Combining magnetic resonance imaging within six-hours of symptom onset with clinical follow-up at 24 h improves prediction of 'malignant' middle cerebral artery infarction

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Background **A large diffusion-weighted imaging lesion ≤six-hours of symptom onset was found to predict the development of 'malignant' middle cerebral artery infarction with high specificity, positive predictive value, and negative predictive value, but sensitivity was low.**

Hypothesis **We tested the hypothesis that sensitivity can be improved by adding information from clinical follow-up examination after 24 h.**

Methods **We analyzed data from a prospective, multicenter, observational cohort study of patients with acute ischemic stroke and middle cerebral artery occlusion studied by stroke magnetic resonance imaging ≤six-hours of symptom onset. We used the National Institutes of Health Stroke Scale to assess severity of symptoms after 24 h. We used the Classification and Regression Trees analysis to define the optimal thresholds of diffusion-weighted imaging lesion volume and the National Institutes of Health Stroke Scale after 24 h in patients developing 'malignant' middle cerebral artery infarction. We calculated sensitivity, specificity, positive predictive value, and negative predictive value for two simple predictive models based on acute diffusion-weighted imaging lesion volume alone and acute diffusion-weighted imaging lesion volume together with the National Institutes of Health Stroke Scale after 24 h.**

Results **Of 135 patients, 27 (20%) developed a 'malignant' middle cerebral artery infarction. The Classification and Regression Trees analysis identified acute diffusion-weighted imaging lesion ≥78 ml and the National Institutes of Health Stroke Scale score after 24 h ≥22 as optimal cut-offs. Inclusion of the National Institutes of Health Stroke Scale score after 24 h in a simple two-step decision tree increased sensitivity from 0·59 to 0·79, while specificity, positive predictive value, and negative predictive value remained largely unchanged.**

Conclusion **Clinical follow-up examination after 24 h helps identify patients at risk of 'malignant' middle cerebral artery infarction that are missed by predictive algorithms based on early diffusion-weighted imaging lesion volume alone.**

Key words: acute stroke, malignant middle cerebral artery infarction, diffusion-weighted, magnetic resonance imaging

Introduction

The prognosis of complete middle cerebral artery (MCA) territory stroke is poor which largely relates to the fact that space-occupying mass effect develops over the initial five-days after onset (1–3). Mortality remains about 80% under conservative treatment (4). Thus, the labeling 'malignant' MCA infarction (MMI) was introduced (1). Randomised controlled trials of decompressive craniectomy demonstrated a marked reduction of mortality and improvement in functional outcome associated with early hemicraniectomy within 48 h of symptom onset while conforming the poor high mortality under conservative treatment (5). Furthermore, there is evidence that mortality rates may be lower the earlier decompressive surgery is performed (6–8). As a consequence, it is of high clinical interest to identify patients who are likely to develop an MMI early in the clinical course of the disease.

Several clinical and imaging parameters were identified as predictors of the development of MMI. While clinical findings such as severe neurological deficit like coma on admission (9) and computed tomography (CT) findings such as extended early ischemic signs (10,11) showed rather low predictive values, acute lesion volume on diffusion-weighted imaging (DWI) was reported to predict the development of MMI with high predictive values (12,13). In a recent prospective multicenter study of patients studied within six-hours of symptom onset a large DWI lesion volume ≥82 ml predicted the development of MMI with high specificity (0·98), positive predictive value (PPV) (0·88), and negative predictive value (NPV) (0·90), but low sensitivity (0·52) (13).

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Hypothesis

In the current study, we tested the hypothesis that sensitivity of the prediction of MMI can be improved by adding information from clinical follow-up examination after 24 h.

Methods

Patients and treatment protocol

We analyzed data from a prospective, multicenter, observational study of patients with acute ischemic stroke due to MCA main stem occlusion studied by DWI within six hours of symptom onset (13). Inclusion criteria were acute ischemic stroke; stroke magnetic resonance imaging (MRI) performed within six-hours of symptom onset including at least DWI and time of flight-magnetic resonance angiography (TOF-MRA); occlusion of the MCA main stem alone or in combination with occlusion of the extra- or intracranial carotid artery (ICA) diagnosed by TOF-MRA; and informed consent. All patients were treated according to national and international guidelines at stroke units or neurological intensive care units including conservative treatment of increased intracranial pressure and decompressive surgery. Treatment decisions were made at the individual centers on an individual basis and independent of the study results (for a detailed description, see the report of the original study (13)).

