Correlation between ASPECTS and core volume on CT Perfusion: Impact of time since stroke onset and presence of large vessel occlusion

Supplementary Material

Supplementary Tables: 5 (Table 1S, 2S, 3S, 4S, 5S)

Supplementary Figures: 5 (Figure 1S, 2S, 3S, 4S, 5S)

Table 1S STROBE Statement checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	In the ASTRAL registry, we reviewed all middle cerebral artery AIS with standardized reconstructions of CTP maps.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1	The association between ASPECTS and CTP-core in 1,046 AIS patients was moderate, but significantly stronger in patients with longer time since stroke onset and presence of LVO.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	Both Alberta Stroke Program Early CT Score (ASPECTS) and automated core volume on CT perfusion (CTP) have been used to estimate infarct volume in the acute phase of stroke.
Objectives	3	State specific objectives, including any prespecified hypotheses	4	The main purpose of our study was to investigate the correlation between ASPECTS and automated core volume on CTP in a

				large cohort of AIS patients with involvement of middle cerebral artery (MCA) territory.
Methods				
Study design	4	Present key elements of study design early in the paper	4	We performed a retrospective analysis of all consecutive patients entered in the Acute STroke Registry and Analysis of Lausanne (ASTRAL).
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	The study period was from January 2003 to December 2018.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4	The inclusion criteria are reported in the Methods section. Details of pre-specified variables collected in the ASTRAL registry and those analyzed in the current study are provided.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5, 7	Clinical outcome was measured at 3 months using the mRS. Statistical correlation between ASPECTS and core volume on CTP was quantified using Spearman's Rho coefficient
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-7	Data source is the ASTRAL registry. Assessment of neuroimaging variables is explained in the "Neuroimaging protocol" section.
Bias	9	Describe any efforts to address potential sources of bias	13	Risk of bias related to the retrospective, single-center nature of the study is acknowledged in the limitations section.
Study size	10	Explain how the study size was arrived at	9, and Figure 1S	Out of 5,049 AIS patients entered in the ASTRAL registry during the study period, 1,046 were included in the current analysis.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7	Categorical and binary variables were summarized with frequencies and percentages, and continuous variables with

				median and interquartile range (IQR).
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8	See 'Statistical Analysis' section
		(*b*) Describe any methods used to examine subgroups and interactions	7-8	See 'Statistical Analysis' section
		(*c*) Explain how missing data were addressed	8	We performed a complete case analysis and no imputation of missing data was done.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA	
		(*e*) Describe any sensitivity analyses	11	As sensitivity analysis, we compared the predictive capabilities of the models for good clinical outcome at 3 months where ASPECTS is replaced with CTP-core
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9,	Out of 5,049 AIS patients entered in the ASTRAL registry during the study

				period, 1,046 were included in the current analysis.
		(b) Give reasons for non-participation at each stage	Figure 1S	-
		(c) Consider use of a flow diagram	Figure 1S	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9 and Table 1	Median age of the included patients was 71.4 years (IQR= 59.8-79.4) and median NIHSS was 12 (6-18), as described in Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA	
Outcome data	15	*Cohort study*—Report numbers of outcome events or summary measures over time	NA	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10	With the linear multiple regression model, we confirmed an independent association between ASPECTS and CTP-core (□=-0.10 per 10 mL; 95%CI= (-0.14;-0.07), p<0.01). The list of confounders is provided in Tables 2S and 3S

