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Identification of Coronary Artery Calcification Can Optimize Risk Stratification in Patients with Acute Chest Pain

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Abstract

Background—The number of patients presenting to the emergency department (ED) with suspected acute coronary syndrome (ACS) is substantial. We tested whether identification of coronary artery calcium (CAC) can improve the negative predictive value (NPV) of clinical risk assessment for ACS in patients with acute chest pain.

Methods and Results—We included 826 consecutive patients (mean age: 53±11 years; 42% female) without known coronary artery disease (CAD) or initially elevated serum biomarkers, whom underwent non-contrast CT, to assess the CAC score, and CT angiography (CTA), to detect coronary stenosis. We analyzed the diagnostic performance of CAC and the Thrombolysis In Myocardial Infarction (TIMI) risk score for our primary outcomes (ACS and obstructive CAD).

No CAC was found in 54% (n=444) of all patients, 63% (n=524) had a TIMI score of 0 and 40% (n=328) had both. The prevalence of obstructive CAD was 16% for 50% stenosis and 8.7% for 70% stenosis. The incidence of ACS was 7.9%, (MI=11, UAP=54). The NPV of CAC=0 was 99.5% for ACS. The NPV of a combination of TIMI score =0 and no CAC was 89% for any CAD (any plaque or stenosis) and 99.7% for 50% stenosis. A 100% NPV was found for 70% stenosis and ACS, correctly identifying 328 (40%) patients.

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Conclusions—The exclusion of CAC, in combination with clinical risk assessment, has high clinical value in patients with acute chest pain, as it identifies patients at low risk for ACS and obstructive CAD more accurately as compared to clinical risk assessment alone.

Keywords

coronary artery calcium; acute coronary syndrome; acute chest pain; TIMI risk score; coronary CT angiography

Introduction

The assessment of patients presenting to the emergency department (ED) with acute chest pain syndrome (ACS) remains challenging but highly important as individuals with ACS are at higher risk for major morbidity and mortality (1, 2). ESC's and ACC/AHA's class I recommendation for assessing the likelihood of ACS and adverse outcome in patients with non-ST-segment elevation stresses the importance for accurate risk stratification. Patient evaluation, the decision to hospitalize a patient and the selection of further diagnostic and treatment options has to be made in a timely manner (1, 2). For this reason, clinical assessment, collection of medical history, assessment of electrocardiographic findings and determination of cardiac biomarkers have been used to develop clinical prediction algorithms like the Thrombolysis In Myocardial Infarction (TIMI) risk score (3). This assessment tool is used clinically, and meant to help identify patients with ACS at increased risk for adverse outcomes (2). The development and evaluation of novel prediction scores for patients presenting with chest pain shows the continuous attempt to further improve risk stratification in the ED, for instance the HEART score (4, 5) among others (6, 7).

Whereas conventional risk factors can indicate the likelihood of CAD, coronary artery calcification (CAC) represents direct evidence of coronary atherosclerosis (8) and thus can significantly improve 10-year CHD risk prediction in combination with traditional risk factors (9). As shown in asymptomatic patients, CAC scoring has been studied extensively and is well established by using non-contrast ECG-gated computed tomography of the heart (9–11). Although the negative predictive value (NPV) was consistently demonstrated to be high, in symptomatic patients the assessment of CAC does not play a major role (1, 12), as obstructive CAD can not be ruled out completely using non-contrast scans of the heart (13–16).

The majority of patients presenting to the ED with chest pain do not have ACS, and are at low risk for major morbidity and mortality. To improve risk stratification, we therefore sought to investigate the negative predictive value of a combination of CAC scoring and clinical risk assessment using TIMI risk score. If successful, this could represent a simple and efficient way to identify patients who are at low risk for obstructive CAD and ACS and might be valuable in settings where advanced downstream testing is not readily available.

Methods

Study design and study population

This is an observational study based on a single tertiary academic medical center registry, which evaluated the use of coronary CTA in consecutive symptomatic patients presenting to the ED with acute chest pain. A detailed description of the main study was previously reported (17).