Clinical assessment

Experienced neurologists assessed the severity of neurological deficit on admission and after 24 h using the National Institute of Health Stroke Scale (NIHSS) (14). The diagnoses of MMI based on the definition used in recent randomized controlled trials are (5): (1) clinical signs of large MCA territory infarction with an NIHSS score >18 and a level of consciousness of ≥1 on item 1a of the NIHSS either on admission or after secondary deterioration; (2) large space-occupying MCA infarction on follow-up MRI or CT of at least two thirds of the MCA territory with compression of lateral ventricles or midline shift; and (3) no other obvious cause for neurological deterioration.

MRI protocol – image acquisition and analysis

MRI studies were performed on 1·5-Tesla echoplanar equipped clinical whole body scanners. Acute stroke MRI protocols were standardized within the study, but details of sequence parameters in MRI protocols varied between the individual centers due to different scanner models and equipment. Acute stroke MRI protocols comprised an axial DWI sequence, a perfusion imaging sequence, a TOF-MRA of the intracranial arteries, a T2*-weighted gradient-echo sequence for the exclusion of intracranial hemorrhage, and a fluid-attenuated inversion recovery sequence with a total scanning time of <15 mins (15). Diagnosis of vessel occlusion was primarily based on intracranial TOF-MRA. In case of diagnostic uncertainty regarding ICA-status, a contrast-enhanced MRA of the supraaortic vessels was added to the protocol. Being part of the inclusion criteria, vessel occlusion on TOF-MRA was determined by experienced neuroradiologists in the individual centers.

All MRI scans were transferred to the coordinating center and analyzed by an investigator blinded to primary outcome. Diffusion and perfusion lesion volumes were measured on apparent diffusion coefficient and time-to-peak maps using a semiautomatic threshold procedure as described previously (16).

Statistical analysis

Patients with MMI and without MMI (No MMI) were compared regarding clinical and imaging baseline parameters using Fisher's exact test or Student's *t*-test as appropriate. *P* values are reported without correction for multiple testing.

Binary logistic regression analysis was used to test the performance of two models incorporating acute DWI lesion volume alone (model A) or combined with NIHSS score after 24 h (model B) to predict MMI. We compared model performance using the −2 log-likelihood test (17).

We used Classification and Regression Trees (CART) analysis to generate binary trees and identify optimal thresholds of acute DWI lesion volume and NIHSS score values after 24 h to predict MMI. We calculated sensitivity, specificity, PPV, and NPV for two simple decision trees based on the cut-offs generated by CART analysis.

Results

A total of 140 patients were enrolled into the original study in four centers. For the current analysis, we excluded five patients because follow-up NIHSS scores after 24 h were missing. Of 135 patients included, 27 (20%) developed MMI while 108 (80%) did not (No MMI). See Table 1 for group comparison. Patients developing MMI presented with more severe symptoms on admission (mean NIHSS 19·7 vs. 15·5). Combined MCA + ICA occlusion was more frequent in MMI patients (51·9 vs. 24·1%). Acute diffusion lesion

Table 1 Group comparison MMI vs. No MMI

	MMI ($n = 27$)	No MMI ($n = 108$)	*P* value
NIHSS on admission	19·7 (18·1–21·3)	15·5 (14·6–16·4)	<0·001
Occlusion ICA + MCA	14 51·9%	26 24·1%	0·009
DWI lesion volume (ml)	57·8 (38·6–86·4)	13·9 (11·4–16·9)	<0·001
NIHSS after 24 h	26·5 (22·9–30·1)	12·8 (11·5–14·0)	<0·001
Female gender	17 63·0%	55 50·9%	0·288
Left hemispheric stroke	15 55·6%	62 57·4%	1
Age	60 (54·4–65·6)	65·5 (63·1–68·0)	0·053

Values are given as mean (95% CI) or count (%). Group comparison was performed using Student's *t*-test or Fisher's exact test as appropriate.
DWI, diffusion-weighted imaging; ICA, intracranial carotid artery; MCA, middle cerebral artery; MMI, malignant middle cerebral artery infarction; NIHSS, National Institutes of Health Stroke Scale.

volumes were larger in MMI patients (mean 57·8 vs. 13·9 ml). Furthermore, NIHSS after 24 h was significantly higher in patients developing MMI (26·5 vs. 12·8) (Table 1). Groups were comparable as regards gender, side of infarction, and stroke etiology. The mean time from symptom onset to imaging was <three hours in both groups (165 vs. 150·5 mins).

