Acute imaging does not improve ASTRAL score's accuracy despite having a prognostic value

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Background **The ASTRAL score was recently shown to reliably predict three-month functional outcome in patients with acute ischemic stroke.**

Aim **The study aims to investigate whether information from multimodal imaging increases ASTRAL score's accuracy.**

Methods **All patients registered in the ASTRAL registry until March 2011 were included. In multivariate logistic-regression analyses, we added covariates derived from parenchymal, vascular, and perfusion imaging to the 6-parameter model of the ASTRAL score. If a specific imaging covariate remained an independent predictor of three-month modified Rankin score > 2, the area-under-the-curve (AUC) of this new model was calculated and compared with ASTRAL score's AUC. We also performed similar logistic regression analyses in arbitrarily chosen patient subgroups.**

Results **When added to the ASTRAL score, the following covariates on admission computed tomography/magnetic resonance imaging-based multimodal imaging were not significant predictors of outcome: any stroke-related acute lesion, any nonstroke-related lesions, chronic/subacute stroke, leukoaraiosis, significant arterial pathology in ischemic territory on computed tomography angiography/magnetic resonance angiography/Doppler, significant intracranial arterial pathology in ischemic territory, and focal hypoperfusion on perfusion-computed tomography. The Alberta Stroke Program Early CT score on plain imaging and any significant extracranial arterial pathology on computed tomography angiography/magnetic resonance angiography/Doppler were independent predictors of outcome (odds ratio: 0·93, 95% CI: 0·87–0·99 and odds ratio: 1·49, 95% CI: 1·08–2·05, respectively) but did not increase ASTRAL score's AUC (0·849 vs. 0·850, and 0·8563 vs. 0·8564, respectively). In exploratory analyses in subgroups of different prognosis, age or stroke severity, no covariate was found to increase ASTRAL score's AUC, either.**

Conclusions **The addition of information derived from multimodal imaging does not increase ASTRAL score's accuracy to predict functional outcome despite having an independent prognostic value. More selected radiological parameters applied in specific subgroups of stroke patients may add prognostic value of multimodal imaging.**

Key words: ASTRAL score, CT angiography, CT, functional outcome, multimodal imaging, perfusion CT

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Introduction

Multimodal imaging (MMI) of acute ischemic stroke (AIS) including noninvasive arterial and perfusion imaging shows promise to improve stroke diagnosis, prognosis, and treatment selection of AIS patients (1–3). With regard to prognosis, the value of the presence, site and extent of arterial occlusion (4–6), of the infarct core (7–9), and of penumbra (8–10) have been shown to be useful for prediction of stroke outcome in selected patient populations.

The ASTRAL score was introduced recently for the prognosis of functional outcome in patients with AIS (11). It is based on six nonradiological items readily available upon arrival of the stroke patient in the emergency department (11). It has been externally validated in three independent and ethnically diverse cohorts, showing remarkable consistency on predicting three-month functional outcome (11,12); recently, it was also validated externally for the prognosis of five-year dependence and mortality (13). Other scores have also been introduced to predict ischemic stroke outcome like the PLAN (14), the iSCORE (15), the SSV (16), the MOSAIC (17), and others (18–22). Most, but not all (17), of these current stroke outcome scores omit imaging technology to remain simple and rapid (11). This is especially the case for the ASTRAL score which can be easily calculated at bedside without any mathematical calculation by using the color chart which may be found in the original publication of the score (11).

The aim of the present study was to investigate whether the addition of information from multimodal imaging increases

ASTRAL score's prognostic accuracy to predict three-month functional outcome in patients with acute ischemic stroke.

Patients and methods

Data selection

All patients who were admitted with AIS between January 2003 and March 2011 and had a prestroke modified Rankin Scale score (mRS) ≤ 2 were selected from the Acute STroke Registry and Analysis of Lausanne (ASTRAL). ASTRAL is the prospective registry of all AIS patients admitted to the stroke unit and/or intensive care unit of the Lausanne University Hospital (CHUV) within 24 h after last proof of well-being (23). Patients with missing three-month mRS and one or more missing component(s) needed to calculate the ASTRAL score were excluded from the analysis. The scientific use of the data registered in ASTRAL was approved by the ethics commission (subcommision III) for research on humans of the Canton of Vaud.

As previously described (23), the ASTRAL score was calculated based on age (1 point for every five-years), stroke severity [1 point for every point of National Institutes of Health Stroke Scale score (NIHSS) at admission], time delay between symptom onset and admission (2 points if >three-hours), presence of any new visual field defect (2 points), glucose at admission (1 point if >7·3 mmol/l or <3·7 mmol/l), and level of consciousness (3 points if impaired item 1a on the NIHSS was >0) (11).

