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Anterior ischemic stroke:

Comparison of two clinical outcome prediction scores through the investigation of cerebral collaterals using multiphase CT angiography

A. Nigron¹, N. Bourgois², S. Dao³, C. Lambert⁴, M. Perrier⁵, S. Akono⁶, R. Moreno⁷, E. Chabert⁸, B. Jean⁹, B. Claise¹⁰, L. Gerbaud¹¹, L. Boyer¹², A. Zerroug¹³

¹University Clermont Auvergne, Clermont-Ferrand University Hospital, Radiology Department, Clermont-Ferrand, France

^{2,5} Clermont-Ferrand University Hospital, Vascular Neurology Department, Clermont-Ferrand, France

^{3, 7, 8, 9, 10, 13} Clermont-Ferrand University Hospital, Interventional Neuroradiology Department, Clermont-Ferrand, France

⁴ Clermont-Ferrand University Hospital, Biostatistics Department, Clermont-Ferrand, France

⁶ Vichy Hospital, Neurology Department, Vichy, France

¹¹ Clermont-Ferrand University Hospital, Public Health and Epidemiology Department, Clermont-Ferrand, France

¹² Clermont-Ferrand University Hospital, Interventional Vascular Radiology Department, Clermont-Ferrand, France

SUMMARY

Purpose:

To compare the evaluation of collaterals on multiphase computed tomography (CT) angiography using the score proposed by the reference study by Menon BK *et al.* and the Alberta Stroke Program Early CT (ASPECT) score for the prediction of favorable clinical outcome in patients with anterior ischemic stroke (IS).

Materials and Methods:

Retrospective single center study including 199 patients with anterior ischemic stroke and evaluated using multiphase CT angiography. Collaterals were assessed using the reference score and ASPECT score. The early clinical outcome (National Institute of Health Stroke Score (NIHSS) over day 1) and later clinical outcome (90-day modified Rankin Scale (mRS)) were collected. The primary analysis related to the association between collateral scores and clinical outcome.

Results:

Collaterals are an independent predictive factor of favorable clinical outcome with the two scores, ranging from an odds ratio (OR) [95% confidence interval (CI)] = 1.84 [1.23; 2.76], $p=0.003$ for the reference score to an OR [95% CI] = 2.63 [1.21; 5.73], $p=0.015$ for the phase 3 ASPECT score. The phase 3 ASPECT score offers better sensitivity (Se) for the prediction of a favorable clinical outcome (Se=95%, specificity (Sp) =37% for a threshold of 7/7) than the reference score (Se=83%, Sp=47% for a threshold of 4/5).

Conclusion:

This study demonstrates the value of the ASPECT score in analyzing collaterals using multiphase CT angiography for the prediction of clinical outcome.

Key words:

Ischemic stroke - vascular collaterals - multiphase CT angiography - ASPECT

INTRODUCTION:

The notion of cerebral collaterals has recently been highlighted as one of the most reliable predictive radiological marker of clinical outcome in anterior ischemic stroke (IS) patients (1-5). The vascular network of leptomeningeal anastomoses quality is of key importance as it could limit the progression of the hypoperfused cerebral area towards necrosis (6-8). Various scores (9-12) and imaging methods, such as magnetic resonance imaging (MRI) (13) and computed tomography (CT) (14-15), have already been proposed to assess arterial collaterals, but there is no recommended non-invasive gold standard at present. The study by Menon BK. *et al.* (16) proposed a 5-point radiological score using multiphase CT angiography, considered as the reference (17). However, this score is still not well known outside of specialist institutions and is therefore underused. The 10-point ASPECT score is more widespread. Recently, it has been used in a simpler 7-point format (18), which take into account only the cortical regions.

The main objective of our study is to determine whether the 7-point ASPECT score adapted to collaterals is as closely correlated to the clinical outcome of a stroke patient as the reference score from the Menon study (16).

