

Original Paper

# Predictors of Outcome following Stroke due to Isolated M2 Occlusions

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## Key Words

M2 occlusion · Outcome · Cortical infarct · Stroke · Thrombolysis

## Abstract

**Background:** Factors influencing outcome after cerebral artery occlusion are not completely understood. Although it is well accepted that the site of arterial occlusion critically influences outcome, the majority of studies investigating this issue has focused on proximal large artery occlusion. To gain a better understanding of factors influencing outcome after distal large artery occlusion, we sought to assess predictors of outcome following isolated M2 middle cerebral artery occlusion infarcts. **Methods:** We retrospectively analyzed patients with isolated acute M2 occlusion admitted to a single academic center from January 2010 to August 2012. Baseline clinical, laboratory imaging, and outcome data were assessed from a prospectively collected database. Factors associated with a modified Rankin Scale (mRS) score  $\leq 2$  in univariable analyses ( $p < 0.05$ ) were entered into multivariable logistic regression analysis. The Admission National Institutes of Health Stroke Scale (aNIHSS) score, age, and infarct volume were also entered as dichotomized variables. Receiver operating characteristic curves were plotted to determine the optimal aNIHSS score, infarct volume, and age cut points predicting an mRS score  $\leq 2$ . Optimal thresholds were determined by maximizing the Youden index. Respective multivariable logistic regression analyses were used to identify independent predictors of a good 90-day outcome (mRS score  $\leq 2$ ; primary analysis) as well as 90-day mortality (secondary outcome). **Results:** 90 patients with isolated M2 occlusion were included in the final analyses. Of these, 69% had a good 90-day outcome which was associated with age  $< 80$

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years ( $p = 0.007$ ), aNIHSS  $<10$  ( $p = 0.002$ ), and infarct volume  $\leq 26$  ml ( $p < 0.001$ ). Notably, 20% of patients (64% of those with a poor outcome) had died by 90 days. Secondary analysis for 90-day mortality was performed. This analysis indicated that infarct volume  $>28$  ml (OR 11.874, 95% CI 2.630–53.604,  $p = 0.001$ ), age  $>80$  years (OR 4.953, 95% CI 1.087–22.563,  $p = 0.039$ ), need for intubation (OR 7.788, 95% CI 1.072–56.604), and history of congestive heart failure (OR 5.819, 95% CI 1.140–29.695) were independent predictors of 90-day mortality (20% of all included patients). **Conclusion:** While the majority of patients with isolated M2 occlusion stroke has a good 90-day outcome, a substantial proportion of subjects dies by 90 days, as identified by a unique subset of predictors. The knowledge gained from our study may lead to an improvement in the prognostic accuracy, clinical management, and resource utilization in this patient population.

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## Introduction

Acute stroke treatment has evolved significantly over the last two decades, which is in part due to an improved understanding of factors that determine outcome [1]. It is now well understood that the site of arterial occlusion critically influences outcome following acute anterior circulation ischemic stroke [2, 3]. However, the majority of studies investigating this issue has focused on proximal large artery occlusion involving the internal carotid artery (ICA) and proximal middle cerebral artery (MCA) as these represent a particular challenge for medical management [2–4]. For example, recanalization following intervention in ICA and proximal MCA occlusion has been reported to be generally poor [2–4], and has been associated with larger infarct volumes and rarely with good functional outcomes ( $<40\%$ ) even in affected patients with aggressive interventions [2–6]. Conversely, distal MCA occlusions have been associated with higher rates of recanalization following intervention, smaller infarct volumes, and a favorable outcome in the majority of patients ( $>50\%$ ) [2–4]. Yet, the number of investigated patients in these studies was relatively small ( $n \leq 100$ ) and most ( $>80\%$ ) were subjected to intravenous (i.v.) or endovascular recanalization approaches. Hence, there remains a paucity of information regarding factors modulating outcome following isolated distal MCA occlusion.

Therefore, we sought to investigate predictors of 90-day functional outcome in patients with infarction due to isolated M2 segment occlusion. Specifically, we assessed for factors associated with a good versus poor 90-day outcome (primary outcome) as well as 90-day mortality (secondary outcome).

## Methods

### Study Population

This study was a retrospective analysis of our prospective database including consecutive acute ischemic stroke patients admitted to a single academic center from January 2010 to August 2012. Only patients with isolated M2 occlusion on computed tomography angiography (CTA) performed at admission were included.