In this analysis, we included symptomatic patients presenting to the ED for the evaluation of suspected ACS from October 1st 2013 to August 31st 2015. Patients with known CAD or initial positive cardiac serum biomarker levels were excluded for this analysis. Medical records were reviewed for cardiovascular risk profile, other baseline characteristics and disposition times. Subsequently, TIMI risk score was calculated with the information available at index presentation. All patients in this cohort underwent non-contrast ECG-gated coronary CT as well as coronary CTA. Eligibility criteria for coronary CTA were previously described (17). Institutional Review Board approval was obtained. Written informed consent was waived by the Institutional Review Board.

CT Imaging and image interpretation

CT data sets were acquired using second- or third-generation dual-source CT scanner (SOMATOM Definition Flash or SOMATOM Force; Siemens Healthcare, Forchheim, Germany). For the evaluation and quantification of CAC, non-contrast image data sets were acquired using a prospective ECG-triggered acquisition mode (120 kVp, 80 mAs) and reconstructed with a slice thickness of 3 mm. CAC was calculated using the Agatston score method (18). Coronary CTA settings and image reconstruction were previously described in detail (17). Coronary arteries were evaluated by a board-certified radiologist or cardiologist in respect to the degree of stenosis, ranging from normal (no plaque or stenosis) to mild stenosis (1–49%), moderate stenosis (50–69%) and severe stenosis (≥ 70%).(19)

Endpoints

To assess the incremental value of CAC in addition to clinical risk assessment using the TIMI risk score, we used ACS as primary endpoint, defined as myocardial infarction (MI) and unstable angina (UAP) during index hospitalization. Diagnosis for each patient was based on a medical record review, including laboratory results, ECGs and related diagnostic test results. An independent cardiologist adjudicated these diagnoses, adhering to previously reported definitions for major adverse cardiovascular events (MACE) (20). Secondary endpoint was the presence of significant coronary artery stenosis using 50% and 70% stenosis thresholds. The 70% stenosis threshold was defined as 50% stenosis in the left main and 70% stenosis in other major epicardial vessels. Both endpoints were used to analyze the diagnostic performance of CAC score and TIMI risk score. CAC score was categorized by strata (0, >0–10, >10–100, >100–400, >400) (21) to display differences in baseline patient characteristics, endpoints and length of stay. CAC was dichotomized by zero for the analysis of length of stay and the diagnostic performance of the primary and secondary endpoints, as was TIMI risk score for the performance analysis.

Statistical analysis

Continuous variables were listed as mean ($\pm$ standard deviation [SD]) and compared using Student t-test for independent samples. Non-normally distributed variables were listed as median (P25, P75) and compared with Mann-Whitney U test. Quantile-quantile plots were generated to determine normal distribution. Categorical variables were listed as frequencies (percentages) and statistical significance was assessed using the chi-square test. All analyses were performed on a per-patient level, grouping patients by their worst stenosis severity. Kaplan-Meier curves were used to depict length of stay until discharge to home. To calculate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) 2 by 2 contingency tables were generated. The areas under the curve (AUC) of receiver operating characteristic (ROC) plots were used to determine overall test performance. A P-value of less than 0.05 was deemed statistically significant. Statistical analyses were performed using SPSS (version 22, IBM, Armonk, New York, USA).

Results

Patient characteristics

We included 826 consecutive symptomatic patients presenting to the ED with suspected ACS. Baseline clinical characteristics are displayed in Table 1, stratified by CAC score groups. Out of 826 patients with a mean age of 52.6 ± 10.7 years (41.9% female), 53.8% (n=444) had no CAC. 63.4% (n=524) of all individuals had a TIMI score of zero and in 39.7% (328) TIMI and CAC score were zero. There were predominately men in the groups with presence of coronary calcification (CAC>0). Among the groups, age was directly proportional to CAC score strata. The number of patients with a TIMI score of zero continuously decreased from 73.9% to 32.0% in patients with an increasing burden of CAC (from 0 to >400, respectively).

Endpoints

As displayed in Table 2, ACS was diagnosed in 65 (7.9%) patients during the index hospitalization, 11 (1.3%) with MI and 54 (6.5%) with unstable angina pectoris. The number of patients with ACS significantly increased with increasing extent of CAC from 2 (0.5%) to 24 (48%) ($p < 0.001$), predominately driven by an increasing number of UAP. In the patient group with absence of CAC, two patients (0.5%) were diagnosed with MI and no one with UAP.

