Journal of the American Heart Association

ORIGINAL RESEARCH

New Electrocardiographic Algorithm for the Diagnosis of Acute Myocardial Infarction in Patients With Left Bundle Branch Block

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BACKGROUND: Current electrocardiographic algorithms lack sensitivity to diagnose acute myocardial infarction (AMI) in the presence of left bundle branch block.

METHODS AND RESULTS: A multicenter retrospective cohort study including consecutive patients with suspected AMI and left bundle branch block, referred for primary percutaneous coronary intervention between 2009 and 2018. Pre-2015 patients formed the derivation cohort (n=163, 61 with AMI); patients between 2015 and 2018 formed the validation cohort (n=107, 40 with AMI). A control group of patients without suspected AMI was also studied (n=214). Different electrocardiographic criteria were tested. A total of 484 patients were studied. A new electrocardiographic algorithm (BARCELONA algorithm) was derived and validated. The algorithm is positive in the presence of ST deviation ≥1 mm (0.1 mV) concordant with QRS polarity, in any lead, or ST deviation ≥1 mm (0.1 mV) discordant with the QRS, in leads with max (R|S) voltage (the voltage of the largest deflection of the QRS, ie, R or S wave) ≤6 mm (0.6 mV). In both the derivation and the validation cohort, the BARCELONA algorithm achieved the highest sensitivity (93%–95%), negative predictive value (96%–97%), efficiency (91%–94%) and area under the receiver operating characteristic curve (0.92–0.93), significantly higher than previous electrocardiographic rules (P<0.01); the specificity was good in both groups (89%–94%) as well as the control group (90%).

CONCLUSIONS: In patients with left bundle branch block referred for primary percutaneous coronary intervention, the BARCELONA algorithm was specific and highly sensitive for the diagnosis of AMI, leading to a diagnostic accuracy comparable to that obtained by ECG in patients without left bundle branch block.

Key Words: acute myocardial infarction ■ electrocardiography ■ left bundle branch block ■ primary percutaneous coronary intervention

See Editorial by Macfarlane

The electrocardiographic diagnosis of acute myocardial infarction (AMI) in patients with left bundle branch block (LBBB) is often challenging. On one hand, most of patients referred for primary percutaneous coronary intervention (pPCI) because of the presence of LBBB are not experiencing an AMI.[1] On the other hand, patients with LBBB and AMI are usually at high risk and often experience delays in reperfusion therapy[1] that may lead to critical consequences.[2,3]

Unfortunately, even the most recent electrocardiographic algorithms[4,5] do not afford a diagnostic certainty for AMI in patients with LBBB.[2,5,6] In the absence

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Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.015573

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For Sources of Funding and Disclosures, see page 14.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- We have identified and validated a new electrocardiographic algorithm, named the BARCELONA algorithm, that significantly improves the performance of previous electrocardiographic criteria to diagnose acute myocardial infarction in patients with left bundle branch block.

What Are the Clinical Implications?

- To improve the electrocardiographic diagnosis of acute myocardial infarction in patients with left bundle branch block will help to reduce many false activations of the protocols for emergent reperfusion and will help to provide timely reperfusion to those patients who are truly experiencing an acute myocardial infarction.

Nonstandard Abbreviations and Acronyms

AMI	acute myocardial infarction
pPCI	primary percutaneous coronary intervention
ROC	receiver operating characteristic

of acute ischemia, the LBBB pattern is characterized by (1) ST-segment displacement in the opposite direction to the polarity of the QRS complex (further referred as discordant ST deviation) and (2) the existence of a certain degree of proportionality between the magnitude of the discordant ST deviation and the voltage of the corresponding QRS complex.[4,5,7] Thus, in addition to the clinical symptoms of acute ischemia, the occurrence of ST elevation concordant with QRS polarity (5 points in Sgarbossa rules, referred to as concordant ST elevation) and the presence of excessive discordant ST deviation (such as the ST/QRS ratio in the Modified Sgarbossa Criteria)[5] are specific for AMI. However, these criteria have a relatively low sensitivity.[2,5,6]

To improve the diagnostic sensitivity of ECG in patients with LBBB and suspected AMI, we have elaborated 2 new approaches. First, since any ST deviation concordant with the QRS should be regarded as abnormal, we hypothesized that not only concordant ST elevation but also concordant ST depression might be a sign of AMI; we therefore extended the Sgarbossa rule of concordant ST depression in leads V1 to V3 to any other lead. It was hypothesized that this would cover the electrocardiographic projection of acute ischemia in different myocardial regions.

Second, we considered as a positive criterion for AMI the presence of an appreciable (≥1 mm or 0.1 mV) discordant ST deviation in low-voltage QRS complexes because, in the absence of ischemia, these complexes usually show isoelectric ST-segment potentials (Figure 1). This latter criterion had not yet been explored and required defining the best cutoff value for QRS voltage below which any discordant ST deviation ≥1 mm (0.1 mV) would be regarded as disproportionate and suggestive of AMI. Of note, leads with low-voltage QRS are a frequent finding in patients with LBBB and AMI, since AMI is associated with lower QRS voltages in patients with LBBB.[8]

The objective of this study was to assess whether the electrocardiographic diagnosis of AMI in the presence of LBBB improved by considering the presence of concordant ST depression in any ECG lead and the occurrence of discordant and disproportionate ST deviation in leads with low-voltage QRS complexes.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patient Selection

This is a retrospective, observational cohort study involving 4 referral hospitals for pPCI in Barcelona, Spain. The "Codi IAM" network[9] in Catalonia (Spain) provides early reperfusion, mainly through pPCI, to all patients with suspected ST-segment–elevation myocardial infarction (STEMI) presenting during the first 12 hours after the onset of symptoms. According to the Codi IAM protocol, the presence of new or presumed new LBBB in association with ischemic symptoms is considered an indication for pPCI.

In this study, we included all consecutive patients referred for pPCI because of new or presumed new LBBB with available ECG recorded at the first medical contact.

The cohort of patients referred for pPCI between October 2009 and December 2014 formed the derivation sample, while patients referred from January 2015 until June 2018 served as the validation sample.

In addition, to evaluate the specificity of the proposed new electrocardiographic criteria in patients not suspected of having an AMI, we included a control group of consecutive patients with complete LBBB who attended the emergency department of Bellvitge University Hospital for any reason other than acute coronary syndrome or who were referred to this center for electrophysiological study or cardiac pacemaker implantation.

The clinical data were retrieved from prospective databases available at each participating hospital. These databases register all patients with STEMI treated within the Codi IAM protocol since the beginning of this