MATERIALS AND METHODS:

Study

This is a retrospective single center observational study carried out at Gabriel Montpied University Hospital in Clermont Ferrand, France, from July 2015 to July 2017.

Population

We selected patients according to the following inclusion criteria:

- Patient aged 18 years or more,
- Presenting to an emergency department of the region with symptoms of IS,
- Then examined at Clermont Ferrand University Hospital with multiphase CT angiography and demonstration of an IS due to occlusion of intracranial anterior circulation large vessel,
- Regardless of received treatment (intravenous thrombolysis (IVT) alone or in association, endovascular thrombectomy (EVT) alone or in association, support care),
- With time frame shorter than 24hours.

Multiphase CT angiography

All patients underwent multimodal CT. The perfusion CT was systematically realized for the patients who had their first CT at the university hospital. It was not available for patients who underwent their CT imagery at a

peripheral hospital. The protocol began with a non-enhanced CT. The multiphase CTA consisted of the acquisition of three phases: for the 1st phase, the Smart Prep acquisition volume extended from the aortic arch to the vertex after injection of 50 ml contrast medium at a rate of 3ml/sec, pulsed with 30 ml saline using an automatic syringe. The acquisition parameters were 120 kV and 600 mA with slices of 0.625 mm every 0.6 mm. For the following two acquisitions, the volume was from the base of the skull to the vertex. The 2nd phase started 13 seconds after the end of the 1st phase and the 3rd phase started 10 seconds after the end of the 2nd phase.

Interpretation of imaging

The post-processing of the images was carried out on an Advantage Windows 4.6 console with multiplanar reconstruction (MPR) and maximum intensity projection (MIP) reconstructions in order to identify and locate the thrombus within the anterior cerebral circulation and evaluate the collaterals by two scoring methods:

- The recognized 5-point score (Fig 1) investigated in the study by Menon BK *et al.* (16) and
- The 7-point ASPECT score (Fig 2) based on the presence or absence of collaterals in the different seven ASPECTS cortical regions for each phase.

There were therefore three ASPECT scores (phase 1, phase 2 and phase 3) and one Menon reference score for each patient (Fig 3 a, b). Double reading of the results, blinded with respect to clinical data, was carried out by a junior radiology doctor (five years of experiment) and a senior radiologist (ten years of experiment).

Clinical outcome

The primary study endpoint was the 90-days clinical outcome.

A good clinical outcome was defined as a mRs 0,1 or 2 while a poor clinical outcome was defined as mRs > 2, mRs 3 designate a moderate disability, mRs 4 and 5 a severe disability and mRS 6 death.

The early clinical outcome was assessed as a secondary endpoint, a good clinical outcome was defined as a decrease of more than 50% in NIHSS over one day while a poor clinical outcome was defined as a decrease of less than 50% in NIHSS.

These scores were collected in patient medical records by a vascular neurologist.

Statistical analyses

The statistical analyses were carried out with the Stata software (version 13; StataCorp, College Station, Texas, USA) and R 3.3.1 (<http://cran.r-project.org/>), taking into account a bilateral risk of type I error of 5%. The population is described by the associated numbers and percentages for categorical variables, and by the mean \pm standard deviation or median [interquartile range] for quantitative variables, as regards their statistical distribution (normality tested using Shapiro-Wilk). In order to study the relationship between the collateral

scores and the clinical outcomes of patients, logistic regressions were used. The results are expressed in the form of odds ratio (OR) and 95% confidence interval (CI). The areas under the ROC curves (AUC) were also calculated and presented with their 95% CI, together with Akaike information criterion (AIC) and Bayesian information criterion (BIC) values. In order to investigate the “optimal” thresholds of these collateral scores for predicting clinical outcome, various statistical indices were used (Youden, Liu, efficiency). The associated sensitivities, specificities and positive and negative predictive values were calculated. Comparisons between the two independent groups (good vs. poor clinical outcome) concerning quantitative parameters were carried out using Student’s t-test or the Mann–Whitney U test if the conditions for the t-test were not met (normality, homoscedasticity using the Fisher-Snedecor test). Comparisons between groups concerning qualitative parameters were carried out using the Chi2 test and Fisher's exact test. Finally, for the multivariate situation, a logistic regression was implemented in order to investigate the factors associated with good clinical outcome, taking into consideration covariables as regards the results of the univariate analysis and their clinical relevance. The results are expressed in terms of OR and 95% CI. A score reproducibility study was carried out using the weighted kappa coefficient method and the software MEDCALC 14.12.0. The results are expressed as kappa value and 95% confidence interval with the rules of interpretation of J.R. Landis and G.G. Koch.

