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# Predictors of mortality in acute ischemic stroke treated with endovascular thrombectomy despite successful reperfusion: subgroup analysis of a multicentre randomised clinical trial

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## ABSTRACT

**Objectives** We sought to determine the predictors of 90-day mortality despite successful reperfusion.

**Design** Subgroup analysis of a multicentre randomised clinical trial (ClinicalTrials.gov Identifier: NCT03469206).

**Setting** This study used data from the Direct Intra-arterial thrombectomy in order to Revascularize AIS patients with large vessel occlusion Efficiently in Chinese Tertiary hospitals: a Multicenter randomized clinical Trial (DIRECT-MT).

**Participants** 622 patients enrolled in DIRECT-MT.

**Results** Overall successful reperfusion rate was 82.0% (510/622), and 18.5% (115/622) of patients died within 90 days. Univariate analysis identified increased risks of mortality for age ≥70 years, history of diabetes mellitus, National Institutes of Health Stroke Scale (NIHSS) score on admission ≥17, NIHSS score after thrombectomy (24±6 hours) ≥11, Alberta Stroke Program Early Computed Tomography Score (ASPECTS) <9, glucose level at hospital arrival ≥130 mg/dL, location of internal carotid artery occlusion, embolisation into a new territory, symptomatic intracranial haemorrhage (ICH) and a decreased risk of mortality for smoking. In multivariable analysis, smoking (OR 0.38; 95% CI 0.17 to 0.83; p=0.015), NIHSS score on admission ≥17 (OR 3.14; 95% CI 1.77 to 5.55; p<0.001), glucose level at hospital arrival ≥130 mg/dL (OR 2.54; 95% CI 1.51 to 4.27; p<0.001), symptomatic ICH (OR 11.70; 95% CI 4.74 to 28.89; p<0.001) and NIHSS score after thrombectomy (24±6 hours) ≥11 (OR 12.04; 95% CI 5.09 to 28.46; p<0.001) were significant independent predictors of 90-day mortality.

**Conclusions** Symptomatic ICH and high post-thrombectomy NIHSS score are strong predictor of 90-day mortality in acute ischaemic stroke treated with mechanical thrombectomy despite successful reperfusion, as well as high NIHSS score and high glucose level at hospital arrival. However, further studies need to be performed to confirm the association between smoking and mortality.

## Strengths and limitations of this study

- The study used a multicentre randomised clinical trial data from Direct Intra-arterial thrombectomy in order to Revascularize AIS patients with large vessel occlusion Efficiently in Chinese Tertiary hospitals: a Multicenter randomized clinical Trial DIRECT-MT (DIRECT-MT).
- The large sample size provides robustness and strong statistical power for the reported outcomes.
- All patients in the DIRECT-MT trial were Chinese, which may limit the generalisability of the findings to other populations.

## INTRODUCTION

The overwhelming benefit of endovascular thrombectomy for acute ischaemic stroke (AIS) with large-vessel occlusion in the anterior circulation has been demonstrated.[1–5] A large number of studies show that successful reperfusion was a powerful predictor of good outcomes in AIS. However, despite the rates of successful reperfusion (modified thrombolysis in cerebral infarction score 2b or 3) up to 71%, the mortality at 90 days remains high, approximately up to 15%.[6] Thus, it remains important to understand which factors influence mortality despite successful reperfusion. Some studies have identified predictors that influence mortality in patients with acute stroke treated with the thrombectomy, such as age, National Institute of Health Stroke Scale (NIHSS) score, vessel occlusion site, passes with the thrombectomy device and use of rescue therapy.[7 8] However, the predictors of mortality despite successful reperfusion have been less intensively addressed thus far.

Direct Intra-arterial thrombectomy in order to Revascularize AIS patients with large vessel occlusion Efficiently in Chinese Tertiary hospitals: a Multicenter randomized clinical Trial (DIRECT-MT) is an investigator-initiated, multicentre, prospective, randomised, open-label trial, designed to determine whether endovascular thrombectomy alone would be non-inferior to combined treatment with endovascular thrombectomy preceded by intravenous alteplase in patients who had AIS with large-vessel occlusion in the anterior circulation.[9] Thus, in this subgroup analysis, using the data from DIRECT-MT trial, we investigated the predictors of 90-day mortality in AIS treated with endovascular thrombectomy despite successful reperfusion.

