Published in final edited form as:

Stroke. 2018 May ; 49(5): 1163–1169. doi:10.1161/STROKEAHA.117.020138.

Predicting Intracerebral Hemorrhage Expansion with non-contrast CT: The BAT Score

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Disclosures
The other authors report no disclosures.

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Abstract

Background and Purpose—While the CT angiography (CTA) spot sign performs well as a biomarker for hematoma expansion (HE), CTA is not routinely performed in the emergency setting. We developed and validated a score to predict HE based on non-contrast CT (NCCT) findings in spontaneous acute intracerebral hemorrhage (ICH).

Methods—After developing the score in a single center cohort of ICH patients (n=344), we validated it in a large clinical trial population (n=954) and in a multicenter ICH cohort (n=241). The following NCCT markers of HE were analyzed: hypodensities, blend sign, hematoma shape and density, and fluid level. HE was defined as hematoma growth>6 mL or>33%. The score was

created using the estimates from multivariable logistic regression after final predictors were selected from bootstrap samples.

Results—Presence of blend sign (odds ratio (OR) 3.09, 95% confidence interval (CI) 1.49-6.40, p=0.002), any intrahematoma hypodensity (OR 4.54, 95% CI 2.44-8.43, p<0.0001) and time from onset to NCCT<2.5 h (OR 3.73, 95% CI 1.86-7.51, p=0.0002) were predictors of HE. A 5–point score was created (BAT score:1 point for Blend sign, 2 points for Any hypodensity and 2 points for Timing of NCCT<2.5h). The c statistic was 0.77 (95% CI 0.70-0.83) in the development population, 0.65 (95% CI 0.61-0.68) and 0.70 (95%CI 0.64-0.77) in the two validation cohorts. A dichotomized score (BAT score≥3) predicted HE with 0.50 sensitivity, 0.89 specificity.

Conclusions—An easy to use 5-point prediction score can identify subjects at high risk of HE with good specificity and accuracy. This tool requires just a baseline NCCT scan and may help select ICH patients for anti-expansion clinical trials.

Keywords

intracerebral Hemorrhage; hematoma expansion; blend sign; hypodensities; score

INTRODUCTION

Intracerebral hemorrhage (ICH) is the deadliest type of stroke, with mortality at one month close to 40% and severe disability in most of the survivors(1). Hematoma size is the strongest predictor of unfavorable outcome and up to half of patients experience early hemorrhage growth(2,3). Hematoma expansion (HE) is potentially preventable, and therefore rapid identification of patients at high risk of active bleeding is crucial for development of anti-expansion therapies. The CT angiography (CTA) spot sign is a strong and validated radiological marker of HE(4,5) and most of the currently available scores to predict HE incorporate this imaging marker(6). However, in many institutions CTA is not part of the routine diagnostic workup of acute ICH. In a large international randomized clinical trial, more than 80% of ICH patients did not receive a CTA and in those who did undergo a CTA, the diagnostic performance of the spot sign for HE was suboptimal(7). Several non-contrast CT (NCCT) predictors of HE have been recently reported and validated, suggesting that these imaging markers may represent a reliable alternative to the CTA spot sign for HE prediction(8–10). NCCT is a widely available technique used for the diagnosis of acute ICH worldwide. We aimed at developing and validating a HE score that is based on NCCT markers and therefore does not require a CTA, using three well characterized ICH cohorts that could reasonably mimic clinical trial populations.

METHODS

All the procedures for this study received approval from the local Institutional Review Board at each site. Written informed consent was either obtained by patients and family members or waived by the Institutional Review Board. Because the data supporting this analysis are an aggregate of three independent studies, the dataset will not be available for access.

Study population

The score was developed in a cohort of consecutive patients with spontaneous ICH admitted to an academic hospital (MGH, Boston)(11). Two different ICH populations were used for validation. First, the score was applied to subjects enrolled in the randomized clinical trial ATACH-II(12). Second, we validated the score in PREDICT, a prospective observational study on the association between the CTA spot sign, HE and outcome after ICH(4). The three study populations characteristics are described in the online-only Data Supplement.