The methods applied to collect and register data, the definitions used in the ASTRAL registry, and the imaging protocols for acute ischemic stroke in our center were previously described (23). With regard to acute MMI, for all patients, parenchymal imaging [mostly computed tomography (CT)] was analyzed if performed within 24 h after stroke onset. The presence of early ischemic changes, the Alberta Stroke Program Early CT score (ASPECTS) (24), the presence of chronic/subacute stroke and of leukoaraiosis [Blenow grade 1 or more (25)] were registered. Acute vascular imaging [mostly CT angiography (CTA)] within the first 24 h after stroke onset was analyzed and classified in significant arterial pathology in extra- and intracranial arteries. Arterial pathology was considered significant if occlusion, >50% stenosis, or any signs of dissection were present; these parameters were combined into a single category to simplify their use in clinical practice and increase the statistical power of the study. Also, perfusion CT (PCT) was performed in most patients with symptoms not clinically limited to the posterior fossa, according to methods described elsewhere (26,27). The presence of focal hypoperfusion on visually inspected slices of cerebral blood flow measurement (corresponding to the combination of infarct core and penumbra) was noted as present or absent. Threshold maps for core and penumbra were not calculated for this project. All patients were treated according to current European Stroke Organization guidelines (28). Unfavorable functional outcome was defined as three-month mRS > 2.

Statistical analysis

To investigate the prognostic accuracy of the ASTRAL score to predict three-month functional outcome, we assessed the discriminatory power of the score, i.e., the degree to which the prognostic score enables the discrimination between patients with favorable and unfavorable outcome by calculating the area-under-the-curve (AUC).

To assess if a specific imaging covariate increases the prognostic accuracy of the ASTRAL score, we first performed a multivariate logistic regression analysis with the specific imaging covariate added in the 6-parameter model of the ASTRAL score (i.e., age, NIHSS score, onset-to-admission time interval, visual field defect, glucose and level of consciousness). In case that a specific imaging covariate remained an independent predictor of three-month functional outcome, the AUC of this new model (i.e., the ASTRAL score plus the specific imaging covariate) was calculated and compared with the AUC of the 6-parameter model of the ASTRAL score. A specific covariate would be considered that it increases the prognostic accuracy of the ASTRAL score if the AUC of the new model was significantly higher than the AUC of the ASTRAL score. The statistical comparison of the AUCs was performed with the DeLong method (29). The imaging covariates included in the multivariate logistic regression analyses were the following: any stroke-related acute lesion on CT or magnetic resonance imaging (MRI), the ASPECTS, any vascular lesions on acute CT or MRI not related to the current stroke (i.e., chronic or subacute stroke or leukoaraiosis), chronic or subacute stroke on acute CT or MRI, leukoaraiosis, focal hypoperfusion on PCT, significant arterial pathology in the ischemic territory in acute CTA or magnetic resonance angiography (MRA) or Doppler, significant intracranial arterial pathology in the ischemic territory in acute CTA or MRA or Doppler, and significant extracranial arterial pathology in the ischemic territory in acute CTA or MRA or Doppler. The ASPECTS was analyzed both as continuous and categorical covariate using different arbitrary cutoffs to reduce the possibility of a type II error (false negative result).

We also investigated whether imaging increased the prognostic accuracy of the ASTRAL score in specific patient subgroups. Hence we performed similar logistic regression analyses in arbitrarily chosen subgroups of patients with regard to their age (<71 and ≥71 years), NIHSS at admission (≤3, 4–19, and >19), and ASTRAL score (0–22, 23–38, and >38).

For continuous variables, data are summarized as medians and interquartile range (IQR). Categorical data are presented as absolute numbers and percentage. Imputation techniques were not implemented for missing data. In the multivariate analyses, the level of statistical significance was set at 95% ($P = 0{\cdot}05$). Associations are presented as odds ratios (OR) with 95% confidence intervals (95% CI). The statistical analysis was performed with STATA Statistical Software (Release 10, College Station, TX, USA: StataCorp LP 2007).

Results

From the entire cohort of 2401 patients in the ASTRAL registry during the observation period, 203 patients were excluded because of a prestroke mRS > 2 and 95 patients because the initial imaging was performed >24 h after stroke onset. One hundred

sixty-four patients were excluded because one or more of the six components of the ASTRAL score were unavailable and 47 because three-month mRS was not available. Finally, 1892 patients [median age: 71·2 years, IQR: 59·4–79·8; 1094 (57·8%) males] were available for analysis. Overall, 1855 (98·0%) had an acute CT, 1626 (85·9%) had acute CTA, and 1268 (67·1%) had PCT. A few patients had MRI as the initial imaging, and others had a CT followed by MRI in the acute phase. Three hundred eighty-one (20·1%) patients were treated with intravenous thrombolysis and 31 (1·6%) with endovascular revascularization. The baseline characteristics of the patients are summarized in Table 1.

