Radiological Eye Deviation as a Predictor of Large Vessel Occlusion in Acute Ischaemic Stroke

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Background: Detection of large vessel occlusion (LVO) is required for endovascular therapy in acute ischemic stroke (AIS) but CT angiography (CTA) is not always performed at primary stroke centers. Eye deviation on CT brain has been associated with improved stroke detection, but comparisons with angiographic status have been limited. This study sought to determine if radiological eye deviation was associated with LVO. *Methods:* All AIS patients given intravenous thrombolysis who had acute CTA performed in 2 stroke units were reviewed over 2013-2015 for the presence of LVO. Eye deviation was determined by 2 clinicians blinded to LVO status. Logistic regression was performed to determine which factors predicated LVO. *Results:* Total 195 AIS patients with acute CTA were identified; 124 (64%) had LVO. Median age was 72 (IQR 64−82) years, median National Institutes of Health Stroke Scale (NIHSS) was 12 (IQR 7-14). LVO patients had a higher NIHSS (15 versus 7, $p < .01$) and were more likely to have eye deviation on CT brain (71% versus 22.5%, $p < .01$). Logistic regression confirmed NIHSS score and eye deviation were associated with LVO, with odds ratios of 1.15 (per point) and 5.13 respectively. NIHSS less than equal to 11 gave greatest sensitivity (78.5%) and specificity (76.1%) for LVO with a positive predictive value of 84.7%. Eye deviation was similar with sensitivity 71%, specificity 77.5%, and 84.6%. *Conclusions:* Eye deviation on CT brain is strongly associated with LVO. Presence of eye deviation on CT should alert clinicians to probability of LVO and for formal angiographic testing if not already performed.

Key Words: Acute stroke—imaging—eye deviation—occlusion

Introduction

Endovascular thrombectomy (EVT) has proven efficacy in acute ischemic stroke (AIS). Because the treatment effect is time dependent, with more rapid reperfusion improving likelihood for good clinical outcome, early identification of potential EVT candidates is crucial. It has been estimated that 7%-15% of AIS patients may be eligible for EVT.[1] However, there are significant logistical barriers to provide EVT for all patients presenting with AIS. Most UK hospitals treating AIS patients do not have EVT available on-site (82%) while some have no access to EVT at all. Even in centers capable of performing EVT, access is typically not possible for 7 days per week, a service constraint expected to continue into the future.[2] Despite recommendations,[3] vascular imaging is not yet performed for all AIS patients nationally, while even high volume centers where CT angiography (CTA) is part of imaging protocols do not perform CTA on all AIS cases for multiple reasons.[4,5]

In order to identify patients earlier who may be eligible for EVT, multiple prediction tools have been investigated for their sensitivity and specificity at predicting large

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vessel occlusion (LVO). These include the National Institutes of Health Stroke Scale (NIHSS), Cincinnati Prehospital Stroke Severity Scale, Los Angeles Motor Scale, Rapid Arterial Occlusion Evaluation , and the 3 Point Stroke scale.[6] All of these scoring systems other than Los Angeles Motor Scale use clinical eye deviation as a predictor of LVO but none have both high sensitivity and specificity. Eye deviation in isolation has been shown to have a positive predictive value (PPV) of 90% for LVO in 1 small study.[6] Despite the usefulness of clinical eye deviation in stroke there is poor inter-rater reliability for detecting this sign with previous studies showing a kappa value of 0.46 between trained neurologists.[7]

Eye deviation detected on CT brain imaging has previously demonstrated clinical usefulness in the assessment of patients with AIS. Eye deviation detected on CT enhances radiologists' ability to detect early signs of brain ischemia.[8] Radiological eye deviation localizes the symptomatic hemisphere in 93% of AIS cases and has superior inter-rater variability in comparison to a clinical assessment of eye deviation.[8] Eye deviation on CT has been associated with larger middle cerebral artery infarct volumes[9] and may infer spatial neglect due to cortical ischemia.[10] Studies comparing radiologically detected eye deviation and LVO status in AIS have been limited to date. This study sought to investigate the usefulness of radiological eye deviation as a predictor of LVO.

