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Clinical and therapeutic variables may influence the association between infarct core predicted by CT perfusion and clinical outcome in acute stroke

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Abstract

Objectives After an acute ischemic stroke, patients with a large CT perfusion (CTP) predicted infarct core (pIC) have poor clinical outcome. However, previous research suggests that this relationship may be relevant for subgroups of patients determined by pretreatment and treatment-related variables while negligible for others. We aimed to identify these variables.

Methods We included a cohort of 828 patients with acute proximal carotid arterial occlusions imaged with a whole-brain CTP within 8 h from stroke onset. pIC was computed on CTP Maps (cerebral blood flow < 30%), and poor clinical outcome was defined as a 90-day modified Rankin Scale score > 2. Potential mediators of the association between pIC and clinical outcome were evaluated through first-order and advanced interaction analyses in the derivation cohort (n = 654) for obtaining a prediction model. The derived model was further validated in an independent cohort (n = 174).

Results The volume of pIC was significantly associated with poor clinical outcome (OR = 2.19, 95% CI = 1.73 – 2.78, p < 0.001). The strength of this association depended on baseline National Institute of Health Stroke Scale, glucose levels, the use of thrombectomy, and the interaction of age with thrombectomy. The model combining these variables showed good discrimination for predicting clinical outcome in both the derivation cohort and validation cohorts (area under the receiver operating characteristic curve 0.780 (95% CI = 0.746–0.815) and 0.782 (95% CI = 0.715–0.850), respectively).

Conclusions In patients imaged within 8 h from stroke onset, the association between pIC and clinical outcome is significantly modified by baseline and therapeutic variables. These variables deserve consideration when evaluating the prognostic relevance of pIC.

Key Points

- *The volume of CT perfusion (CTP) predicted infarct core (pIC) is associated with poor clinical outcome in acute ischemic stroke imaged within 8 h of onset.*
- *The relationship between pIC and clinical outcome may be modified by baseline clinical severity, glucose levels, thrombectomy use, and the interaction of age with thrombectomy.*
- *CTP pIC should be evaluated in an individual basis for predicting clinical outcome in patients imaged within 8 h from stroke onset.*

Keywords Brain imaging · Cerebral blood flow · Cerebrovascular circulation · Acute ischemic stroke · Thrombolysis

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Abbreviations

AAI	Advanced analysis of interaction
ASPECTS	Alberta Stroke Program Early CT Score
AUC-ROC	Area under the receiver operating characteristic curve
CV	Cross-validation
CTP	CT perfusion
ICA-T	Internal carotid artery terminal segment
IVT	Intravenous treatment
MT	Mechanical thrombectomy
mRS	Modified Rankin Scale score
mTICI	Modified thrombolysis in cerebral infarction
NIHSS	National Institute of Health Stroke Scale
PO	Poor outcome
pIC	Predicted infarct core
rCBF	Relative cerebral blood flow threshold
SE	Standard error
TOAST	Trial of Org 10 172 in acute stroke treatment
VAR	Variance

Introduction

The evaluation of non-viable tissue or core of the infarct is one of the most relevant baseline imaging markers in acute stroke patients. Infarct core can be estimated by several different techniques, such as the Alberta Stroke Program Early CT Score (ASPECTS) in non-contrast CT, the volume of tissue with severely reduced cerebral blood volume or cerebral blood flow (CBF) on CT perfusion (CTP), or the volume of hyperintense signal on acute diffusion weighted imaging on magnetic resonance imaging [1, 2].

Due to the availability of CTP, this technique is extensively used in the acute stroke setting to obtain a predicted infarct core (pIC) volume, which is a perfusion-based estimation of the non-viable tissue based in threshold-derived hemodynamic maps [1, 2]. Despite the overall association between pIC and clinical outcome metrics, a number of pretreatment and treatment-related variables have been shown to modify these relationships including age, baseline National Institute of Health Stroke Scale (NIHSS), ASPECTS, time to CTP acquisition, degree of reperfusion, collaterals, or hyperglycemia [3–9]. Specifically, CTP-derived pIC may overestimate substantially ischemic changes, especially in the early time window and particularly in the context of early and complete reperfusion [4]. However, the joint relevance of baseline and therapeutic variables that may influence the association between infarct core predicted by CTP and clinical outcome in acute stroke is not well characterized at the time being. Thus, a better delineation of the interaction between these variables would be relevant for assuring better outcome predictions at the early stroke setting.

Under the hypothesis that the prognostic accuracy of pIC might be modified by a number of baseline and treatment-related variables, we analyzed a cohort of acute ischemic stroke patients with large-vessel anterior circulation occlusions imaged with CTP within 8 h from stroke onset in order to identify the most relevant modifiers of the association between pIC and clinical outcome.

Materials and methods

Study design and included population

The study population included consecutive acute stroke patients admitted in a referral comprehensive stroke center between March 2010 and December 2017 (derivation cohort) and between January 2018 and December 2018 (validation cohort) who had a whole-brain CTP scan within the first 8 h from stroke onset showing a perfusion deficit due to a proximal arterial occlusion in the carotid territory (Fig. 1). The study protocol was approved by the Hospital Clinic of Barcelona Research Ethics Committee under the requirements of Spanish legislation in the field of biomedical research, the protection of personal data (15/1999), and the standards of good clinical practice, as well as with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Given the retrospective nature of the study, the individual consent to participate was not required after the approval from the local Clinical Research Ethics Committee. The datasets analyzed during the current study are available from the corresponding author on reasonable request. We adhered to the Standards for Reporting of Diagnostic Accuracy (STARD) guidelines (http://www.stard-statement.org/).