As accurate prediction of HE is particularly relevant in the setting of clinical trials, we selected patients with clinical characteristics similar to those usually included in acute phase ICH randomized controlled trials. We included patients with the following characteristics: primary spontaneous supratentorial hemorrhages with baseline volume≤60 mL, presentation to the ED within 6 h from symptom onset, lack of anticoagulant treatment and international normalized ratio (INR)<1.5. We applied the following exclusion criteria to all study samples: traumatic intracranial bleeding, tumor or vascular malformation underlying the hemorrhage, hemorrhagic conversion of ischemic stroke, primary intraventricular hemorrhage, missing follow-up NCCT. In the development and validation cohort #2, blood pressure was managed according to the American Heart Association/American Stroke Association guidelines(13).

Clinical data

Clinical variables were acquired with different modalities across the three cohorts, as described in the online-only Data Supplement(4,11,12). Briefly, the following clinical data were collected: age, sex, medical history of hypertension, medical history of diabetes mellitus, admission systolic and diastolic blood pressure, admission INR, Glasgow coma scale (GCS) score, time from symptom onset to baseline NCCT, and three months mortality.

Images Acquisition and Analysis

Baseline NCCT images were collected at each center with different scanners and acquisition parameters using local CT protocols. All the images were reviewed for determination of hemorrhage location (deep versus lobar) and presence of intraventricular bleeding (IVH). Baseline ICH volume was calculated with semi-automated software (Analyze Direct Sofware version 11.0 for development and validation cohort #1 and Cybertrial Inc, Calgary, Canada for validation cohort #2). HE was defined as relative hematoma growth>33% or absolute hematoma growth>6 mL from baseline hemorrhage volume. All patients underwent a follow-up NCCT scan at 24h from onset or earlier in case of clinical deterioration. In a sensitivity analysis the performance of the score was tested using a different definition of HE (ICH growth>33% or 12.5 mL)(14). NCCT images were analyzed to determine the presence of the following NCCT markers: blend sign, intrahematoma hypodensities, irregular hematoma shape, heterogeneous hematoma density and presence of a fluid level, according to previously described radiological criteria(9). Briefly, blend sign was defined as a hypoattenuating area next to a hyperattenuating area of the hematoma, with sharp separation between the two regions and a density difference of at least 18 hounsfield units. Intrahematoma hypodensities were defined as a hypodense region inside the hemorrhage with any shape and dimension and lack of connection with the surrounding brain

parenchyma. Hematoma density and shape were rated with an ordinal scale ranging from 0 to 5 (higher irregularity in shape and heterogeneous hematoma density as the score increases) as previously described by Barras and Colleagues and dichotomized defining as irregular and heterogeneous all the hemorrhages with a Barras score equal or greater than 3(15). Different raters analyzed the three cohorts, blinded to the results of the follow-up NCCT and did not undertake a training before reading the scans. More details are provided in table I in the online-only Data Supplement.

Statistical Analysis

Data were summarized using mean with standard deviation or median with interquartiles, whichever more appropriate, for continuous variables and frequency with percentage for categorical variables. We used the data from the development sample to derive a new risk score for predicting HE and validated the score in two independent samples. Potential predictors of HE known from the literature were included as candidate variables(3,8–10,15). We pre-selected the following fourteen candidate predictor variables: patient demographics (age, sex), history of hypertension, clinical information such as initial measurement of systolic and diastolic blood pressure at ED, ICH volume at baseline, baseline INR measurement, time from hemorrhage onset to baseline NCCT, and imaging findings (hemorrhage location, hypodensities, blend sign, irregular shape, heterogeneous density, and fluid level). Cutoffs for continuous variables were explored using quartiles, graphical display, and recursive partitioning approach. We conducted bivariate analysis between these predictors and outcome using chi-square tests. To avoid the issues associated with the traditional variable selection methods, we constructed 1,000 bootstrap samples based on the development sample data. For each sample, we used a stepwise logistic regression model to determine predictors significant at 0.05 level. Variables consistently chosen in>80% of the bootstrap samples were included in the final model. The prediction score was created based on the parameter estimates (β coefficients) from the final regression model. The assigned scores for each item were derived by summing the β coefficients (B), calculating the point for each risk factor as 5*(βi/B) and the point was rounded to the nearest integer(16). Subsequently, the scoring system was tested in the external validation datasets. Traditional measures of model performance were calculated for both the development sample and the validation samples, including c-index for discrimination and the Hosmer-Lemeshow goodness-of-fit statistic for calibration. For the scoring system, cutoff value was chosen to group patients into low and high risk categories. The test characteristics (sensitivity, specificity, positive and negative predictive value and accuracy [true positive+true negative/ cohort sample size]) were calculated based on the dichotomized categories. Inter-rater reliability was assessed with Cohen’s Kappa statistic. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.,Cary,NC).