All patients underwent head CT or brain magnetic resonance imaging (MRI) within 7 days after ischemic stroke. Patient demographics, comorbidities, preadmission medications, laboratory data, intubation, requirement for admission at the intensive care unit (ICU), length of hospital stay (LOS), treatment modality [conservative management vs. acute intervention (i.v. thrombolysis and endovascular recanalization)], and stroke etiology [according to the

Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification] [7] after completion of diagnostic evaluation were collected in all patients. Admission National Institutes of Health Stroke Scale (aNIHSS) and modified Rankin Scale (mRS) scores were assessed at the time of presentation and at 90 days by a stroke-trained physician or study nurse certified in mRS [8]. This study was reviewed and approved by our Institutional Review Board.

#### *Image Review and Analysis*

CT, CTA, and diffusion-weighted imaging were reviewed independently by study physicians masked to clinical data, follow-up scans, patient variables, and outcomes. Details of the used imaging protocols have been previously described [9]. The MCA-M2 segment was defined as the segment extending from the bifurcation/trifurcation of the MCA to the top of the Sylvian fissure to further division [10]. The M2 portion was conceptually further divided into three segments of equal length: proximal, middle, and distal. The ischemic lesion volume was measured manually on follow-up imaging. Hemorrhagic transformation was defined according to the European Cooperative Acute Stroke Study II (ECASS II) criteria [11]. For analysis, hemorrhagic transformation was dichotomized into parenchymal hemorrhage (PH) versus non-PH.

#### *Statistics*

Continuous variables are reported as mean  $\pm$  SD or as median  $\pm$  interquartile range (IQR). Categorical variables are reported as proportions. The primary analysis was performed to determine factors associated with a good 90-day outcome (mRS 0–2). In light of significant mortality, we further sought to investigate for factors that were independently associated with 90-day mortality in a secondary analysis. Receiver operating characteristic (ROC) curves were plotted to determine the optimal cut point for continuous variables (aNIHSS, age, and infarct volume) predicting a good 90-day outcome and mortality, respectively.

Between-group comparisons for continuous variables were made with unpaired t test, Mann-Whitney U test, and Kruskal Wallis with post hoc Dunn's method. Categorical variables were compared using the  $\chi^2$  test or Fisher exact test as appropriate. Variables significantly associated with 90-day outcome in the univariable analysis ( $p < 0.05$ ) were included in the multivariable logistic regression model with backward elimination (likelihood ratio) to identify independent predictors for a good 90-day outcome or 90-day mortality, respectively.

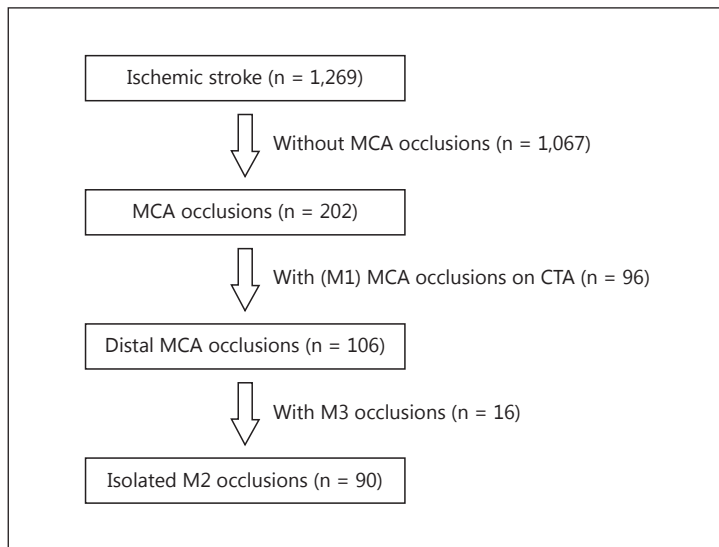
Two-sided significance tests were used throughout and  $p < 0.05$  was considered statistically significant. All statistical analyses were performed using IBM® SPSS® Statistics 20.0.0 (IBM®, Armonk, N.Y., USA).

## **Results**

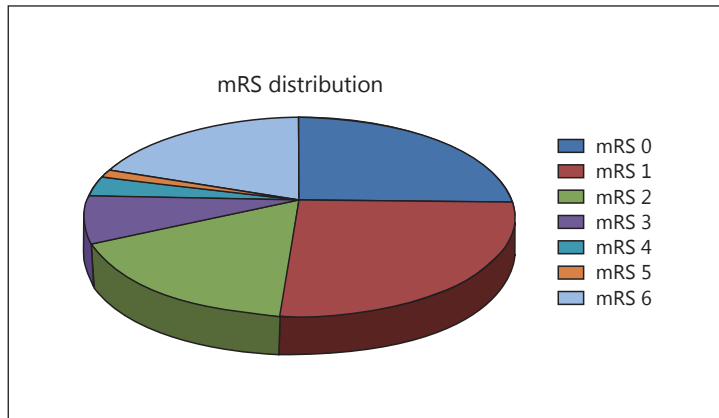
During the study period, 1,269 patients were admitted for acute ischemic stroke. Of these, 202 patients had an MCA occlusion confirmed by imaging and 106 of them had an occlusion distal to the bifurcation. Sixteen patients with an M3 occlusion were excluded. Thus, 90 patients with isolated M2 occlusions were included for analysis (fig. 1).