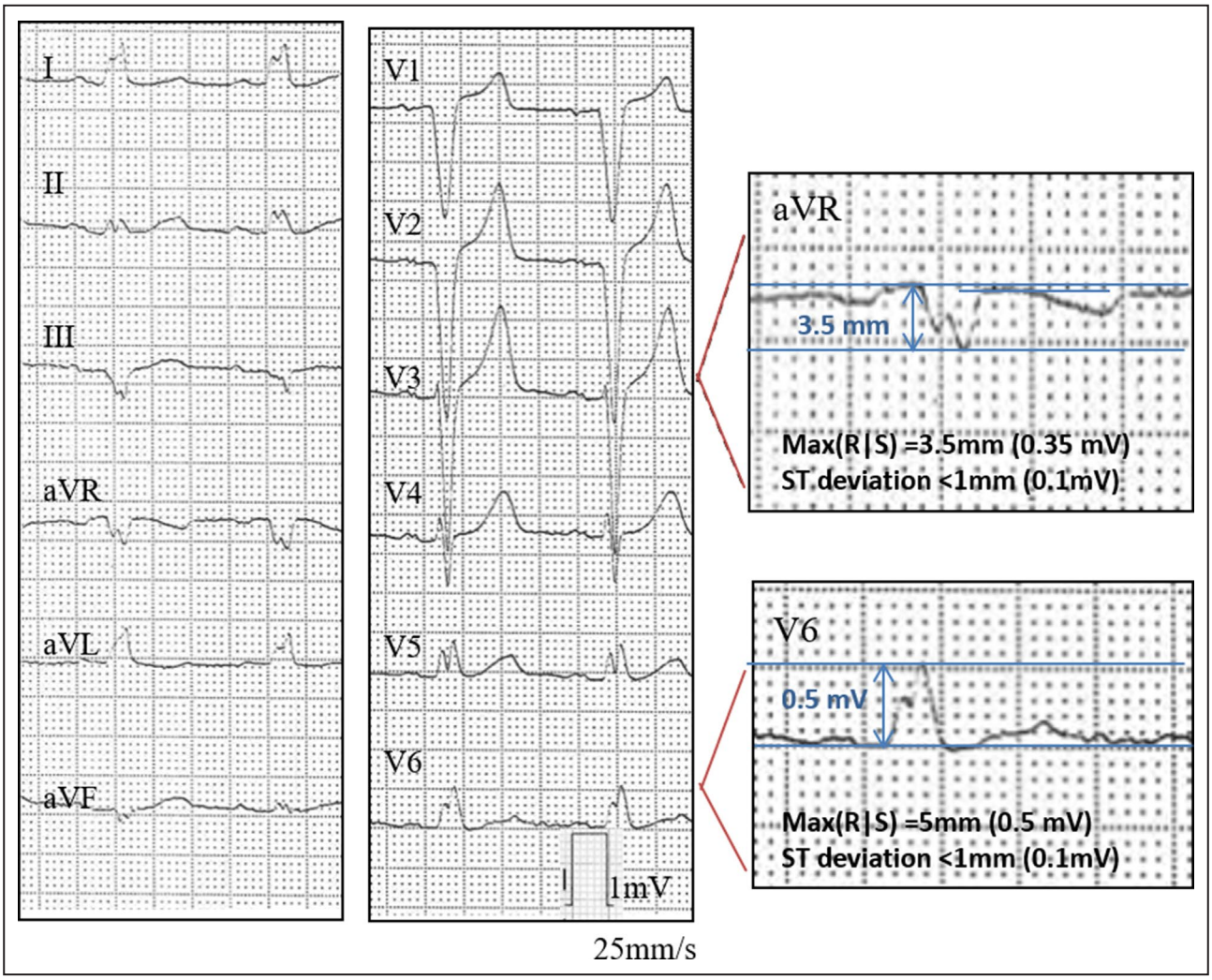


Figure 1. ECG from a patient without acute myocardial infarction showing isoelectric ST segment or minimal ST deviation <1 mm (0.1 mV) in leads with low-voltage QRS and the absence of any ST deviation ≥1 mm (0.1 mV) concordant with QRS polarity.

network in 2009. The study protocol was approved by the Institutional Ethics Committee; the Committee considered that, given the retrospective nature of the analysis and the use of anonymized data, written informed consent from patients was not needed.

Electrocardiographic Analysis

All ECGs were recorded at 25 mm/s speed, 10 mm/mV amplitude.

The ECGs were analyzed by 2 independent cardiologists from the coordinating center (Bellvitge Hospital), who were blinded to the clinical and angiographic data. In case of discordance, the evaluation of a third cardiologist was required. LBBB was defined by the presence of QRS complex duration >120 ms; QS or rS pattern in lead V1; R-wave peak time >60 ms in leads DI, V5, or V6; and absence of Q wave in these leads.[4,10] The ST deviation was measured at the J point relative to the QRS onset, and all voltage measurements >1 mm (0.1 mV) were rounded to the nearest 0.5 mm (0.05 mV); ST deviations <1 mm (0.1 mV) were not taken into account. To mitigate the potential influence of an unstable recording baseline and interbeat ST and QRS variability on our results, we considered an electrocardiographic criterion positive when it was present in >50% of the beats available in 1 lead.

The new electrocardiographic criteria evaluated in this study are (1) the presence of ST depression ≥1 mm (0.1 mV) concordant with QRS polarity in any lead of the ECG (Figure 2 and Figure S1) and (2) the occurrence of discordant ST deviation ≥1 mm (0.1 mV) in leads with a low-voltage QRS (Figure 3, Figure 4, and Figure S1). QRS polarity was considered as positive or negative whenever the largest

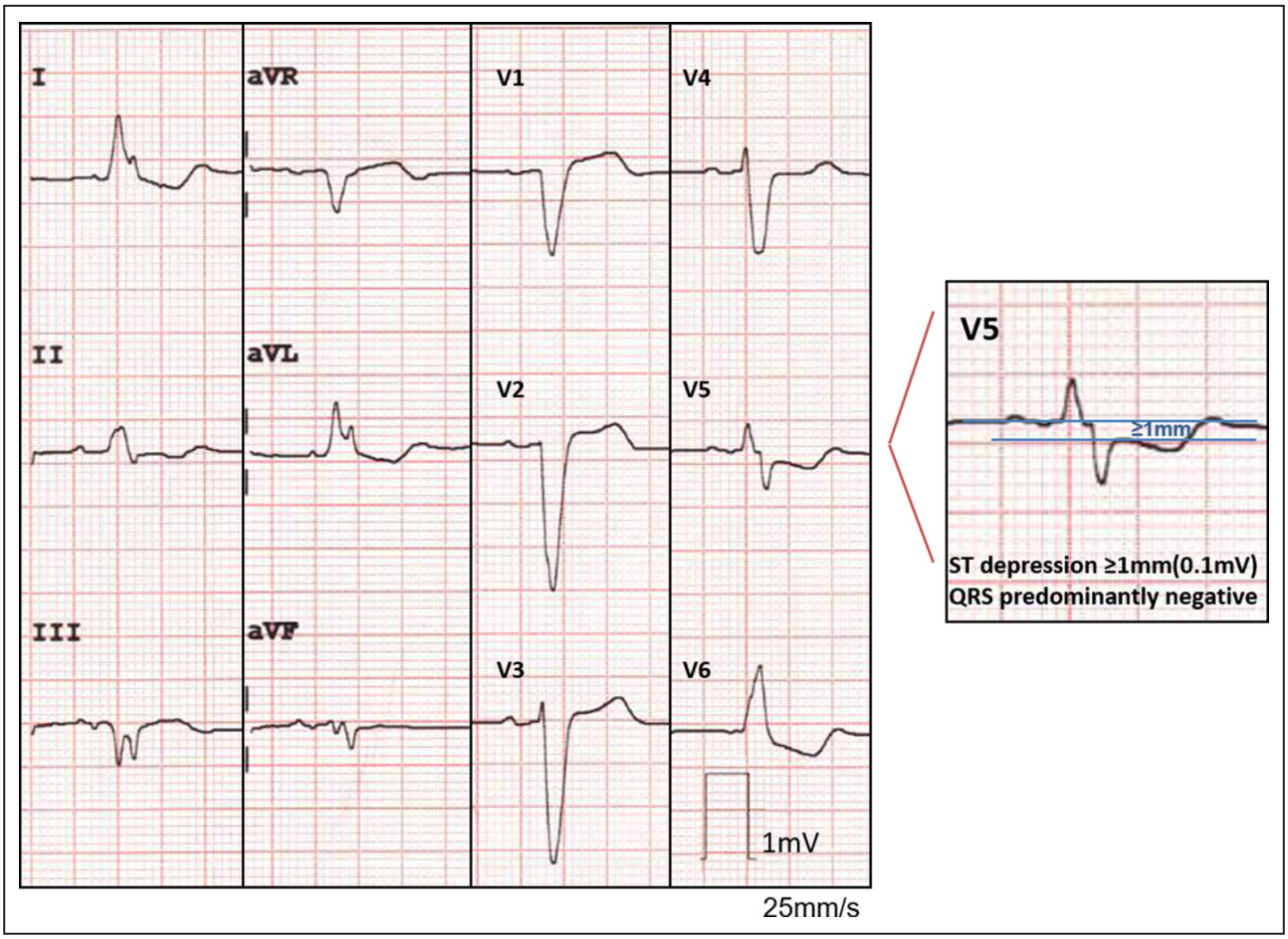


Figure 2. **ECG from a patient with acute myocardial infarction and culprit lesion in the right coronary artery, showing ST-segment depression ≥1 mm (0.1 mV) concordant with negative QRS polarity in lead V5.**

deflection of the QRS was ≥1.5mm (0.15mV) higher as compared to the opposite deflection. Leads where the difference between the voltages of the R wave and the Q or S waves were ≤1mm (0.1mV) were not taken into account. To evaluate low-voltage QRS, we considered the voltage of the largest deflection of the QRS (ie, the R wave in leads with a predominantly positive QRS and the Q or S wave in leads with a predominantly negative QRS), measured with respect to QRS onset; we defined this variable as max (R|S) voltage.[5]To accomplish this second criterion, we needed to find the best cutoff value for max (R|S) voltage, below which any discordant ST deviation ≥1 mm (0.1 mV) would be regarded as abnormal and then support the diagnosis of AMI. This cutoff value was derived from the receiver operating characteristic (ROC) curves for max (R|S) voltages ranging from 4 mm (0.4 mV) to 8 mm (0.8 mV). The best cutoff was defined by the highest area under the ROC curve and the highest efficiency.

We hypothesized that the highest sensitivity would be achieved by an algorithm that took into account all potential aspects of repolarization abnormalities in LBBB, that is, concordant ST elevation, concordant ST depression, and disproportionate discordant ST deviation in leads with a low-voltage QRS.

The Sgarbossa and Modified Sgarbossa Criteria were applied according to previously published definitions[4,5] (Table S1).