		(*b*) Report category boundaries when continuous variables were categorized	9 and Table 1	Median age of the included patients was 71.4 years (IQR= 59.8-79.4) and median NIHSS was 12 (6-18), as described in Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11	As sensitivity analysis, we compared the predictive capabilities of the models for good clinical outcome at 3 months where ASPECTS is replaced with CTP-core (Table 5S).
Discussion				
Key results	18	Summarise key results with reference to study objectives	11	In a large cohort of consecutive AIS patients involving the MCA territory, we showed a moderate correlation between ASPECTS and core volume on CTP in the acute phase of stroke. This correlation was significantly better in the presence of an LVO (ICA, M1 or proximal M2 occlusion) and was time-dependent, being stronger in the subgroup of patients

				potentially eligible for late endovascular treatment.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13	Several limitations of our study need to be acknowledged.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12	Our results confirm that in a mixed population of AIS patients, some treated with IVT and/or EVT, baseline ASPECTS is a major determinant of good clinical outcome at three months.
Generalisability	21	Discuss the generalisability (external validity) of the study results	13	The clinical implications of our findings include that ASPECTS appears a quite reliable surrogate marker for ischemic core in patients with LVO in the later time window. Such a finding supports the possible role of ASPECTS as a selection tool for late mechanical thrombectomy.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page	The study was funded by the Swiss National Science Foundation (SNSF) (grant 320030_182654).

Table 2S. Variables included in the multivariate regression model to identify associations with ASPECTS (used as dependent variable), and the p-values obtained in the univariate analysis.

Variable	*p-value*
Age	**<0.01**
Unknown stroke onset	**<0.01**
LPGH to hospital arrival, h	**<0.01**
Pre-stroke antiplatelet therapy	0.55
Pre-stroke anticoagulation therapy	0.20
Pre-stroke antihypertensive therapy	0.26
Pre-stroke statin therapy	0.28
Hypertension	0.21
Diabetes	0.58
Hyperlipidaemia	0.89
Current smoking	**0.01**
Atrial fibrillation	0.64
Systolic blood pressure on admission, *per* 10 mmHg	**0.04**
Blood glucose on admission, (g/L)	**<0.01**
Hyperdense MCA sign	**<0.01**
Chronic stroke on NCCT	**<0.01**
Severe leukoaraiosis	**<0.01**
LVO	**<0.01**
Good Collaterals	**0.03**
Clot Burden Score	**<0.01**
Infarct volume on CTP, mL	**<0.01**
Penumbra volume on CTP, mL	**<0.01**

Table 3S. Variables included in multivariate regression model for 3-month good clinical outcome prediction.

Variable
Age
Pre-stroke modified Rankin Scale
NIHSS on admission
Decreased level of consciousness on admission
Unknown stroke onset
LPGH to hospital arrival, h
Blood glucose on admission, (g/L)
ASPECTS
Severe leukoaraiosis
LVO
Good Collaterals
Clot Burden Score
Tandem occlusion
Etiology: cardioembolism
IVT
EVT

Table 4S. Demographics, clinico-radiological characteristics, stroke etiology and clinical outcome of the 1,046 patients included in the study. Continuous variables are summarized as medians and interquartile range (IQR), categorical variables as frequencies and percentages.

Variable	Patients (n=1,046)
Age, y	71.4 (59.8-79.4)
Sex, F	501 (47.9%)
Pre-stroke mRS	0 (0-1)
Vascular risk factors	
Hypertension	606 (57.9%)
Hyperlipidemia	375 (35.9%)
Atrial fibrillation	210 (20.1%)
Current smoking	256 (24.7%)
Diabetes	130 (12.4%)
Stroke characteristics	
NIHSS on admission	12 (6-18)
Hemiparesis	940 (90.7%)
Visual field defects	566 (54.8%)
Aphasia	522 (50.3%)
Neglect	423 (41.1%)
Vigilance impairment	137 (13.3%)
Onset stroke type	
Unwitnessed onset	99 (9.5%)
Wake-up stroke	217 (20.7%)
Process measures	
LPGH to arrival, min	154 (79-416)
LPGH to CT time, min	206 (115-508)
Baseline measurements	
SBP on admission (mmHg)	153 (137-172)
DBP on admission (mmHg)	85 (75-99)
Blood glucose on admission (g/L)	6.5 (5.7-7.6)
Body temperature (°C)	36.3 (36.0-36.7)
Radiological variables	
ASPECTS	9 (7-10)
Hyperdense MCA sign	286 (34.2%)
Leukoaraiosis	291 (28.6%)
Chronic strokes	234 (23.0%)