RESULTS:

Population

In total, 199 patients were included in this study. Their description is presented in Table 1.

Mean age was 75.8 ± 13.1 years. Patients with a poor clinical outcome were significantly older than the others (78.5 ± 11.7 years vs. 70.5 ± 13.7 years, $p < 0.001$). The distribution of occlusion sites was as follows: distal internal carotid artery (13.6%), M1 middle cerebral artery (MCA) (56.6%), M2 MCA (29.8%).

Clinical outcome

With regard to good clinical outcome at 24 hours, 32% of patients presented at least a 50% decrease in NIHSS over one day.

With regard to good clinical outcome at 3 months, 33.3% of patients presented a minimal disability (mRS between 0 and 2), 14.4% a moderate disability (mRS = 3) and 52.3% a severe disability or death (mRS between 4 and 6).

Collateral scores

With univariate analysis (Table 2), regardless of the score used, we found a significant association between the quality of vascular collaterals and clinical outcome at 24 hours and 3 months. The phase 3 ASPECTS analysis offered the best correlation with good clinical outcome: OR [95% CI] = 3.42 [1.66; 7.05], $p=0.001$ vs. OR [95% CI] = 1.87 [1.37; 2.53], $p<0.001$ for the reference score.

In light of the ROC curves (Fig 4), the predictive capacity of collaterals for clinical outcome was modest (AUC between 0.65 and 0.68). Regardless of the collateral score used, collaterals as a predictive test for clinical outcome presented a good level of sensitivity: this varied from 77% for the lowest sensitivity (phase 1 ASPECT score) to 95% for the highest (phase 3 ASPECT score). However, collaterals as a predictive test for clinical outcome offered poor specificity, ranging from 37% (phase 3 ASPECT score) to 44% (reference score).

The multivariate analysis which adjusts on confounding factors such as patient age, treatment, time from onset to imagery, wake up stroke, neoplasia context, and stroke history, confirmed a significant independent association (p between 0.015 for 0.002) of all collateral scores with good clinical outcome at 24 hours and 3 months (Fig 5). The phase 3 ASPECT score presented the best correlation: OR [95% CI] = 2.63 [1.21; 5.73], $p=0.015$ vs. OR [95% CI] = 1.84 [1.23; 2.76], $p=0.003$ for the reference score.

Clinical outcome according to assessed collateral status is presented in Figure 6. The proportion of patient with a favorable clinical outcome is higher in patient with a high collateral status.

Sensitivity analysis

In sensitivity analyses restricted to patients independent without cancer history, the OR was higher with ASPECT score on phase 3 (OR [95% CI] = 2.80 [1.31; 5.96], $p=0.008$) than reference score (OR [95% CI] = 1.64 [1.09; 2.46], $p=0.02$). In sensitivity analyses restricted to patients who underwent efficient EVT (thrombolysis in cerebral infarction (TICI) =3 or 2b), the OR was highest with ASPECT score on phase 3 (OR [95% CI] = 3.00 [1.15; 7.80], $p=0.02$) than reference score (OR [95% CI] = 1.67 [1.09; 2.56], $p=0.02$).

Reproducibility analysis

Concordance analyses between the two readers for the different scores were carried out with good, significant weighted kappa values between 0.659 [0.516; 0.803] and 0.735 [0.625; 0.846]. The rating of collaterals using the ASPECT score and with the score recommended by Menon, therefore seems reproducible.