Demographics, clinical course, functional outcome, and reperfusion-therapy modality (no treatment, intravenous thrombolysis and primary or rescue mechanical thrombectomy (MT)) were prospectively recorded. Reperfusion therapies were administered following contemporary guideline recommendations, as previously described [6]. Systemic rtPA was given within 4.5 h from stroke onset at a dose of 0.9 mg per kg. MT was performed within 8 h in eligible patients with proximal arterial occlusions on CT angiography. During the study period, the presence of a malignant profile in CTP (infarct core higher than 70 ml) and the absence of mismatch in patients with symptoms lasting > 4.5 h from the onset of stroke were exclusion criteria for receiving MT according to specific contemporary local guidelines. Qualifying strokes were classified according to the Trial of Org 10 172 in Acute Stroke

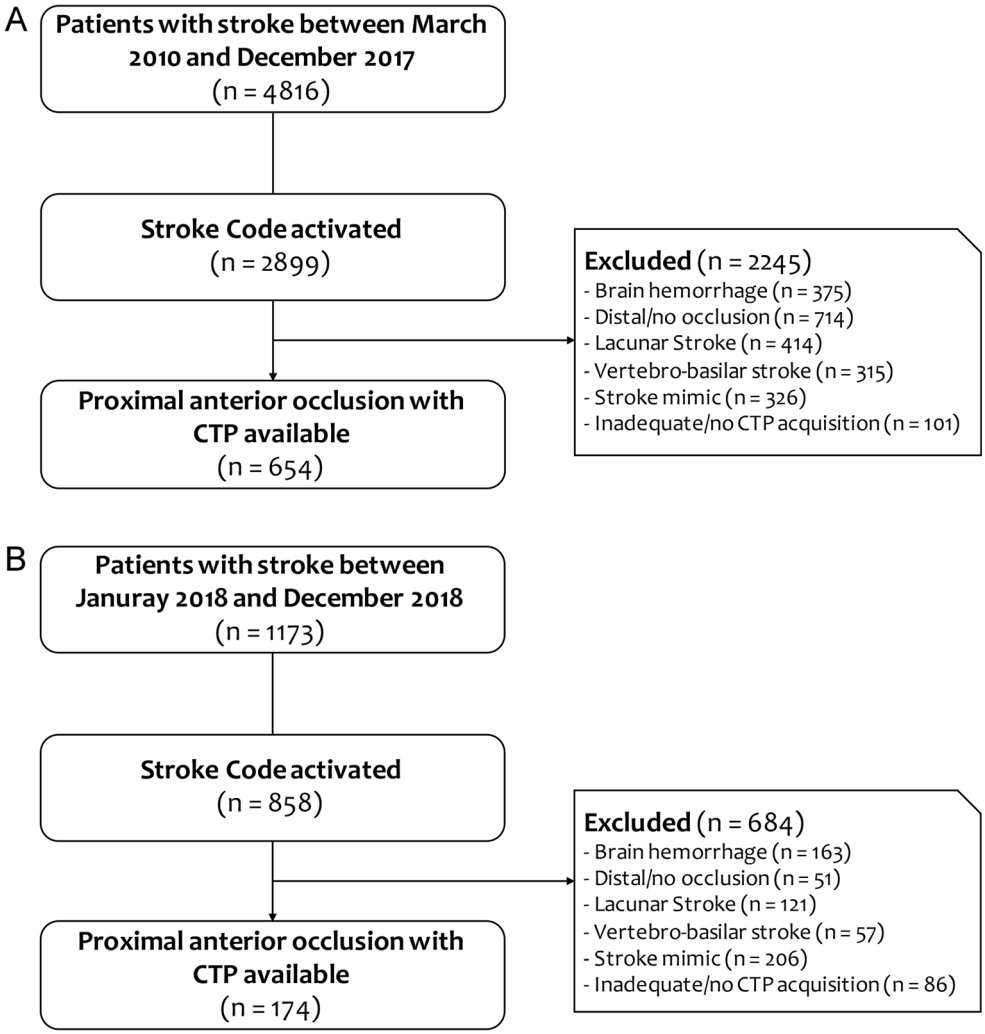


Fig. 1 Flow chart of the included population

Treatment (TOAST) criteria [10]. Neurological status was monitored with the NIHSS score. Functional outcome was scored with the modified Rankin Scale score (mRS) at 3 months, and poor clinical outcome was defined as an mRS > 2.

Imaging protocol

The imaging protocol included a baseline multimodal whole-brain CT scan (SIEMENS Somatom 128-section dual-source CT scanner), which included a non-contrast CT, a CT angiography, and a CTP (98 mm z-coverage, total acquisition time of 59 s). CTP maps were calculated through a model-free singular value decomposition algorithm with a delay and dispersion correction (MIStar, Apollo Medical Imaging Technology). A delay time threshold of 3 s was used to obtain the hypoperfusion area, and a relative CBF (rCBF) of 30% was used to define the pIC. ASPECTS on non-contrast CT and collaterals were defined according to validated methods [11, 12]. In patients receiving MT, early reperfusion was graded on digital subtraction angiography according to the modified thrombolysis in cerebral infarction (TICI) classification and complete recanalization was defined if a grade 2b–3 was obtained at the end of the procedure. Investigators blinded to clinical data evaluated all imaging studies.