Vascular imaging variables	
LVO	612 (58.5%)
ICA occlusion	195 (18.6%)
M1 occlusion*	441 (42.2%)
M2 occlusion*	518 (49.5%)
Good collaterals	382/612 (62.4%)
Clot burden score	7 (4-9)
Tandem occlusion	167 (16.0%)
CTP parameters	
Infarct volume, mL	13.6 (0.6-52.8)
Penumbra volume, mL	49.1 (6.3-106.5)
Mismatch ratio	2.6 (1.3-6.9)
Acute reperfusion therapies	
IVT	359 (34.3%)
LPGH-IVT, min	150 (110-195)
EVT (± preceding IVT)	94 (9.0%)
LPGH-groin puncture, min	353 (218-590)
TICI 2b-3 at the end of EVT	62 (66.0%)
Stroke Mechanism	
Atherosclerotic	157 (15.0%)
Cardioembolism	393 (37.7%)
Dissection	69 (6.6%)
Lacunar	15 (1.4%)
ESUS	153 (14.7%)
Multiple	65 (6.2%)
PFO-related	38 (3.6%)
Other causes/rare	56 (5.4%)
Undetermined/incomplete work-up	97 (9.3%)
Outcome measures	
NIHSS at 24 hours	9 (4-17)
Symptomatic HT at 24 hours	139 (13.3%)
3-month mRS 0-2	536 (51.9%)
Death within 3 months	185 (17.9%)

*Means with or without more proximal occlusion.

Table 5S. Independent predictors for good clinical outcome at 3 months (mRS≤2), in the overall population and in late arriving (>6 hours from LPGH) AIS patients with LVO, with the ASPECTS variable being replaced by the variable CTP-core. Results are adjusted for pre-stroke mRS and expressed as OR and relative 95% CI.

Variables associated with good outcome	**Study cohort** (n=1, 046)	**Late AIS with LVO** (n=151)
Age, years	0.96 (0.94-0.97)	ns
NIHSS on admission	0.88 (0.84-0.91)	0.88 (0.81-0.95)
Decreased LOC on admission	0.45 (0.24-0.83)	ns
LPGH to arrival time, hour	0.94 (0.90-0.98)	0.84 (0.73-0.96)
CTP-core	0.99 (0.99-1.00)	0.98 (0.97-1.00)
CBS	1.18 (1.08-1.28)	ns
Tandem occlusion	0.56 (0.33-0.96)	0.21 (0.06-0.72)
	AIC= 693.34	*AIC=140.64*

Legends for Tables 1-4S: AIC=Akaike's Information Criteria; ASPECTS=Alberta Stroke Program Early CT Score; CBS=Clot Burden Score; DBP=Diastolic Blood Pressure; ESUS= Embolic stroke of undetermined source; EVT=Endovascular treatment; HT=Hemorrhagic transformation according to ECASS-II criteria; IVT=Intravenous thrombolysis; LOC=level of consciousness; LPGH=Last proof of good health; mRS=modified Rankin scale; NCCT=non-contrast CT scan; NIHSS=National Institutes of Health stroke scale; ns= non-significant; PFO=Patent foramen ovale; TICI= Thrombolysis in cerebral infarction.

Figure 1S. Flow-chart for patient selection in the current analysis. Results from the univariate comparison between included (n=1,046) and excluded patients (n=4,003) showed that the included patients were younger (median age =71.4 vs 74.4; p<0.001), more frequently female (47.9% vs 43.8%; p=0.017), had a higher NIHSS on admission (median value=12 vs 5; p<0.001), and a lower ASPECTS (median value= 9 vs 10; p<0.001).