The AUC of the ASTRAL score in the overall population was 0·850, which is similar with the AUC of the score during the analysis which introduced the ASTRAL score (11). When added to the ASTRAL score in logistic regression analyses, the following covariates were not significant predictors of three-month functional outcome: any stroke-related acute lesion on CT or MRI, any vascular lesions on acute CT or MRI not related to the current stroke, significant arterial pathology in the ischemic territory, significant intracranial arterial pathology in the ischemic territory, and focal hypoperfusion on PCT. There was no interaction between any of the aforementioned covariates and time delay since stroke onset.

In a logistic regression analysis including the ASTRAL score as a covariate, significant extracranial arterial pathology in the ischemic territory on acute CTA or MRA or Doppler was an independent predictor of three-month functional outcome (OR: 1·49, 95% CI: 1·08–2·05, $P = 0·014$). However, the AUC of the combined model (which included both covariates) was similar to the AUC of the ASTRAL score (0·849 vs. 0·850), which means that significant extracranial arterial pathology does not increase significantly the prognostic accuracy of the ASTRAL score (despite being an independent predictor).

There were 1262 patients with an ASPECTS of 10, and 215 patients with an ASPECTS of <7. In a logistic regression analysis including the ASTRAL score as a covariate, the ASPECTS – when analyzed as a continuous covariate – was a significant predictor of three-month functional outcome (OR: 0·93, 95% CI: 0·87–0·99, $P = 0·023$). However, the AUC of the combined model (which included both covariates) was similar to the AUC of the ASTRAL score (0·8563 vs. 0·8564, $P = 0·893$), which means that the ASPECTS (as a continuous covariate) does not increase significantly the prognostic accuracy of the ASTRAL score (despite being an independent predictor).

The ASPECTS was also analyzed as a categorical covariate using different cutoff values (3, 5, 7, and 9) in a logistic regression analysis including the ASTRAL score as a covariate. For the cutoffs 3 and 5, it was a significant predictor of three-month functional outcome (OR: 2·32, 95% CI: 1·15–4·65, $P = 0·018$ and OR: 1·95, 95% CI: 1·21–3·12, $P = 0·006$, respectively). However, the AUC of the combined model (which included both covariates) was similar to the AUC of the ASTRAL score (0·857 vs. 0·856, $P = 0·318$, for the cutoff value of 3; 0·857 vs. 0·856, $P = 0·5695$, for the cutoff value of 5). For the cutoffs of 7 and 9, the ASPECTS was not a significant predictor of three-month outcome.

Table 1 Baseline characteristics of analyzed patients

Total number of eligible patients	1892
Median age (years)	71·2 (59·4–79·8)
Male gender	1094 (57·8%)
NIHSS at admission	6 (3–14)
Onset-to-admission time (minutes)	204 (93–624)
Prestroke mRS	
0	1215 (64·3%)
1	472 (24·9%)
2	205 (10·8%)
Serum glucose at admission (mmol/l)	6·5 (5·7–7·7)
Blood pressure at admission (mmHg)	
Systolic	157 (140–176)
Diastolic	89 (78–100)
Visual field deficit	635 (33·6%)
Decreased level of consciousness	200 (10·6%)
Stroke risk factors	
Smoking*	460 (24·5%)
Hypertension†	1266 (67·1%)
Atrial fibrillation (AF)‡	478 (25·3%)
Diabetes mellitus	312 (16·6%)
Dyslipidemia	1299 (68·8%)
Acute CT < 24 h of onset	1855 (98·0%)
Acute arterial imaging performed	
Any vascular imaging	1695 (89·7%)
None	195 (10·3%)
CTA	1626 (85·9%)
MRA	66 (3·5%)
Doppler	333 (17·6%)
Perfusion CT performed	1268 (67·1%)
ASPECTS score on admission	
10	1262 (67·8%)
7–9	383 (20·6%)
<7	215 (11·6%)
Stroke mechanism (TOAST classification)	
Large-artery atherosclerotic stroke	265 (14·1%)
Cardioembolic stroke	624 (33·1%)
Lacunar stroke	263 (14·0%)
Stroke of other determined etiology	72 (3·8%)
Stroke of undetermined origin or multiple etiologies	659 (35·0%)
Treatment	
Intravenous thrombolysis	381 (20·1%)
Endovascular revascularization	31 (1·6%)

*Defined as current smoking or smoking stopped <2 years before the stroke.
†Known or newly diagnosed hypertension.
‡Known history or newly diagnosed AF; patients with one single episode of AF are not included.
Numbers represent medians and interquartile range for continuous covariates, and absolute count and proportion for categorical covariates.
ASPECTS, Alberta Stroke Program Early CT score; CT, computed tomography; CTA, CT angiography; MRA, magnetic resonance angiography; mRS, modified Rankin Scale score; NIHSS, National Institute of Health Stroke Scale score.