DISCUSSION

This study shows that the ASPECT score applied to collaterals using multiphase CT angiography is significantly associated with clinical outcome in anterior ischemic stroke. This association is the strongest when using phase 3 CT angiography with a higher sensibility than the reference score established by Menon et al.

Population and outcome

The mean age in our study was relatively high (75.8 ± 13.1 years) in comparison to key studies in ischemic stroke (19). This age criterion appeared significantly different ($p < 0.001$) with regard to clinical outcome: 70.5 ± 13.7 years in the good outcome group vs. 78.5 ± 11.7 years in the poor outcome group.

We did not apply the same exclusion criteria as Menon's study, which automatically excluded patients with an initial Rankin score of 3. Sixty-four patients of our study were therefore considered to have a poor clinical outcome, although eleven of them displayed the same level of disability as before the stroke. Despite including these patients in the poor clinical outcome group of our main analysis, the correlation was significant. We also carried out a subgroup analysis excluding them; our statistical results did not display significant change.

Menon's study also excluded patients with terminal-stage cancer, considering them to have a low life expectancy at 3 months. As this data is difficult to evaluate, we decided to include them. There was 17 patients with neoplasia (including 5 with Rankin 3). In our study, only one patient had a good outcome, although we frequently noted poor collateral scores for these patients.

Methods

Although we did not carry any comparative analysis about whether the patients underwent a perfusion CT before the CTA or not, we did not observe any difference between the two groups during CTA assessment. Due to the time laps between the first contrast injection and the acquisition of multiphase CT angiography, persistent arterial filling from the first contrast injection would require a severe cardiac failure. Neither we, nor Menon et al did encounter such a case. However, the slow flow due to either a cardiac failure or a pre occlusive carotid stenosis is clearly considered as a potential weakness to the assessment of collaterals on CTA.

Collaterals and predictive capacity

We found similar values to the Menon study with regard to the association between collaterals (evaluated using the reference score) and clinical outcome. The score that best forecasts 3-month clinical outcome appears to be the phase 3 ASPECT score. The statistical values have the same trend with regard to early clinical outcome at 24 hours. The phase 3 ASPECT score also offers the best sensitivity ($Se=95\%$) for a threshold of 7 points, versus a sensitivity of 83% for the reference score with a threshold of 4 points. A phase 3 ASPECT score of less than 7 points essentially makes it possible to exclude the possibility of a good clinical outcome. However, collaterals as a predictive test of clinical outcome present low specificity. This lack of specificity can be explained by the multiplicity of factors that influence favorable clinical outcome for stroke patients as vascular recanalization, time onset, age and comorbidities.

Collateral score and imaging

The reference score presented in Menon's study offer the advantage over ASPECT score in providing temporal information. Besides, it offers both quantitative and qualitative analysis of the collaterals. The ASPECT score which is purely quantitative is more objective. Furthermore, as the 7-point score is a derivative of the ASPECT score which was initially created for non-contrast CT and became over time the best known scale in stroke neuroimaging, it is potentially more usable and more accessible to more non expert radiologist and neurologist or even untrained fellows than Menon score which needs further training in multimodal CT reading.

Our results indicate that it is possible to carry out the collateral analysis using the ASPECT score for phase 3 alone. It would therefore be possible to do without phase 2, which would enable a significant radiation dose reduction.

Study limitations

This study was retrospective and only included patients treated at Clermont Ferrand University Hospital. Although the overall sample offers satisfactory statistical power, the analysis of some subgroups like the subgroup of patients treated by EVT with good recanalization rates lack statistical power given their low numbers.

CONCLUSION

In summary, we describe an ASPECT score applied to collaterals on multiphase CT angiography and demonstrates its significant association with clinical outcome at 24hours and three months in patients with AIS; its association with clinical outcome is at least as strong as that of the reference score used in Menon's study. Nevertheless, it need more validation by prospective and larger studies to be established as a reliable tool to the triage of AIS patients.

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