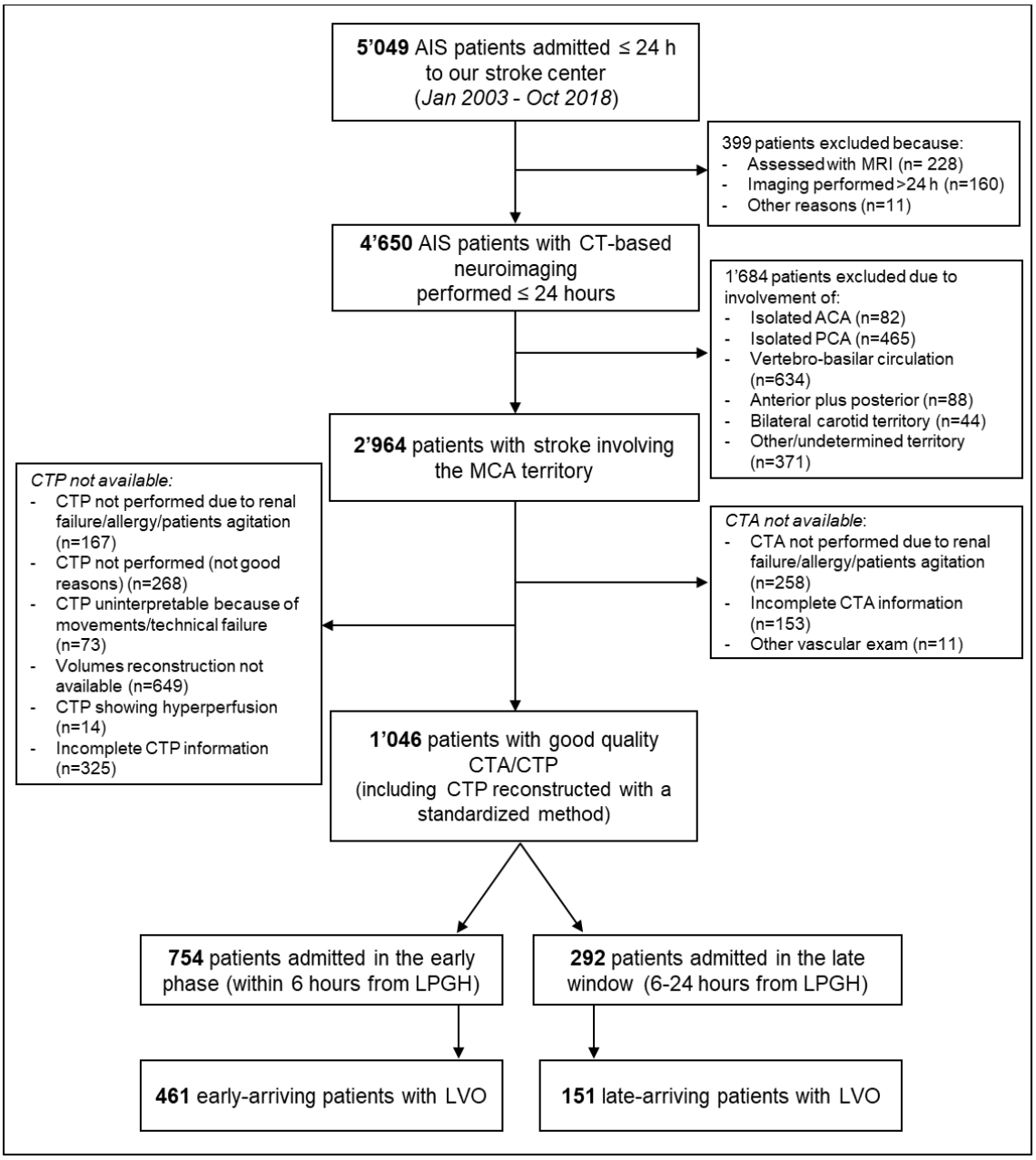
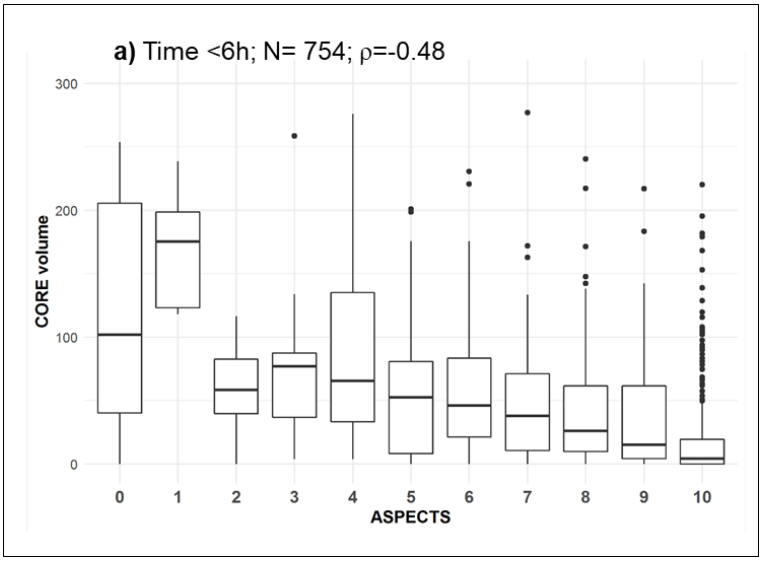