The prevalence of obstructive CAD by coronary CTA was 15.7% and 8.7% using a 50% and 70% stenosis threshold respectively. The degree of stenosis according to CAC strata is displayed in Supplemental Figure 1. The number of patients with 50% stenosis increased from 0.9% to 74.0% according to increasing CAC score strata (from 0 to >400 respectively). The same trend was obvious for 70% stenosis (from 0.7% to 44.0%). In the vast majority of patients without CAC (392/444 (87.6%)), no coronary atherosclerosis was identified by coronary CTA. Out of 444 (53.8%) patients with a CAC score of zero, 50% stenosis was detected in two (0.5%) patients and 70% stenosis in one (0.2%) patient. Two patients were false positive by coronary CTA (compare Table 2), one with suspected severe proximal RCA stenosis and another patient with apparently subtotal occlusion of the mid circumflex artery

by coronary CTA. Invasive coronary angiography (ICA) showed a normal, small, non-dominant RCA in the first case and minimal disease in the latter. For this reason, both patients were reclassified for the diagnostic performance analysis (Table 3). One patient had uninterpretable coronary CTA results, and was therefore only included in the performance analysis for ACS.

Diagnostic performance of CAC and TIMI risk score

The discriminatory power of CAC score strata for the presence of 50% stenosis and 70% stenosis on CTA was 0.90 and 0.88, according to the AUC respectively. The AUC for the presence of ACS at discharge was 0.88 (see Supplemental Figure 2). Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) as well as AUC for the dichotomized TIMI risk score, the dichotomized CAC score and their combination are listed in Table 3. The NPV for the presence of any plaque or stenosis was 55.8% for TIMI score, 88.7% for CAC and 89.0% for CAC+TIMI. The NPV for 50% stenosis threshold was 88.9%, 99.5% and 99.7% for TIMI score, CAC score and a combination of both respectively. Using a 70% stenosis threshold, the NPV was highest in the combination of both (100.0%), as compared to TIMI score (93.7%) or CAC score alone (99.8%). The combination of TIMI and CAC score provided also the highest NPV for the diagnosis of ACS, which was 100% as compared to 94.5% (TIMI risk score) and 99.5% (CAC score). The PPV for presence of CAC to predict 50%, 70% stenosis and ACS was 33.1%, 18.1% and 16.5% respectively. The PPV for a combination of presence of any CAC and TIMI score >0 to predict ACS was 13.1%.

Length of stay

Although the decision for discharge was not based on CAC scans, we looked at the association of CAC with the length of stay. The displayed times refer to the duration of the in-hospital workup including CTA. When dichotomizing CAC score, Kaplan Meyer curves in Figure 1A indicate, that 50% of all individuals without CAC were discharged within 7.0 hrs compared to 18.4 hrs for patients with any presence of CAC ($p<0.001$). Figure 1B shows an increasing median length of stay with increasing extent of CAC. The length of stay reflects complexity of patient care, in line with the trend we saw for severity of CAD across CAC strata. The longest hospital course was found in patients with CAC >400 (35.1 hrs), again consistent with the highest incidence of ACS and prevalence of obstructive CAD (Table 2).

Discussion

In a real-world clinical scenario, our study demonstrated strong association of the extent of CAC to the severity of CAD and the incidence of ACS. Identification of CAC provides an excellent negative predictive value in addition to clinical risk assessment using TIMI risk score to identify patients at low risk for obstructive CAD and ACS. To date, this is one of the largest studies demonstrating the clinical value of CAC for pretest likelihood estimation in patients with acute chest pain.