Statistical methods

Continuous variables were reported as mean (standard deviation, SD) or median (interquartile range, IQR) and were compared with the Student *t* test, one-way analysis of variance, Mann–Whitney, or Kruskal–Wallis tests as appropriate. Categorical variables were compared with the $\chi 2$ and Fisher exact tests as appropriate. Unadjusted and adjusted logistic regression models were used to obtain the association between pIC and poor clinical outcome. The dependent variable was

the clinical outcome at 90 days, and the independent variables were pIC volume and the interaction between pIC and several potential modulators. Before inclusion in the regression, we applied the fourth root transformation to pIC volume to approach normality. The variables included in the adjusted models were those that showed an independent association with poor clinical outcome in the whole derivation cohort after applying a stepwise backwards procedure. Treatment-related variables and those neuroimaging variables that were highly correlated with pIC were not included in order to avoid losing not-treated patients from the analysis and to prevent colinearity issues.

We followed an advanced analysis of interaction (AAI) to select significant first- and second-order interactions in the regression applied to the derivation cohort (Fig. 2). The analysis of interaction was performed in two stages. First, we evaluated the first-order interaction between pIC and the potential mediators in unadjusted and adjusted binary logistic regression models and subgroup analyses were performed in the presence of a significant interaction term (p value lower than 0.1). Second, we implemented a three-step advanced analysis of interaction (AAI) including first- and second-order interactions. In AAI step 1 a binary logistic regression was applied for every interacting variable to predict poor clinical outcome (PO) in a model including four terms: intercept, pIC, the interacting variable, and the first-order interaction term pIC-interacting variable (Eq. 1). In this stage, all the interacting variables that had a significant first-order interaction term in the model were stored. The interaction variable alone was also stored if it was significant together with the interaction term. In the AAI step 2, a binary logistic regression was applied for every pair of interacting variables identified in the previous step into a model with seven terms including second-order interaction terms (Eq. 2). In this step, all the pairs of interacting variables that had a significant second-order interaction term in the model were stored. In the AAI third step, a final logistic regression model was constructed with all the significant interacting variables stored in previous steps, including significant variables alone, first-order interaction terms, and second-order interaction terms (Eq. 3). In the final model, the sum of all the beta values of the terms related to pIC provided the strength of the association between pIC and poor outcome taking into account the interacting variables. Finally, before applying the AAI to the whole cohort of patients, twofold cross-validation (CV) was

