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Original Article

Clinical Predictors of Acute Ischemia in Patients with Low-Risk Neurological Deficits

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ABSTRACT: ***Background:*** Diagnosis of acute ischemia typically relies on evidence of ischemic lesions on magnetic resonance imaging (MRI), a limited diagnostic resource. We aimed to determine associations of clinical variables and acute infarcts on MRI in patients with suspected low-risk transient ischemic attack (TIA) and minor stroke and to assess their predictive ability. ***Methods:*** We conducted a post-hoc analysis of the Diagnosis of Uncertain-Origin Benign Transient Neurological Symptoms (DOUBT) study, a prospective, multicenter cohort study investigating the frequency of acute infarcts in patients with low-risk neurological symptoms. Primary outcome parameter was defined as diffusion-weighted imaging (DWI)-positive lesions on MRI. Logistic regression analysis was performed to evaluate associations of clinical characteristics with MRI-DWI-positivity. Model performance was evaluated by Harrel's c-statistic. ***Results:*** In 1028 patients, age (Odds Ratio (OR) 1.03, 95% Confidence Interval (CI) 1.01–1.05), motor (OR 2.18, 95%CI 1.27–3.65) or speech symptoms (OR 2.53, 95%CI 1.28–4.80), and no previous identical event (OR 1.75, 95%CI 1.07–2.99) were positively associated with MRI-DWI-positivity. Female sex (OR 0.47, 95%CI 0.32–0.68), dizziness and gait instability (OR 0.34, 95%CI 0.14–0.69), normal exam (OR 0.55, 95%CI 0.35–0.85) and resolved symptoms (OR 0.49, 95%CI 0.30–0.78) were negatively associated. Symptom duration and any additional symptoms/symptom combinations were not associated. Predictive ability of the model was moderate (c-statistic 0.72, 95%CI 0.69–0.77). ***Conclusion:*** Detailed clinical information is helpful in assessing the risk of ischemia in patients with low-risk neurological events, but a predictive model had only moderate discriminative ability. Patients with clinically suspected low-risk TIA or minor stroke require MRI to confirm the diagnosis of cerebral ischemia.

RÉSUMÉ : Prédicteurs cliniques de l'ischémie aiguë chez des patients présentant des déficits neurologiques à faible risque ***Contexte :*** Le diagnostic d'ischémie aiguë repose généralement sur la mise en évidence de lésions ischémiques dans le cadre d'un examen d'imagerie par résonance magnétique (IRM), une ressource diagnostique limitée. À cet égard, nous avons cherché à déterminer les associations entre les variables cliniques et les infarctus aigus détectés au moyen d'un examen d'IRM chez des patients soupçonnés d'avoir été victimes d'un accident ischémique transitoire (AIT) à faible risque ou d'un accident vasculaire cérébral (AVC) mineur. Qui plus est, nous avons cherché à évaluer les capacités de prédiction de ces associations. ***Méthodes :*** Nous avons effectué une analyse post-hoc de l'étude DOUBT (*Diagnosis of Uncertain-Origin Benign Transient Neurological Symptoms)*. Il s'agit d'une étude de cohorte prospective et multicentrique portant sur la fréquence des infarctus aigus chez des patients présentant des symptômes neurologiques à faible risque. Le principal paramètre en matière de résultat a été défini comme des lésions détectées par imagerie de diffusion lors d'un examen d'IRM. Une analyse de régression logistique a été réalisée pour évaluer les associations entre les caractéristiques cliniques des patients et la positivité des résultats par imagerie de

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diffusion. La performance de notre modèle a été ensuite évaluée à l'aide de l'indice *C* de Harrel. ***Résultats :*** Chez 1028 patients, l'âge (RC 1,03 ; IC 95 % 1,01-1,05), les symptômes moteurs (RC 2,18 ; IC 95 % 1,27-3,65) ou liés à l'élocution (RC 2,53 : IC 95 % 1,28-4,80), de même que l'absence d'événement identique antérieur (RC 1,75 ; IC 95 % 1,07-2,99) ont été positivement associés à la positivité des résultats d'imagerie par diffusion. En revanche, le sexe féminin (RC 0,47 ; IC 95 % 0,32-0,68), les vertiges et l'instabilité de la démarche (RC 0,34 : IC 95 % 0,14-0,69), un examen normal (RC 0,55 ; IC 95% 0,35-0,85) et des symptômes résolus (RC 0,49 : IC 95% 0,30-0,78) ont été négativement associés à la positivité des résultats d'imagerie par diffusion. La durée des symptômes et toutes les combinaisons de symptômes supplémentaires n'étaient pas associées. Enfin, la capacité prédictive du modèle était modérée (indice *C* : 0,72 ; IC 95 % 0,69-0,77). ***Conclusions :*** Des renseignements cliniques détaillés sont utiles pour évaluer le risque d'ischémie chez les patients présentant des événements neurologiques à faible risque. Cela dit, notre modèle prédictif n'avait qu'une capacité de discrimination modérée. Sur le plan clinique, les patients chez lesquels on soupçonne un AIT à faible risque ou un AVC mineur ont besoin d'un examen d'IRM pour confirmer un diagnostic d'ischémie cérébrale.