The inclusion of NIHSS after 24 h in model B significantly improved model performance as compared with model A (−2 log-likelihood ratio 54·9 vs. 88·6, $P < 0·001$). CART analysis identified a DWI lesion ≥78 ml and an NIHSS score after 24 h ≥22 as best cut-off values. The predictive values for two simple decision trees incorporating these cut-offs are given in Table 2. Adding NIHSS after 24 h to the decision tree sensitivity increased from 0·59 to 0·79, while specificity (0·98 vs. 0·96), PPV (0·89 vs. 0·85), and NPV (0·91 vs. 0·94) remained largely unchanged. The proportion of correct classifications slightly increased from 122/135 (90%) to 125/135 (93%). However, within the group of patients with MMI, the number of correct classifications markedly increased from 16/27 (59%) to 23/27 (85%) (see Fig. 1).

Table 2 Predictive values for both models for the prediction of MMI

	Sensitivity	Specificity	NPV	PPV
Model A (acute DWI lesion volume ≥78 ml)	0·59	0·98	0·91	0·89
Model B (acute DWI lesion volume ≥78 ml and NIHSS after 24 h)	0·79	0·96	0·94	0·85

DWI, diffusion-weighted imaging; NIHSS, National Institutes of Health Stroke Scale; NPV, negative predictive value; PPV, positive predictive value130.

Discussion

The main finding of our study is the improvement of sensitivity of predicting space-occupying MCA infarction by combining acute MRI with clinical follow-up at 24 h. In a large multicenter study, we previously demonstrated that acute DWI lesion volume measured as early as within the first six-hours of stroke predicts the development of MMI with high specificity, PPV, and NPV, but low sensitivity (13). We now demonstrate that the addition of a simple clinical examination 24 h after admission improves sensitivity by 20% to almost 80%, while the other predictive values continue to be high. The combined model of acute DWI lesion volume and clinical examination using the NIHSS after 24 h correctly predicted the clinical course (MMI or No MMI) in 93% of patients and correctly identified 85% of patients developing MMI. The suggested model is simple and easy to incorporate into clinical decision making in patients with large MCA infarction and will help identify patients for early decompressive surgery.

It was noted previously that the dynamics of acute ischemic lesion evolution sets limitations to the prediction of space-occupying MCA infarction by measurements of DWI lesion at a very early stage (13,18). Further lesion growth beyond the first six hours of stroke depends on vessel occlusion, recanalization, collateral status, and numerous other factors which cannot be captured at the time-point of acute brain imaging within the first six hours. Thus, the incorporation of a follow-up measurement at a time-point when the largest part of infarct growth has happened to improve the prediction of malignant course is straightforward. While follow-up MRI might be challenging in this group of severely affected patients, a clinical follow-up examination using a standardized and well-established scale as the NIHSS is quick and