#### *Primary Analysis*

The majority of patients (69%) had a good 90-day outcome (fig. 2). Baseline characteristics of the included patients as stratified by good (mRS score  $\leq 2$ ) versus poor (mRS score  $> 2$ ) outcome are summarized in table 1. In univariable analysis (table 1), factors associated with a poor 90-day outcome were older age ( $p = 0.014$ ), a higher aNIHSS ( $p < 0.001$ ), admission at the intensive care unit ( $p = 0.002$ ), intubation ( $p = 0.001$ ), LOS ( $p = 0.003$ ), presence of



**Fig. 1.** Flowchart showing the process of patient selection for inclusion in the study.



**Fig. 2.** Distribution of the 90-day mRS score. The majority of our cohort patients achieved functional independence at 90 days.

proximal M2 occlusion ( $p = 0.024$ ), greater infarct volume ( $p < 0.001$ ), presence of both cortical and subcortical infarcts ( $p = 0.004$ ), and PH-type conversion ( $p = 0.036$ ). ROC curve analyses indicated that an aNIHSS  $\leq 10$  (sensitivity = 0.836, specificity = 0.931, AUC = 0.917,  $p < 0.001$ ), age  $\leq 80$  years (sensitivity = 0.721, specificity = 0.690, AUC = 0.673,  $p = 0.008$ ), and infarct volume  $\leq 26$  ml (sensitivity = 0.902, specificity = 0.862, AUC = 0.925,  $p < 0.001$ ) best predicted a good 90-day outcome.

Multivariable logistic regression analysis indicated that age  $\leq 80$  years (OR 0.045, 95% CI 0.005–0.435,  $p = 0.007$ ), aNIHSS  $\leq 10$  (OR 0.073, 95% CI 0.014–0.387,  $p = 0.002$ ), and infarct volume  $\leq 26$  ml (OR 0.018, 95% CI 0.002–0.166,  $p < 0.001$ ) were significant predictors of good 90-day outcome (mRS score 0–2) (table 2). When aNIHSS, age, and infarct volume were entered as continuous variables, multivariable analysis showed that a lower aNIHSS and smaller infarct volume ( $p = 0.001$ ) were independently associated with a good 90-day outcome (online suppl. table 1; for all online suppl. material, see [www.karger.com/doi/10.1159/000360075](http://www.karger.com/doi/10.1159/000360075)).

#### Secondary Analysis

In contrast to the overall good outcome in our patient cohort, a significant proportion of patients with a poor outcome (64%) had died by 90 days. In secondary analyses, we sought

**Table 1.** Baseline characteristics (unadjusted) of the studied patient population as stratified by good 90-day outcome (mRS score 0–2)