Keywords: magnetic resonance imaging; stroke; transient ischemic attack

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Introduction

Accurate diagnosis of acute ischemia in patients presenting with transient or minor neurological deficits is important because a diagnosis of true cerebral ischemia further influences risk stratification and treatment decisions. Patients with transient ischemic attacks (TIA) or minor stroke carry a substantial early risk of recurrent ischemic events,[1,2] and appropriate and early secondary prevention is essential to reduce the risk of future ischemic events and disability.[3] This risk can be stratified by clinical and imaging factors. It is known that motor or speech symptoms, longer duration[4] and associated vascular disease (e.g., extracranial carotid artery stenosis)[5] are predictors of a higher risk of recurrent stroke. Consequently, these features define a "high-risk" event[5] and are the basis for clinical prediction scores of recurrent ischemia such as the "ABCD2" score.[4,6] Available prediction scores are largely driven by the "C" – the clinical presentation with motor and speech symptoms.[7] However, there is also evidence of a comparable risk of recurrent ischemia in patients presenting with non-classical symptoms.[8] Additionally, if early magnetic resonance imaging (MRI) can be performed, the presence of diffusion-weighted imaging (DWI)-positive lesions has been shown to be associated with an increased risk of recurrent ischemic events.[5,9–11] Approximately one third of all patients presenting with transient neurological symptoms show one or more DWI-positive lesions on brain MRI.[12]

In contrast, "low-risk" transient or persistent minor neurological symptoms are defined by the lack of "high-risk" factors. Low-risk events were studied in the Diagnosis of Uncertain-Origin Transient Neurological Symptoms (DOUBT) study which reported that clinical low-risk neurological events were associated with acute ischemic lesions on DWI-MRI in over 13%. Furthermore, while the rate of clinical recurrent stroke events was low (0.7% at one year), consistent with the clinically low-risk population, the presence of DWI-positive MRI was associated with an increased risk of recurrent ischemic stroke.[13]

MRI has significant resource implications with limited access in many countries.[14,15] If clinical factors alone could predict the risk of stroke in patients with transient or minor neurological deficits, it might mitigate the need for early MRI. Therefore, we aimed to assess associations of easily available clinical parameters with the presence or absence of acute infarcts defined as DWI-positive lesions on brain MRI in patients with low-risk transient and minor neurological symptoms and evaluate their predictive ability for acute ischemia.

Methods

Patient sample – DOUBT study population

DOUBT was a prospective, international, multicenter cohort study investigating the frequency of acute ischemic infarcts on MRI in patients with low-risk neurological symptoms.[13] A total of 1028 patients were enrolled between June 2010 and October 2016. Inclusion criteria were: age > 40 years, possible low-risk TIA or minor stroke, a National Institute of Health Stroke Scale ≤ 3 in case of persistent symptoms and brain MRI within 8 days from symptom onset. Possible low-risk TIA or minor stroke was defined as either nonmotor or nonspeech symptoms of any duration, or motor or speech symptoms lasting for ≤ 5 minutes. Patients were excluded if they had high-risk clinical features (motor or speech symptoms > 5 minutes), had experienced an episode of isolated monocular vision loss, had a history of prior stroke, a modified Rankin Scale (mRS) > 2, a limited life expectancy of less than 12 months, a contraindication to perform MRI or a definite alternative cause for their presenting symptoms according to the investigator. Patients were enrolled within 8 days of symptom onset and prior to performing brain MRI. Patient assessment included a detailed neurological examination and provisional diagnosis by a stroke neurologist. Clinical neurological symptoms were classified as lateralized or non-lateralized symptoms. Lateralized symptoms included sensory, motor and visual afferent symptoms (further differentiated into negative and positive visual phenomena), as well as limb ataxia and gait instability. Non-lateralized symptoms included diplopia, dizziness, aphasia, dysarthria, confusion without aphasia and altered level of consciousness. Brain MRI including DWI-sequences was performed according to local standards on 1.5 or 3.0 tesla MRI machines; acquired images were centrally reviewed by a neuroradiologist blinded to patients' clinical symptoms.[13]