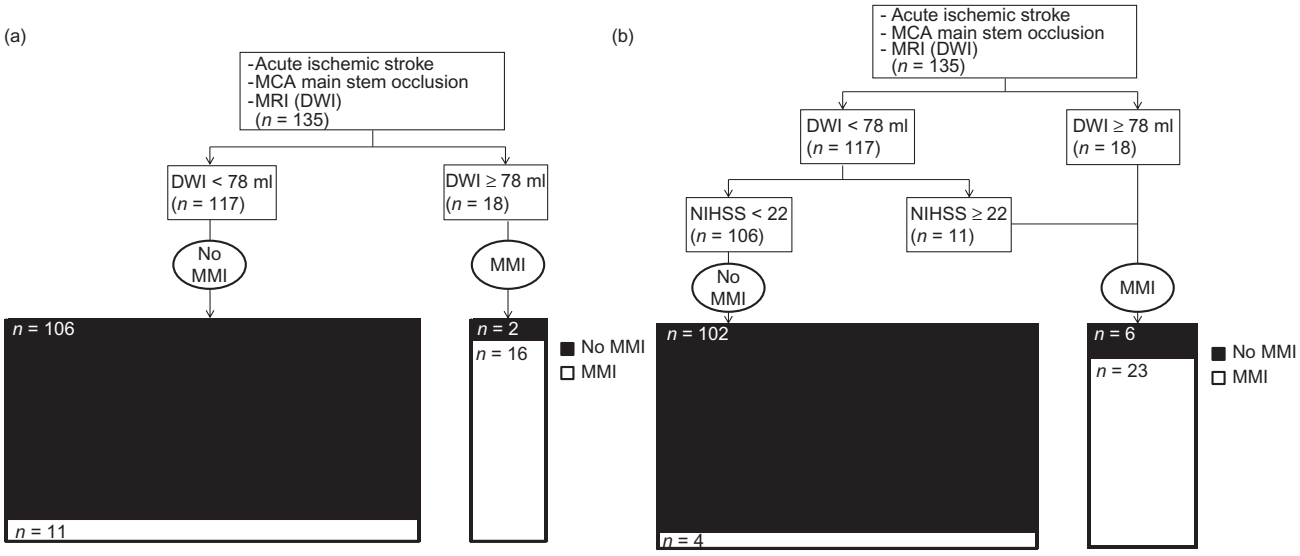

Fig. 1 Model A shows the single-step decision tree dividing patients into two groups based on DWI lesion volume (< or ≥78 ml). The correct classifications is shown by the color of the bars (MMI = white, No MMI = black). There were 11 false negative and two false positive predictions while 106/108 patients were correctly classified negative (No MMI) and 16/27 patients were correctly classified positive (MMI). Model B shows the two-step decision tree model classifying patients based on DWI lesion volume and NIHSS score after 24 h (< or ≥22). This algorithm results in four false negative and six false positive predictions, while 102/108 patients are correctly classified negative and 23/27 patients are correctly classified positive. DWI, diffusion-weighted imaging; MCA, middle cerebral artery; MMI, malignant middle cerebral artery infarction; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale.

easily performed. Adding clinical information in terms of the NIHSS score after 24 h to the acute DWI lesion volume in our predictive model clearly improved sensitivity and the total number of correctly classified patients with MMI. Thus, we conclude that a large number of patients developing malignant MCA stroke who are missed by a predictive model based on acute DWI lesion volume alone can be detected by a simple clinical test after 24 h.

There were still a number of patients misclassified even after incorporation of clinical follow-up into the predictive model. This might result from the fact that 24 h still represents a rather early time-point in the development of space-occupying brain edema following ischemic stroke. It is well known that the maximum of brain swelling is reached at some time between days two and five after symptom onset (2,3). In previous studies, neurological deterioration was found to occur as late as beyond 48 h in one third of patients with massive MCA infarction (19). This might limit the predictive value of a clinical follow-up test performed as early as after 24 h.

Our study has certain limitations. Although one of the largest case series of large MCA stroke patients reported, the sample size is still small, making the results susceptible to effects of chance and precluding reasonable subgroup analyses, for example, the analysis of specific NIHSS cut-off values for depending on the side of infarction. Although a well-established standardized rating scale, the NIHSS has its limitations, including its stronger weighting of left hemispheric strokes, and a limited use in mechanically ventilated patients. In these cases, follow-up imaging by either MRI or CT might be needed to identify patients developing space-occupying brain swelling. It is well known that the NIHSS performs differently in right and left hemispheric strokes (20). Looking at right and left MCA strokes separately in our sample resulted in different optimal 24 h NIHSS threshold values for the improvement of prediction of MMI by clinical follow-up (right MCA stroke: NIHSS >18; left MCA stroke: NIHSS >22). However, as patient numbers in these subgroups are rather small, these analyses have to be looked at with caution. Nevertheless future studies should take into account the interaction between clinical scales and side of infarction in predictive models of outcome of severe stroke. In our sample follow-up imaging was not part of the prospective evaluation and not standardized as toward modality and time-point. Thus, we do not have the data to judge the predictive value of early follow-up brain imaging. Future studies will have to elucidate the role of follow-up imaging in the prediction of MMI.

In our study, the optimal threshold for DWI lesion volume to predict MMI identified by CART analysis was ≥78 ml which is very close to the previously reported threshold of ≥82 ml (12). The second splitting revealed an NIHSS score ≥22 as the optimal threshold to predict MMI in patients with initial DWI lesion <78 ml. A score of ≥22 on the NIHSS reflects a very severe neurological deficit with corresponding poor outcome. An NIHSS score of ≥16 at day 7 after stroke onset was previously reported to be associated with severe disability (21). It is of further interest that age was found to be different between both groups in the descriptive analysis, with MMI patients being younger. However, this relation did not survive in multivariate analysis (13), nor was CART analysis able to generate a specific age threshold that would have allowed to separate patients with MMI from those without.