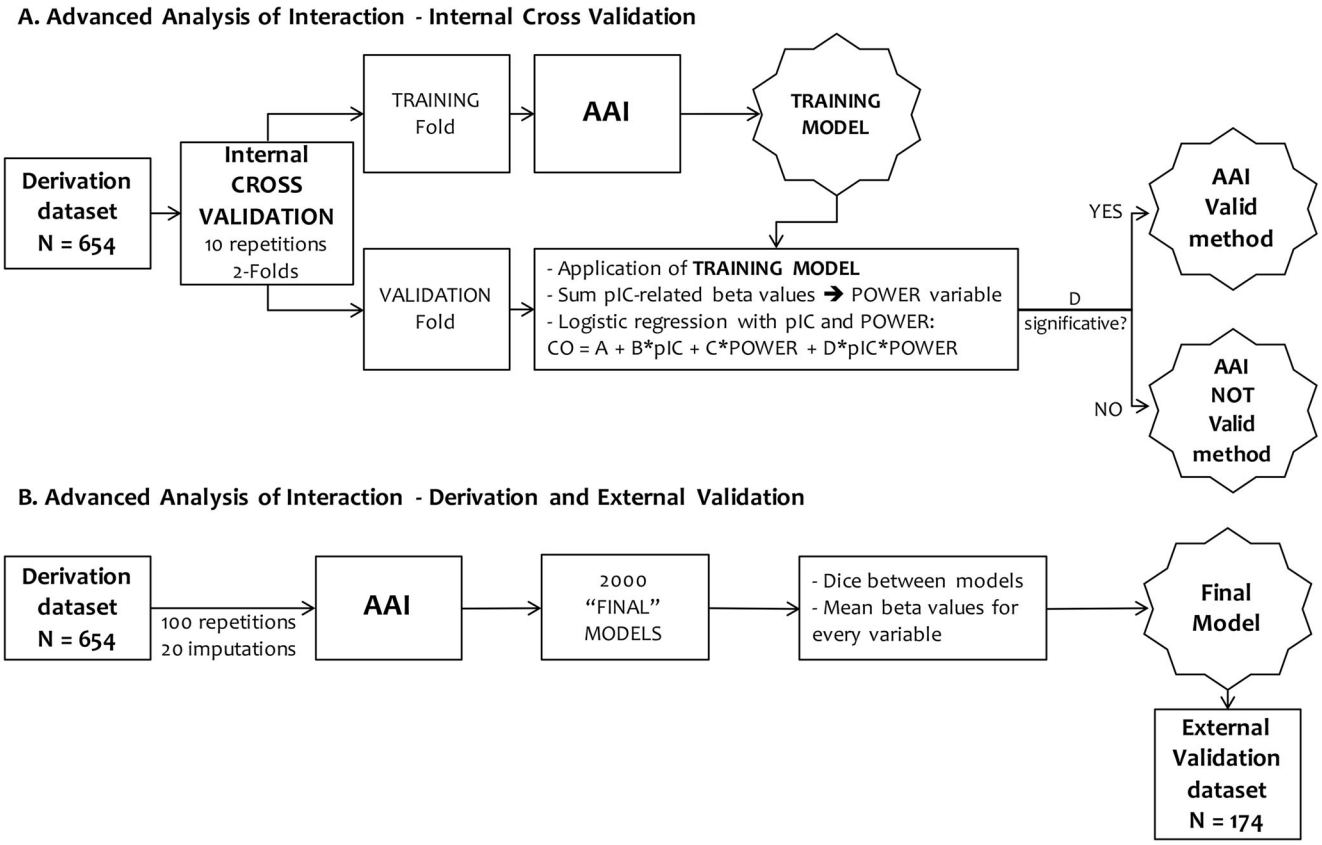


Fig. 2 Graphical representation of the study design and analysis. AAI: advanced analysis of interaction; CO: clinical outcome; pIC: predicted infarct core

carried out ten times to test the validity of the AAI approach. The allocation of patients in the 2 folds of the internal CV was controlled through balancing the distribution of mRS between both groups. To test if the interacting variables influenced the relationship between pIC and poor outcome, the final model obtained in the training fold was applied to the validation fold and the beta values of the terms related to pIC were stored in a new continuous variable called POWER and the beta value for the interaction term pIC*POWER was stored (Eqs. 4 and 5, respectively). A meta-analysis using fixed and random effects was then applied to the ten 2-folds. The mean of the 20 meta-analytic beta values, variances, and global Z and p values were recorded (significant global Z and p values were considered as indicative of model validity). After the internal CV, the AAI procedure was applied to all the databases of the 654 patients. A hundred iterations of the procedure were processed (20 models per iteration, 2000 models), and the Dice coefficient was calculated for every pair of 2000 models. Finally, the models with a maximum Dice coefficient were stored and the mean beta values for every variable were computed to obtain a representative unique final model. Finally, we estimated the validity of the model in the validation cohort with the area under the receiver operating characteristic (AUC-ROC) curve. This statistic may range from 0.5 (tossing a coin) to 1 (perfect prediction). We conducted all analyses with SPSS v.20 (IBM) and R (v.3.4.4, https://www.R-project.org).

Table 1 Demographics, baseline, and procedure-related variables according to clinical outcome at day 90 in the derivation cohort

	mRS ≤ 2 *n* = 294	mRS > 2 *n* = 360	*p*
Age (years)	69 (59 – 78)	74 (65 – 80)	< 0.001#
Prior mRS	0 (0 – 1)	0 (0 – 1)	< 0.001
Females, *n* (%)	130 (44)	178 (49)	0.183
Smoking, *n* (%)	37 (13)	32 (9)	0.126
Hypertension, *n* (%)	166 (57)	239 (66)	0.009
Diabetes, *n* (%)	43 (15)	75 (21)	0.040
Dyslipidemia, *n* (%)	121 (41)	147 (41)	0.933
Atrial fibrillation, *n* (%)	76 (26)	114 (32)	0.103
Glucose (mg/dl)	116 (102 – 136)	127 (111 – 152)	< 0.001#
NIHSS	13 (8 – 18)	18 (13 – 22)	< 0.001#
ASPECTS	9 (8 – 10)	9 (7 – 10)	< 0.001
Collateral score	2 (2 – 3)	2 (1 – 2)	< 0.001
Time to CTP (min)	172 (107 – 245)	194 (116 – 289)	0.089
TOAST classification			0.541
Atherothrombotic, *n* (%)	49 (17)	61 (17)	
Cardioembolic, *n* (%)	141 (48)	186 (52)	
Other etiologies, *n* (%)	104 (35)	113 (31)	
Location of the occlusion			0.474
Tandem, *n* (%)	39 (13)	51 (14)	
ICA-T or M1, *n* (%)	196 (67)	250 (69)	
M2, *n* (%)	59 (20)	59 (17)	
pIC (ml)	14 (6 – 29)	27 (10 – 67)	< 0.001#

Data are median (IQR) unless otherwise specified. # means $p < 0.05$ in the multivariate binary regression model constructed through a stepwise backwards procedure after removing the treatment-related variables and the neuroimaging-based variables that were highly correlated with pIC (to avoid collinearity)

ASPECTS Alberta Stroke Program Early CT Score, *CTP* computed tomography perfusion, *ICA-T* internal carotid artery terminal occlusion, *mRS* modified Rankin Scale score, *NIHSS* National Institutes of Health Stroke Scale, *pIC* predicted infarct core, *TOAST* Trial of ORG 10172 in acute stroke treatment

$$PO = A + B*pIC + C*var + D*pIC*var \quad (1)$$

$$PO = A + B*pIC + C*var_1 + D*var_2 + E*pIC*var_1 + F*pIC*var_2 + G*pIC*var_1*var_2 \quad (2)$$

$$PO = A + B*pIC + \sum_n (C_n*var_n) + \sum_n (D_n*pIC*var_n) + \sum_n \sum_m (E_{nm}*pIC*var_n*var_m) \quad (3)$$

$$POWER = B + \sum_n D_n + \sum_n \sum_m E_{nm} \quad (4)$$

$$PO = A + B*pIC + C*POWER + D*pIC*POWER \quad (5)$$

Results

During the 2010–2018 timeframe, 828 patients were admitted to the unit, of which we assigned 654 to the derivation cohort (2010–2017) and 174 to the validation cohort (2018). The main baseline clinical and radiological traits of the derivation cohort are shown in Table 1 and Table 2. The variables independently associated with poor clinical outcome at 3 months are shown in Table 1 and included older age and higher pretreatment glucose levels, NIHSS, and pIC volume. A description of the sample population according to acute reperfusion treatment is shown in Table 2.