All patients provided informed consent prior to enrollment in the DOUBT study; local ethics boards approved the study at all participating sites.[13]

Data analysis

This is a post-hoc analysis of prospectively collected data in the DOUBT study.

Baseline characteristics including demographic variables, detailed symptomatology and time metrics as well as outcome parameters were descriptively evaluated for the overall population. The primary outcome was the same as in the main study, defined as

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the presence of DWI-positive lesions on MRI indicating an acute ischemic stroke.

Clinical symptoms were included according to the above-mentioned classification. To investigate a potential association between specific symptoms and symptom combinations with MRI-DWI-positivity, absolute numbers for all possible symptom pairs and symptom triplets were assessed. In a second step, associations between symptoms and symptom combinations with at least one observation and MRI-DWI-positivity were assessed by univariable logistic regressions.

Next, significant results for symptoms (irrespective of any symptom combinations) and symptom pairs and triplets obtained from univariable analysis and clinical variables shown to be significantly associated with MRI-DWI-positivity in the primary DOUBT analysis (age, sex, resolved symptoms, neurological exam and history of a previous identical event)[13] were combined in a multivariable logistic regression model to evaluate associations of clinical findings and MRI-DWI-positivity. Subsequently, significant variables from this model were transferred to a final model including overall symptom duration as an additional independent variable. For sensitivity analysis, calculation of this model was restricted to patients with resolved symptoms at the time of presentation. Furthermore, we evaluated a potential effect modification by symptom duration on each included symptom/symptom combination by adding interaction terms of each symptom/symptom combination and symptom duration. Additionally, the analysis was repeated in the subgroup of patients without any motor or speech symptoms (excluding patients with any motor symptoms, aphasia or dysarthria).

Model performance of the final logistic regression model was assessed by calculating its discriminative ability, which is reported as Harrel's c-statistic (ranging from 0.5 to 1.0; good discriminative ability is characterized by a c-statistic approaching 1).[16]

Statistical analyses were performed in STATA (version 16.0) and R (version 3.6.1). All tests were two-sided; levels of statistical significance were defined as alpha < 0.05.

Data availability

Data supporting the reported findings are currently not publicly available; requests about data access should be addressed to the corresponding author.

Results

This post-hoc analysis was conducted in the whole patient sample of the DOUBT study, comprising a total of 1028 patients. Detailed baseline characteristics of enrolled patients have been published previously.[13] In summary, median age was 63.0 years (IQR: 54.1–71.5), 522 patients (50.8%) were female, 238 patients (23.2%) had a previous identical event, 370 patients (36.0%) had ongoing symptoms at the time of assessment and 740 patients (72.0%) had a normal neurological exam. A total of 139 patients (13.5%) had DWI-positive lesions on brain MRI. Patients with acute infarcts on DWI-MRI were older, less frequently female, presented less frequently with a previous identical event, were less likely to have a normal exam and more likely to have ongoing symptoms.[13] Median symptom duration was 370 min (IQR: 45–2160 min); in the subgroup of patients with resolved symptoms, median symptom duration was 120 min (IQR: 15–360 min). For patients with ongoing symptoms, median symptom duration (defined as time from symptom onset until first clinical assessment) was 2340min (IQR: 900–5760 min).

Table 1. Univariable analysis–statistically significant associations of symptoms and symptom combinations with MRI-DWI-positivity

	Number of observations	Odds Ratio	95%CI
Any motor symptoms	116	1.92	1.17–3.08
Limb ataxia	42	2.38	1.12–4.72
Dizziness	327	0.60	0.39–0.91
Aphasia	66	1.99	1.05–3.56
Positive visual symptoms	56	0.1	0.01–0.51
Any sensory symptoms + Limb ataxia	10	4.36	1.10–15.46
Gait instability + Dizziness	117	0.44	0.19–0.86

MRI = Magnetic Resonance Imaging; DWI = Diffusion-Weighted Imaging; OR = Odds Ratio; CI = Confidence Interval.