In conclusion, MRI with DWI predicts the development of malignant MCA infarction in patients with severe MCA stroke within the first six-hours of stroke with high specificity, NPV, and PPV, while sensitivity remains low. Sensitivity can be markedly improved by adding early clinical follow-up examination using the NIHSS after 24 h. Both the measurement of acute DWI lesion volume and clinical follow-up after 24 h using the NIHSS can easily be incorporated in routine clinical practice and will help in guiding acute treatment decisions in patients with severe MCA stroke, such as the performance of decompressive surgery.

References

1 Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. *Arch Neurol* 1996; **53:**309–15.
2 Ng LK, Nimmannitya J. Massive cerebral infarction with severe brain swelling: a clinicopathological study. *Stroke* 1970; **1:**158–63.
3 Shaw CM, Alvord EC, Jr, Berry RG. Swelling of the brain following ischemic infarction with arterial occlusion. *Arch Neurol* 1959; **1:**161–77.
4 Berrouschot J, Sterker M, Bettin S, Koster J, Schneider D. Mortality of space-occupying ('malignant') middle cerebral artery infarction under conservative intensive care. *Intensive Care Med* 1998; **24:**620–3.
5 Vahedi K, Vicaut E, Mateo J *et al.* Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (decimal trial). *Stroke* 2007; **38:**2506–17.
6 Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB. Surgical decompression for space-occupying cerebral infarction (the hemicraniectomy after middle cerebral artery infarction with life-threatening edema trial [hamlet]): a multicentre, open, randomised trial. *Lancet Neurol* 2009; **8:**326–33.
7 Cho DY, Chen TC, Lee HC. Ultra-early decompressive craniectomy for malignant middle cerebral artery infarction. *Surg Neurol* 2003; **60:**227–32; discussion 232-223.
8 Schwab S, Steiner T, Aschoff A *et al.* Early hemicraniectomy in patients with complete middle cerebral artery infarction. *Stroke* 1998; **29:**1888–93.
9 Pullicino PM, Alexandrov AV, Shelton JA, Alexandrova NA, Smurawska LT, Norris JW. Mass effect and death from severe acute stroke. *Neurology* 1997; **49:**1090–5.
10 Krieger DW, Demchuk AM, Kasner SE, Jauss M, Hantson L. Early clinical and radiological predictors of fatal brain swelling in ischemic stroke. *Stroke* 1999; **30:**287–92.
11 Kasner SE, Demchuk AM, Berrouschot J *et al.* Predictors of fatal brain edema in massive hemispheric ischemic stroke. *Stroke* 2001; **32:**2117–23.
12 Oppenheim C, Samson Y, Manai R *et al.* Prediction of malignant middle cerebral artery infarction by diffusion-weighted imaging. *Stroke* 2000; **31:**2175–81.
13 Thomalla G, Hartmann F, Juettler E *et al.* Prediction of malignant middle cerebral artery infarction by magnetic resonance imaging within 6 hours of symptom onset: a prospective multicenter observational study. *Ann Neurol* 2010; **68:**435–45.
14 Brott T, Adams HP, Jr, Olinger CP *et al.* Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989; **20:**864–70.
15 Fiebach JB, Schellinger PD, Gass A *et al.* Stroke magnetic resonance imaging is accurate in hyperacute intracerebral hemorrhage: a multicenter study on the validity of stroke imaging. *Stroke* 2004; **35:**502–6.

16 Thomalla GJ, Kucinski T, Schoder V *et al.* Prediction of malignant middle cerebral artery infarction by early perfusion- and diffusion-weighted magnetic resonance imaging. *Stroke* 2003; **34:**1892–9.
17 R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria, R Foundation for Statistical Computing, 2009.
18 Neumann-Haefelin T, Sitzer M, du Mesnil de Rochemont R, Lanfermann H. Prediction of malignant MCA infarction with DWI: pitfalls in hyperacute stroke. *Stroke* 2001; **32:**580–3.
19 Qureshi AI, Suarez JI, Yahia AM *et al.* Timing of neurologic deterioration in massive middle cerebral artery infarction: a multicenter review. *Crit Care Med* 2003; **31:**272–7.
20 Woo D, Broderick JP, Kothari RU *et al.* Does the National Institutes of Health stroke scale favor left hemisphere strokes? *Stroke* 1999; **30:**2355–9.
21 Adams HP, Jr, Davis PH, Leira EC *et al.* Baseline NIH stroke scale score strongly predicts outcome after stroke: a report of the trial of org 10172 in acute stroke treatment (toast). *Neurology* 1999; **53:**126–31.