Methods

We retrospectively examined clinical and imaging data for consecutive AIS patients admitted to 2 acute stroke services over a 3-year period (January 1, 2013 until December 31, 2015) as part of a national audit and quality improvement program. The institutional quality improvement board for each center approved the study. From this cohort we selected all AIS patients who had CTA performed acutely to determine LVO for presence of radiological eye deviation.

Demographic data and admission NIHSS scores were collected from hospital records. Individual patients were reviewed for angiography (CTA/magnetic resonance angiography) during the acute admission and a LVO classified as an internal carotid artery, proximal middle cerebral artery, M1 or M2 branch, posterior cerebral artery, or basilar artery occlusion.

Two stroke neurologists independently reviewed the admission CT brain slices around the orbits of all included patients to determine the presence of eye deviation. Eye deviation was recorded as present or absent based on subjective assessment of the radiological appearance. In order to reflect clinical practice as closely as possible, a formal measurement of eye deviation angle was not used. The clinicians were blinded to clinical information including NIHSS, symptomatic cerebral hemisphere CT brain report, and angiography imaging and report. Any discrepancies were resolved through consensus.

Analyses were carried out using IBM SPSS Statistics for Windows, Version 25.0. Normality of continuous data was determined using the Shapiro-Wilk test and where nonuniformity was identified, nonparametric tests were performed. Univariate analyses were performed using chi-square tests. Binomial logistic regression was carried out on univariate analyses approaching significance. Sensitivity, specificity, positive and negative predictive values (NPVs), and receiver operating characteristic curves for predictors of LVO were calculated on significant factors from the logistic regression model. Inter-rater variability in determining radiological eye deviation and clinical versus radiological assessment of eye deviation were analyzed using Cohen's kappa statistic.

Results

Total 195 AIS patients treated with intravenous thrombolysis were identified. Of these 124 patients (64%) had a LVO. Shapiro-Wilk testing showed that NIHSS score and age were non-normally distributed ($p < .01$ for both). The median age in the entire cohort was 72 (interquartile range 64-82) and the median NIHSS score was 12 (interquartile range 7-14). NIHSS scores were negatively skewed as shown in Figure 1.

Age, gender, NIHSS score, common risk factors for stroke as well as the presence of eye deviation on CT brain were analyzed using chi-square tests. Patients with LVO had a significantly higher median NIHSS (15 versus 7, $p < .01$), were more likely to be female (48.4% versus 31%, $p < .01$) and were more likely to have radiological eye deviation (71% versus 22.5%, $p < .01$) than patients without LVO. The risk factor data distributions among patients with and without LVO are shown in Table 1.

Logistic regression was carried out on all variables with a p value approaching significance (<0.25). The logistic regression model was statistically significant (chi-square 72.8, $p < .01$) and was able to successfully predict the outcome in 78.5% of cases, with a Nagelkerke R^2 value 0.427. This confirmed that radiological eye deviation (OR 5.13) and increasing NIHSS score (OR 1.15 for each point increase in score) were associated with LVO as shown in Table 2.

Sensitivity, specificity, positive, and NPVs were calculated for NIHSS score and radiological eye deviation. To determine the optimum NIHSS value for this sensitivity and specificity were calculated for each cut off score on the NIHSS as shown in Figure 2. An NIHSS score of less than equal to 11 gave the maximum sensitivity for specificity with a sensitivity of 78.5%, specificity 76.1%, PPV 84.7%, and NPV 65.3%. Using the presence solely of eye deviation on CT as a predictor of LVO gave a sensitivity 71%, specificity 77.5%, PPV 84.6%, and NPV 60.4%. Receiver operating characteristic curves were calculated for NIHSS score and the presence of eye deviation on CT, with an area under the curve of 0.8 and 0.74 respectively, as seen in Figure 3.

