore, model_LGBM can perform excellently under the condition of many low-importance parameters, such as in the present study.

The SHAP method is novel and can show both feature importance and correlation (positive or negative). In statistical comparison by multivariate analysis, it is difficult to compare the importance of all parameters when there are pairs with significant correlation/confounding/multicollinearity. However, in ML (especially ensemble learning models using decision trees), most models are adjusted by internal regularization, and their predictive value is not affected. The explainability of features is somewhat affected (weakened) when there is significant correlation, confounding, or multicollinearity; as opposed to statistical models, parameters are recognized not to exclude because of internal regularization.

Study limitations
This study was performed with a small sample size of patients; therefore, several limitations were inevitable: no external validation (using separate external test data), no ECG variations, and no validation in other similar clinical populations (acute pericarditis, inferior AMI, atypical TTS, no sinus rhythm, etc). The precision of the study became relatively low because of the small sample size of test data. We did not perform deep learning as ML method because of the size. Because STEMI and NSTEMI cases are treated differently, it was ideal to separate the 2 groups. Combining multiple leads seems to produce good results, but in our preliminary data, it induced overfitting to prediction data and we could not show the usefulness of the combination. Although the V1 STJ was essential in both ML models, other important features of the models were not the same; hence, the diagnosis by the 2 models might be different in several patients. An automated system of ECG (ECAPs12c) with μV-level measurement demonstrated a higher diagnostic performance; however, this system is not commonly used worldwide.

Conclusion
ML on the parameters of the automated ECG system with μV measurement showed superior diagnostic performance compared to conventional single ECG parameters to distinguish between TTS and Ant-AMI. Although the results of the present study were limited by the small sample size, it may be a clinically useful ECG-based discriminator.

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Disclosures
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Authorship
All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent
Written informed consent was obtained from all participants prior to the study.

Ethics Statement
The ethics committee of Yokohama Minami Kyosai Hospital approved the study protocol and the research has adhered to the relevant ethical guidelines.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.cvdhj.2022.07.001.

References
1. Ghadri JR, Wittstein IS, Prasad A, et al. International expert consensus document on takotsubo syndrome (part i): clinical characteristics, diagnostic criteria, and pathophysiology. Eur Heart J 2018;39:2032–2046.
2. Kosuge M, Kimura K. Clinical implications of electrocardiograms for patients with anterior wall ST-segment elevation acute myocardial infarction in the interventional era. Circ J 2012;76:32–40.
3. Jim M-H, Chan AO-O, Tsui P-T, et al. A new ECG criterion to identify takotsubo cardiomyopathy from anterior myocardial infarction: role of inferior leads. Heart Vessels 2009;24:124–130.
4. Makimoto H, Höckmann M, Lin T, et al. Performance of a convolutional neural network derived from an ECG database in recognizing myocardial infarction. Sci Rep 2020;10:8445.
5. Cho Y, Kwon J, Kim K-H, et al. Artificial intelligence algorithm for detecting myocardial infarction using six-lead electrocardiography. Sci Rep 2020;10:20495.
6. Tyggesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Circulation 2018;138:e618–e651.
7. Ezaki K, Nakagawa M, Taniguchi Y, et al. Gender differences in the ST segment. Circ J 2010;74:2448–2454.
8. Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant 2012;48:452–458.
9. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2016, https://www.R-project.org/.
10. Nakamura T, Nagata Y, Nitta G, et al. Prediction of premature ventricular complex origins using artificial intelligence-enabled algorithms. Cardiovasc Digit Health J 2021;2:76–83.
11. Gain U, Hotti V. Low-code AutoML-augmented data pipeline – a review and experiments. J Phys Conf Ser 2021;1828:012015.
12. Maré E, Geurts P, Wehnkel L. Random subwindows and extremely randomized trees for image classification in cell biology. BMC Cell Biol 2007;8(Suppl 1):S2.
13. Basha SM, Rajput D, Vandhan V. Impact of gradient ascent and boosting algorithm in classification. Int J Intell Eng Syst 2018;11:41–49.
14. Lundberg SM, Lee S. A unified approach to interpreting model predictions. Adv Neural Inf Process Syst. https://arXiv.org/abs/1705.07874.
15. Molnar C, Casalicchio G, Bischl B. Interpretable machine learning – a brief history, state-of-the-art and challenges. arXiv:201009337 [cs, stat] [Internet]. 2020 [cited 2021 Aug 15], http://arxiv.org/abs/2010.09337.
16. Mugnai G, Pasqualin G, Benfari G, et al. Acute electrocardiographic differences between Takotsubo cardiomyopathy and anterior ST elevation myocardial infarction. J Electrocardiol 2015;48:79–85.
17. Frangieh AH, Obeid S, Ghadri J, et al. ECG criteria to differentiate between takotsubo (stress) cardiomyopathy and myocardial infarction. J Am Heart Assoc 2016;5:e003418.
18. George A, Arumugham PS, Figueredo VM. aVR – the forgotten lead. Exp Clin Cardiol 2010;15:e36–e44.
19. Tsuchihashi K, Ueshima K, Uchida T, et al. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. Angina Pectoris-Myocardial Infarction Investigations in Japan. J Am Coll Cardiol 2001;38:11–18.
20. Ogura R, Hiasa Y, Takahashi T, et al. Specific findings of the standard 12-lead ECG in patients with ‘Takotsubo’ cardiomyopathy: comparison with the findings of acute anterior myocardial infarction. Circ J 2003;67:687–690.
21. Inoue M, Shimizu M, Ino H, et al. Differentiation between patients with takotsubo cardiomyopathy and those with anterior acute myocardial infarction. Circ J 2005;69:89–94.
22. Chia BL, Yip JW, Tan HC, Lim YT. Usefulness of ST elevation II/III ratio and ST deviation in lead I for identifying the culprit artery in inferior wall acute myocardial infarction. Am J Cardiol 2000;86:341–343.
23. Ghiasi MM, Zendehboudi S. Application of decision tree-based ensemble learning in the classification of breast cancer. Comput Biol Med 2021;128:104089.
24. Rufo DD, Debelee TG, Ibenthal A, Negera WG. Diagnosis of diabetes mellitus using gradient boosting machine (LightGBM). Diagnostics (Basel) 2021;11:1714.
25. Crowley G, Kim J, Kwon S, et al. PEDF, a pleiotropic WTC-L1 biomarker: machine learning biomarker identification and validation. PLoS Comput Biol 2021;17:e1009144.