Symptom durations for different patient subgroups stratified by MRI-DWI-positivity are illustrated in Supplemental Figure 1.

The most frequent symptoms irrespective of any symptom combination were any sensory symptoms ($n = 595$, 57.9% of the total study population), dizziness ($n = 327$, 31.8%) and gait instability ($n = 307$, 29.9%). Patient characteristics stratified by symptom subgroups are provided in Supplemental Table 1; importantly, for the entire analysis, motor or speech symptoms were limited to a duration of ≤ 5 minutes as per the main study inclusion/exclusion criteria. The most frequent symptom pairs were dizziness and gait instability ($n = 117$, 11.4%), any motor and any sensory symptoms ($n = 53$, 5.2%), and any sensory symptoms and dizziness ($n = 42$, 4.1%). The most frequent symptom triplets were any sensory symptoms, gait instability and dizziness ($n = 22$, 2.1%) and diplopia, gait instability and dizziness ($n = 18$, 1.8%). Detailed information on frequencies of different symptoms and symptom combinations (pairs and triplets) and corresponding frequencies of acute infarcts on DWI-MRI is provided in Supplemental Tables 2-4.

On univariable analysis, any motor symptoms (≤5min), limb ataxia, and aphasia (≤5min; all irrespective of any symptom combinations) and the symptom pair of any sensory symptoms/limb ataxia were associated with increased odds of MRI-DWI-positivity. Positive visual symptoms, dizziness (both irrespective of any symptom combinations) and the symptom pair of gait instability/dizziness were negatively associated with MRI-DWI-positivity. Odds ratios and corresponding 95% confidence intervals are provided in Table 1.

A statistically significant association of symptoms and symptom combinations with MRI-DWI-positivity on multivariable analysis was preserved for any motor symptoms (≤5 min, OR 2.18, 95%CI 1.27–3.65, irrespective of symptom combinations), aphasia (≤5 min, OR 2.53, 95%CI 1.28–4.80, irrespective of symptom combinations) and the symptom pair gait instability/dizziness (OR 0.34, 95%CI 0.14–0.69; odds ratios are derived from the final regression model, Table 2). On final multivariable logistic regression analysis, we further observed a positive association of MRI-DWI-positivity with age (OR 1.03, 95%CI 1.01–1.05, per year of older age), and having no previous identical event (OR 1.75, 95% CI 1.07–2.99), and a negative association with female sex (OR 0.47, 95%CI 0.32–0.68), normal neurological exam (OR 0.55, 95%CI 0.35–0.85) and resolved symptoms (OR 0.49, 95%CI 0.30–0.78). There was no statistically significant association between overall symptom duration and MRI-DWI-positivity (Table 2) and no evidence of effect modification by symptom duration on any

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Table 2. Multivariable analysis–association of clinical findings with MRI-DWI-positivity

	OR	95%CI
Age (years)	1.03	1.01–1.05
Female sex	0.47	0.32–0.68
Any motor symptoms	2.18	1.27–3.65
Aphasia	2.53	1.28–4.80
Gait instability/dizziness	0.34	0.14–0.69
Normal neurological exam	0.55	0.35–0.85
Resolved symptoms	0.49	0.30–0.78
No previous identical event	1.75	1.07–2.99
Symptom duration (min)	1.00	1.00–1.00

MRI = Magnetic Resonance Imaging; DWI = Diffusion-Weighted Imaging; OR = Odds Ratio; CI = Confidence Interval.

symptom variable. Similarly, sensitivity analysis in the subgroup of patients with resolved symptoms did not show a statistically significant influence of overall symptom duration on MRI-DWI-positivity (Supplemental Table 5).

Harrel's c-statistic illustrating model performance of the final multivariable logistic regression model including symptom duration was 0.72 (95%CI 0.69-0.77).

In the subgroup of patients without any motor or speech symptoms ($n = 810/1028$ (78.8%)), limb ataxia (OR 2.71, 95%CI 1.17–5.79) and the symptom pair any sensory symptom/limb ataxia (OR 4.89, 95%CI 1.23–17.42) were significantly associated with MRI-DWI-positivity on univariable analysis, but this was not preserved on multivariable logistic regression analysis (Supplemental Table 6). Again, overall symptom duration was not significantly associated with MRI-DWI-positivity in this subgroup (OR 1.00, 95%CI 0.99–1.00).