Figure 2S. ASPECTS-CTP core correlations in the subgroup of AIS patients admitted in: a) the early time window (< 6 hours since LPGH), b) the late time window (6-24 hours since LPGH). The correlation was moderate in the early phase (ρ=-0.48) and moderately strong (ρ=-0.56) in the later phase, with a statistically significant difference (*p*=0.05) between the two groups.



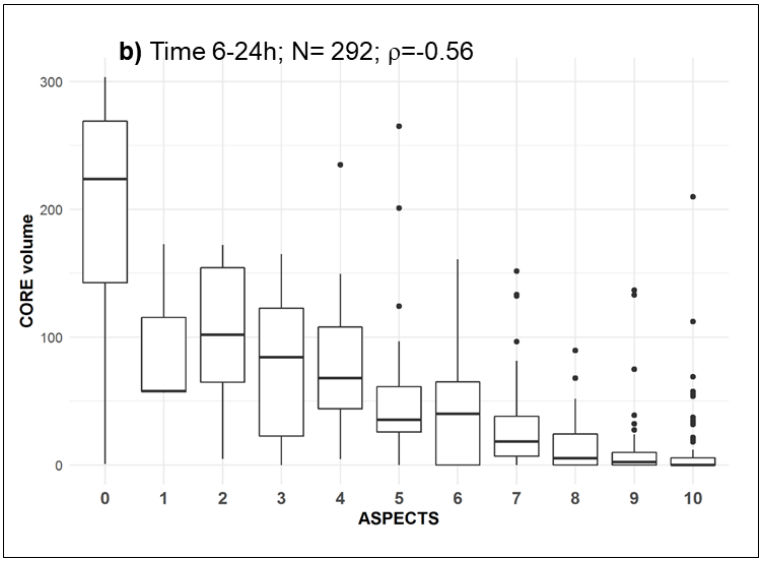
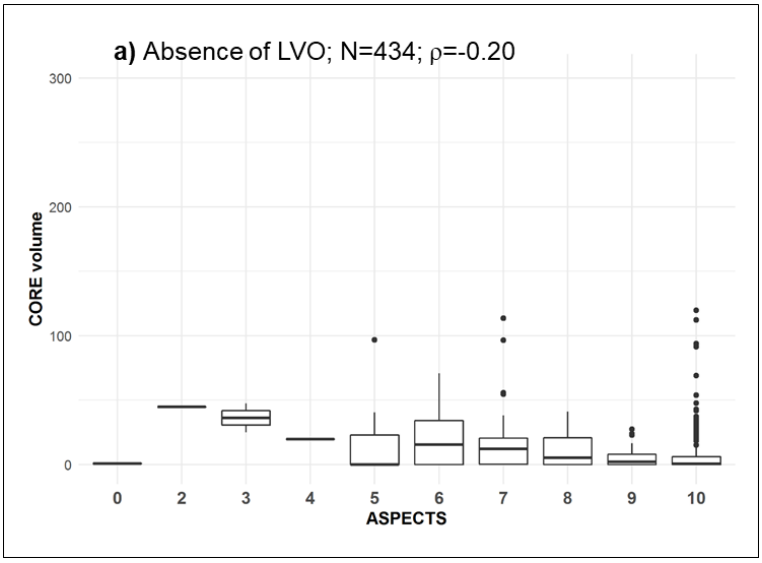