Overall, a larger pIC volume was significantly associated with poorer clinical outcome in both unadjusted and adjusted analyses, as shown in Fig. 3. However, the strength of the association was modified by different baseline variables, indicating that the prediction of clinical outcome by infarct core volume differed by clinical and radiological stroke severity scales. In the first-order analyses of multiplicative interaction, the strength of the association was significantly modified by

Table 2 Demographics, baseline, and procedure-related variables for all patients included in the derivation cohort and according to treatment modality

	All patients $n = 654$	No IVT/MT $n = 92$	IVT alone $n = 129$	MT ± IVT $n = 433$	p
Age (years)	72 (62 – 80)	75 (66 – 80)	74 (64 – 79)	73 (61 – 80)	0.354
Prior mRS	0 (0 – 1)	0 (0 – 1)	0 (0 – 0)	0 (0 – 1)	0.187
Females, *n* (%)	308 (47)	44 (48)	58 (45)	206 (48)	0.863
Hypertension, *n* (%)	405 (62)	59 (64)	86 (67)	260 (60)	0.356
Diabetes, *n* (%)	118 (18)	23 (25)	26 (20)	69 (16)	0.095
Dyslipidemia, *n* (%)	268 (41)	35 (38)	55 (43)	178 (41)	0.788
Atrial fibrillation, *n* (%)	190 (29)	29 (32)	30 (23)	131 (30)	0.262
Glucose (mg/dl)	124 (107 – 146)	125 (109 – 160)	128 (111 – 154)	119 (105 – 142)	0.008
NIHSS, median (IQR)	16 (10 – 20)	15 (6 – 21)	16 (9 – 20)	17 (11 – 20)	0.067
ASPECTS, median (IQR)	9 (8 – 10)	8 (6 – 10)	8 (7 – 10)	9 (8 – 10)	< 0.001
Collateral score	2 (1 – 3)	2 (1 – 3)	2 (1 – 2)	2 (1 – 3)	0.015
Time to CTP (min)	181 (103 – 288)	245 (114 – 636)	179 (110 – 251)	179 (100 – 285)	0.002
Time to MT onset (min)		–	–	251 (180 – 360)	–
Recanalization (yes), *n* (%)		–	–	376 (87)	–
Time to recanalization (min)		–	–	300 (217 – 398)	–
TOAST classification					0.160
Atherothrombotic, *n* (%)	110 (17)	15 (16)	19 (15)	76 (18)	
Cardioembolic, *n* (%)	327 (50)	52 (57)	56 (43)	219 (51)	
Other etiologies, *n* (%)	217 (33)	25 (27)	54 (42)	138 (32)	
Location of the occlusion					< 0.001
Tandem, *n* (%)	90 (14)	11 (12)	18 (14)	61 (14)	
ICA-T or M1, *n* (%)	446 (68)	50 (54)	79 (61)	317 (73)	
M2, *n* (%)	118 (18)	31 (34)	32 (25)	55 (13)	
pIC (ml)	20 (8 – 37)	23 (6 – 83)	28 (9 – 81)	19 (8 – 36)	0.002

Data are median (IQR) unless otherwise specified

ASPECTS Alberta Stroke Program Early CT Score, *CTP* computed tomography perfusion, *ICA-T* internal carotid artery terminal occlusion, *IVT* intravenous treatment, *mRS* modified Rankin Scale score, *MT* mechanical thrombectomy, *NIHSS* National Institutes of Health Stroke Scale, *pIC* predicted infarct core, *TOAST* Trial of ORG 10172 in acute stroke treatment

pretreatment NIHSS, glucose levels, and MT, as illustrated in Fig. 3.

The internal cross-validation based on ten twofold replicates demonstrated that the interaction terms significantly modified the association between pIC and clinical outcome (final beta value 0.80, variance 0.12, Z value 2.3, and p value 0.02). The beta values, standard errors, and Z and p values for the interaction terms for each of the ten 2-folds and the results of the internal CV metagen analysis are shown in Table 3. After the internal CV, the AAI applied to the derivation cohort generated 2000 models (100 repetitions, 20 models per repetition). Of those, 289 models were identical and were the most similar to the other models (Dice = 0.77). This final AAI model included baseline NIHSS, blood glucose levels, MT use, age, and the interaction age × MT as significant interacting variables (Table 4). Representative examples of applying the model for different levels of the identified modifiers are shown in Fig. 4.

As shown in Fig. 5, the model combining the variables identified through the AAI approach had higher accuracy than the prediction yielded by pIC alone (AUC-ROC = 0.780 (95% CI = 0.746–0.815) for the final model, AUC-ROC = 0.648 (95% CI = 0.607–0.690) for the model with pIC alone; $p < 0.001$). Reassuringly, the obtained model showed good discrimination in both the derivation cohort (AUC-ROC = 0.780 (95% CI = 0.746–0.815)) and the validation cohort (AUC-ROC = 0.782 (95% CI = 0.715–0.850)), respectively (Fig. 5).