Discussion

In this post-hoc analysis of patients selected by their presentation with low-risk transient or persistent minor neurological symptoms, we observed an association of various clinical factors with the presence of DWI-positive brain MRI performed within 8 days from symptom onset. Increasing age, presentation with motor or speech symptoms ≤ 5 min, and no history of a previous identical event were positively associated with the presence of DWI-positive MRI whereas female sex, presentation with dizziness and gait instability, normal neurological exam and resolved symptoms showed a negative association. Additional clinical factors, namely symptom duration, did not show a significant association with MRI-DWI-positivity. Predictive ability for MRI-DWI-positivity of these easily available clinical factors was only moderate. In comparison to the main analysis of the DOUBT study, this post-hoc analysis provides a more extensive and detailed assessment of clinical characteristics and symptoms and their associations with MRI-DWI-positivity even though the majority of those additional characteristics was not significantly associated.

Associations of clinical factors with the presence of DWI-positive brain MRI in patients with TIA and minor stroke have been investigated and reported previously, including age and presentation with motor or speech symptoms.[6,17,18] Most of these previous analyses were performed in an overall population of patients diagnosed with a TIA, and we could now confirm these associations also for the subgroup of patients presenting with low-risk transient or minor persistent neurological symptoms. The negative association of female sex and MRI-DWI-positivity might be explained by higher a proportion of stroke mimics in women,[19] and sex-specific differences in clinical presentation and diagnosis of events in the DOUBT population have been investigated in detail previously.[20] In addition, we observed an influence of any abnormal findings on neurological exam (potentially revealing subtle persistent deficits), the absence of previous identical episodes (decreasing the likelihood of differential diagnoses of stroke mimics such as epileptic seizures or migraines, which usually present as stereotypical and identical episodes) and ongoing symptoms at the time of neurological assessment on the presence of DWI-positive MRI. These easily available clinical characteristics might be able to add information about the possibility of finding acute infarcts on MRI to the abovementioned, already established clinical factors.

In addition to knowing which clinical parameters help to identify patients with DWI-positive MRI, it is also important to be aware of clinical variables that have limited ability to predict acute ischemic lesions. In contrast to previous studies reporting associations of symptom duration with an increased risk of recurrent ischemic events and the presence of acute ischemic lesions on brain MRI,[6,18,21] we did not observe a statistically significant association between overall symptom duration and MRI-DWI-positivity in our patient sample. Furthermore, there was no significant influence of interactions between specific symptoms and symptom duration. According to a previously published analysis, physicians interpret short duration symptoms as less consequential and prefer to perform MRI in patients with TIA or minor stroke if neurological deficits last for more than 6 hours.[22] In light of our results however, symptom duration alone might not be an optimal choice to guide decisions about whether to perform MRI in patients with low-risk neurological events or not.

Patient assessment in the DOUBT study included a thorough evaluation of neurological symptoms and detailed clinical symptom classification. We investigated all possible symptom pairs and triplets to cover a broad spectrum of clinical presentations of included patients. However, in addition to the abovementioned and previously often reported association of motor and speech symptoms with MRI-DWI-positivity, we only observed a statistically significant negative association for the symptom pair gait instability and dizziness. Any other symptoms or symptom combinations were not significantly associated with MRI-DWI-positivity. In a sensitivity analysis restricted to patients without any motor or speech symptoms no clinical symptom or symptom combination was significantly associated with MRI-DWI-positivity on multivariable analysis. Even though this analysis might be limited in its power by low numbers of patients in many of these symptom subgroups, this fact also highlights the heterogeneity of clinical presentations of patients with low-risk transient or minor ischemic events. Overall, our findings indicate that apart from motor and speech symptoms and dizziness/gait instability, presenting symptoms are not reliable enough to predict the presence or absence of DWI-positive MRI. In addition, the overall discriminative ability of the logistic regression model to predict MRI-DWI-positivity in the individual patient was moderate, indicated by a c-statistic of 0.72. In comparison, a previous study reports a discriminative ability of different versions of the ABCD-score as well as the Dawson-score for the prediction of MRI-DWI-positivity in patients with TIA ranging between an Area Under the Curve (AUC)/c-statistic of 0.63 and 0.85.[23] Even though in clinical practice knowledge of certain clinical

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phenotypes of patients with low-risk events which are highly associated with MRI-DWI-positivity or a clinical prediction score of MRI-DWI-positivity in these patients would be very helpful, we are unfortunately not able to provide such information based on these results. Given the heterogeneity of clinical presentations, larger trials covering higher numbers of these different phenotypes would be needed to improve prediction capability.