As coronary artery calcification (CAC) represents direct evidence of coronary atherosclerosis (8) with excellent negative predictive values in patients without presence of CAC (13–16), it suggests itself to be beneficial for risk stratification of patients with suspected ACS and potentially advantageous as opposed to clinical risk scores alone. In fact, in this low-intermediate risk population only 10% of patients without CAC were shown to have any coronary plaque by CTA, whereas in 44% of patients with TIMI=0, plaque was present on CTA. Still, using CAC as isolated risk prediction tool carries a small residual risk for potential misclassification (13–16, 22), which could be confirmed in the underlying analysis. This is also in line with results from a subanalysis of the Rule Out Myocardial Infarction using Computer-Assisted Tomography (ROMICAT) II trial (22), including 473 patients presenting with chest pain. The majority of all individuals (53%) in ROMICAT had no CAC out of which two (0.8%) developed ACS, one due to unstable angina caused by a non-calcified severe stenosis and a second patient with coronary anomaly and non-ST-segment-elevation MI. A similar proportion of patients without CAC was found in our study (54%), but despite a significantly higher total number of patients (n=826), the absolute number of patients with ACS (n=2) was equivalent, suggesting an overall lower incidence of ACS in patients without CAC (0.5%) in this contemporary cohort. In a combined effort of CAC and TIMI risk scoring, all patients without CAC and TIMI score of zero could be correctly identified as being at low risk for obstructive CAD (70%) and ACS. Despite a substantial prevalence of obstructive CAD (8.7% for 70% stenosis) and incidence of ACS (7.9%), no patient was misclassified in the pre-specified analysis.

Interestingly, in every category of this analysis (0%, 50% and 70% stenosis and ACS), the discriminatory power of CAC score alone was higher as compared to TIMI risk score alone or the combination of both, according to the c-statistic. However, a NPV of 100% was found only for the combination of CAC score plus TIMI risk score, obviously further minimizing the risk for obstructive CAD (70% stenosis) and ACS, again highlighting the clinical importance of a combination of both.

Value and limitations of CAC

Several advantageous aspects support the identification of CAC in addition to clinical risk assessment for risk stratification in patients presenting to the ED. First, it is fast, as the time to perform a CAC scan is comparable to a conventional chest CT and scoring of CAC can be performed within minutes. Second, CAC scoring is a straightforward approach, without high levels of expertise being necessary for adequate performance and interpretation of CT scans. Neither the presence of a cardiologist nor radiologist is required, as protocols are standardized (23). Most importantly, this study showed that the combination of CAC measurement and clinical evaluation would be a safe strategy to reliably risk stratify patients presenting with acute chest pain. Hence, this might be primarily useful for medical centers without the capability to perform advanced functional or anatomic testing to potentially avoid resource-inefficient and expensive scenarios, for instance weekend-long observation. Under careful consideration, it could also be a viable option for special clinical scenarios, for instance in patients with comorbidities where the ad hoc application of contrast media is either relatively contraindicated or needs special consideration, e.g. hyperthyroidism or

contrast allergy. In these cases, availability for follow-up with a qualified expert to carefully discuss results and any further management would be required.

In this context, it seems appropriate to mention limitations of CAC scoring. Although the likelihood for significant CAD and ACS is little with absence of CAC in a low-intermediate risk population as proven with this analysis, there will remain uncertainty about the diagnosis, as the non-contrast scan does not provide visualization of coronary artery lumen and degree of stenosis. Coronary CTA however provides granular information in regard to presence of plaque and luminal narrowing with excellent diagnostic accuracy (24–26). This information can subsequently be used to direct downstream testing as well as medical management. Also, the simultaneous enhancement of the aorta and pulmonary arteries will provide additional information at least partly allowing for the assessment of non-coronary structures, even though the CTA protocol is normally not particularly timed to rule out e.g. aortic dissection or pulmonary embolism. Notably, CAC scoring might not be of value for patients with very low likelihood of classic atherosclerotic disease but rather a different coronary pathology, such as spontaneous coronary artery dissection, being an important differential diagnosis in e.g. young women or patients with connective tissue disorders (27–29). For cases like this, definite diagnoses are essential and again can only be made using modalities clearly depicting anatomy (30).

Beyond CAC – The importance of additional clinical information

Previously, Korley et al. (31) demonstrated the value of CAC scoring and initial high-sensitive troponin measurements in a registry with 314 patients. Similar to our study, a NPV of 100% was achieved. However, the prevalence of obstructive CAD (70% stenosis) as well as the incidence of ACS (1.9% and 1.6% respectively) was significantly lower as compared to our analysis. Despite a substantial disease burden, we could also demonstrate a NPV of 100% using a combined effort with CAC and TIMI risk scoring. In the prospective, observational ADAPT trial (32), a 2-hour accelerated diagnostic protocol, including TIMI risk score and serial troponin measurements, was performed to assess patients with chest pain symptoms. Out of 1,975 patients, 20% were identified as being at low risk for MACE within 30 days. Ultimately, only one patient in this group had a MACE, resulting in a NPV of 99.7%. In comparison, 40% of all patients included in our cohort could be identified as being at low risk without misclassifying one single patient.

