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## Accepted Manuscript

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**Algorithm for the Automatic Computation of the Modified Anderson-Wilkins Acuteness Score of Ischemia from the Pre-hospital ECG in ST-segment Elevation Myocardial Infarction**

Running title: Automated algorithm for evaluation of ischemia acuteness in pre-hospital ECG in STEMI patients

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**Disclosures:** None

**Key words:** Prehospital ECG, Acuteness of Ischemia, STEMI

**Abstract**

**Background:** The acuteness score (based on the modified Anderson-Wilkins score) estimates the acuteness of ischemia based on ST-segment, Q-wave and T-wave measurements obtained from the electrocardiogram (ECG) in patients with ST Elevation Myocardial Infarction (STEMI). The score (range 1 (least acute) to 4 (most acute)) identifies patients with substantial myocardial salvage potential regardless of patient reported symptom duration. However, due to the complexity of the score, it is not used in clinical practice. Therefore, we aimed to develop a reliable algorithm that automatically computes the acuteness score.

**Methods:** We scored 50 prehospital ECGs from STEMI patients, manually and by the automated algorithm. We assessed the reliability test between the manual and automated algorithm by interclass correlation coefficient (ICC) and Bland-Altman plot.

**Results:** The ICC was 0.84 (95% CI 0.72-0.91),  $P < 0.0001$ . The mean difference between manual and automated acuteness score was  $0.17 \pm 0.66$ . In only two cases, there was a major disagreement between the two scores. There was an excellent agreement between the scores for the remaining 48 ECGs, all within the upper (1.46) and lower (-1.12) limits of agreement.

**Conclusion:** In conclusion, we have developed an automated algorithm for measurement of the modified Anderson-Wilkins ECG acuteness score from the pre-hospital ECG in STEMI patients. This automated algorithm is highly reliable, can be applied in daily practice for research purposes and may be implemented in commercial automated ECG analysis programs to achieve practical use for decision support in the acute phase of STEMI.

## Background

Rapid revascularization of the acute occluded coronary artery, either by percutaneous coronary intervention (PCI) or thrombolytic therapy, is of major importance to both myocardial salvage, risk of subsequent heart failure and survival in patients with ST-segment elevation myocardial infarction (STEMI) [1-3]. It is recommended that reperfusion of the occluded artery with primary PCI (pPCI) is provided within 120 minutes (<60 – 90 minutes preferable) of the first medical contact in patients with STEMI and symptom onset <12 hours [4]. However, time of symptom onset might be inaccurately assessed due to inaccurate patient recollection, silent angina pectoris or pre-infarction angina pectoris, which pre-conditions the ischemic myocardium leading to cardioprotection. An objective electrocardiographic (ECG) method for quantifying the timing of evolving acute myocardial infarction, the Anderson-Wilkins acuteness score has previously been developed and modified. The acuteness score quantifies the acuteness of myocardial ischemia from the electrocardiogram (ECG) [5,6], and has been shown to be superior to treatment delay (time from pain-to-balloon) in predicting final infarct size (FIS), salvage and mortality in patients with symptom duration within 12 hours [7-9] and 12-72 hours [10]. This score represents a more objective and quantitative ECG measure of the time course of ongoing myocardial ischemia compared to subjective patient-reported symptom duration. The patient-reported time from symptom onset and the ECG acuteness score have been shown to provide complementary value in predicting final infarct size after reperfusion therapy [7]. Although the acuteness score is well-established, and might become a reliable tool for pre-hospital risk stratification and choice of treatment in STEMI patients, manual calculation of this score is a time-consuming task unlikely to be performed in the acute setting of STEMI [11]. Automatic calculation of the acuteness score could facilitate prospective research for usefulness of the score and ultimately enhance clinical

implication. Thus, the purpose of this study was to develop a reliable algorithm that automatically computes the acuteness score.

## **Methods**

### *Study sample size and design*

A total of 50 randomly chosen pre-hospital 12-lead ECGs from patients with STEMI and treated with pPCI were used in this project. Electrocardiograms satisfying the following criteria were included in this study: 1) an available digital pre-hospital standard 12-lead ECG recorded in the ambulance, 2) the pre-hospital ECG meeting the current recognized ECG criteria [1] for STEM and 3) no bundle brunch block or excessive signal noise that could confound quantitative ECG evaluation. The expert ECG reader (YF) scored the 50 ECGs electronically. In case of challenging or questionable scoring, the ECG acuteness scores were reviewed, discussed and matched with two other experts (MS, MMS). This dataset was used to set the detection and recognition rules of our automatic algorithms. All three ECG experts were blinded to the results from the automated scores, as the manual scores were performed before the automated algorithm was done. The 50 digital ECGs were then automatically processed using our developed automatic algorithm of acuteness score. The levels of agreement between the fully automated acuteness score and the manual score were evaluated.