## METHODS

### Patients selection

Study patients were obtained from the DIRECT-MT trial of patients with good quality final angiographic images (performed with digital subtraction angiography) could be assessed for eTICI by the core laboratory. Details of the DIRECT-MT patient selection can be found in the original report.[9]

### Data

In addition to patient demographic and baseline characteristics, data included information on radiological imaging, procedural complications, symptomatic ICH, NIHSS score after thrombectomy (24±6 hours) and clinical outcomes. Successful reperfusion was defined as achieving the eTICI score (range: 0 (no reperfusion) to 3 (complete reperfusion)) of 2b, 2c or 3 on the final angiogram after thrombectomy.[10] Symptomatic intracranial haemorrhage (ICH) was defined on the basis of Heidelberg criteria.[11] Cause of stroke was determined according to the medical history, clinical features and results on digital subtraction angiography, including cardioembolism, large-artery occlusion and undetermined. All radiological imaging was assessed by an independent imaging core-lab blinded to the trial group assignments. All imaging was read by two independent readers, and a consensus reading was performed by a senior reader of each team in case of discrepancies. More details of the design, methods and results of DIRECT-MT trial have been reported previously.[12]

### Statistical analysis

Since for age, NIHSS score at baseline, NIHSS score after thrombectomy (24±6 hours), Alberta Stroke Program Early Computed Tomography Score and glucose level at hospital arrival we observed a non-linear relationship, we determined the optimal cut-off value discriminating between mortality and survival using restricted cubic spline functions. Data are presented as numbers with percentages. Pearson $\chi^2$ test or Fisher's exact test was used to compared baseline characteristics, angiographic outcomes, procedural complications and symptomatic ICH between the mortality and survival groups in univariate analysis. In the first multivariable model, variables with $p \le 0.05$ in the univariate analysis were included in the multivariable logistic regression model-building process, except symptomatic ICH and NIHSS score after thrombectomy (24±6 hours), to evaluate association with 90-day mortality. In the second multivariable model, symptomatic ICH was included as covariate to determine whether symptomatic ICH modifies the estimated effect of the baseline characteristics as predictors of mortality. In the third multivariable model, NIHSS score after thrombectomy (24±6 hours) was included, except NIHSS score at baseline and symptomatic ICH, to evaluate association with 90-day mortality. Multivariable models were built basing on backwards selection. The retention criterion was set at $p \le 0.05$. All data were processed using the SAS software V.9.2 (SAS Institute).

### Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

## RESULTS

The DIRECT-MT enrolled 656 consecutive patients with AIS treated with endovascular thrombectomy with or without intravenous alteplase. A total of 17 patients were primarily excluded, because poor quality angiographic images could not be assessed for eTICI, thus leaving 622 patients to participate in the analysis. Of these, 510 patients (77.7%) achieved successful reperfusion (eTICI ≥2b). Mortality was lower in patients with successful reperfusion compared with those without successful reperfusion (15.3% (78/510) vs 33.0% (37/112); $p<0.001$). In successful reperfusion patients, procedural complications (vessel dissection, contrast extravasation, embolisation into a new territory and femoral access complications) occurred in 73 patients (14.3%).

The shape of the relationship with age, NIHSS score on admission, NIHSS score after thrombectomy (24±6 hours), ASPECTS score and glucose level appeared to be nonlinear (online supplemental figure 1). We identified a value of 70 years for age, 17 for NIHSS score on admission, 11 for NIHSS score after thrombectomy (24±6 hours), 9 for ASPECT score and 130 mg/dL for glucose level as optimal cut-off value for discriminating deceased from survived patients. Baseline characteristics, angiographic outcomes, procedural complications, NIHSS score after thrombectomy (24±6 hours) and symptomatic ICH for study patients are summarised in table 1.The mortality group had a significantly higher prevalence of age ≥70 years, diabetes mellitus, NIHSS score on admission ≥17, NIHSS score after thrombectomy (24±6 hours) ≥11, ASPECTS score <9, glucose level at hospital arrival ≥130 mg/dL, location of internal carotid artery occlusion, embolisation into a new territory and symptomatic ICH than the survival group had. Inversely, prevalence of