Clinical Variables

In each patient, we recorded clinical and anthropometric variables, laboratory tests, and electrocardiographic and angiographic data. AMI was diagnosed in the presence of either an acute coronary artery occlusion (grade 0 of the thrombolysis in myocardial infarction flow grading) or an acute coronary lesion with thrombolysis in myocardial infarction flow ≥1 associated with a troponin rise and fall above the 99th percentile upper reference limit. Coronary stenosis was considered acute when

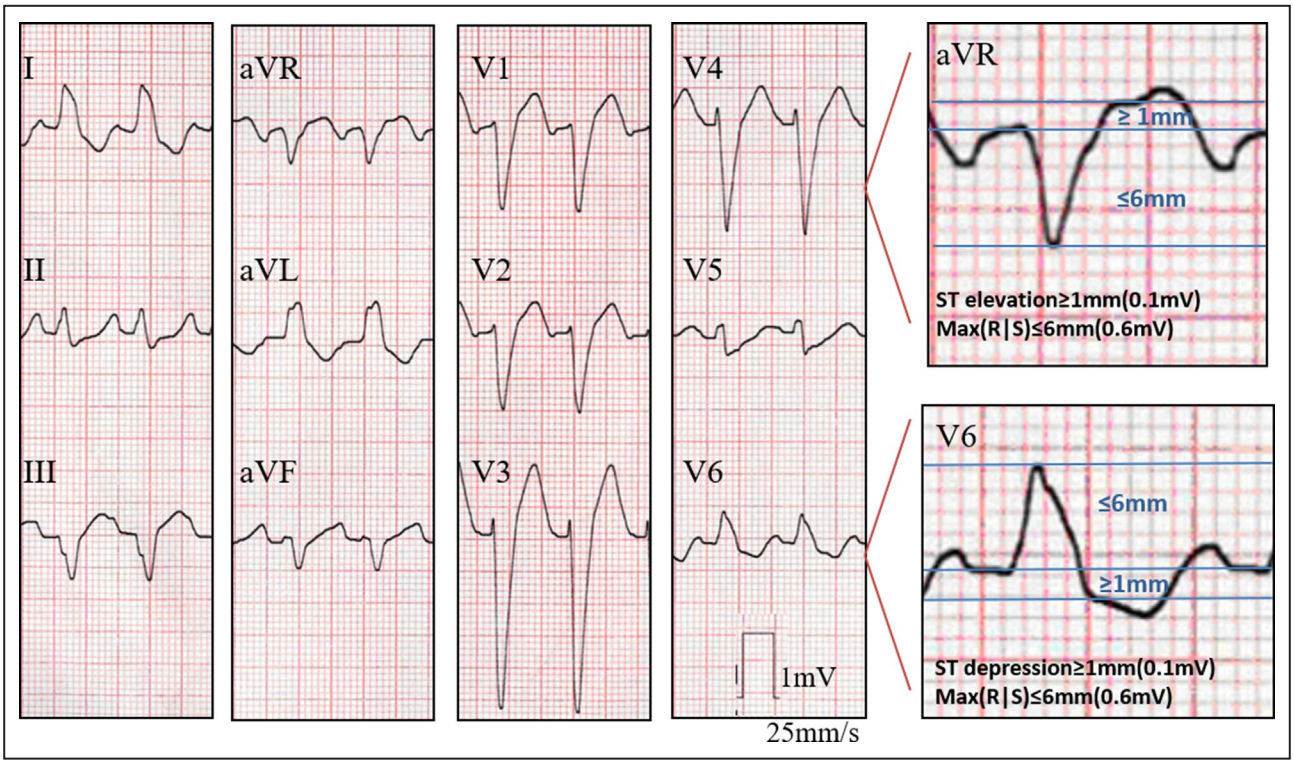


Figure 3. ECG from a patient with acute myocardial infarction and culprit lesion in the left circumflex artery, showing discordant ST deviation ≥1 mm (0.1 mV) in 2 leads with a QRS voltage ≤6 mm (0.6 mV).

signs of thrombosis or ulceration were identified by angiography.

The diagnosis of STEMI is based on electrocardiographic criteria that do not apply to patients with LBBB. To test the diagnostic performance of the Modified Sgarbossa rules, Smith and coworkers[5] elaborated a definition of STEMI equivalent based on angiographic findings and the amount of the release of biomarkers of cardiac injury. To get closer to the concept of STEMI equivalent used in the Modified Sgarbossa Criteria, we elaborated a similar definition of STEMI equivalent (see Data S1) and tested the diagnostic performance of the new electrocardiographic criteria by including patients with STEMI equivalent in a separate analysis (see Data S1 and Table S2).

Statistical Analysis

Continuous variables are presented as mean and SD or median and interquartile range. Categorical variables are expressed as numbers and percentages. Comparisons between groups were performed using the *t* test or the Mann–Whitney *U* test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. The 95% CIs were obtained using Wald's or Wilson's method when appropriate. Sensitivity and specificity of each electrocardiographic algorithm were compared using McNemar's test. Global performance of each algorithm was assessed by calculating the efficiency and the area under the ROC curve. Efficiency is a parameter that expresses the percentage of correct classifications by a diagnostic test, and it is calculated as follows: 100×(true negatives+true positives)/all cases. Areas under the ROC curve were compared using the algorithm proposed by De Long et al.[11] The added value of the new criteria was calculated by the Integrated Discrimination Improvement index and the Net Reclassification Improvement index.[12] The agreement between the 2 cardiologists who interpreted the ECGs was evaluated with the Cohen's kappa coefficient. Differences were considered statistically significant at the 2-sided $P<0.05$ level. The statistical analysis was performed with STATA Release 12 software (StataCorp LP, College Station, TX).

RESULTS

The study included 484 patients divided into 3 groups: (1) a derivation cohort formed by 163 patients who were referred for pPCI between October 2009 and December 2014, (2) a validation cohort including 107 patients referred for pPCI from January 2015 until June 2018, and (3) a control group of 214

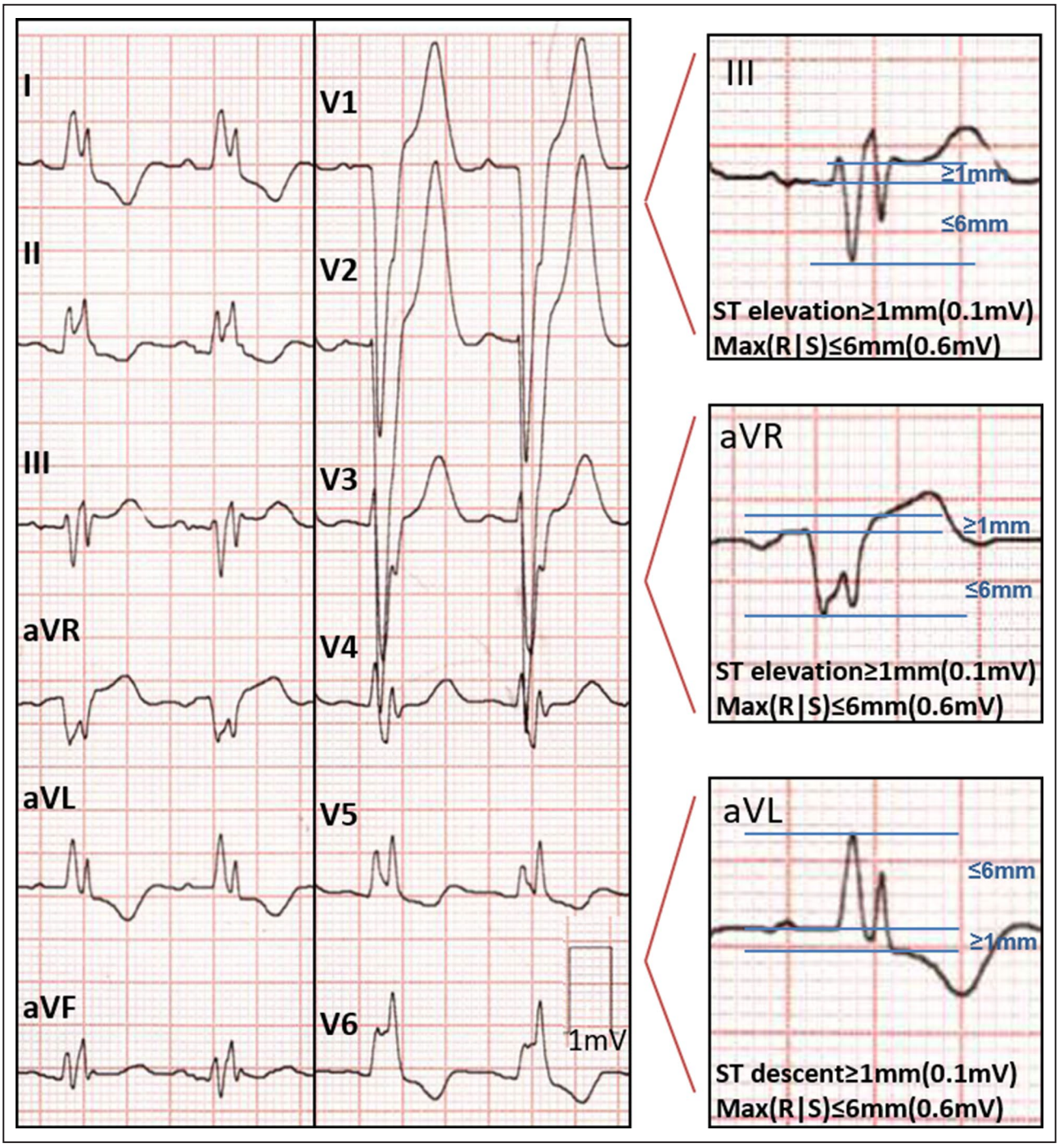


Figure 4. ECG from a patient with acute myocardial infarction and culprit artery in the left main.
Discordant ST deviation ≥1 mm (0.1 mV) in leads with max (R|S) voltage ≤6 mm (0.6 mV) is present in leads III, aVR, and aVL.

patients with LBBB and no suspected acute coronary syndrome. The 2 cardiologists who analyzed the ECGs agreed completely on the evaluation of the Sgarbossa criteria. There were 4 cases (1.5%) of disagreement concerning the Modified Sgarbossa Criteria and 2 cases (0.7%) of disagreement with the BARCELONA algorithm, all in patients referred for pPCI. The Cohen's kappa coefficient was 0.96 for the Modified Sgarbossa criteria and 0.98 for the BARCELONA algorithm.