### *Acuteness score*

The ECG acuteness score is a continuous variable and ranges from 1 (least acute/late ischemia) to 4 (most acute/early ischemia). Also, it has been shown that STEMI patients with ECG acuteness score  $\geq 3$  and treated with pPCI, have better outcome independent of symptom durations [7,9,10].

Accordingly, the ECG acuteness score was dichotomized as  $\geq 3$  and  $< 3$ . We defined acute ischemia as ECG acuteness score  $\geq 3$  and non-acute ischemia as ECG acuteness score  $< 3$ .

### ***ECG measurement***

#### *The manual ECG acuteness score:*

All digital 12-lead ECG waveform measurements were measured electronically (using CODE-STAT-Reviewer version 9.0 Software, Physio-Control, Inc.). Each lead was designated an acuteness phase (1A, 1B, 2A or 2B) based on the presence or absence of a tall T-wave or an abnormal Q-wave [5,6] (Table 1); phase 1A, tall T-wave and no abnormal Q-wave; phase 1B, positive T-wave and no abnormal Q-wave; phase 2A, tall T-wave and an abnormal Q-wave; phase 2B, positive or initial  $>50\%$  positive T-wave and an abnormal Q-wave [5]. In addition, leads with ST elevation, negative T-wave and Q-wave were designated phase 2B. Leads with ST elevation, negative T-wave and no Q-wave were excluded, if any. ST elevation  $\geq 0.10$  mV was considered significant. The overall ECG acuteness score was calculated from the following formula:

$$\text{Acuteness score} = \frac{4(\# \text{ leads } 1A) + 3(\# \text{ leads } 1B) + 2(\# \text{ leads } 2A) + 1(\# \text{ leads } 2B)}{\sum \# \text{ leads with } 1A, 1B, 2A \text{ or } 2B}, \text{ where } \# \text{ means "number of"}$$

and  $\sum$  means "sum of". Figure 1 shows an example of an ECG, designating acuteness phases in relevant leads and using formula for calculating the acuteness score.

#### *The automated algorithm:*

Using the software (using CODE-STAT-Reviewer version 9.0 Software, Physio-Control, Inc.), 12SL measurements were used directly from digital 12-lead ECG XML source files output from the

recording system, thus enabling near real-time analysis. The threshold for digital ST-segment elevation was changed from 0.1 mV to 0.085 mV to more closely reflect visual impression of manual coding of ST-segment elevation due to line thickness on a printed ECG. Further, the criteria for “any Q” in leads V1-V3 was coded as Q-waves longer than 8ms duration to minimize noise deflections being interpreted as Q-waves. We also required the presence of either ST-segment elevation in 2 consecutive leads.

### Statistical analysis

Categorical variables are reported as numbers (percentages) and continuous variables as median (25<sup>th</sup> – 75<sup>th</sup> quartiles). Wilcoxon matched pairs test was done to test the differences in the acuteness scores between the manual and the automated score. The automated acuteness score was correlated with the manual acuteness score by Spearman correlation. The reliability between the manual score and the automated score (absolute agreement) was assessed by intraclass correlation coefficient (ICC) with corresponding 95% confidence intervals (CI). A two-way mixed model was used to calculate the ICCs. To further investigate the presence of systematic differences between the manual and automated scores, a Bland-Altman plot was made. The Kappa coefficient with corresponding 95% CI was used to measure the agreements between manual score and automated score on acute ischemia (acuteness score  $\geq 3$ ) vs non-acute ischemia (acuteness score  $< 3$ ) among all 50 ECGs.

The reading of the ICC and Kappa was according to the following usually recognized scale: poor,  $\leq 0.20$ ; fair,  $> 0.20$  and  $0.40 <$ ; moderate,  $> 0.40$  and  $0.60 <$ ; good,  $> 0.60$  and  $0.80 <$ ; very good,  $> 0.80$  and  $0.90 <$ ; or excellent,  $> 0.90$ .



All statistical tests were two-sided and the level of statistical significance was defined as  $p < 0.05$ . All analyses were performed using SPSS statistical software (SPSS version 22.0, SPSS Inc, Chicago, IL).