**Table 1** Baseline characteristics, angiographic outcomes, procedural details and complications in mortality and survival at 90 days

| Variable | Mortality n=78 | Survival n=432 | P value |
|---|---|---|---|
| Age ≥70 | 49 (62.82) | 198 (45.83) | 0.0057 |
| Sex (male) | 44 (56.41) | 250 (57.87) | 0.8102 |
| Diabetes mellitus | 23 (29.49) | 72 (16.67) | 0.0074 |
| Hypertension | 51 (65.38) | 259 (59.95) | 0.3659 |
| Hypercholesterolaemia | 1 (1.28) | 18 (4.17) | 0.3611 |
| Previous ischaemic stroke | 11 (14.10) | 59 (13.66) | 0.9163 |
| Peripheral artery disease | 0 (0.00) | 3 (0.69) | 1.0000 |
| Heart disease | 44 (56.41) | 221 (51.16) | 0.3928 |
| Atrial fibrillation | 43 (55.13) | 192 (44.44) | 0.0815 |
| Chronic heart failure | 4 (5.13) | 26 (6.02) | 0.9632 |
| Myocardial infarction | 6 (7.69) | 23 (5.32) | 0.5717 |
| Mechanical aorta and/or mitral valve rep | 1 (1.28) | 10 (2.31) | 0.8773 |
| Smoking | 8 (10.26) | 112 (25.93) | 0.0027 |
| Statin | 4 (5.13) | 37 (8.56) | 0.3042 |
| Antiplatelet agents | 13 (16.67) | 72 (16.67) | 1.0000 |
| Anticoagulant pretreatment | 6 (7.69) | 34 (7.87) | 0.9571 |
| NIHSS score on admission ≥17 | 60 (76.92) | 214 (49.54) | <0.0001 |
| NIHSS score after thrombectomy (24±6 hours) ≥11 | 72 (92.31) | 197 (45.60) | <0.0001 |
| ASPECTS <9 | 47 (61.04) | 201 (46.74) | 0.0208 |
| Intravenous thrombolysis | 40 (51.28) | 227 (52.55) | 0.8370 |
| Glucose level ≥130 mg/dL | 50 | 171 | <0.0001 |
| Location of intracranial artery occlusion | | | |
| ICA | 40 (51.28) | 142 (32.87) | 0.0075 |
| M1 middle cerebral artery segment | 32 (41.03) | 248 (57.41) | |
| M2 middle cerebral artery segment | 6 (7.69) | 42 (9.72) | |
| Cause of stroke | | | |
| Cardioembolic | 39 (50.00) | 189 (43.75) | 0.510 |
| Large-artery occlusion | 14 (17.95) | 76 (17.59) | |
| Undetermined | 25 (32.05) | 167 (38.66) | |
| Anaesthesia | | | |
| Local anaesthesia | 27 (35.06) | 158 (37.26) | 0.2423 |
| Sedation | 18 (23.38) | 129 (30.42) | |
| General anaesthesia | 32 (41.56) | 137 (32.31) | |
| Extracranial stent placement | 2 (2.56) | 37 (8.56) | 0.0664 |
| Intracranial stent placement | 11 (14.10) | 37 (8.56) | 0.1232 |
| Procedural complications | | | |
| Vessel dissection | 2 (2.56) | 6 (1.39) | 0.7843 |
| Contrast extravasation | 3 (3.85) | 7 (1.62) | 0.3891 |
| Embolisation into a new territory | 14 (17.95) | 40 (9.26) | 0.0217 |
| Femoral access complications | 0 (0.00) | 1 (0.23) | 1.0000 |
| Symptomatic ICH | 16 (20.51) | 11 (2.55) | <0.0001 |

ASPECTS, Alberta Stroke Program Early Computed Tomography Score; ICA, internal carotid artery; ICH, intracranial haemorrhage; NIHSS, National Institutes of Health Stroke Scale.