Baseline Characteristics of Patients Referred for pPCI

There were no significant differences in terms of cardiovascular risk factors, cardiac history, and in-hospital

Table 1. Clinical Characteristics of the Study Population

	Patients With Suspected AMI Referred for pPCI (N=270)						Patients With No Suspected AMI (Control Group) (N 214)
	Derivation Cohort (N 163)	Validation Cohort (N 107)	*P* Value	AMI (N 101)	No AMI (N 169)	*P* Value	
Age, y, median (IQR)	72 (62–78)	73 (65–82)	0.23	73 (64–80)	71 (63–79)	0.53	79 (72–85)
Sex, male	97 (60%)	60 (56%)	0.58	75 (74%)	82 (49%)	<0.01	97 (46%)
Risk factors/comorbidities							
Hypertension	125 (77%)	78 (73%)	0.48	81 (80%)	122 (72%)	0.14	179 (84%)
Dyslipidemia	97 (60%)	66 (62%)	0.72	76 (75%)	87 (51%)	<0.01	128 (60%)
Diabetes mellitus	58 (36%)	45 (42%)	0.28	46 (46%)	57 (34%)	0.05	87 (41%)
Active smoker	29 (18%)	17 (16%)	0.68	24 (24%)	22 (13%)	0.02	19 (9)
Cardiac history							
Known structural heart disease	73 (45%)	46 (43%)	0.77	45 (45%)	75 (44%)	0.98	99 (46%)
Prior MI	24 (15%)	21 (20%)	0.29	24 (24%)	21 (13%)	0.02	25 (12%)
History of AF	28 (17%)	15 (14%)	0.49	11 (11%)	32 (19%)	0.08	65 (30%)
LVEF (%), median (IQR)	45 (35–60)	47 (35–60)	0.66	40 (33–50)	50 (35–60)	<0.01	56 (46–60)*
Admission data							
Hospital stay (d), median (IQR)	4 (1–9)	5 (1–10)	0.03	6 (4–11)	2 (1–8)	<0.01	NA
In hospital death	11 (7%)	13 (12%)	0.13	15 (15%)	9 (5%)	<0.01	NA

Chi squared or the Fisher exact test when appropriate were used to calculate differences between proportions; the Mann–Whitney *U* test was used to calculate differences between medians. AF indicates atrial fibrillation; AMI, acute myocardial infarction; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not available; and pPCI, primary percutaneous coronary intervention.

*LVEF was not available for 17 patients in the control group.

death between the derivation and the validation samples (Table 1).

AMI was diagnosed in 61 patients (37%) in the derivation cohort and in 40 patients (37%) in the validation sample. As compared with those without a diagnosis of AMI, patients with AMI were more frequently men, had higher prevalence of diabetes mellitus, dyslipidemia, and prior myocardial infarction, as well as lower left ventricular ejection fraction (Table 1). Clinical and angiographic details of patients with AMI are presented in Table 2. There were no significant differences in AMI characteristics and severity between the derivation and validation cohort (Table 2). Overall, the clinical presentation of the AMI was often severe: 40% of patients were in Killip class III or IV, the median left ventricular ejection fraction was 40%, and the in-hospital mortality was 15%.

Baseline Characteristics of Patients With No Suspected AMI

The control group included 23 cases referred for electrophysiological study after syncope, 96 patients referred for pacemaker implantation and 95 patients attended at the emergency department. The complete list of final diagnoses at the emergency department is reported in Table S3. The baseline characteristics of the control group are reported in Table 1. Almost half of patients (46%) had structural heart disease, and the median left ventricular ejection fraction was 56%.

ECG Analysis in the Derivation Cohort

The Sgarbossa and Modified Sgarbossa rules showed a high specificity (up to 98% for Sgarbossa score ≥3) but a low sensitivity (range, 26%–62%) for the diagnosis of AMI in the presence of LBBB (Table 3).

The Sgarbossa rule of ST depression limited to ECG leads V1 to V3 had a sensitivity of 13%. By extending the analysis to concordant ST depression ≥1 mm (0.1 mV) in any ECG lead the sensitivity increased to 51% ($P<0.01$) still maintaining a 97% specificity (Table 4).

The best cutoff value of max (R|S) voltage indicating low-voltage QRS with disproportionate discordant ST deviation was 6 mm (0.6 mV). This max (R|S) voltage gave the highest efficiency (86%) and the highest area under the ROC curve (0.84), significantly higher than other values (Figure 5). Thus, the new criterion was positive in the presence of discordant ST deviation ≥1 mm (0.1 mV) in any ECG lead with a max (R|S) voltage ≤6 mm (0.6 mV). Of note, in line with previous studies,[7] patients with AMI had lower QRS voltage (mean max [R|S] voltage 9.6 mm or 0.96 mV versus 10.8 mm or 0.108 mV; $P=0.01$)

Table 2. Angiographic, Clinical, and Laboratory Data of Patients With Left Bundle Branch Block and Acute Myocardial Infarction

	All Patients, N=101 (%)	Derivation Sample, N=61 (%)	Validation Sample, N=40 (%)	*P* Value
Acute occlusion (TIMI 0)	49 (49)	29 (48)	20 (50)	0.81
Acute lesion with TIMI 1–2	24 (24)	15 (25)	9 (23)	0.81
Acute lesion with TIMI 3	28 (28)	17 (28)	11 (28)	0.97
Multivessel disease*	57 (56)	37 (61)	20 (50)	0.29
Culprit artery				0.39
Left main	9 (9)	4 (7)	5 (14)	
LAD territory	48 (48)	29 (48)	19 (48)	
LCx territory	21 (21)	15 (25)	6 (16)	
RCA territory	18 (18)	10 (16)	8 (22)	
Intermediate artery	3 (3)	3 (5)	0 (0)	
Killip class at admission				0.78
I	53 (52)	32 (52)	21 (53)	
II	8 (8)	4 (7)	4 (11)	
III	22 (23)	15 (25)	7 (18)	
IV	18 (19%)	10 (17)	8 (21)	
TnT or TnI ratio, median (IQR)	171 (53–680)	194 (55–857)	149 (47–677)	0.52
CK-MB ratio, median (IQR)	23 (5–64)	23 (5–64)	23 (7–78)	0.94

The Pearson chi-squared or the Fisher exact test when appropriate was used to calculate differences between proportions; the Mann–Whitney *U* test was used to calculate differences between medians. CK-MB indicates creatine kinase isoenzyme MB; LAD, left anterior descendending artery; LCx, left circumflex artery; RCA, right coronary artery; STEMI, ST-segment–elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction flow grade; TnI, troponin I; and TnT, troponin T.

*Significant coronary stenosis in at least 2 coronary arteries.

and the median number of leads with max (R|S) voltage ≤6 mm (0.6 mV) was higher in patients with AMI (5 versus 3; *P*=0.02).