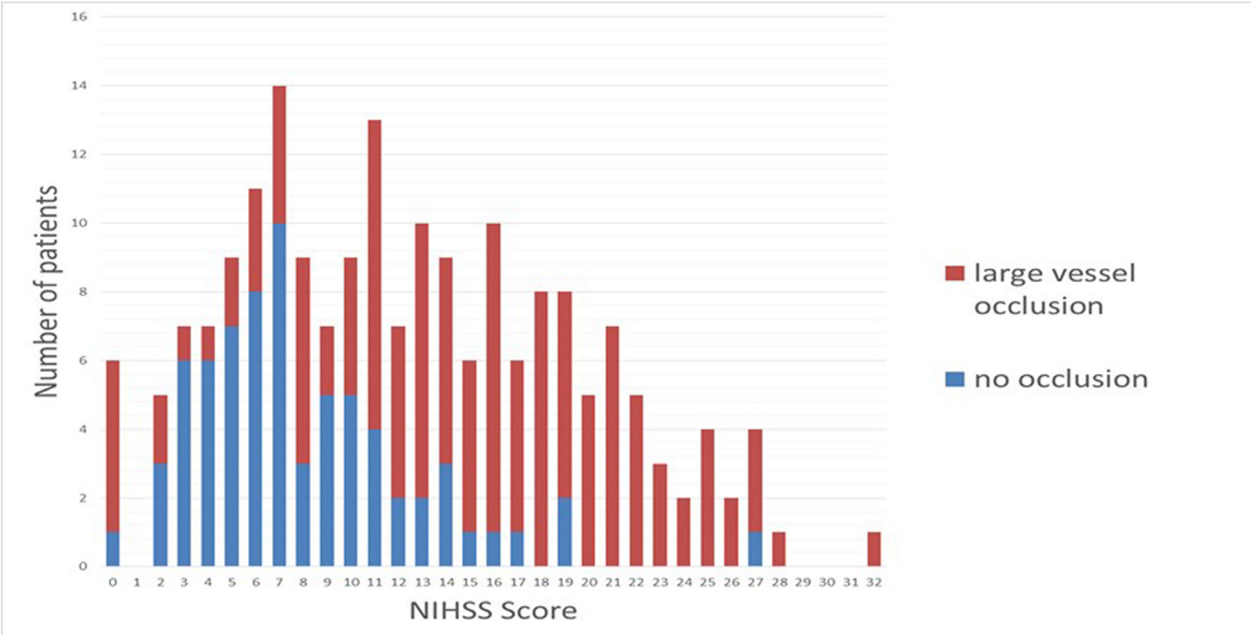

Figure 1. *Distribution of NIHSS scores. Abbreviation: NIHSS, National Institutes of Health Stroke Scale. (Color version of figure is available online.)*

Clinical eye deviation was compared to radiological eye deviation on CT. Clinical eye deviation was significantly associated with LVO ($p < .01$). However clinical eye deviation was identified less frequently than radiological eye deviation (43.5% compared to 71%). As NIHSS score already includes the clinical measurement of eye deviation, the clinical assessment could not be used as part of the logistic regression model. The sensitivity of clinical eye deviation was 57.6%, specificity 78.3%, PPV 81.9%, and NPV 51.9%. Eye deviation was directed towards the symptomatic hemisphere in the majority of cases (81%). There was fair inter-rater agreement of clinical and radiological evidence of eye deviation for predicting LVO, with Kappa 0.3 (95% CI 0.17, 0.44).

To determine the clinical ease of identifying radiological eye deviation (Ferghal McVerry and Mark O McCarron) independently reviewed the admission CT brain blinded to the result of the angiography. Inter-rater variability was again assessed using Cohen's Kappa showing a good agreement with Kappa 0.56 (95% CI 0.44, 0.68).

Table 1. *Risk factors associated with stroke in patients with and without LVO*

Risk factor	Large vessel occlusion (N = 124)	No large vessel occlusion (N = 71)	*p* value
Median (interquartile range)			
Age	72 (65-83)	71 (58-81)	.24
NIHSS score	**15 (11-20)**	**7 (5-10)**	**<.01**
Number (percentage)			
Hypertension	35 (28.2)	9 (12.7)	0.09
Diabetes	14 (11.3)	4 (5.6)	0.35
Current/ Ex-smoker	21 (16.9)	10 (14.1)	.42
Atrial fibrillation	20 (16.1)	7 (9.9)	.22
Previous stroke	15 (12.1)	7 (9.9)	.53
Congestive cardiac failure	5 (4.0)	1 (1.4)	.15
Anticoagulant	6 (4.8)	4 (5.6)	.78
Gender (Female)	**60 (48.4)**	**22 (31.0)**	**.02**
Eye deviation on CT	88 (71.0)	16 (22.5)	<.01
Clinical eye deviation (NIHSS point 2)	**54 (43.5)**	**8 (11.3)**	<.01

Bold variables were statistically significantly different between both groups. (P<0.05).