RESULTS

A total of 1539 patients with spontaneous ICH met the inclusion criteria for the present study (344 in the development cohort, 954 in validation cohort #1 and 241 in validation cohort #2). The cohort selection process is shown in Figure I in the online-only Data Supplement.

Subjects included in the ATACH-II trial (validation cohort #1) were overall less severely affected compared to ICH patients in the other cohorts, as highlighted by younger age, smaller hematoma volumes, lower rate of IVH and mortality at 90 days. The baseline demographic, clinical and imaging characteristics of the three study populations are summarized in Table 1.

Hematoma expansion score development

Table 2 shows the bivariate analysis comparing patients with and without HE in the development cohort. All the NCCT markers except the presence of a fluid level were significantly more prevalent in patients with HE. Known predictors of HE such as larger baseline volume and shorter time from onset to NCCT were associated with greater likelihood of HE as well in univariate analysis. The multivariable logistic regression analysis using the bootstrap samples yielded three predictors: blend sign, intrahematoma hypodensisites and time from onset to NCCT, as shown in table 3. Using the estimates obtained from the logistic regression model, a 3 items prediction algorithm was created with a total score ranging from 0 to 5 (Table 4). The inter-rater reliability results and an illustrative example of blend sign and intrahematoma hypodensity are provided in the online-only Data Supplement.

Validation of the prediction score

The c statistic was 0.77 (95%CI 0.70-0.83) in the development sample, 0.65 (95%CI 0.61-0.68) and 0.70 (95%CI 0.64-0.77) respectively when applied to validation cohort #1 and #2. For calibration, the score performed well in all three samples as indicated by the lack-of-fit tests. A graphical illustration of the score calibration is provided in figure III in the online-only Data Supplement. The proportion of patients experiencing HE by score is shown in Table 5. In general, this proportion increased with higher scores. When the score was dichotomized, the rate of HE in the development cohort was 50.8% in subjects with a score≥3 (high risk) compared with 11.0% in those with a score<3 (low risk). This cutoff was chosen because it was the point at which the proportion of patients with HE went above the average incidence rate in the development sample. Patients with a score≥3 had a higher risk of HE compared with subjects with a score<3 also in both the validation cohorts. The test characteristics of the dichotomized score for HE are also shown in Table 5. A total of 61 (17.7%) of subjects in the development sample had a score≥3 and this predicted HE with 0.50 sensitivity, 0.89 specificity and 0.82 accuracy.

All the results were confirmed in a sensitivity analysis using a different definition of HE (hematoma growth>33% or 12.5 mL).

DISCUSSION

We developed and validated a NCCT based HE score using two large spontaneous ICH cohorts and a well characterized spontaneous ICH clinical trial population. Blend sign, intrahematoma hypodensities and baseline NCCT timing were the independent predictors included in our algorithm, with a total score ranging from 0 to 5. We demonstrated that rapid

identification of ICH patients at high risk of HE, with high specificity, is possible with an easy to use prediction tool with 3 items that simply requires a NCCT scan.

We noted great heterogeneity in the demographic, clinical and radiological characteristics of the subjects included in the three populations of our study. In particular we observed variability in the prevalence of NCCT markers and rate of HE across the study populations. A potential explanation for this is cohort differences in variables associated with HE and specific NCCT signs such as hemorrhage size and NCCT timing. These discrepancies may also be explained by the lack of consensus on the diagnostic criteria to identify NCCT markers of HE, with overlap between different signs. Another possibility is the lack of standardized training of the raters that evaluated the NCCT images.

We also observed diversity in outcome, with clinical trial patients being less severely affected and having a lower rate of 90 day mortality. In our opinion this variability represent a strength of our analysis because the proposed score showed a good performance across a range of different ICH cohorts. This is relevant because early identification of HE is important not just in clinical practice, but currently even more in the setting of clinical trials testing therapeutic strategies to limit HE(17).