We tested several ECG algorithms incorporating the new criteria (Table 4). The best performance and the highest sensitivity were obtained by the algorithm

Table 3. Diagnostic Performance for AMI of the BARCELONA Algorithm and Previously Proposed Electrocardiographic Algorithms

Algorithm	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Efficiency % (95% CI)	AUC ROC (95% CI)
Derivation cohort (N=163)						
Sgarbossa score ≥3	34 (24–47)	98 (93–100)	91 (73–98)	71 (64–78)	74 (67–80)	0.66 (0.60–0.72)
Sgarbossa score ≥2	48 (36–60)	84 (76–90)	64 (50–77)	73 (64–80)	71 (63–77)	0.66 (0.59–0.73)
Mod. Sgarbossa III	62 (50–73)	91 (84–95)	81 (68–89)	80 (72–86)	80 (74–86)	0.77 (0.70–0.83)
Mod. Sgarbossa IV	51 (39–63)	96 (90–99)	89 (74–96)	77 (69–83)	79 (72–85)	0.73 (0.67–0.80)
Mod. Sgarbossa V	26 (17–38)	97 (92–99)	84 (62–95)	69 (61–76)	71 (63–77)	0.62 (0.56–0.67)
BARCELONA	95 (86–98)	89 (82–94)	84 (74–91)	97 (91–99)	91 (86–95)	0.92 (0.88–0.96)
Validation cohort (N=101)						
Sgarbossa score ≥3	33 (20–48)	99 (92–100)	93 (69–99)	71 (61–80)	74 (65–81)	0.66 (0.58–0.74)
Sgarbossa score ≥2	40 (26–55)	85 (75–92)	62 (43–78)	70 (60–79)	68 (59–76)	0.63 (0.54–0.72)
Mod. Sgarbossa III	68 (52–80)	94 (86–98)	87 (71–95)	83 (73–90)	84 (76–90)	0.80 (0.72–0.88)
Mod. Sgarbossa IV	50 (35–65)	96 (88–99)	87 (68–96)	76 (66–84)	79 (70–85)	0.73 (0.65–0.82)
Mod. Sgarbossa V	28 (17–44)	97 (90–99)	85 (58–96)	70 (60–78)	72 (63–79)	0.63 (0.55–0.70)
BARCELONA	93 (80–97)	94 (86–98)	90 (78–96)	96 (88–98)	94 (87–97)	0.93 (0.88–0.98)

AMI indicates acute myocardial infarction; AUC, area under the curve; Mod. Sgarbossa III, IV and V Smith's Modified Sgarbossa rule III, IV and V; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; and STEMI, ST-segment-elevation myocardial infarction.

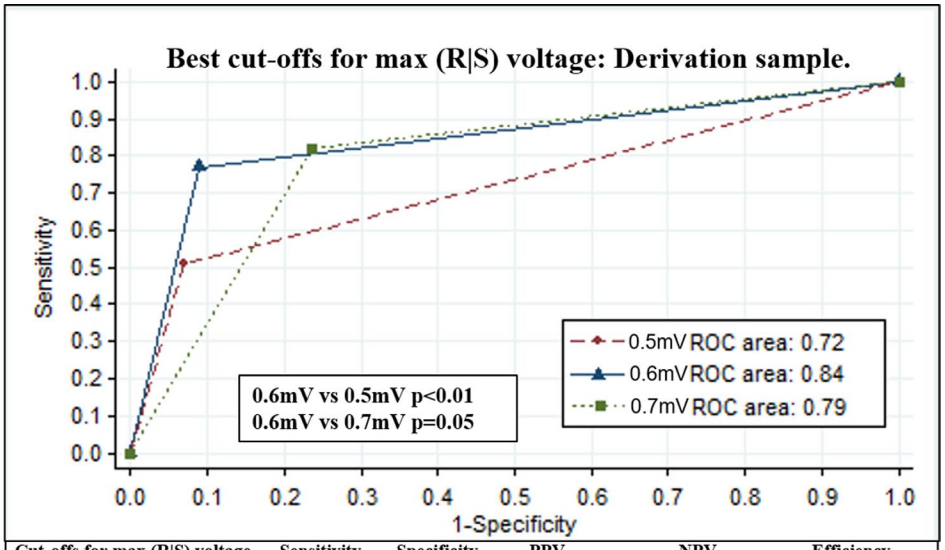
that provided the most comprehensive approach to repolarization abnormalities in LBBB and included concordant ST deviation >1 mm (0.1 mV) in any lead and discordant ST deviation ≥1 mm (0.1 mV) in leads with max (R|S) voltage ≤6 mm (0.6 mV). This algorithm was named BARCELONA algorithm and is described in detail in Table 5.

The BARCELONA algorithm attained the highest sensitivity (95%), significantly higher (P<0.01) than Sgarbossa and Modified Sgarbossa rules, as well as the highest negative predictive value (97%), while maintaining 89% specificity (Table 3 and Table 6). The global performance of the BARCELONA algorithm was significantly better than previous algorithms: It achieved the highest efficiency (91%) and the highest area under the ROC curve (0.92), which was significantly higher (P<0.01) than the ones obtained by the Sgarbossa and Modified Sgarbossa rules (Figure 6). The BARCELONA algorithm also afforded a significant improvement in the ability to predict the occurrence of an AMI, as shown by Integrated Discrimination Improvement and Net Reclassification Improvement indexes (both indexes showed P<0.01 comparing BARCELONA algorithm with Sgarbossa and Modified Sgarbossa rules).

Table 4. Performance of New Criteria and Different Algorithms for the Diagnosis of AMI

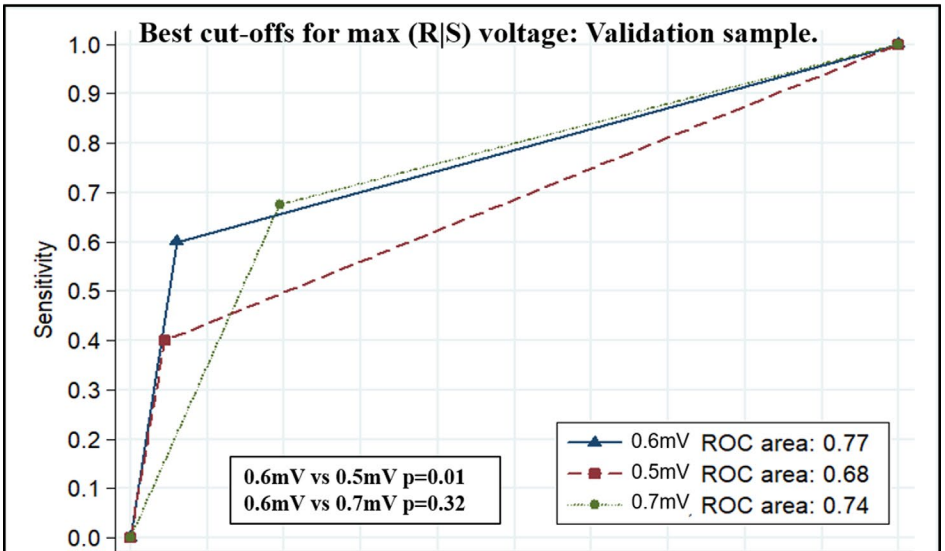
Algorithm	Sensitivity % (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI)	Efficiency% (95% CI)	AUC ROC (95% CI)
Derivation cohort (N=163)						
Concordant ST depression	51 (39–63)	97 (92–99)	91 (77–97)	77 (69–83)	80 (73–85)	0.74 (0.67–0.80)
Disc-ST-max (R|S) ≤6 mm (0.6 mV)	77 (65–86)	91 (84–95)	84 (72–91)	87 (79–92)	86 (80–90)	0.84 (0.78–0.90)
Any of						
Conconcordant ST depression	85 (74–92)	90 (83–95)	84 (73–91)	91 (84–95)	88 (83–92)	0.88 (0.82–0.93)
Disc-ST-max (R|S) ≤6 mm (0.6 mV)						
Any of						
Concordant ST Depression	69 (56–79)	96 (90–99)	91 (80–97)	84 (76–89)	86 (80–90)	0.82 (0.76–0.89)
Concordant ST elevation						
Any of						
Disc-ST-max (R|S) ≤6 mm (0.6 mV)	92 (82–96)	90 (83–95)	85 (74–92)	95 (85–94)	91 (85–94)	0.91 (0.86–0.96)
Concordant ST elevation						
BARCELONA algorithm	95 (86–98)	89 (82–94)	84 (74–91)	97 (91–99)	91 (86–95)	0.92 (0.88–0.96)
Validation cohort (N=101)						
Concordant ST Depression	40 (26–55)	99 (92–100)	94 (72–99)	74 (64–82)	77 (68–84)	0.69 (0.61–0.77)
Disc-ST-max (R|S) ≤6 mm (0.6 mV)	60 (45–74)	94 (86–98)	86 (69–94)	80 (70–87)	81 (73–88)	0.76 (0.68–0.84)
Any of						
Conconcordant ST depression	78 (63–88)	94 (86–98)	89 (74–96)	88 (78–93)	88 (80–93)	0.85 (0.78–0.93)
Disc-ST-max (R|S) ≤6 mm (0.6 mV)						
Any of						
Concordant ST depression	55 (40–69)	99 (92–99)	96 (79–99)	79 (69–86)	82 (74–88)	0.78 (0.70–0.86)
Concordant ST elevation						
Any of						
Disc-ST-max (R|S) ≤6 mm (0.6 mV)	83 (68–91)	94 (86–98)	89 (75–96)	90 (81–95)	90 (83–94)	0.88 (0.81–0.95)
Concordant ST elevation						
BARCELONA algorithm	93 (80–97)	94 (86–98)	90 (78–96)	96 (88–98)	94 (87–97)	0.93 (0.88–0.98)

Concordant ST depression, ST depression ≥1 mm (0.1 mV) concordant with QRS polarity, in any lead; Disc-ST-max (R|S)≤6 mm (0.6 mV), ST deviation ≥1 mm (0.1 mV) discordant with the QRS in any lead with max (R|S) voltage ≤6 mm (0.6 mV); Concordant ST elevation, ST. Elevation ≥1 mm (0.1 mV) concordant with QRS polarity, in any lead ST, corresponding to Sgarbossa score of 5. AUC indicates area under the curve; NPV, negative predictive value; PPV, positive predictive value; and ROC, receiver operating characteristic.