Abbreviations: NIHSS, National Institutes of Health Stroke Scale.

Discussion

This study demonstrates that LVO status in thrombolysis eligible AIS patients can be predicted with high specificity and positive predictive value in the presence of radiological eye deviation on acute CT brain. The sensitivity and specificity for LVO prediction using radiological eye deviation was 71% and 77.5% respectively. Other methods for determining likelihood for LVO include both the hyperdense vessel sign on noncontrast CT brain and NIHSS. The hyperdense vessel sign has a sensitivity of 52.4% and specificity of 94.9% although PPV for this sign has not been reported.[11] A recent meta-analysis suggested NIHSS was the best clinical predictor of LVO but prospective studies to examine other LVO prediction tools are still needed.[6] In this study NIHSS less than equal to 11 had a PPV for LVO of 84.7 % while radiological eye deviation performed similarly to NIHSS with a PPV of 84.6 % with a similar AUC (Fig 3). NIHSS requires specific training

Table 2. *Binomial logistic regression model for factors predictive of LVO*

Risk factor	Odds ratio (95% confidence Intervals)	*p* value
Age	1.01 (0.98-1.04)	.37
NIHSS score	**1.15 (1.08-1.23)**	**<.01**
Hypertension	0.907 (0.43-1.92)	.80
Atrial fibrillation	1.17 (0.44-3.07	.75
Congestive cardiac failure	0.42 (0.03-5.17)	.50
Gender (Female)	1.33 (0.63-2.8)	.45
Eye deviation on CT	**5.13 (2.35-11.2)**	**<.01**

Bold variables were statistically significantly different between both groups. ($P<0.05$).

Abbreviations: NIHSS, National Institutes of Health Stroke Scale.

and has limited observer agreement, takes time to perform, and absolute score varies with symptomatic hemisphere.[7,12] In this study presence/absence of radiological eye deviation was detected rapidly in order to assess its potential for use in clinical practice and performed similarly to NIHSS. It is a dichotomous test, meaning it may be more feasible in some situations such as remote assessment via telemedicine for making clinical decisions. Eye deviation was more frequently identified on CT than within the NIHSS clinical assessment (Table 1), suggesting that clinical eye deviation may be under-recognized in routine clinical practice.[7] Lack of eye fixation to a target because of eye closure during the CT scanning procedure may theoretically make subtle gaze paresis more likely to be detected on CT rather than NIHSS, although this hypothesis requires further study.

Guidelines report the importance of obtaining vascular imaging in EVT eligible patients where feasible.[3] Despite this, it remains unclear what proportion of AIS patients on a nationwide basis will receive CTA or an equivalent vascular imaging modality. A temporal trend for increasing use of CTA over time has been demonstrated[13] and is likely to increase given the proven benefit of EVT. Despite the evidence base, CTA is not yet a routine for all AIS patients and specific challenges relating to CTA access in small or remote hospitals are acknowledged.[3] Lack of access to EVT at weekends/out of hours in the UK for example as well as considerations regarding prevalence of LVO in AIS and other logistical issues may result in ongoing barriers to CTA being performed routinely for *all* AIS patients.[2,14] As access to noncontrast CT brain is not associated with major barriers and is even available in some mobile stroke unit ambulances, the presence of radiological eye deviation could potentially provide additional diagnostic, therapeutic, and prognostic information in resource limited settings.[15] A high proportion of patients in the study were identified with LVO (64%). This is higher than rates of LVO in acute stroke reported in other studies which range from 39-48.5%[1,16] Possible reasons for this are that angiography was not routinely performed