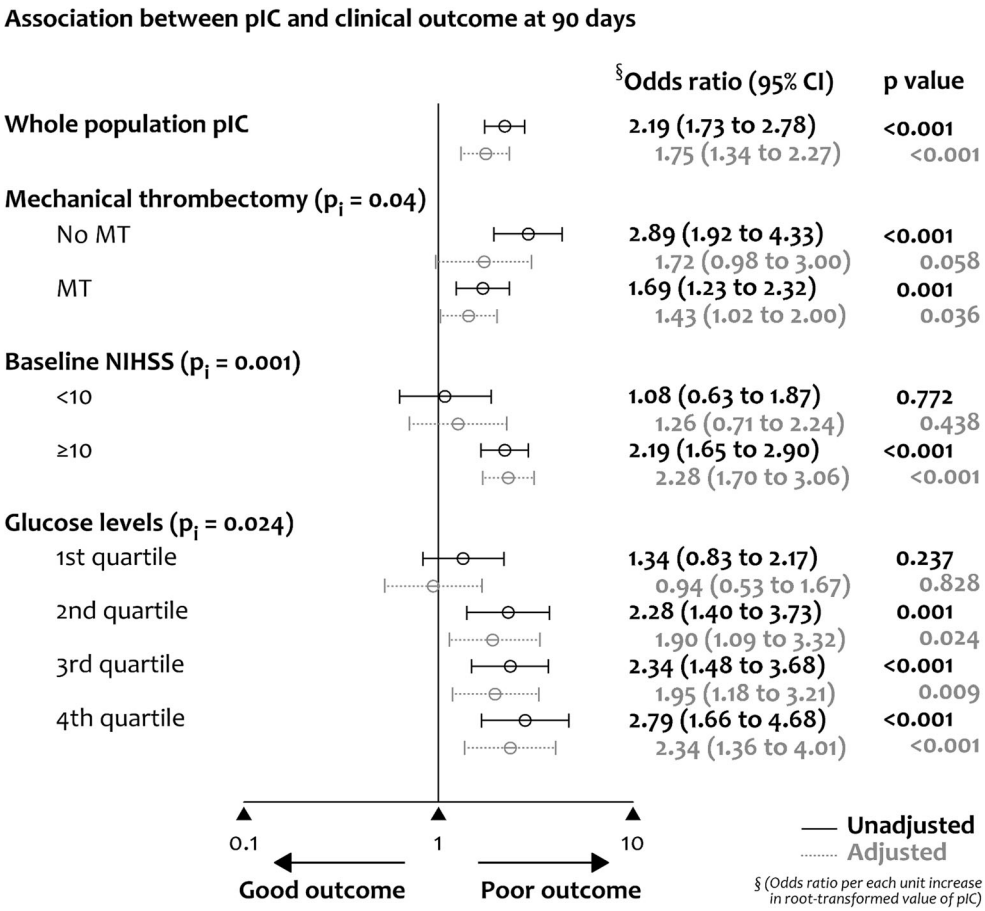


Fig. 3 Forest plot of the association between predicted infarct core (pIC) and poor outcome. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) of the association between pIC and clinical outcome in the whole derivation cohort and in subgroups defined by significant interaction variables. Age, glucose levels, and NIHSS were used for obtaining adjusted OR. mRS: modified Rankin Scale score; MT: mechanical thrombectomy; NIHSS: National Institutes of Health Stroke Scale; pi: interaction *p* value; pIC: predicted infarct core

Discussion

In this study, we specifically explored the interaction between pIC and several baseline and treatment-related variables on the prediction of clinical outcome under the hypothesis that in certain subgroups of patients the association of pIC with clinical outcome would be lost. Expectedly, we found that higher volumes of pIC were associated with poor clinical outcome, although this association was significantly modified by the combination of baseline stroke severity, pretreatment glucose levels, thrombectomy use, and age.

There have been shown strong correlations between pIC volume estimation with both final infarct volume and clinical outcome [3, 4, 11, 13–16]. However, a number of pretreatment and treatment-related variables, including baseline imaging features and acute reperfusion treatment modality, have been extensively proved to modify the performance of CTP for final infarct prediction [3, 17–19]. In this context, we analyzed a total of 828 patients with acute proximal arterial occlusions in the carotid territory imaged with a whole-brain CTP within 8 h from stroke onset and evaluated the potential mediators of the association between pIC and clinical outcome in a derivation cohort for obtaining a prediction model that was further validated in an independent cohort. In first-order analyses of interaction, we found that the strength of the association between pIC and clinical outcome was significantly modified by baseline NIHSS, glucose levels, and MT. Moreover, by means of an advanced analysis of interaction including first- and second-order interaction terms, we also identified age and its interaction with the use of MT as additional modifying variables. Overall, our data support previous observations from experimental and clinical studies showing that both elevated glucose levels and older age are associated with enhanced and faster conversion of ischemic brain tissue into infarction thus supporting their role as biological markers of tissue fate variability [3, 20–22]. Moreover, the accuracy of the most extended and validated perfusion thresholds used for the pre-

Table 3 Results of the metagen analysis on the ten two-folds of the internal cross-validation procedure