Cut-offs for max (R|S) voltage	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Efficiency % (95% CI)
≤0.5mV	51 (39-63)	93 (87-97)	82 (67-91)	76 (68-83)	77 (70-83)
≤0.6mV	77 (65-86)	91 (84-95)	84 (72-91)	87 (79-92)	86 (80-90)
≤0.7mV	82 (71-90)	77 (67-84)	68 (56-77)	88 (79-93)	79 (72-84)

PPV, positive predictive value; NPV, negative predictive value.



Cut-offs for max (R|S) voltage	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Efficiency % (95% CI)
≤0.6mV	60 (45-74)	94 (86-98)	86 (69-94)	80 (70-87)	81 (73-88)
≤0.5mV	40 (26-55)	916(88-99)	84 (62-95)	73 (63-81)	75 (66-82)
≤0.7mV	68 (52-80)	81 (70-88)	68 (52-80)	81 (70-88)	76 (67-83)

PPV, positive predictive value; NPV, negative predictive value.

Figure 5. Diagnostic performance and receiver operating characteristic (ROC) curves for the diagnosis of acute myocardial infarction using discordant ST deviation ≥1 mm (0.1 mV) in leads with a low-voltage QRS.
We show the results of the best cutoffs for the max (R|S) voltage used to define low-voltage QRS, in the derivation and in the validation cohort separately.

ECG Analysis in the Validation Cohort

Sgarbossa and Modified Sgarbossa rules showed a high specificity (up to 99%) but a limited sensitivity (28%–68%) (Table 3), confirming the results of the derivation cohort.

A max (R|S) voltage value ≤6 mm (0.6 mV) also achieved the highest efficiency (81%) and highest area under the ROC curve (0.77) among the cutoff values tested to define a low-voltage QRS where disproportionate discordant ST deviation ≥1 mm (0.1 mV) is suggestive of AMI (Figure 5). Likewise, the validation cohort confirmed that, extending the analysis of concordant ST depression ≥1 mm (0.1 mV) to any ECG lead (instead of limiting it to leads V1–V3) resulted in a significant increase of diagnostic sensitivity (from 10% to 40%; $P<0.01$).

The BARCELONA algorithm attained a 93% sensitivity, which was significantly higher than that of the Sgarbossa and Modified Sgarbossa rules ($P<0.01$ and $P<0.01$, respectively). It also reached the highest negative predictive value (96%) and maintained a 94% specificity, which was not inferior to Sgarbossa and Modified Sgarbossa rules (Tables 3 and 7). The global performance of the BARCELONA algorithm was significantly better than previous algorithms: It achieved the highest efficiency (94%) and the highest area under the ROC curve (0.93), which was significantly higher ($P<0.01$) than the ones obtained by the Sgarbossa and Modified Sgarbossa rules (Figure 6).

Diagnostic Yielding of the ECG in the Entire Cohort of Patients Referred for pPCI

The application of a Sgarbossa score ≥3 and the Modified Sgarbossa rules in our entire cohort of 270 patients with LBBB referred for pPCI (101 diagnosed with AMI) would have missed 67 and 36 patients with AMI, respectively. By contrast, the BARCELONA algorithm would have missed only 6 patients.

The influence of coronary reperfusion on the electrocardiographic algorithms could be evaluated in 75 patients with AMI in whom an ECG recorded within the first 48 hours after pPCI was available. After pPCI, the BARCELONA algorithm became negative in 93% of patients with AMI who were positive before reperfusion.

Table 5. Definition of the BARCELONA Algorithm to Diagnose AMI in the Presence of LBBB

The BARCELONA algorithm is positive if any of the following criteria are present:
(1) ST deviation ≥1 mm (0.1 mV) concordant with QRS polarity in any ECG lead, thus including either: • ST depression ≥1 mm (0.1 mV) concordant with QRS polarity, in any ECG lead. • ST elevation ≥1 mm (0.1 mV) concordant with QRS polarity, in any ECG lead (Sgarbossa score 5).
(2) ST deviation ≥1 mm (0.1 mV) discordant with QRS polarity, in any lead with max (R|S) voltage ≤6 mm (0.6 mV).

AMI indicates acute myocardial infarction; and LBBB, left bundle branch block.

Control Population

The BARCELONA algorithm was positive in 21 of 214 patients (10%), thus achieving a 90% specificity. Among these 21 patients, 2 had ST elevation ≥1 mm (0.1 mV) concordant with QRS polarity, 1 had concordant ST depression ≥1 mm (0.1 mV), 17 had discordant ST deviation ≥1 mm (0.1 mV) in leads with max (R|S) voltage ≤6 mm (0.6 mV), and 1 had both ST-segment elevation ≥1 mm (0.1 mV) concordant with QRS polarity and discordant ST deviation ≥1 mm (0.1 mV) in leads with max (R|S) voltage ≤6 mm (0.6 mV). Thus, in this control group, the majority (81%) of false-positive cases of the BARCELONA algorithm were attributable to the presence of discordant ST deviation ≥1 mm (0.1 mV) in leads with max (R|S) voltage ≤6 mm (0.6 mV).

DISCUSSION

Main Findings and Strengths of the Study

This study shows that the diagnostic accuracy for AMI in the presence of LBBB was significantly improved by considering 2 new electrocardiographic criteria: (1) the finding of ST depression ≥1 mm (0.1 mV) concordant with QRS polarity in any ECG lead and (2) the existence of ST deviation ≥1 mm (0.1 mV) discordant with QRS polarity in any ECG lead with low-voltage QRS, with the optimal cutoff for low-voltage QRS established as max (R|S) voltage ≤6 mm (0.6 mV).

To our knowledge, this is the largest cohort of patients with LBBB referred for pPCI used to evaluate electrocardiographic algorithms to diagnose AMI. Patients

Table 6. Comparison of the Main Algorithms Regarding Sensitivity and Specificity for AMI in the Derivation Sample

Algorithm	Sensitivity % (95% CI)	*P* Value	Specificity % (95% CI)	*P* Value
BARCELONA algorithm	95 (86–98)		89 (82–94)	
Sgarbossa score ≥3	34 (24–47)	<0.01	98 (93–100)	<0.01
Sgarbossa score ≥2	48 (36–60)	<0.01	84 (76–90)	0.33
Modified Sgarbossa rule III	62 (50–73)	<0.01	91 (84–95)	0.69
Modified Sgarbossa rule IV	51 (39–63)	<0.01	96 (90–99)	0.07
Modified Sgarbossa rule V	26 (17–38)	<0.01	97 (92–99)	0.04

The reference value to calculate the *P* value is the BARCELONA algorithm. The *P* value is obtained with McNemar's test. AMI indicates acute myocardial infarction.