Characteristics	All patients (n = 90)	Good outcome (mRS 0–2; n = 61)	Poor outcome (mRS 3–6; n = 29)	p value
Age, years	73±15	70±16	78±13	0.014
Female sex	50 (55.6)	31 (50.8)	19 (65.5)	n.s.
Median aNIHSS (IQR)	8 (4–16)	6.8 (4–8)	18 (12–24)	<0.001
Final TOAST stroke mechanisms				n.s.
Large artery atherosclerosis	8 (9)	7 (11.5)	1 (3.4)	
Cardioembolic stroke	49 (54)	31 (51)	18 (62)	
Stroke of other/undetermined cause	32 (36)	22 (36)	10 (34.5)	
Acute intervention				n.s.
Conservative management	67 (74)	45 (74)	22 (76)	
i.v. rtPA	23 (26)	16 (26)	7 (24)	
Endovascular intervention*	5 (5.6)	5 (8.2)	0 (0)	
Imaging data				
Final infarct volume, ml	28±32	12.5±14.7	60.4±35	<0.001
PH type conversion	5 (5.6)	1 (1.6)	4 (14)	0.036
Proximal M2 occlusion	37 (41)	20 (33)	17 (59)	0.024
Cortical plus subcortical infarction	11 (12)	3 (5)	8 (28)	0.004
Serum markers				
HbA1c	6.3±1.1	6.4±1.1	6.3±1.2	n.s.
Glucose at admission, mg/dl	140±55	140±57	141±50	n.s.
Creatinine at admission, mg/dl	1.06±0.51	1.1±0.37	1.14±0.69	n.s.
White blood cells at admission, ×10 <sup>3</sup> /μl	8.6±2.7	8.4±2.9	9.3±2.2	n.s.
LDL-C, mg/dl	93±38	97±39	85±36	n.s.
HDL-C, mg/dl	46±15	45±14	48±16	n.s.
Preadmission medications				
Antiplatelets	40 (44)	30 (49)	10 (34)	n.s.
Oral anticoagulation	9 (10)	6 (10)	3 (10)	n.s.
Statin	30 (33)	20 (33)	10 (34)	n.s.
Antiglycemic	19 (21)	15 (25)	4 (14)	n.s.
Antihypertensive	57 (63)	38 (62)	19 (66)	n.s.
Preexisting risk factors				
Hypertension	71 (79)	47 (77)	24 (83)	n.s.
Dyslipidemia	51 (56)	37 (60)	14 (48)	n.s.
Diabetes	31 (34)	24 (39)	7 (24)	n.s.
Prior stroke or transient ischemic attack	13 (14)	8 (13)	5 (17)	n.s.
Atrial fibrillation	28 (31)	17 (28)	11 (38)	n.s.
Coronary artery disease	27 (30)	17 (28)	10 (34)	n.s.
Congestive heart failure	18 (20)	9 (15)	9 (31)	n.s.
Renal failure	2 (2)	1 (2)	1 (3)	n.s.
Cancer	7 (8)	5 (8)	2 (7)	n.s.
Peripheral vascular disease	6 (7)	6 (10)	0 (0)	n.s.
Current smoking	22 (24)	18 (29)	4 (14)	n.s.
Alcohol abuse	7 (8)	5 (8.2)	2 (7)	n.s.
Admission at ICU	61 (68)	35 (58)	26 (90)	0.002
Intubation	12 (13)	3 (5)	9 (31)	0.001
Length of stay, days	4 (2–6)	3 (2–5)	6 (3–11)	0.003

Data are n (%) or mean ± SD, except otherwise indicated. \* With or without i.v. rtPA.

**Table 2.** Multivariable logistic regression analysis with backward elimination of factors independently associated with a good 90-day outcome (mRS score 0–2)

Independent variable	Coefficient (95% CI)	p value
Infarct volume $\geq 26$ ml	0.018 (0.002–0.166)	<0.001
aNIHSS $\geq 10^*$	0.073 (0.014–0.387)	0.002
Age $\geq 80$ years	0.045 (0.005–0.435)	0.007

\* When entered as continuous variables, the results did not meaningfully change.

**Table 3.** Multivariable logistic regression analysis with backward elimination of factors independently associated with 90-day mortality

Independent variable	Coefficient (95% CI)	p value
Infarct volume $\geq 28$ ml	11.874 (2.630–53.604)	0.001
CHF	5.819 (1.140–29.695)	0.034
Age $\geq 80$ years	4.953 (1.087–22.563)	0.039
Intubation required	7.788 (1.072–56.604)	0.043

to investigate for potential unique predictors of mortality. Baseline characteristics of patients as stratified by mortality are shown in online supplementary table 2. Older age ( $p = 0.011$ ), congestive heart failure (CHF) ( $p = 0.007$ ), higher aNIHSS ( $p < 0.001$ ), ICU admission ( $p = 0.009$ ), intubation ( $p = 0.002$ ), LOS ( $p = 0.026$ ), proximal M2 occlusion ( $p = 0.017$ ), greater infarct volume ( $p < 0.001$ ), and presence of both cortical and subcortical infarcts ( $p = 0.039$ ) were predictors of 90-day mortality. ROC curve analyses indicated that an aNIHSS  $> 10$  (sensitivity = 0.944, specificity = 0.722, AUC = 0.852,  $p < 0.001$ ), age  $> 80$  years (sensitivity = 0.778, specificity = 0.681, AUC = 0.685,  $p = 0.015$ ), and infarct volume of  $> 28$  ml (sensitivity = 0.833, specificity = 0.806, AUC = 0.877,  $p < 0.001$ ) best predicted 90-day mortality (online suppl. table 2).

Multivariable analysis showed that an infarct volume  $> 28$  ml (OR 11.874, 95% CI 2.630–53.604,  $p = 0.001$ ) and age  $> 80$  years (OR 4.953, 95% CI 1.087–22.563,  $p = 0.039$ ) were independently associated with 90-day mortality (table 3). In addition, need for intubation (OR 7.788, 95% CI 1.072–56.604) and history of CHF (OR 5.819, 95% CI 1.140–29.695) emerged as unique predictors of 90-day mortality (table 3). When infarct volume, aNIHSS, and age were entered as continuous variables, need for intubation ( $p = 0.009$ ) and CHF ( $p = 0.036$ ) remained significantly associated with 90-day mortality (online suppl. table 3).