Fold beta POWER*pIC	Fold SE POWER*pIC	Fold *Z* POWER*pIC	Fold *p* POWER*pIC	Meta weight	Meta beta POWER*pIC	Meta VAR POWER*pIC	Meta *Z* POWER*pIC	Meta *p* POWER*pIC
1.43	0.49	2.9	0.0038	4.09	1.11	0.09	3.8	0.0001
0.94	0.36	2.6	0.0096	7.59				
1.46	0.45	3.3	0.0011	5.01	1.15	0.07	4.2	0.0000
0.97	0.34	2.8	0.0047	8.47				
0.42	0.43	1.0	0.3239	5.49	0.40	0.14	1.1	0.2799
0.34	0.76	0.5	0.6526	1.73				
1.39	0.45	3.1	0.0021	4.91	1.37	0.13	3.8	0.0002
1.35	0.62	2.2	0.0300	2.59				
0.78	0.46	1.7	0.0848	4.83	0.85	0.09	2.8	0.0048
0.91	0.41	2.2	0.0251	6.06				
1.29	0.35	3.7	0.0002	8.31	0.81	0.04	4.0	0.0001
0.40	0.25	1.6	0.1066	16.25				
0.56	0.47	1.2	0.2397	4.48	0.45	0.17	1.1	0.2797
0.09	0.85	0.1	0.9115	1.39				
0.14	0.38	0.4	0.7221	6.93	0.73	0.09	2.5	0.0125
1.38	0.46	3.0	0.0026	4.79				
− 0.72	0.86	− 0.8	0.4043	1.34	0.38	0.30	0.7	0.4851
1.36	0.70	1.9	0.0529	2.02				
0.98	0.38	2.6	0.0099	6.88	0.78	0.10	2.5	0.0120
0.38	0.55	0.7	0.4894	3.36				

Beta values, standard errors, *Z* values, and *p* values for the 20 models constructed in the internal cross-validation process to explore the validity of the advanced analysis of interaction are shown in the first four columns. Metagen weights, beta values, variances, *Z* values, and *p* values of the 10 two-folds are shown in the last 5 columns

pIC predicted infarct core, *SE* standard error, *VAR* variance

diction of established infarct tissue (e.g., CBFr lower than 30% of normal tissue) has been shown to be reduced in the setting of successful recanalization achieved through MT thus reducing the prognostic yield of those predictions [6]. Accordingly, our AAI identified MT use as one of the more potent modifiers of the association between pIC and clinical outcome.

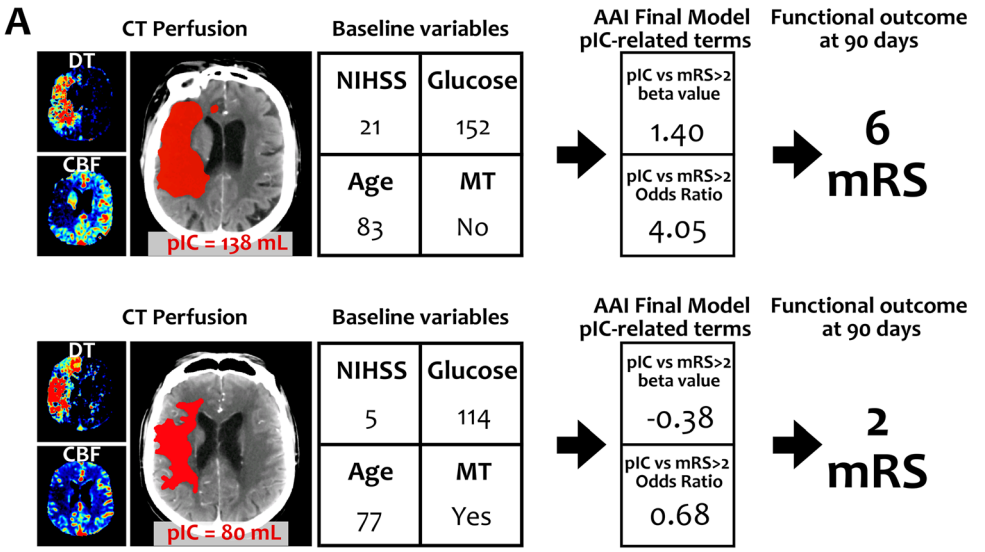
Table 4 Clinical variables and coefficients of the final derived model

Variable	Coefficient
Intercept	− 0.629416935
pIC	− 1.549562775
pIC:age	0.015214074
pIC:glucose	0.003234035
pIC:NIHSS	0.056892900
pIC:MT	0.021245386
pIC:MT:age	− 0.008793370

MT mechanical thrombectomy, *NIHSS* National Institutes of Health Stroke Scale, *pIC* predicted infarct core

Importantly, the AAI model performed better than the model containing pIC alone, thus suggesting that the addition of certain simple baseline clinical variables could improve the accuracy of outcome predictions. The model was internally validated through cross-validation and showed similar accuracy at both derivation and external validation cohorts. According to our data, the prognostic relevance of pIC would be weakened in the context of milder stroke syndromes and lower baseline glucose levels, and in younger patients, especially when the odds of performing MT are high. Overall, these observations are in line with current guidelines that discourage the use of CTP-derived pIC as a screening tool to establish the need or lack thereof of reperfusion therapies in the early time window [1, 4].