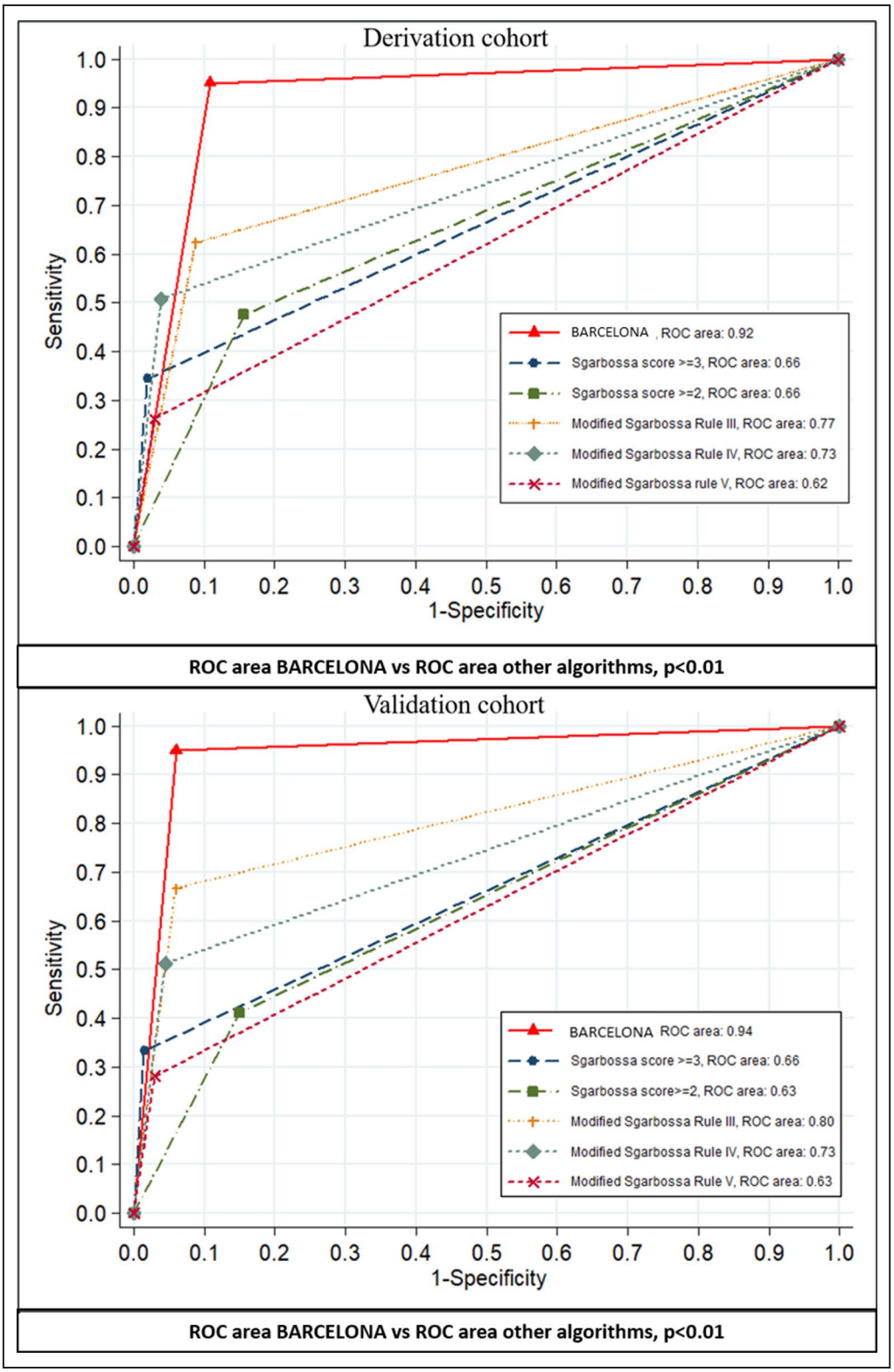


Figure 6. Receiver operating characteristic (ROC) curves of ECG algorithms for the diagnosis of acute myocardial infarction in the presence of left bundle branch block, in the derivation and validation sample.

with LBBB referred for pPCI are the target population that could benefit the most from an improved electrocardiographic diagnosis of AMI. Because of the lack of a reliable electrocardiographic diagnosis of AMI, these patients are often overtreated. Indeed, in our study, 63% of patients were unnecessarily exposed to

Table 7. Comparison of the Main Algorithms Regarding Sensitivity and Specificity for AMI in the Validation Sample

Algorithm	Sensitivity % (95% CI)	*P* Value	Specificity % (95% CI)	*P* Value
BARCELONA	93 (80–97)		94 (86–98)	
Sgarbossa score ≥3	33 (20–48)	<0.01	99 (92–100)	0.08
Sgarbossa score ≥2	40 (26–55)	<0.01	85 (75–92)	0.08
Smith III	68 (52–80)	<0.01	94 (86–98)	>0.99
Smith IV	50 (35–65)	<0.01	96 (88–99)	0.32
Smith V	28 (17–44)	<0.01	97 (90–99)	0.16

The reference value to calculate the *P* value is the BARCELONA algorithm. The test used to calculate the *P* value is the McNemar's test. AMI indicates acute myocardial infarction.

an emergent reperfusion protocol, which has inherent risks and an elevated economic cost. Moreover, the availability of angiographic data in patients referred for pPCI allowed us to establish a reliable diagnosis of AMI, overcoming the limitation of some previous studies where the diagnosis of AMI was confirmed only by cardiac biomarkers.[4]

The type of study (cohort study) also permitted calculation of positive predictive value and negative predictive value, which could not be performed in previous case-control studies.[4,5] This was an "all comers" study, as we did not select or exclude patients with certain clinical variables. Therefore, the results may be widely applicable to patients with LBBB and suspected AMI. Finally, the specificity of the proposed criteria was also tested in a control population without suspected acute coronary syndrome.

Electrocardiographic Diagnosis of AMI in the Presence of LBBB

Our results show that concordant ST deviations are extremely specific for AMI. This was already known for concordant ST elevation ≥1 mm (0.1 mV) (Sgarbossa score 5) but had not been demonstrated for concordant ST depression ≥1 mm (0.1 mV) in any lead. As described in Table 1 in their manuscript,[4] Sgarbossa and colleagues analyzed the ST-segment concordance or discordance with QRS polarity only for ST elevation. By contrast, they evaluated the presence of ST depression in any lead without correlating it with QRS polarity. They found that ST depression in leads V1 to V3 was suggestive of AMI, since leads V1 to V3 generally display a negative QRS in patients with LBBB. However, such analysis without correlating ST depression with QRS polarity could miss the clinical relevance of concordant ST deviations occurring in those ECG leads that can have either a negative or a positive QRS in different patients with LBBB. In our series, when concordant ST depression was present, it occurred in leads other than V1 to V3 in the vast majority of patients with AMI, and these patients would have been missed by the Sgarbossa rules. Thus, we confirmed the hypothesis that by evaluating concordant ST depression in any lead, we could improve the sensitivity of the ECG to detect ischemia in different myocardial regions.

In patients with LBBB, it has been demonstrated that acute ischemia is associated with an increase in the magnitude of ST deviations discordant with QRS polarity[7,13] so that they become disproportionately greater than would be expected by the voltage of the QRS in the corresponding lead. By using a new approach, we could identify a max (R|S) voltage of 6 mm (0.6 mV) as the best cutoff for disproportionate discordant ST deviations ≥1 mm (0.1 mV) suggestive of AMI.

The BARCELONA algorithm incorporated a comprehensive approach to repolarization abnormalities in patients with LBBB by including concordant ST deviations ≥1 mm (0.1 mV) in any lead and discordant ST deviations in leads with max (R|S) voltage ≤6 mm (0.6 mV). This algorithm significantly improved the sensitivity of the ECG to diagnose AMI in patients with LBBB, achieving similar results to those obtained by the ECG in patients without LBBB.[14] It also had a high negative predictive value: When the algorithm is negative, the probability of AMI seems very low.

The BARCELONA algorithm also had good specificity and positive predictive value: only 9% of patients without AMI would have still been transferred for emergent reperfusion by using the new algorithm. This percentage is in agreement with the prevalence of false-positive activation of the pPCI protocol in the general population, including patients without LBBB.[15] Moreover, the BARCELONA algorithm confirmed a 90% specificity in a large cohort of patients with LBBB without suspected acute coronary syndrome.

Of note, among patients with LBBB and AMI included in the present study, there was a wide range of culprit arteries, including all major coronary branches as well as the left main. Thus, the good performance of the new algorithm could apply to any AMI location. Finally, this new algorithm is simpler as compared with the Modified Sgarbossa Criteria and could be widely applied without determining a relevant delay in diagnosis and reperfusion.

LBBB and Suspected AMI: To Treat or to Wait?

The presence of LBBB in patients with ischemic symptoms has traditionally been considered an ECG equivalent to ST-segment elevation and the 2017 European Society of Cardiology guidelines[16] still recommend emergent reperfusion in such cases.

However, increasing evidence suggests that LBBB is a major cause of false activation of the pPCI protocol.[1] In view of these findings, the 2013 American guidelines stated that LBBB should not be considered diagnostic of AMI in isolation.[17]

Until a reliable diagnosis of AMI with LBBB is available, both strategies have major drawbacks. On the one hand, if LBBB is considered an equivalent to ST-segment elevation, a majority of patients who have not experienced an AMI are unnecessarily exposed to the aggressive and costly protocol of emergent reperfusion. This was also confirmed in our cohort where, among patients with LBBB referred for pPCI, only 37% actually had an AMI (a result in line with previous report from other groups).[1] On the other hand, if the pPCI protocol is not directly activated in patients with LBBB and ischemic symptoms, the high-risk subgroup of patients with LBBB and AMI may not receive timely reperfusion treatment with potential consequences over their prognosis.

These considerations highlight the urgent need for new ECG criteria to diagnose AMI in the presence of LBBB and underline the clinical and also economic importance of the present findings to improve the efficiency of pPCI networks.

Recently, clinical algorithms based on the hemodynamic status, on cardiac biomarkers and echocardiographic findings have also been proposed to improve the management of patients with LBBB and suspected AMI.[18,19] However, these algorithms may be limited by the high prevalence of initially elevated cardiac biomarkers among patients with LBBB without AMI[2] and by the limited echocardiographic availability in small hospitals and emergency services. The possibility to achieve a reliable electrocardiographic diagnosis of AMI in patients with LBBB would represent a major step forward. If our results are confirmed by other groups, the BARCELONA algorithm could be integrated into a wider clinical algorithm, to optimize the diagnosis and treatment of patients with LBBB and suspected AMI.