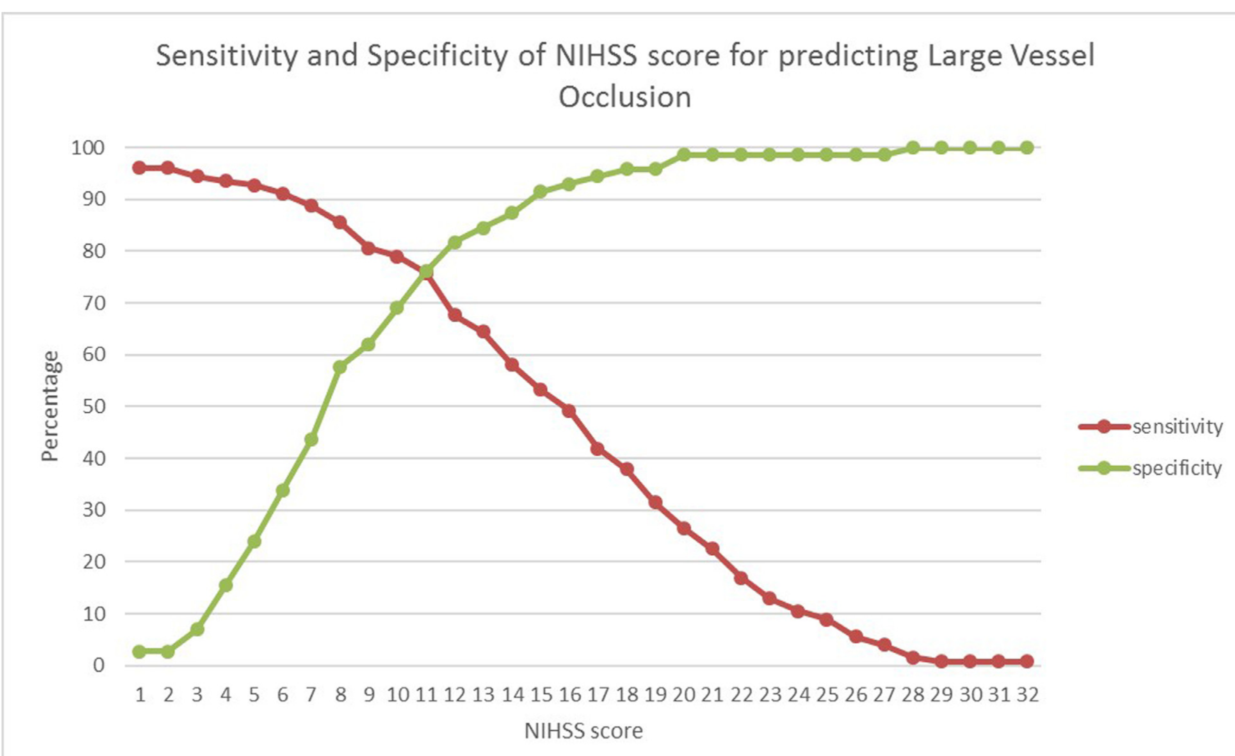

Figure 2. *Sensitivity and Specificity for NIHSS cut points to predict LVO. Abbreviations: LVO, large vessel occlusion; NIHSS, National Institutes of Health Stroke Scale. (Color version of figure is available online.)*