Figure 3S. ASPECTS-CTP core correlations in the subgroup of AIS patients: a) without large vessel occlusion (LVO), b) who had LVO. The correlation was weak in patients without LVO (ρ=-0.20) and moderate in the presence of LVO (ρ=-0.40), with a statistically significant difference (p<0.01) between the two groups.



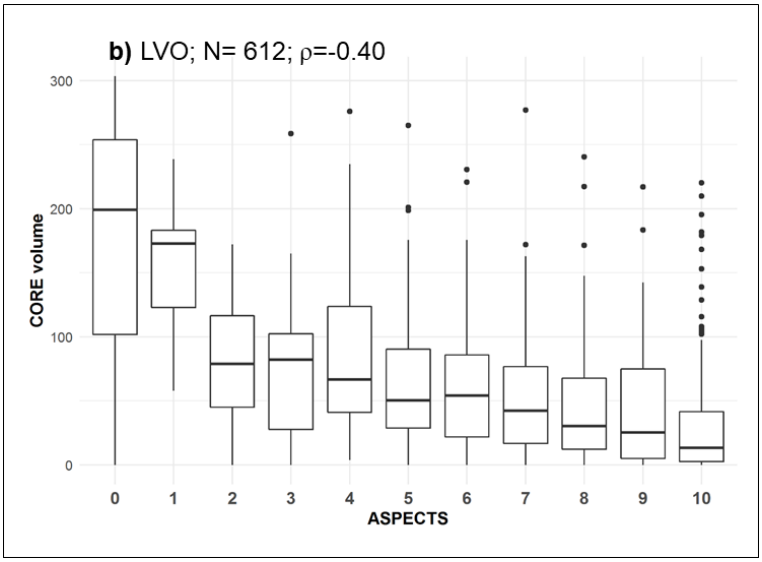
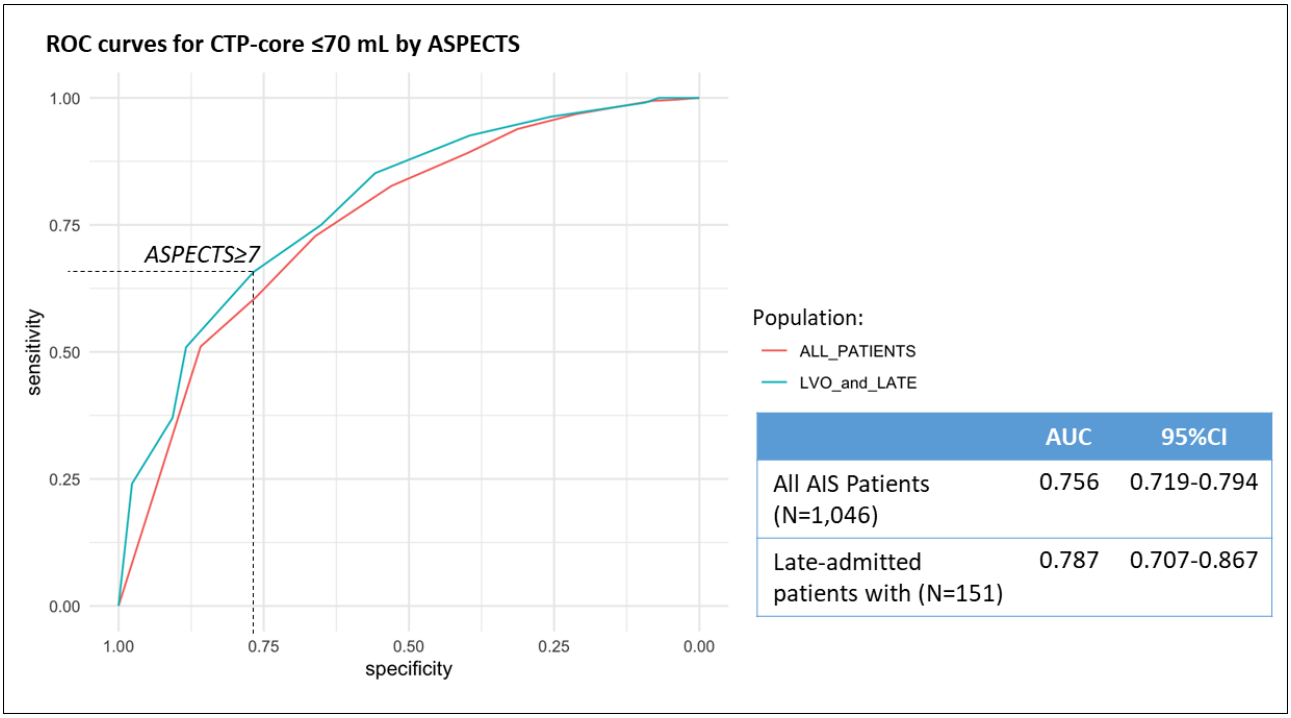
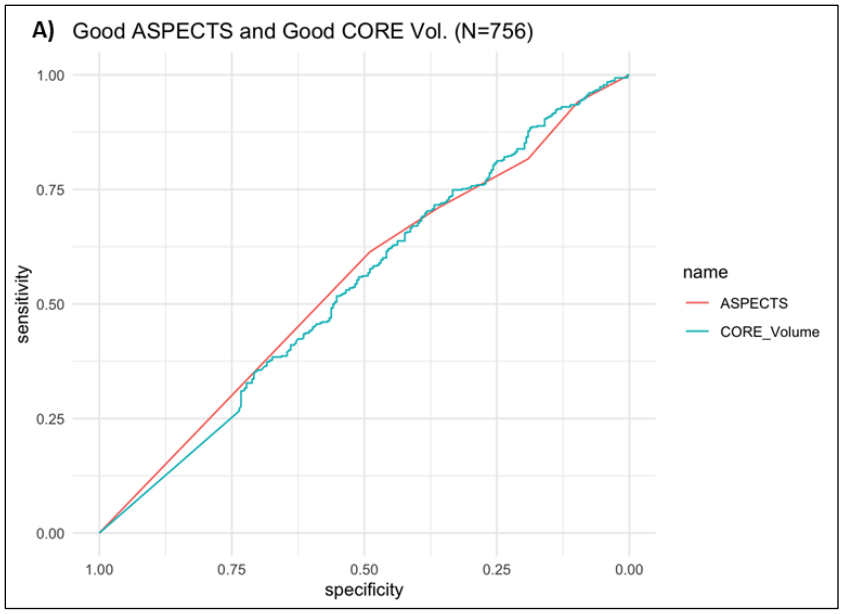