The CTA spot sign is the strongest predictor of HE in most of the currently available scores to identify ICH patients at risk of HE(6,18,19). Therefore a CTA is required to apply these prediction tools. However, many institutions do not have 24/7 CTA capability. In the ATACH-II trial more than 80% of the subjects did not receive a CTA, and in those who did, the diagnostic performance of the spot sign was worse than had been seen in prior studies(7). In addition, two randomized trials using the spot sign to select subjects for hemostatic treatment were prematurely terminated because of a slow recruitment rate (“Spot Sign” Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy(SPOTLIGHT) ClinicalTrials.gov:NCT01359202 and The Spot Sign for Predicting and Treating ICH Growth Study(STOP-IT) ClinicalTrials.gov:NCT00810888)(20). As a result, there appears to be a need for a non-CTA dependent prediction tool.

HE prediction scores that did not require the CTA spot sign assessment have been published. The HEP prediction algorithm includes 6 items with a total score ranging from 0 to 18 whereas the BRAIN scale contains 5 parameters with a total score of 24(19,21). The discriminative ability of our scale was similar to the performance obtained with the HEP and BRAIN scores. Compared with previously published HE risk grading scales our tool may be easier to apply having a total score ranging from 0 to 5 and 3 parameters that can be rapidly evaluated with a baseline NCCT scan that is available in virtually all ICH patients. Another practical score was proposed by Takeda et. al, including only three parameters: ICH volume, hematoma heterogeneity and elevated systolic blood pressure(22). In this score hematoma heterogeneity was the strongest predictor of HE whereas it was not associated with HE in the HEP score(21). Again, these conflicting findings may derive from the lack of strict criteria and consensus on how hematoma heterogeneity should be graded. In addition, the prediction tool published by Takeda and Colleagues included only patients with deep ICH and has not been validated.

In the development and validation cohort #1 our prediction tool showed high specificity for HE. A prediction tool with good specificity may be valuable in clinical trials testing hemostatic anti-expansion drugs, to minimize the exposure to potential thrombotic side effects in patients with a low risk of HE. Conversely, our score showed low sensitivity for HE in the development cohort and this may be explained by the low proportion of patients having a BAT score equal or greater than 3. The dissimilar prevalence of NCCT markers may account for the differences in sensitivity and specificity for HE in the three study populations.

The findings of our study may have relevant implications for future ICH research. The possibility to stratify the risk of HE without the CTA spot sign might indeed expand the pool of patients eligible for clinical trials testing anti-expansion therapies. NCCT is a widely available tool that may allow recruitment of ICH patients for clinical trials. HE is a potentially preventable event that is strongly associated with unfavorable outcome and therefore is an appealing target for acute ICH treatment. Time is brain in ICH as well because most of the patients experience HE in the first 6 hours after symptoms onset(3), leaving a narrow time window for anti-expansion strategies. Our NCCT-based score may allow pre-hospital identification of subjects at high risk of HE through mobile stroke units in the future.

Some limitations should be considered in the interpretation of our results. First, to maximize the applicability of the score in the setting of clinical trials we selected patients with spontaneous ICH with relatively small baseline hematoma volume and absence of anticoagulant treatment. This may have influenced our findings since hemorrhage size and coagulopathy are known predictors of HE(3) and previously published prediction tools such as the BRAIN score did not exclude warfarin-associated hemorrhages(19). In our study baseline ICH volume was not significantly associated with HE. This discrepancy with previous studies may be explained by the exclusion of patients with large ICH volume. In addition non-contrast CT predictors of HE are more prevalent in larger hemorrhages(8,10) and this may also account for the observed lack of association between ICH volume and HE in multivariable analysis. Second, patients received different blood pressure treatment in the three study cohorts and previous studies suggested that blood pressure management may modify the odds of HE(23,24). However this was not the case in the ATACH-II trial that specifically addressed this research question. Third, we previously showed that there is not a strong spatial correlation between intrahematoma hypodensities and the CTA spot sign, and both these markers remained independent predictors of HE in multivariable analysis(8). Therefore it’s possible that integration of CTA spot sign and NCCT markers may provide additional yield in the identification of ICH patients at high risk of HE. We have shown good inter-observer agreement for the identification of intrahematoma hypodensities and blend sign on NCCT. However, these markers were analyzed by raters with a strong expertise in ICH imaging. It remains unclear whether rapid and accurate identification of these NCCT markers is possible also for raters with less experience in ICH neuroimaging.