This study has several limitations. First, patients were treated within the first 8 h from stroke onset following local guidelines where treatment decisions were not randomized and included the use of information derived from CTP. Consequently, our findings might not apply to acute stroke patients evaluated without CTP in the acute phase. Although we used validated software, our results may not be



B

			Baseline NIHSS											
			5-10			11-15			16-20			21-25		
			Glucose			Glucose			Glucose			Glucose		
			60-100	101-140	141-180	60-100	101-140	141-180	60-100	101-140	141-180	60-100	101-140	141-180
MT	Age	40-50	0.6	0.7	0.7	0.8	0.9	1.0	1.0	1.2	1.3	1.3	1.5	1.7
		51-60	0.6	0.7	0.8	0.8	0.9	1.1	1.1	1.2	1.4	1.4	1.6	1.9
		61-70	0.7	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.5	1.5	1.7	2.0
		71-80	0.7	0.8	0.9	0.9	1.1	1.2	1.2	1.4	1.6	1.6	1.9	2.1
		81-90	0.7	0.8	1.0	1.0	1.1	1.3	1.3	1.5	1.7	1.7	2.0	2.3
No MT	Age	40-50	0.8	1.0	1.1	1.1	1.3	1.4	1.5	1.7	1.9	2.0	2.2	2.5
		51-60	1.0	1.1	1.3	1.3	1.5	1.7	1.7	2.0	2.2	2.3	2.6	3.0
		61-70	1.1	1.3	1.5	1.5	1.7	2.0	2.0	2.3	2.6	2.7	3.0	3.4
		71-80	1.3	1.5	1.7	1.8	2.0	2.3	2.3	2.7	3.0	3.1	3.5	4.0
		81-90	1.5	1.7	2.0	2.0	2.3	2.6	2.7	3.1	3.5	3.6	4.1	4.7

Fig. 4 Representative examples of the application of the model in individual patients (**A**). Summary table for different levels of exposition to the identified modifiers (**B**). Values are odds ratios of the association between predicted infarct core and poor clinical outcome (mRS > 2) across different exposition levels of the modifiers. CBF: cerebral blood flow; DT: delay time; mRS: modified Rankin Scale score; MT: mechanical thrombectomy; NIHSS: National Institutes of Health Stroke Scale; pIC: predicted infarct core

generalizable to other CTP postprocessing platforms or in the population of patients reperfused beyond 8 h. Otherwise, the main strength of the study was the use of a comprehensive statistical methodology to assess the strength of the interactions between pIC and relevant pretreatment- and treatment-related variables. Although the obtained prediction model was supported by internal cross-validation and performed similarly well at derivation and validation cohorts, it deserves external validation in larger observational studies.

Overall, these data highlight the limited accuracy of CTP-derived pIC for predicting clinical outcome in certain subgroups of acute ischemic stroke patients imaged within 8 h from stroke onset and defined by specific baseline or therapeutic variables. In parallel, the addition

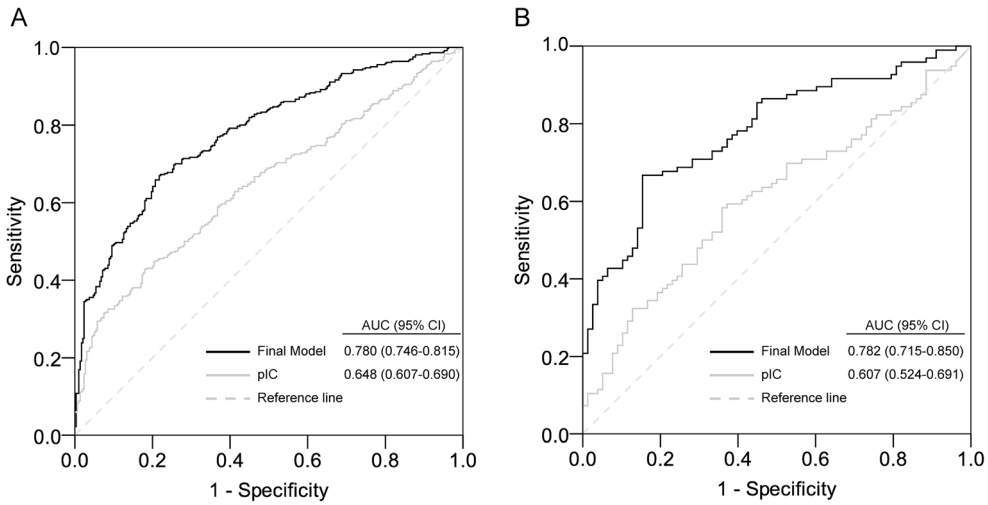


Fig. 5 Discrimination of the derived model assessed through ROC analysis in the derivation (**A**) and validation (**B**) cohorts. pIC: predicted infarct core

of certain simple baseline clinical variables might improve the accuracy of outcome predictions derived from pIC estimations. Thus, our findings point towards the importance of considering these variables when evaluating the prognostic value of pIC. Whether these findings may also apply to patients imaged in the extended temporal window deserves further study.

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Declarations

Guarantor The scientific guarantor of this publication is Sergio Amaro, MD, PhD.

Conflict of Interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and Biometry Two of the authors have significant statistical expertise.

Informed Consent Written informed consent was waived by the Institutional Review Board.

Ethical Approval Institutional Review Board approval was obtained.

Methodology

- Retrospective
- Cross-sectional study
- Performed at one institution

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