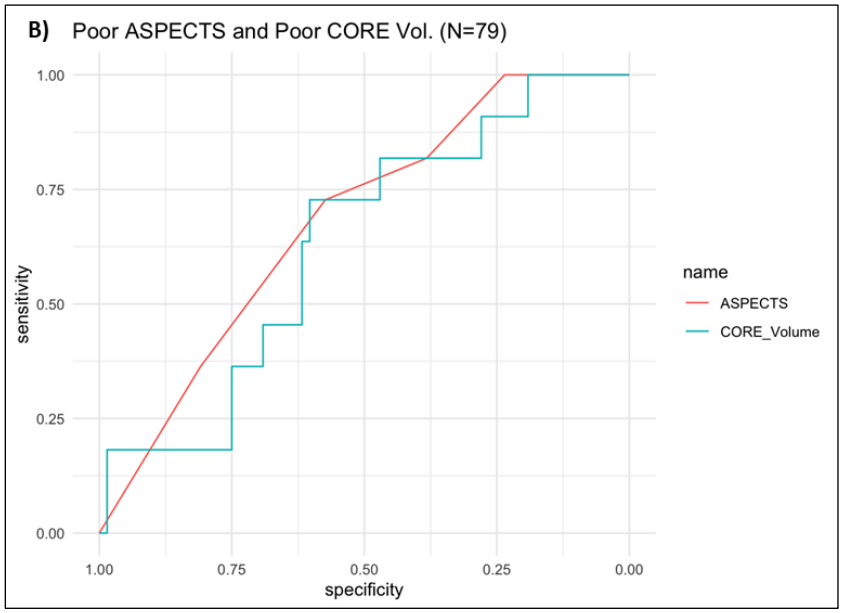
Figure 4S. Receiver Operating Characteristic (ROC) curve analyses for the prediction of CTP-core volume<70 mL by ASPECTS, in all included patients (red line) and in the late-arriving patients with LVO (blue line). AUC indicates the area under the curve for each model (with its 95% confidence interval, CI). In LVO patients admitted after 6 hours, a cut off ASPECTS≥7 identified patients with a CTP-core <70 mL with a sensitivity of 65.7% and a specificity of 76.7%.