Hence, the combination of CAC scanning, clinical assessment, serial troponin/high-sensitive troponin measurements seems to be promising and will most likely further improve risk stratification with excellent safety profile. Therefore, it seems to be timely to test this approach, especially by using novel risk stratification tools like HEART(4, 5), the Vancouver chest pain rule (6) or the Emergency Department Assessment of Chest pain Score (EDACS) (7) for instance, in a contemporary and adequately sized population to optimize ED management and resource utilization sustainably.

Study limitations

Some limitations of our study need to be mentioned. First, this is a registry with less strict inclusion criteria than a randomized controlled trial. However, it reflects a real world clinical

practice scenario at a tertiary medical center and therefore can be easily translated into clinical practice. Second, we investigated a low-intermediate risk population by excluding patients with prior history of CAD or initially elevated troponin values, as CAC scoring is of very limited value in this population. Consequently, it is difficult to draw any conclusions about the overall value of TIMI risk score. Third, the serial follow up troponin test is missing in a substantial number of patients, especially in patients who had a normal CTA result within 6–7 hours of presentation, and high sensitive troponin was not available for the majority of patients at the time of coronary CTA. As such, we could not perform an analysis combining CAC scoring with a serial Troponin approach. Last, we do not report MACE rates for follow-up. However, CTA has been shown to have an excellent predictive and prognostic value for MACE in patients with acute chest pain, according to the ROMICAT II trial (33).

Conclusion

In this large real-world clinical scenario of patients with acute chest pain, we could demonstrate a strong association of the extent of CAC to the severity of CAD and the incidence of ACS. Identification of CAC in addition to clinical risk assessment using TIMI risk score provides an excellent negative predictive value to identify patients at low risk for obstructive CAD and ACS. The clinical value of this combined effort might improve patient management in settings where more advanced imaging is not available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACS	acute coronary syndrome
AUC	area under the receiver-operating curve
CAC	coronary artery calcium
CAD	coronary artery disease
CI	confidence interval
(C)CTA	(coronary) computed tomography angiography
ED	emergency department
MI	myocardial infarction

TIMI	Thrombolysis In Myocardial Infarction
UAP	unstable angina pectoris

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Figure 1. Kaplan-Meier curves demonstrating the proportion of patients discharged (%) as function of length of stay (in hrs) stratified by [Panel A] presence of CAC and [Panel B] extent of CAC. The presence of CAC is associated with a significant increase in length of stay ($p < 0.001$).

Table 1

Patient characteristics, CV-risk factors and TIMI risk score according to CAC score strata

Characteristics	CAC score strata				
	Full cohort (n=826)	0 (n=444)	>0-10 (n=110)	>10-100 (n=123)	>100-400 (n=99)
Age (years)	52.6±10.7	48.6±9.5	54.1±9.6	56.1±8.6	58.5±10.4
Male (%)	480 (58.1)	221 (49.8)	74 (67.3)	83 (67.5)	70 (70.7)
BMI (kg/m ²)	39.0±5.7	28.4±5.6	30.1±6.1	29.4±5.5	29.7±5.3
Current smoker (%)	187 (22.6)	82 (18.5)	30 (27.3)	31 (25.2)	30 (30.3)
Diabetes Mellitus (%)	87 (10.5)	35 (7.9)	18 (16.4)	18 (14.6)	11 (11.1)
Dyslipidemia (%)	223 (27.0)	88 (19.8)	29 (26.4)	41 (33.3)	42 (42.4)
Hypertension (%)	340 (41.2)	135 (30.4)	52 (47.3)	56 (45.5)	60 (60.6)
Family history of CAD	118 (14.3)	68 (15.3)	16 (14.5)	14 (11.4)	14 (14.1)
TIMI score					
0	524 (63.4)	328 (73.9)	66 (60.0)	70 (56.9)	44 (44.4)
1	220 (26.6)	96 (21.6)	28 (25.5)	38 (30.9)	35 (35.4)
2	72 (8.7)	20 (4.5)	15 (13.6)	13 (10.6)	15 (15.2)
3	10 (1.2)	0 (0.0)	1 (0.9)	2 (1.6)	5 (5.1)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 2