CONCLUSION

We developed and validated a 5-point prediction algorithm to identify patients at high risk of HE. The score does not need a CTA, and rapid identification of high risk patients requires only 3 parameters that can be easily evaluated on a baseline NCCT scan. This may help optimize the ability to select patients for anti-expansion therapies across a wide range of centers. Prospective validation of our prediction score in other datasets is required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding

The present study was supported by the following awards from the NINDS: 5R01NS073344,1U01NS062091-01A2,K23NS086873. PREDICT was supported by Canadian Stroke Consortium and NovoNordisk Canada. The funding sources did not have any involvement in study design; data collection, analysis, and interpretation; writing of the manuscript; or decision to submit the study for publication.

Christopher D. Anderson reports NIH research grants. Jonathan Rosand reports clinical trial monitoring for Pfizer and NIH research grants. Joshua Goldstein reports research grant and clinical trial monitoring from Pfizer, and research grant from Portola.

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Table 1

Characteristics of the development and validation cohorts

	Development Cohort (n=344)	Validation Cohort #1 (n=954)	Validation Cohort #2 (n=241)
Age, mean (SD)	70.0 (13.7)	61.9 (13.0)	66.2 (15.0)
Male, n (%)	188 (54.7)	590 (61.8)	145 (60.2)
Hypertension, n (%)	281 (81.7)	754 (79.0)	171 (71.0)
Admission SBP, mean (SD)	182 (36)	201 (27)	175 (32)
Admission DBP, mean (SD)	97 (26)	111 (21)	95 (19)
Admission INR, mean (SD)	1 (0.1)	1 (0.1)	1 (0.1)
Baseline ICH volume, median, (IQR)	15.0 (7.4-29.0)	10.2 (5.1-18.2)	11.9 (6.2-24.1)
ICH location			
Deep, n (%)	227 (66.0)	850 (89.1)	175 (72.6)
Lobar, n (%)	117 (34.0)	104 (10.9)	66 (27.4)
GCS, median (IQR)	14 (10-15)	15 (13-15)	15 (13-15)
IVH, n (%)	142 (41.3)	248 (26.0)	77 (32.0)
Time from onset to NCCT scan			
Median, (IQR), h	3.1 (1.6-4.8)	1.4 (1.0-2.2)	2.3 (1.5-3.3)
<2.5 h, n (%)	106 (30.8)	781 (81.9)	142 (58.9)
>2.5 h, n (%)	146 (42.4)	172 (18.0)	99 (41.1)
Unknown, n (%)	92 (26.7)	1 (0.1)	N/A
Hypodensities, n (%)	84 (24.4)	252 (26.4)	148 (61.4)
Blend Sign, n (%)	54 (15.7)	83 (8.7)	49 (20.3)
Irregular Shape, n (%)	160 (46.5)	381 (39.9)	200 (83.0)
Heterogeneous Density, n (%)	67 (19.5)	296 (31.0)	131 (54.4)
Fluid Level, n (%)	16 (4.7)	7 (0.7)	13 (5.4)
Hematoma expansion, n (%)	62 (18.0)	236 (24.7)	71 (29.5)
90-day Mortality, n (%)	82 (23.8)	53 (5.6)	41 (17.0)

SD indicates standard deviation; SBP,systolic blood pressure; DBP, diastolic blood pressure; INR, International normalized ratio; ICH, intracerebral hemorrhage; GCS, Glasgow coma scale; IVH, intraventricular hemorrhage; IQR, interquartile range; NCCT, non-contrast computed tomography.