## Discussion

In this observational cohort study of stroke patients with M2 occlusions, we found that functional outcomes predominantly fall in two extremes. While most patients will have a good functional outcome by 90 days, the majority of patients with a poor outcome will have died by that time point. The former observation adds to the notion that patients with M2 occlusion have a generally favorable outcome. Prior studies on patients receiving intravenous thrombolysis and/or endovascular therapy showed high recanalization rates and good outcomes in 50–70% of cases [2–4, 12–14]. However, since the majority of studied patients received i.v. recombinant tissue plasminogen activator (rtPA), it is difficult to extrapolate these findings to patients that are ineligible to systemic (or endovascular) recan-

alization strategies. Interestingly, despite the fact that ~75% of patients in our study were not subjected to acute recanalization therapy, the good outcome rates were at the upper limit of previously published ranges [2–4, 12–14]. This observation is important because it might explain why some studies did not note robust functional improvement with i.v. rtPA treatment in patients with distal MCA occlusion [15–17]. The reasons for overall good outcome in untreated patients are likely related to smaller clot burden leading to spontaneous recanalization as well as sparing of lenticulostriate arteries, which together results in smaller infarct volumes [5, 6, 12, 17–22]. Our data supports this hypothesis, as surrogate markers of a large lesion volume such as proximal M2 occlusion and cortical plus subcortical infarction were associated with worse outcome in unadjusted (but not adjusted) analyses. More importantly, consistent with other stroke studies, the absolute lesion volume was the most significant outcome predictor [4–6, 19]. In this respect, it is notable that the herein defined lesion volume cut point best predicting a favorable outcome was  $\leq 26$  ml, which is remarkably consistent with previously defined lesion size cutoffs associated with a good outcome [5, 6, 17].

In addition to lesion volume, our data confirms the importance of advanced age as well as higher aNIHSS as critical determinants of outcome [23–25]. Specifically, we found that age  $\geq 80$  years was associated with a worse prognosis consistent with generally worse outcome after ischemic stroke in octogenarians.

Recent endovascular therapy-based trials did not show a significant benefit over i.v. thrombolysis with rtPA [26]. In this respect our findings may provide valuable information for a future endovascular trial design as it may help identify and exclude patients that are ‘too good’ (or too poor) to be treated.

Notably, 64% of patients with a poor outcome had died by 90 days. This is in stark contrast to the observed good outcome in  $>70\%$  of investigated patients. Advanced age, greater infarct volume, history of CHF and need for intubations were independently associated with 90-day mortality. Thus, our study expands on previous observations by confirming these as important risk factors allowing for the identification of a subpopulation of patients with likely very poor outcome after isolated M2 occlusion, and thus aid guiding clinicians in patient management as well as counseling family members.

The strengths of our study relate to the analysis of a large and well-defined patient population with investigation of prospectively collected variables that have been associated with clinical outcome after ischemic stroke as well as masked assessment of data and standardized assessment of 90-day outcome in all patients. Our inclusion of a high number of untreated patients provides important information regarding the natural history of isolated M2 occlusions. Finally, we included volumetric analyses in our predictive models, which is important because infarct volume is increasingly recognized as a key predictor of outcome. The prospective collection of a large number of clinically relevant variables contributed to improved data quality while limiting the potential for misclassification.

Limitations of our study relate to its retrospective design. Further, CTA was obtained at the treating stroke physician’s discretion, which may have biased the selection of patients having worse clinical presentation and outcomes. However, outcome rates were comparable to those published as part of prior studies rendering this possibility less likely [2–4, 12–14]. Given our study design and the limited number of patients that received thrombolytic therapy, the therapeutic efficacy of rtPAs could not be ascertained in this patient population. Lastly, future studies may benefit from assessing the acute lesion volume by defining the Alberta Stroke Program Early Computed Tomography Score (ASPECTS), which has the potential for risk stratification in the hyperacute setting [27, 28].

In conclusion, this study shows generally good outcome after isolated M2 occlusion and confirms the predictive importance of age, aNIHSS, and lesion volume. Additionally, we

provide novel information regarding unique predictors for mortality in this group of patients with otherwise favorable outcome. Such information may aid in risk stratification to help with clinical management as well as to counsel patients and their families.

### Disclosure Statement

The authors have no conflicts of interest to disclose.

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