## Results

Patient characteristics are summarized in table 2. The median ECG acuteness score in each lead and the overall score are summarized in table 3. There were no significant difference in acuteness scores between the manual and the automated measures. There was a strong correlation between the manual and automated overall acuteness score (Spearman correlation coefficient  $r = 0.84$ ,  $p < 0.0001$ ).

### Reliability for automated ECG acuteness score

The reliability test for the overall acuteness score between the manual and automated measures was ICC = 0.84 (95% CI 0.72 – 0.91),  $p < 0.0001$ . The correlation and reliability tests between the manual and automated acuteness score for each lead were similarly strong and are summarized in table 4.

A Bland-Altman plot of differences between manual and automated acuteness scores with the corresponding upper (1.46) and lower (-1.12) limits of agreement is shown in figure 2. The mean of differences in overall acuteness score between manual and automated score was 0.17 ( $\pm 0.66$ ). Only two outliers (ECG1 and ECG2) were observed above the upper limit of agreement. The differences between the manual and automated acuteness score were 3.33 for ECG1 and 2.17 for ECG2, figure 3.

**Reliability of the automated algorithm for designating acute ischemia on ECG**

Acute ischemia (ECG acuteness score  $\geq 3$ ) was obtained in 32 (64.0%) vs 29 (59.2%) ECGs by manual and automated score, respectively. The reliability test between the manual and automated score for acute ischemia was kappa = 0.83 (95% CI 0.64 – 0.96),  $p < 0.0001$ .

**Discussion**

In this study we aimed to develop a useful and reliable automated algorithm for the acuteness score that digitally measures the modified Anderson-Wilkins acuteness of ischemia from the pre-hospital ECG in patients with STEMI. We demonstrated that our developed automated algorithm showed statistically (by ICC calculation) and visually (by Bland-Altman plot) excellent reliabilities when compared to the manual acuteness score.

The acuteness score has been shown to be superior to treatment delay (time from pain to balloon inflation) in predicting final infarct size (FIS), salvage and mortality in patients with symptom duration within 12 hours [7-9] and 12-72 hours [10]. The patient-reported time-from-symptom-onset and ECG acuteness score have been shown to provide complementary value in predicting final infarct size after reperfusion therapy [7]. The acuteness scores also identifies STEMI patients with substantial myocardial salvage potential from pPCI even with symptom durations up to 72 hours [10]. Although, this score could be useful in the clinical setting, its clinical application is very limited due to its complexity and the time it takes to obtain the score manually. Ripa et al. demonstrated that the use of digital waveform measurements was more precise than waveform measurements obtained from a printed ECG, where an ECG-ruler for calculating the acuteness

score is applied [11]. These automatically retrieved waveform measurements from the GE-Marquette 12SL ECG Analysis Program were entered into a Microsoft Excel spreadsheet for the calculation of the acuteness score using Excel's built-in formulas. The authors recommended that an automated algorithm would be more precise than the manual score in a clinical setting and that an automatic algorithm could possibly be implemented in commercially available ECG analysis programs [11]. In the present study, we extended this approach to develop a computerized automated algorithm for the acuteness score and validated it against our manual score, based on electronically waveform measurements from the digital standard 12-lead ECGs using CODE-STAT-Reviewer version 9.0 Software, Physio-Control, Inc.

The automated acuteness score could provide decision support in the acute phase of STEMI by implementation in commercially available ECG analysis programs, which additionally could ease research purposes that deal with the ECG acuteness score in patients with STEMI. However, further prospective studies are warranted prior to commercial implementation. Using the automatic calculation of the acuteness score, prospective studies should first investigate whether the acuteness score appropriately identifies patients in the very early acute phase of STEMI, e.g. to correlate the acuteness score to post-PCI left ventricular function, release of cardiac biomarkers as a biomarker estimate of myocardial infarct size or clinical outcome.

## **Conclusion**

In conclusion, we have developed an automated modified Anderson-Wilkins acuteness score quantifying the acuteness of ischemia from the pre-hospital ECG in STEMI patients. The reliability of the automated acuteness score was excellent when compared to manually measured acuteness scores.