Table 2

Univariate analysis comparing subjects with and without hematoma expansion

	Hematoma Expansion		
	YES (n=62)	**NO (n=282)**	***p***
Age, mean (SD)	70.0 (13.9)	70.1 (13.6)	0.99
Sex, n (%)			0.38
Male	37 (59.7)	151 (53.5)	
Female	25 (40.3)	131 (46.5)	
Hypertension, n (%)	49 (79.0)	232 (82.3)	0.72
Admission SBP, mean (SD)	177.7 (40.3)	182.5 (34.8)	0.40
Admission DBP, mean (SD)	94.8 (25.4)	97.6 (26.1)	0.45
Admission INR, mean (SD)	1.0 (0.1)	1.1 (0.1)	0.45
Antiplatelet treatment, n (%)	33 (53.2)	117 (41.5)	0.08
Baseline ICH volume, median (IQR)	14.0 (7.0-27.5)	23.2 (10.4-38.3)	0.003
ICH location			0.75
Deep, n (%)	42 (67.7)	185 (65.6)	
Lobar, n (%)	20 (32.3)	97 (34.4)	
GCS, median (IQR)	13.0 (10.0-15.0)	14.0 (10.0-15.0)	0.42
IVH, n (%)	26 (41.9)	118 (41.8)	0.99
Time from onset to NCCT scan,			
Median, (IQR), h	1.8 (1.2-3.5)	3.4 (2.0-5.0)	<0.0001
<2.5 h, n (%)	36 (58.1)	70 (24.8)	<0.0001
>2.5 h, n (%)	16 (25.8)	130 (46.1)	
Unknown, n (%)	10 (16.1)	82 (29.1)	
Hypodensities, n (%)	33 (53.2)	51 (18.1)	<0.0001
Blend Sign, n (%)	17 (27.4)	37 (13.1)	0.005
Irregular Shape, n (%)	36 (58.1)	124 (44.0)	0.044
Heterogeneous Density, n (%)	25 (40.3)	42 (14.9)	<0.0001
Fluid Level, n (%)	2 (3.2)	14 (5.0)	0.56
90-day Mortality, n (%)	29 (46.8)	53 (18.8)	<0.0001

SD indicates standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; INR, International normalized ratio; ICH, intracerebral hemorrhage; GCS, Glasgow coma scale; IVH, intraventricular hemorrhage; IQR, interquartile range.

Table 3

Multivariable Logistic Regression Model from Development Sample

Variable	aOR (95% CI)	*p*
Blend Sign Presence vs. Absence	3.09 (1.49-6.40)	0.002
Any Hypodensity Presence vs. Absence	4.54 (2.44-8.43)	<0.0001
Time from onset to NCCT<2.5 h vs ≥2.5 h or unknown	3.73 (1.86-7.51)	0.0002

aOR indicates adjusted odds ratio; CI, confidence interval; NCCT, non-contrast computed tomography.

Table 4

Individual components of the BAT score

Variable	Points
Blend Sign	
Present	1
Absent	0
Any Hypodensity	
Present	2
Absent	0
Time from onset to NCCT	
<2.5 h	2
≥2.5 h or unknown	0

NCCT indicates non-contrast computed tomography.

Table 5

Hematoma Expansion Rate by BAT Score

	Hematoma expansion, n (%)		
	Development Cohort	**Validation Cohort #1**	**Validation Cohort #2**
C-statistics (95% CI)	0.77 (0.70-0.83)	0.65 (0.61-0.68)	0.70 (0.64-0.77)
Score			
0 – 1	14/193 (7.3)	15/145 (10.3)	3/46 (6.5)
2	17/90 (18.9)	114/541 (21.1)	18/83 (21.7)
3	10/22 (45.5)	14/44 (31.8)	8/17 (47.1)
4	18/35 (51.4)	74/192 (38.5)	26/65 (40.0)
5	3/4 (75.0)	19/32 (59.4)	16/30 (53.3)
Dichotomized			
<3	31/283 (11.0)	129/686 (18.8)	21/129 (16.3)
≥3	31/61 (50.8)	107/268 (39.9)	50/112 (44.6)
Dichotomized test characteristics (95% CI)			
Sensitivity	0.50 (0.37-0.63)	0.45 (0.38-0.51)	0.70 (0.58-0.81)
Specificity	0.89 (0.85-0.93)	0.78 (0.74-0.81)	0.64 (0.56-0.71)
PPV	0.51 (0.38-0.64)	0.40 (0.34-0.46)	0.45 (0.35-0.54)
NPV	0.89 (0.85-0.92)	0.81 (0.78-0.84)	0.84 (0.76-0.90)
Overall Accuracy	0.82 (0.78-0.86)	0.70 (0.66-0.72)	0.66 (0.59-0.72)

CI indicates confidence interval; PPV, positive predictive value; NPV, negative predictive value.