Extent of coronary artery disease by CTA and ACS according to CAC score strata

Characteristics	CAC score strata					
	Full cohort (n=826)	0 (n=444)	>0-10 (n=110)	>10-100 (n=123)	>100-400 (n=99)	>400 (n=50)
						<i>P value</i>
CCTA 0%	392 (47.5)	392 (87.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CCTA 0-49%	303 (36.7)	48 (10.8)	96 (87.3)	96 (78.0)	50 (51.0)	13 (26.0)
CCTA 50%	130 (15.7)	4 (0.9)	14 (12.7)	27 (22.0)	48 (49.0)	37 (74.0)
CCTA 70%	72 (8.7)	3 (0.7)	6 (5.5)	16 (13.0)	25 (25.5)	22 (44.0)
ACS at discharge	65 (7.9)	2 (0.5)	5 (4.5)	12 (9.8)	22 (22.2)	24 (48.0)
MI	11 (1.3)	2 (0.5)	0 (0.0)	2 (1.6)	6 (6.1)	1 (2.0)
UAP	54 (6.5)	0 (0.0)	5 (4.5)	10 (8.1)	16 (16.2)	23 (46.0)

Table 3

Diagnostic performance of a dichotomized TIMI risk score (0 vs. >0), a dichotomized CAC score (0 vs. >0) and the combination of both in respect to 50% and 70% stenosis and ACS.

Test	Sensitivity	Specificity	PPV	NPV	AUC
50% stenosis on CCTA					
TIMI	54.7 [70/128] (45.7–63.5)	66.9 [465/695] (63.3–70.4)	23.3 [70/300] (18.7–28.5)	88.9 [465/523] (85.9–91.5)	0.61 (0.57–0.64)
CAC	98.4 [126/128] (94.5–99.8)	63.3 [440/695] (59.6–67.9)	33.1 [126/381] (28.4–38.0)	99.5 [440/442] (98.4–99.9)	0.81 (0.78–0.84)
CAC+TIMI	99.2 [127/128] (95.7–100.0)	47.1 [327/695] (43.3–50.8)	25.7 [127/495] (21.9–29.7)	99.7 [327/328] (98.3–100.0)	0.73 (0.70–0.76)
70% stenosis on CCTA					
TIMI	52.9 [37/70] (40.6–64.9)	65.1 [490/753] (61.5–68.5)	12.3 [37/300] (8.8–16.6)	93.7 [490/523] (91.3–95.6)	0.59 (0.56–0.62)
CAC	98.6 [69/70] (92.3–100.0)	58.6 [411/753] (55.0–62.1)	18.1 [69/381] (14.4–22.4)	99.8 [441/442] (98.7–100.0)	0.79 (0.76–0.81)
CAC+TIMI	100.0 [70/70] (94.9–100.0)	43.6 [328/753] (40.0–47.2)	14.1 [70/495] (11.2–17.5)	100.0 [328/328] (98.9–100.0)	0.72 (0.69–0.75)
ACS					
TIMI	55.4 [36/66] (42.5–67.7)	65.1 [495/761] (61.5–68.4)	11.9 [36/302] (8.5–16.1)	94.5 [495/524] (92.1–96.3)	0.60 (0.57–0.64)
CAC	96.9	58.1	16.5	99.5	0.78

Test	Sensitivity	Specificity	PPV	NPV	AUC
CAC+TIMI	[63/65]	[442/761]	[63/382]	[442/444]	
	(89.3–99.6)	(54.5–61.6)	(12.9–20.6)	(98.4–99.9)	(0.75–0.80)
	100.0	43.1	13.1	100.0	0.72
	[65/65]	[328/761]	[645/498]	[328/328]	
	(94.4–100.0)	(39.5–46.7)	(10.2–16.3)	(98.9–100.0)	(0.68–0.75)

PPV = positive predictive value; NPV = negative predictive value; AUC = area under the receiver operating characteristic curve. Number of patients between []. 95% confidence interval between parentheses.