**Acknowledgments**

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## Figure legends

Figure 1: A: A pre-hospital standard 12-lead ECG (25mm/s, 10mm/mV, 150Hz) from a STEMI patient with RCA culprit lesion. There are ST-segment elevation  $> 0.1$  mv in leads II, III and aVF. The T-wave amplitudes are 0.76 mV, 0.85 mV and 0.80 mV in lead II, III and aVF, respectively. Neither of the leads had pathological Q-waves (Q-wave duration were  $< 30$  msec in all 3 leads). B: Designating acuteness phase in each lead; Lead II, III and aVF are designated *IA* since ST-segment elevation, Tall T-wave and no abnormal Q-wave. C: Using the formula, the acuteness score is calculated to 4. (amp; amplitude, dur; duration, msec; millisecond, mV; millivolt, RCA; Right Coronary Artery, #; number of,  $\Sigma$ ; sum of)

Figure 2: Bland-Altman plot and limits of agreement between the manual and automated overall acuteness score.

Figure 3: ECG examples (50mm/s, 20mm/mV, 150Hz): ECG1; the automated algorithm measured ST elevation in one lead (III) and found no significant ST elevation in two contiguous leads, hence acuteness score was null. The manual score found ST elevation in lead III, aVF and V1 a tall T-wave in lead V1, hence overall acuteness score 3.33. ECG2; the manual acuteness score was 3.50, while the automated score was 1.33. This discordance was due to interpretation of abnormal Q-wave in lead II, III and aVF which were measured to be  $\geq 30$  msec by automated score while the manual score measured correctly the Q-waves to be  $< 30$  msec (electronically measured using CODE-STAT-Reviewer version 9.0 Software, Physio-Control, Inc.).