In exploratory logistic regression analyses, to identify arbitrarily chosen subgroups of patients in which the addition of imaging could increase the prognostic accuracy of the ASTRAL score, no covariate was found to significantly increase the prognostic accuracy of the ASTRAL score in any subgroup (Table 2).

Table 2 Logistic regression analyses in arbitrarily chosen patient subgroups

	ASTRAL score 0–22	ASTRAL score 23–38	ASTRAL score > 38	Age < 71	Age ≥ 71	NIHSS ≤ 3	NIHSS 4–19	NIHSS > 19
Any stroke-related acute lesion on CT or MRI	0·93 (0·52–1·67)	1·21 (0·85–1·71)	2·96 (1·05–8·37)	0·99 (0·64–1·55)	1·44 (1·00–2·08)	1·00 (0·44–2·25)	1·17 (0·84–1·61)	1·87 (0·79–4·45)
Chronic or subacute stroke	1·13 (0·66–1·94)	1·35 (0·91–2·00)	0·44 (0·13–1·47)	1·10 (0·66–1·83)	1·25 (0·85–1·85)	1·49 (0·73–3·07)	1·15 (0·81–1·64)	0·84 (0·28–2·50)
Leukoaraiosis	1·62 (0·80–3·26)	1·62 (0·97–2·71)	2·67 (0·29–24·87)	1·54 (0·60–3·94)	1·60 (1·01–2·52)	1·75 (0·72–4·25)	1·50 (0·93–2·42)	3·94 (0·47–33·32)
Any vascular lesions on acute CT or MRI not related to the current stroke	0·80 (0·49–1·30)	0·70 (0·49–1·02)	1·42 (0·45–4·48)	0·86 (0·53–1·37)	0·73 (0·51–1·04)	0·64 (0·33–1·24)	0·91 (0·58–1·13)	0·79 (0·29–2·16)
Focal hypoperfusion on PCT-CBF	0·59 (0·32–1·07)	1·14 (0·64–2·03)	6·95 (0·80–60·44)	1·09 (0·60–2·00)	0·80 (0·48–1·35)	0·78 (0·32–1·90)	0·92 (0·58–1·47)	3·72 (0·52–26·79)
Significant arterial pathology in the ischemic territory on CTA/MRA/Doppler	0·98 (0·57–1·69)	1·23 (0·82–1·84)	2·21 (0·58–8·46)	1·54 (0·95–2·52)	1·07 (0·71–1·61)	1·05 (0·48–2·33)	1·17 (0·82–1·68)	1·58 (0·44–5·71)
Significant intracranial arterial pathology in the ischemic territory	0·92 (0·50–1·70)	1·35 (0·92–1·98)	1·66 (0·46–6·05)	1·67 (1·05–2·67)*	1·01 (0·66–1·55)	1·02 (0·40–2·57)	1·21 (0·85–1·70)	1·52 (0·48–4·86)
Significant extracranial arterial pathology	1·16 (0·59–2·29)	1·39 (0·93–2·06)	3·80 (1·02–14·13)†	1·61 (1·02–2·56‡)	1·42 (0·90–2·22)	1·76 (0·71–4·36)	1·38 (0·95–2·00)	1·84 (0·75–4·56)

*, † and ‡: Although significant associations with outcome were identified in these specific subgroups, these parameters did not actually add to the prognostic accuracy of the ASTRAL score in these subgroups because they just substituted some of the ASTRAL score components in the final multivariate model (i.e., glucose in * and ‡; NIHSS, onset-to-admission time and glucose in †). To be considered that they add to the prognostic accuracy of the ASTRAL score, not only should these parameters be identified as independent predictors of outcome, but also all components of the ASTRAL score should remain as independent predictors (which was not the case for *, †, and ‡).

The covariates included in the analyses are several imaging parameters and the components of the ASTRAL score.

ASTRAL, Acute STroke Registry and Analysis of Lausanne; CBF, cerebral blood flow; CT, computed tomography; CTA, CT angiography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PCT, perfusion CT.