LIMITATIONS

The main limitation of the present study is its observational nature. The relatively wide time frame for post-pPCI ECG recordings (immediate to 48 hours) does not allow a description of the time course of ECG changes after revascularization. Adjustments for multiplicity were not performed.

CONCLUSIONS

In 2 cohorts of patients with LBBB referred for pPCI, we identified and validated the new ECG algorithm BARCELONA based on the presence of concordant ST deviation ≥1 mm (0.1 mV) in any ECG lead and/or discordant ST deviation ≥1 mm (0.1 mV) in leads with max (R|S) voltage ≤6 mm (0.6 mV). This algorithm significantly improved the diagnosis of AMI as compared with previous ECG rules, achieving a diagnostic performance for AMI similar to that of ECG in patients without LBBB. The high specificity of the algorithm was confirmed in a large and heterogeneous control group of patients without suspected AMI.

ARTICLE INFORMATION

Received December 9, 2019; accepted April 14, 2020.

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Acknowledgments

We thank the Bellvitge Institution of Biomedical Investigation (IDIBELL) and the CERCA Programme/Generalitat de Catalunya for institutional support.

Sources of Funding

None.

Disclosures

None.

Supplementary Materials

Data S1
Tables S1–S3
Figure S1
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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Definition of a STEMI equivalent

Patients with acute coronary occlusion were considered to have a STEMI equivalent. However, between one quarter and one third of STEMI patients have no complete acute occlusion of the culprit artery at the time of pPCI.[20,21] Therefore the definition of a STEMI equivalent needs to be extended also to patients with acute non-occlusive coronary lesions. In cases of patent culprit artery, cardiac biomarkers may be a useful discriminator since STEMI is associated with higher biomarker release than non-STEMI (NSTEMI).[22] Several studies analyzed biomarkers ratio (the peak level divided by the upper normal limit): 25% of STEMI patients were found to have a cardiac troponin I (cTnI) ratio lower than 45[22] and 11% fitted in a category of low cardiac troponin (cTn) defined by a lower limit of cTn ratio of 10.[23] Creatine kinase isoenzyme MB (CK-MB) ratio is usually lower than cTnI[22,24,25] ratio and the upper limit of the first quartile for CK-MB ratio in STEMI was found to be 8 in a previous study that included the largest population investigated so far.[22]

In the present study patients with acute non-occlusive coronary lesions were considered to have a STEMI if their cardiac troponin I (cTnI) or cardiac troponin T (cTnT) ratios were ≥10 or when the creatine kinase MB isozyme (CK-MB) ratio was ≥5.

Supplemental Results

STEMI equivalent

In the derivation cohort, out of 61 patients with AMI, 58 (95%) had a STEMI equivalent; similar results were obtained in the validation cohort, where, among the 40 patients with AMI, 38 (95%) had a STEMI equivalent. Both in the derivation and validation cohort, the BARCELONA algorithm showed the highest sensitivity, highest NPV and highest efficiency for the diagnosis of a STEMI equivalent (Table S3). Moreover, both in the derivation and in the validation cohort the BARCELONA algorithm had the highest area under the ROC curve, significantly higher ($p<0.01$) than previous ECG rules.

Table S1. Definition of previously described algorithms.

Algorithm	Criteria
Sgarbossa score ≥3	- ST elevation ≥1mm (0.1mV) in any lead concordant with the QRS and/or - ST depression ≥1mm (0.1mV) in leads V1-V3
Sgarbossa score ≥2	- Sgarbossa score ≥3 and/or - ST elevation ≥5mm (0.5mV) in any lead, discordant with the QRS
Modified Sgarbossa rule III	- Sgarbossa score ≥3 and/or - ST elevation/S ≤-0.25 in any lead with ST elevation ≥1mm (0.1mV)
Modified Sgarbossa rule IV	- Sgarbossa score ≥3 and/or - ST deviation/S or R ≤-0.3 in any lead with ST deviation ≥1mm (0.1mV)
Modified Sgarbossa rule V	- ST deviation/S or R ≤-0.3 in any lead with ST deviation ≥1mm (0.1mV)

Table S2. Diagnostic performance of different ECG algorithms for the diagnosis of STEMI equivalent.

Algorithm	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Efficiency % (95% CI)	AUC ROC (95% CI)
Derivation cohort (N 163)						
Sgarbossa score ≥3	36 (25-49)	98 (93-100)	91 (73-98)	74 (66-80)	76 (69-82)	0.67 (0.61-0.74)
Sgarbossa score ≥2	50 (38-63)	85 (77-90)	64 (50-77)	75 (67-82)	72 (65-79)	0.67 (0.60-0.75)
Mod. Sgarbossa III	66 (53-76)	91 (85-95)	81 (68-90)	83 (75-89)	82 (76-87)	0.78 (0.71-0.85)
Mod. Sgarbossa IV	53 (41-66)	96 (91-99)	89 (74-96)	79 (71-85)	81 (74-86)	0.75 (0.68-0.82)
Mod. Sgarbossa V	28 (18-40)	97 (92-99)	84 (62-95)	71 (63-78)	72 (65-78)	0.62 (0.56-0.68)
BARCELONA	95 (86-98)	87 (79-92)	80 (69-88)	97 (91-99)	90 (84-93)	0.91 (0.86-0.95)
Validation cohort (N 107)						
Sgarbossa score ≥3	34 (21-50)	99 (92-100)	93 (69-99)	73 (63-81)	76 (67-83)	0.67 (0.59-0.75)
Sgarbossa score ≥2	42 (28-58)	86 (75-92)	62 (43-78)	73 (62-81)	70 (61-78)	0.64 (0.55-0.73)
Mod. Sgarbossa III	68 (53-81)	93 (84-97)	84 (67-93)	84 (74-91)	84 (76-90)	0.80 (0.72-0.88)
Mod. Sgarbossa IV	50 (35-65)	94 (86-98)	83 (63-93)	77 (67-85)	79 (70-85)	0.72 (0.64-0.81)
Mod. Sgarbossa V	27 (15-43)	96 (88-99)	77 (50-92)	71 (61-79)	72 (63-79)	0.61 (0.54-0.69)
BARCELONA	95 (83-99)	93 (84-97)	88 (75-95)	97 (90-99)	94 (87-97)	0.95 (0.91-0.99)

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; STEMI, ST elevation myocardial infarction; Mod. Sgarbossa III, IV and V, Smith's Modified Sgarbossa rule III, IV and V.

Table S3. Within the control group of patients with LBB without suspected AMI, 95 patients were included after a visit at the emergency department due to symtpoms other than chest pain and with a final diagnosis different from acute coronary syndrome.

Diagnosis	**N (%)**
Decompensated heart failure	16 (17%)
Syncope/Lipothymia	10 (11%)
Atrial fibrillation/flutter	9 (9%)
Decompensated COPD	9 (9%)
Stroke/TIA	5 (5%)
Trauma	3 (3%)
Anemia	3 (3%)
Pneumonia	3 (3%)
Seizures	3 (3%)
Subarachnoid hemorrage	3 (3%)
Gastritis	3 (3%)
Rectal bleeding	2 (2%)
Lower limb ischemia	2 (2%)
Hepatic encephalopathy	2 (2%)
Gastroenteritis	2 (2%)
Perianal abscess	2 (2%)
Acute kidney failure	2 (2%)
Sepsis	2 (2%)
Complications of neoplasm	2 (2%)
Urinary tract infection	2 (2%)
Hemoptisis	1 (1%)
Dehydration	1 (1%)
Acute confusion	1 (1%)
Peripheral vertigo	1 (1%)
Acute pancreatitis	1 (1%)
Back pain	1 (1%)
Bipolar disorder	1 (1%)
High INR (>6)	1 (1%)
Acute colangitis	1 (1%)
Deep vein thrombosis	1 (1%)

The final diagnosis at the emergency department of these patients is reported in the table.

COPD, chronic ostructive pulmonary disease; TIA, transient ischemic attack; INR, international normalized ratio.

Figure S1. ECG from a patient with acute myocardial infarction and culprit lesion in the left anterior descending artery. Concordant ST depression ≥1mm (0.1mV) is present in lead V4. Discordant ST deviation ≥1mm (0.1mV) in a lead with max (R|S) voltage ≤6mm (0.6mV) is present in lead V5. In this figure the Modified Sgarbossa criteria could be considered positive in lead V5. However, the ST depression in lead V5 is just below 2mm (0.2mV) and falls between 1.5mm (0.15mV) and 2mm (0.2mV); considering this ST deviation 1.5mm (0.15mV) or 2mm (0.2mV) make a complete difference with respect to the Modified Sgarbossa criteria that become either negative or positive. This example shows how the Modified Sgarbossa criteria, which are based on an exact measurement of both QRS amplitude and ST deviation, may be difficult to evaluate, especially in the setting of emergency care. By contrast, the BARCELONA algorithm, based on simpler cut-offs, may be easier to evaluate and in this case it was undoubtedly positive.