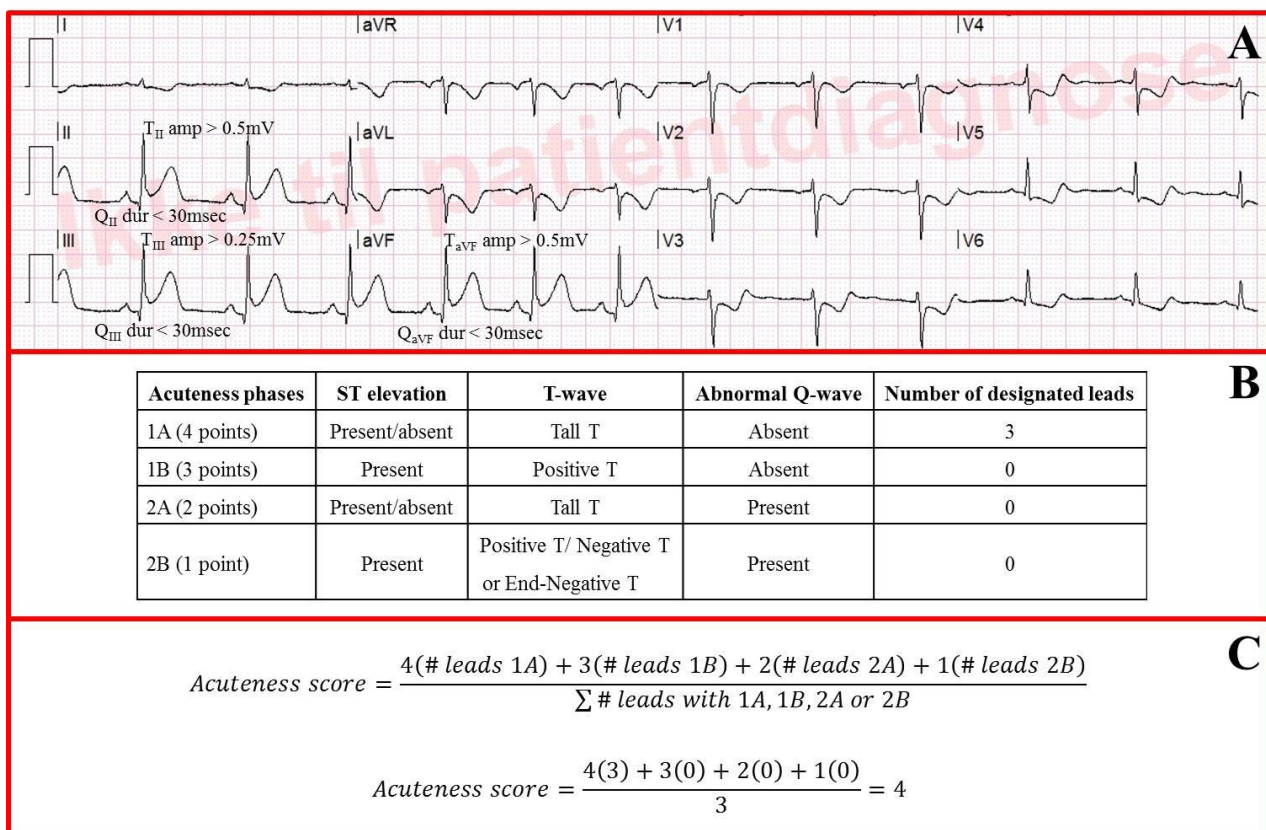


Fig. 1

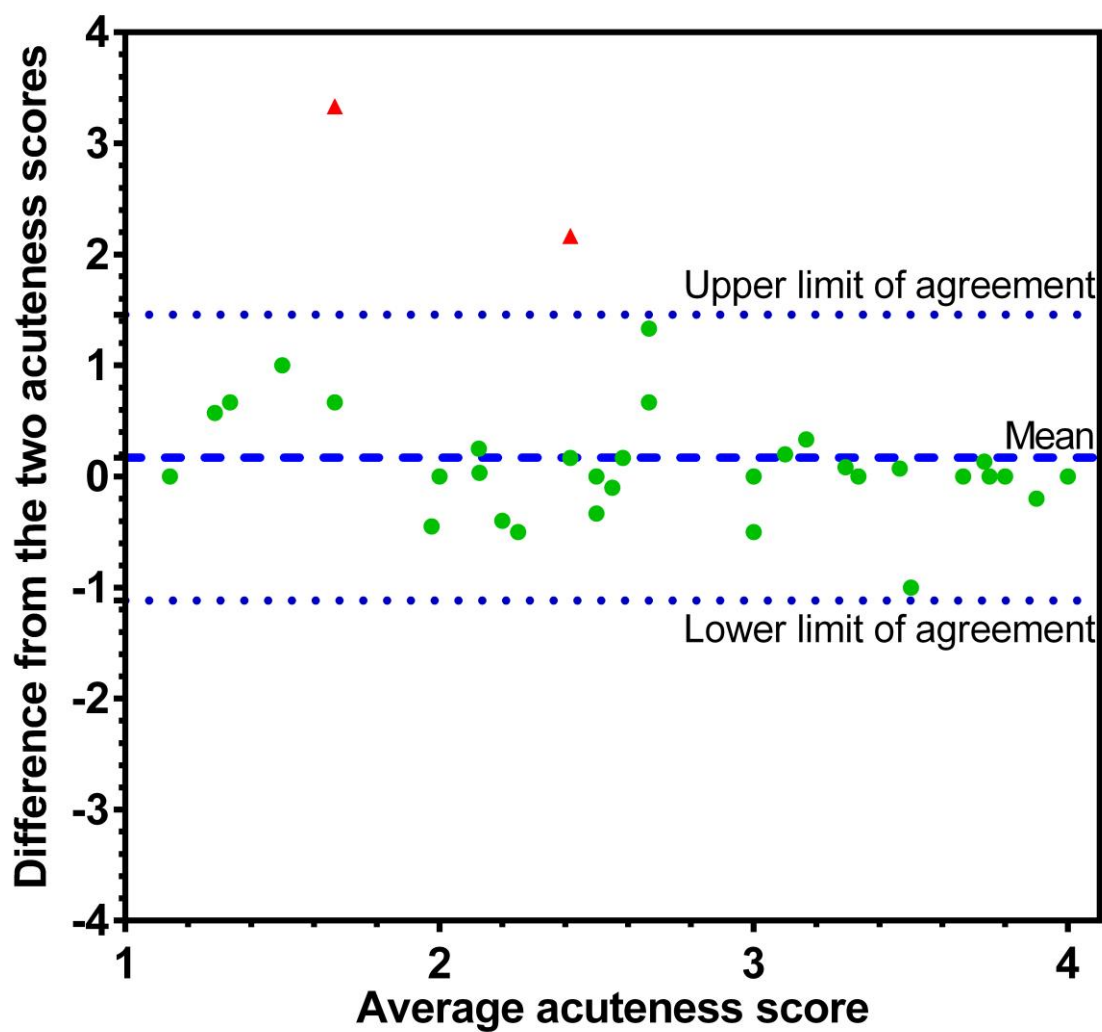


Fig. 2





Fig. 3

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Table 1: Baseline characteristics of the study population