Importantly, there are limitations to MR-imaging. First, even though MRI-DWI-positivity is highly reliable in detecting acute ischemia on MRI, not all patients with true ischemia might be captured by MRI (DWI-negative ischemia). Therefore, a DWI-positive MRI can confirm the diagnosis of an ischemic event, but a DWI-negative MRI cannot completely rule out that an event was ischemic in nature; these patients could not be accounted for in our analysis. In addition, an observed DWI-lesion might not be causative for a patient's symptoms. A detailed analysis of infarct patterns and a correlation to presenting symptoms was not performed within the scope of this analysis. However, any DWI-lesion, even if it might not necessarily anatomically correspond to a patient's symptoms, can still be considered a marker of ischemia, and support the diagnosis of an ischemic event.

Our study has further limitations; first, this is a post-hoc analysis of a prospective cohort study, which had the primary purpose of evaluating the frequency of MRI-DWI-positivity, but not to assess predictors of acute ischemia. Second, frequencies of specific symptoms and especially frequencies of specific symptom combinations were relatively low, which limits the possibilities to accurately assess their influence on MRI-DWI-positivity. Third, the restriction of a maximum symptom duration of 5 minutes for the presentation with motor or speech symptoms as per the main study inclusion/exclusion criteria might affect calculations of the influence of symptom duration on MRI-DWI-positivity. However, this restriction is necessary to comply with the definition of low-risk ischemic events and cannot be avoided for this analysis. Last, the DOUBT-dataset might not cover all potential predictors of MRI-DWI-positivity and there might be additional, unmeasured characteristics which could improve the model's predictive capability.

Conclusion

Previously reported associations of age, motor symptoms and aphasia with MRI-DWI-positivity in clinically high-risk patients also apply to patients with low-risk neurological events. In addition, an abnormal neurological exam, ongoing symptoms and absence of any previous identical event are also associated with MRI-DWI-positivity in low-risk patients. However, additional clinical characteristics such as overall symptom duration or any other lateralized or non-lateralized neurological symptoms and symptom combinations were not associated with the diagnosis of acute ischemic lesions on brain imaging, and the overall predictive ability for MRI-DWI-positivity of easily available clinical characteristics was only moderate. In conclusion, the combination of clinical characteristics based on a detailed history of a neurological event and neurological exam can be helpful in assessing the risk of acute ischemia on MRI, but their predictive ability is limited by the heterogeneity of clinical presentations. Based on these results, even the clinically suspected low-risk TIA/minor stroke patient still needs an MRI to confirm the diagnosis of acute ischemia and future studies will need to evaluate the benefit of a thorough etiological work up and secondary preventive measures in this population. In addition, further research in larger and more diverse cohorts might be helpful in improving the prediction of MRI-DWI-positivity in patients with low-risk events early during the course of their presentation (i.e. in the emergency department setting) and to improve real-world clinical practice (e.g. adequate triaging of patients for admission and outpatient work-up).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2024.274.

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References

1. Wu CM, McLaughlin K, Lorenzetti DL, Hill MD, Manns BJ, Ghali WA. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. *Arch Intern Med*. 2007;167:2417–22. DOI: 10.1001/archinte.167.22.2417.
2. Amarenco P, Lavallée PC, Labreuche J, et al. One-year risk of stroke after transient ischemic attack or minor stroke. *N Engl J Med*. 2016;374:1533–42. DOI: 10.1056/NEJMoa1412981.

3. Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet*. 2007;370:1432–42. DOI: 10.1016/s0140-6736(07)61448-2.
4. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007;369:283–92. DOI: 10.1016/s0140-6736(07)60150-0.
5. Coutts SB, Modi J, Patel SK, Demchuk AM, Goyal M, Hill MD. CT/CT angiography and MRI findings predict recurrent stroke after transient ischemic attack and minor stroke: results of the prospective CATCH study. *Stroke*. 2012;43:1013–7. DOI: 10.1161/strokeaha.111.637421.
6. Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet*. 2005;366:29–36. DOI: 10.1016/s0140-6736(05)66702-5.
7. Sheehan OC, Merwick A, Kelly LA, et al. Diagnostic usefulness of the ABCD2 score to distinguish transient ischemic attack and minor ischemic stroke from noncerebrovascular events: the North Dublin TIA study. *Stroke*. 2009;40:3449–54. DOI: 10.1161/strokeaha.109.557074.
8. Tuna MA, Rothwell PM. Diagnosis of non-consensus transient ischaemic attacks with focal, negative, and non-progressive symptoms: population-based validation by investigation and prognosis. *Lancet*. 2021;397:902–12. DOI: 10.1016/s0140-6736(20)31961-9.
9. Hurford R, Li L, Lovett N, Kubiak M, Kuker W, Rothwell PM. Prognostic value of "tissue-based" definitions of TIA and minor stroke: population-based study. *Neurology*. 2019;92:e2455–e61. DOI: 10.1212/wnl.0000000000007531.
10. Yaghi S, Rostanski SK, Boehme AK, et al. Imaging parameters and recurrent cerebrovascular events in patients with minor stroke or transient ischemic attack. *JAMA Neurol*. 2016;73:572–8. DOI: 10.1001/jamaneurol.2015.4906.
11. Coutts SB, Simon JE, Eliasziw M, et al. Triaging transient ischemic attack and minor stroke patients using acute magnetic resonance imaging. *Ann Neurol*. 2005;57:848–54. DOI: 10.1002/ana.20497.
12. Brazzelli M, Chappell FM, Miranda H, et al. Diffusion-weighted imaging and diagnosis of transient ischemic attack. *Ann Neurol*. 2014;75:67–76. DOI: 10.1002/ana.24026.
13. Coutts SB, Moreau F, Asdaghi N, et al. Rate and prognosis of brain ischemia in patients with lower-risk transient or persistent minor neurologic events. *JAMA Neurol*. 2019;76:1439–45. DOI: 10.1001/jamaneurol.2019.3063.
14. Geethanath S, Vaughan JT Jr. Accessible magnetic resonance imaging: a review. *J Magn Reson Imaging*. 2019;49:e65–e77. DOI: 10.1002/jmri.26638.
15. Bhat SS, Fernandes TT, Poojar P, et al. Low-field MRI of stroke: challenges and opportunities. *J Magn Reson Imaging*. 2021;54:372–90. DOI: 10.1002/jmri.27324.
16. Harrell FE Jr., Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA*. 1982;247:2543–6.
17. Crisostomo RA, Garcia MM, Tong DC. Detection of diffusion-weighted MRI abnormalities in patients with transient ischemic attack: correlation with clinical characteristics. *Stroke*. 2003;34:932–7. DOI: 10.1161/01.Str.0000061496.00669.5e.
18. Purroy F, Montaner J, Rovira A, Delgado P, Quintana M, Alvarez-Sabín J. Higher risk of further vascular events among transient ischemic attack patients with diffusion-weighted imaging acute ischemic lesions. *Stroke*. 2004;35:2313–9. DOI: 10.1161/01.Str.0000141703.21173.91.
19. Merino JG, Luby M, Benson RT, et al. Predictors of acute stroke mimics in 8187 patients referred to a stroke service. *J Stroke Cerebrovasc Dis*. 2013;22:e397–403. DOI: 10.1016/j.jstrokecerebrovasdis.2013.04.018.
20. Yu AYX, Hill MD, Asdaghi N, et al. Sex differences in diagnosis and diagnostic revision of suspected minor cerebral ischemic events. *Neurology*. 2021;96:e732–e9. DOI: 10.1212/wnl.0000000000011212.
21. Shah SH, Saver JL, Kidwell CS, et al. A multicenter pooled, patient-level data analysis of diffusion-weighted MRI in TIA patients. *Stroke*. 2007;38:463.
22. Chaturvedi S, Ofner S, Baye F, et al. Have clinicians adopted the use of brain MRI for patients with TIA and minor stroke? *Neurology*. 2017;88:237–44. DOI: 10.1212/wnl.0000000000003503.
23. Yuan J, Jia Z, Song Y, et al. Incidence and predictors of acute ischemic lesions on brain magnetic resonance imaging in patients with a clinical diagnosis of transient ischemic attack in China. *Front Neurol*. 2019;10:764. DOI: 10.3389/fneur.2019.00764.