Discussion

The present study analyzed a large series of previously independent consecutive AIS patients and found that the addition of readily available information derived from mostly CT-based MMI does not increase the accuracy of the ASTRAL score to predict three-month functional outcome despite the fact that certain imaging parameters (i.e., the ASPECTS and the presence of extracranial arterial pathology in the ischemic territory) had an independent prognostic value.

The fact that the prognostic accuracy of the ASTRAL score did not increase by the addition of information from (parenchymal, vascular, and perfusion) MMI neither in the overall study population nor in selected arbitrarily chosen patient subgroups, should only be regarded as a further confirmation of the excellent performance of the ASTRAL score, and, of course, by no means does it suggest that acute imaging does not need to be performed during acute stroke. The most plausible explanation for this finding could be that most of the information derived from acute MMI is already incorporated into (certain components of) the ASTRAL score: there is a causal chain in acute ischemic stroke which originates from the vascular lesion and predicts clinical severity and imaging findings. The ASTRAL score gives considerable weight to the initial NIHSS and level of consciousness which were previously shown to be closely associated with the presence of acute intracranial arterial occlusions (30) and with the extent of core and penumbra (10,31,32). Therefore, the clinical variables included in the ASTRAL score may eliminate MMI radiological covariates from being independent predictors, or make them of little additive value. It may also be that we did not analyze sufficient details of MMI, such as threshold-based volumes of nonviable and at-risk tissue, site and extent of occlusion, or collaterals. Also, it may be due to the fact that we did not target specific stroke types but have analyzed a consecutive real-world AIS population. Still, the analysis of defined subgroups within our population did not improve the prognostic score either.

We found that the ASPECTS based on plain imaging and the presence of significant extracranial arterial pathology on CTA/MRA/Doppler were independent predictors of functional outcome. These results confirm previous observations that the ASPECTS [based on noncontrast CT (24)] and diffusion weighted imaging (DWI) (33) are prognostic predictors independently of clinical and epidemiological variables. Regarding other parameters of MMI, we limited our analysis to readily available parameters to avoid the additional time required for detailed analysis and the sometimes difficult decisions of thresholds (34). Doing so, the presence of any extracranial stenosis ≥50% or occlusion was associated with worse three-month prognosis, but intracranial arterial pathology or focal tissue hypoperfusion was not. Other MMI parameters did not add independent information in this consecutive AIS population. MMI in AIS has been shown in some studies to add prognostic value in addition to clinical parameters (8,10,35). Collateral status, which we did not measure, was also an independent predictor in some studies (36,37) as were certain threshold tissue viability parameters (10). These MMI parameters which will require more time and expertise to assess could be added in further similar studies. Moreover, MMI was shown to predict response to revascularization treatment in selected stroke patients and situations, such as mismatch imaging in territorial infarct of the middle cerebral artery (MCA) territory with visible hypoperfusion (38–41) or arterial imaging in MCA strokes before thrombolysis (6); our study was not designed to address the question of treatment response.

Strengths of the present study are the inclusion and analysis of a large series of consecutive AIS over an eight-year period. Also, we analyzed information derived from MMI (including vascular and perfusion imaging) performed during the acute phase of stroke (within 24 h after stroke onset). Moreover, this analysis was performed on the same dataset which was used to develop the ASTRAL score (11). Also, we tried several statistical analyses to identify potential covariates which could increase the prognostic accuracy of the ASTRAL score, e.g., the ASPECTS was analyzed both as a continuous and a categorical covariate using different cutoffs. Finally, we also analyzed several patient subgroups to identify potential populations for which the addition of imaging could increase the predictive accuracy of the ASTRAL score.

Limitations of the study are that information about the volume of the initial infarct and the penumbra, the degree of vascular stenosis, thrombus length in occlusions, and a clot burden score were not available for the analysis. Also, information about collateral circulation in patients with intracranial occlusions, which was previously shown to predict stroke outcome (36,42), was not available for the analysis. Therefore, it cannot be excluded that more specific imaging may eventually increase the prognostic accuracy of the ASTRAL score. Moreover, not all patients had available all imaging examinations (i.e., parenchymal, vascular, and perfusion brain imaging), which, however, would be impossible to achieve given the large series of included patients and the pragmatic real-world nature of this study. Finally, the present analysis was performed in the same patient population which was used to develop the ASTRAL score, which may have introduced selection bias.

In conclusion, the ASTRAL score is a reliable tool to predict three-month functional outcome in patients with AIS; further studies are necessary to investigate whether collateral or penumbral imaging could increase its prognostic accuracy.

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