<b>Baseline variables</b>	<b>n = 50</b>
Age, years (mean $\pm$ SD)	62 $\pm$ 11
Male gender, n (%)	41 (82)
LAD culprit, n (%)	23 (46)
MVD, n (%)	13 (26)
Time from symptom-onset to primary PCI, minutes (median (25 <sup>th</sup> – 75 <sup>th</sup> interquartiles))	281 (144-311)
Time from first-medical-contact to primary PCI, minutes (median (25 <sup>th</sup> – 75 <sup>th</sup> interquartiles))	127 (113-149)
LAD; Left Anterior Descending coronary artery, MVD; Multivessel Disease, PCI; Percutaneous Coronary Intervention	

Table 2: Limits of abnormal Q-waves and tall T-waves morphology criteria in different ECG leads, as used for designating each lead an acuteness score

<b>Leads</b>	<b>Abnormal Q-wave criterion</b>	<b>Tall T-wave criterion</b>
I	$\geq 30$ ms	$\geq 0.50$ mV
II	$\geq 30$ ms	$\geq 0.50$ mV
III	$\geq 30$ ms and abnormal Q in aVF	$\geq 0.25$ mV
aVR	–	–
aVL	$\geq 30$ ms	$\geq 0.25$ mV
aVF	$\geq 30$ ms	$\geq 0.50$ mV
V <sub>1</sub>	Any Q	$\geq 0.50$ mV
V <sub>2</sub>	Any Q	$\geq 1.0$ mV
V <sub>3</sub>	Any Q	$\geq 1.0$ mV
V <sub>4</sub>	$\geq 30$ ms	$\geq 1.0$ mV
V <sub>5</sub>	$\geq 30$ ms	$\geq 0.75$ mV
V <sub>6</sub>	$\geq 30$ ms	$\geq 0.50$ mV
ms, milliseconds; mV, millivolts		

Table 3: Lead and the overall median scores between manual and automated ECG acuteness score

Lead	ECG Acuteness score		Wilcoxon matched pairs test
	Manual	Automated	P-value
I	3.0 (1.5-3.8)	3.0 (1.5-3.0)	0.655
II	4.0 (3.0-4.0)	4.0 (3.0-4.0)	0.098
III	4.0 (3.0-4.0)	4.0 (2.3-4.0)	0.199
aVL	3.0 (2.0-4.0)	2.0 (1.0-4.0)	0.854
aVF	4.0 (3.0-4.0)	4.0 (1.3-4.0)	0.609
V1	1.0 (1.0-3.0)	1.0 (1.0-3.0)	0.443
V2	2.5 (1.8-3.0)	3.0 (1.0-3.0)	0.414
V3	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.480
V4	3.0 (2.0-3.0)	3.0 (2.0-3.0)	0.731
V5	3.0 (3.0-3.0)	3.0 (2.3-3.0)	0.102
V6	3.0 (2.3-4.0)	3.0 (3.0-4.0)	0.102
Overall	3.1 (2.5-3.8)	3.0 (2.3-3.8)	0.099

Table 4: Correlation and reliability tests between manual and automated acuteness scores

Leads	Spearman's correlation		Intraclass correlation coefficient (95% CI)	
		P-value		p-value
I	0.71	<0.0001	0.73 (0.53-0.85)	<0.0001
II	0.84	<0.0001	0.92 (0.82-0.95)	<0.0001
III	0.60	<0.0001	0.74 (0.54-0.85)	<0.0001
aVL	0.68	<0.0001	0.72 (0.50-0.84)	<0.0001
aVF	0.84	<0.0001	0.91 (0.83-0.95)	<0.0001
V1	0.55	<0.0001	0.69 (0.46-0.83)	<0.0001
V2	0.86	<0.0001	0.92 (0.87-0.96)	<0.0001
V3	0.89	<0.0001	0.92 (0.86-0.95)	<0.0001
V4	0.74	<0.0001	0.83 (0.71-0.91)	<0.0001
V5	0.91	<0.0001	0.94 (0.89-0.97)	<0.0001
V6	0.88	<0.0001	0.93 (0.87-0.96)	<0.0001
Overall	0.84	<0.0001	0.84 (0.72-0.91)	<0.0001

## Highlights

- Electrocardiographic objective evaluation of the acuteness of ischemia in STEMI
- Using Anderson-Wilkins acuteness score
- We developed an automatic algorithm for the acuteness score
- Validation results show that the algorithm is highly reliable
- The automatic algorithm can be applied in the clinical setting

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