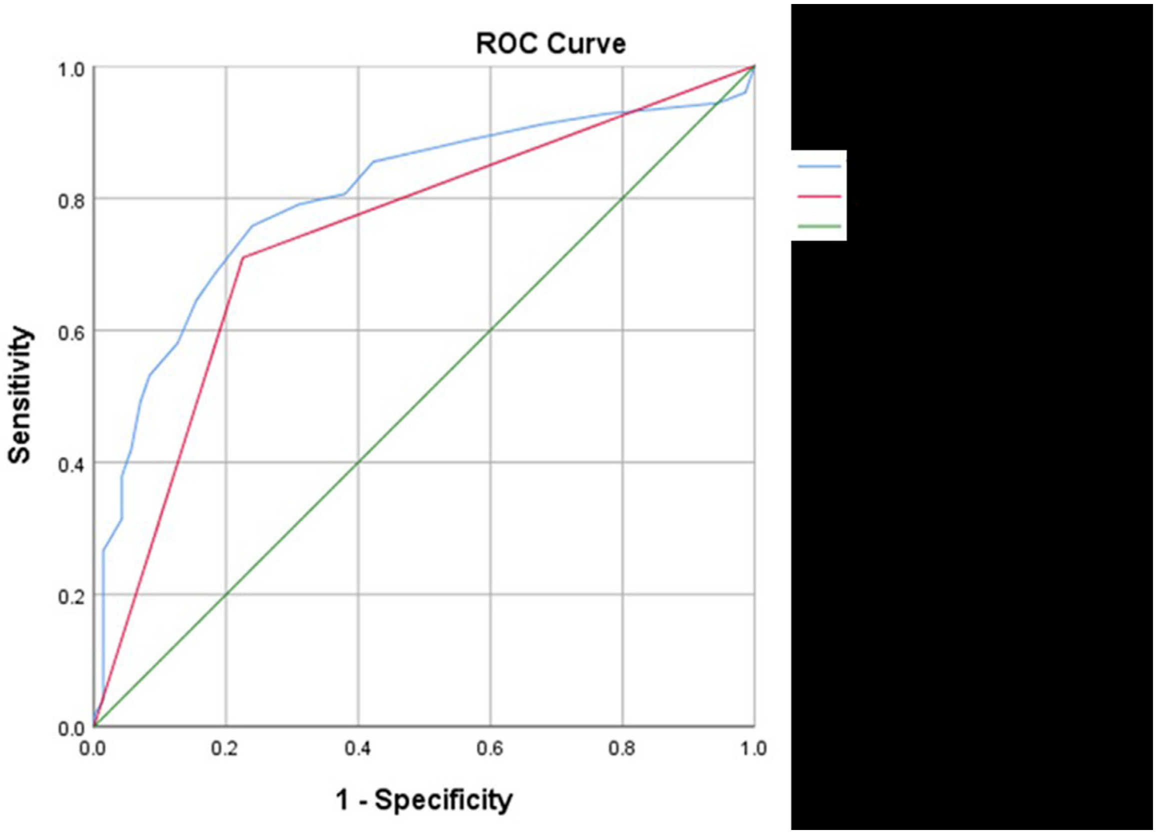

Figure 3. *Receiver operating characteristic curves for NIHSS score and radiological eye deviation for the presence of LVO. Abbreviation: LVO, large vessel occlusion; (Color version of figure is available online.)*

in AIS in the centers investigated and therefore angiography may have only been performed on patients deemed to be high risk e.g. high NIHSS score or who presented during normal working hours reflecting local practice.

There was no statistical difference in baseline characteristics of the groups for known risk factors of LVO. There was a higher proportion of females in the LVO group (48.4% versus 31%) but this difference was not significant in the regression model. The multivariate analysis showed that eye deviation on CT and NIHSS were strongly associated with LVO with an OR of 5.13 and 1.15 respectively. An NIHSS score of less than equal to 11 had the best sensitivity and specificity for LVO. This compares with other studies that have found the best cut off between 7 and 11.[17,18]

Limitations of Study

This study was a retrospective analysis of AIS patients who received intravenous thrombolysis therapy and had angiography performed. As CTA was not routinely performed for 100% of patients over the study period we cannot exclude a patient selection bias in the cohort. Examining the predictive value for eye deviation in suspected stroke patients with CTA+/-CT perfusion would be an appropriate next step in validating the predictive value of radiological eye deviation.

Also the neurologists analyzing the imaging had not been formally trained to identify eye deviation and no formal cut-off angle was agreed. Small studies have shown 15° of deviation are strongly associated with LVO but the lack of specific training or measurement requirement demonstrates the feasibility for detecting this sign in routine practice.[19]

Other potential causes for eye deviation include vestibular lesions and seizures. This work was performed in a population who presented with signs or symtpoms suggesting acute stroke prior to imaging being undertaken, meaning radiological eye deviation should not be used to predict LVO without appropriate clinical suspicion for stroke.[20,21]

Conclusion

Radiological eye deviation is a strong predictor of LVO in AIS patients treated with IV thrombolysis. CTA is the most widely performed imaging modality to detect LVO but as barriers to CTA access persist in some settings additional methods to predict LVO such as radiological eye deviation may be clinically useful. Prospective evaluation of radiological eye deviation in larger populations incorporating CT perfusion and CT angiography in all suspected stroke patients is required to determine the predictive value of this finding in wider clinical practice.

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