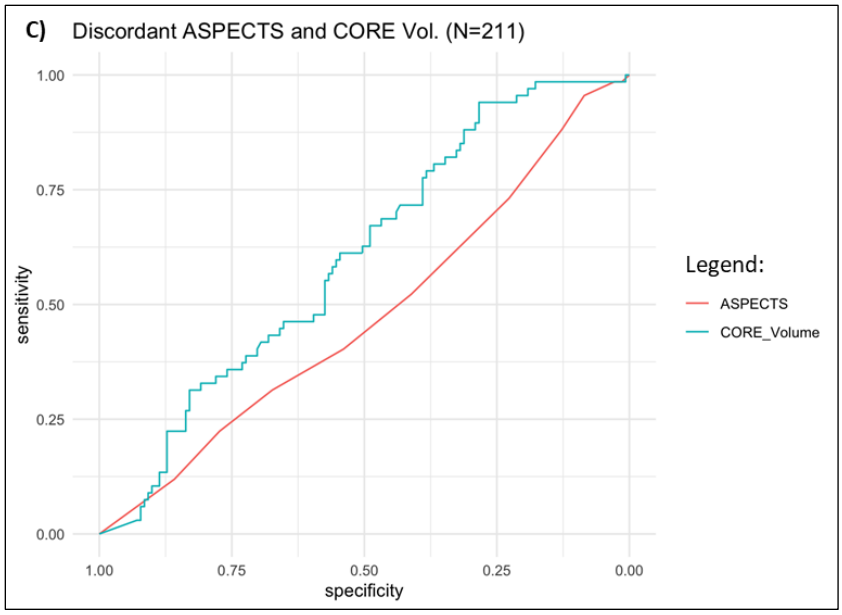


	AUC	95%CI
All AIS Patients (N=1,046)	0.756	0.719-0.794
Late-admitted patients with (N=151)	0.787	0.707-0.867

Figure 5S. Receiver Operating Characteristic (ROC) curve analyses for prediction of good outcome at 3 months, by ASPECTS (red line) and CTP (blue line). The performance of the two imaging modalities was tested in patients showing concordant and favorable NCCT/CTP (n=756), concordant and unfavorable NCCT/CTP (n=79) and discordant NCCT/CTP (n=211), and reported as the area under the curve (AUC) with 95% confidence interval (CI).







	ASPECTS		CTP		p-value
	AUC	95%CI	AUC	95%CI	
A) Favorable ASPECTS/CTP (N=756)	0.548	0.510-0.586	0.538	0.496-0.581	0.683
B) Unfavourable ASPECTS/CTP (N=79)	0.680	0.528-0.831	0.567	0.446-0.687	0.641
C) Discordant ASPECTS/CTP (N=211)	0.475	0.391-0.558	0.603	0.524-0.681	0.099