Table 2 Independent predictors of 90-day mortality

| | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value |
| Smoking | 0.38 (0.17 to 0.83) | 0.015 | 0.30 (0.13 to 0.70) | 0.005 | 0.450 (0.202 to 1.003) | 0.051 |
| NIHSS score on admission ≥17 | 3.14 (1.77 to 5.55) | <0.001 | 3.08 (1.70 to 5.60) | <0.001 | – | – |
| Glucose level | 2.54 (1.51 to 4.27) | <0.001 | 2.62 (1.52 to 4.52) | <0.001 | 2.174 (1.270 to 3.721) | 0.005 |
| Symptomatic ICH | Not included | – | 11.70 (4.74 to 28.89) | <0.001 | Not included | – |
| NIHSS score after thrombectomy ≥11 | Not included | – | Not included | – | 12.04 (5.09 to 28.46) | <0.001 |

ICH, intracranial haemorrhage; NIHSS, National Institutes of Health Stroke Scale.

smoking was lower in mortality group. There was no difference was found for sex, hypertension, hypercholesterolaemia, previous ischaemic stroke, peripheral artery disease, heart disease, atrial fibrillation, chronic heart failure, myocardial infarction, mechanical aorta and/or mitral valve rep, statin, antiplatelet agents, anticoagulant pretreatment, intravenous thrombolysis, cause of stroke, anaesthesia, extracranial stent placement, intracranial stent placement, vessel dissection, contrast extravasation and femoral access complications.

In the first multivariable analysis model (table 2), NIHSS score on admission ≥17 (OR 3.14; 95% CI 1.77 to 5.55; p<0.001) and glucose level at hospital arrival ≥130 mg/dL (OR 2.54; 95% CI 1.51 to 4.27; p<0.001) remained independently associated with a higher risk of mortality. The rate of smoking (OR 0.38; 95% CI 0.17 to 0.83; p=0.015) remained lower in mortality group. In the second multivariable model, symptomatic ICH was significant (OR 11.70; 95% CI 4.74 to 28.89; p<0.001) when added to the model but did not substantively change the estimated effects of smoking, NIHSS score on admission ≥17 and glucose level at hospital arrival ≥130 mg/dL. In the third multivariable model, NIHSS score after thrombectomy ≥11 (OR 12.04; 95% CI 5.09 to 28.46; p<0.001) was also a significant independent predictors of 90-day mortality.

## DISCUSSION

In the present study, we used data from the DIRECT-MT trial to identify potential clinical, angiographic, procedural complications and symptomatic ICH factors of 90-day mortality in AIS treated with endovascular thrombectomy despite successful reperfusion. We found that NIHSS score at baseline ≥17 and glucose level at hospital arrival ≥130 mg/dL were independently associated with higher mortality, whereas smoking was associated with lower risk of mortality. Furthermore, symptomatic ICH significantly increased mortality, whereas procedural complications were not associated with mortality. Similar to the original report of DIRECT-MT, intravenous thrombolysis was not associated with 90-day mortality in successful reperfusion patients. Other factors, such as age, proximal occlusion and diabetes mellitus, although reported in previous studies,[8 13] were not related to mortality in our analysis.

For anterior circulation stroke, a high NIHSS score on admission has been correlated with 90-day mortality after endovascular thrombectomy despite successful reperfusion,[8] in line with the present study. This suggests that it is difficult to reverse the outcome of stroke with severe neurological deficit (as indicated by a high NIHSS score) despite successful reperfusion, because a substantial volume of brain tissue is already irreversibly injured in AIS patients by the time reperfusion occurs. In DIRECT-MT, 36.6% of the patients had a good functional recovery at 90 days despite more than 80% of the patients achieved successful reperfusion, which also can be explained by the above reasons. We determined an NIHSS score cut-off value of 17 on admission and 11 at 24±6 hours after thrombectomy, respectively, and NIHSS score higher than cut-off value increased the risk of a mortality approximately threefold and 12 times, respectively. It indicates that post-thrombectomy (24±6 hours)NIHSS score was a stronger predictor than NIHSS score on admission.

In our study, we found that glucose level at hospital arrival ≥130 mg/dL can increase the risk of 90-day mortality. Hyperglycemia (defined as admission serum glucose >140 mg/dL), similarly to present study previously has been correlated with poor outcomes or mortality in AIS patients with large vessel occlusion after endovascular thrombectomy.[14 15] In previous studies and present study, hyperglycaemic was defined in accordance with the absolute glucose concentration, failing to distinguish between poor management of diabetes and a physiological stress response to acute stroke. Recently, a novel index of stress hyperglycaemic ratio (SHR; the admission random blood glucose divided by the glycosylated haemoglobin level) was proved to be a better predictor of poor outcome or mortality than absolute hyperglycaemic in patients treated with endovascular thrombectomy.[16 17] However, we did not collect haemoglobin level and could not calculate SHR to assess the association between SHR and mortality after endovascular thrombectomy for acute occlusion in the anterior circulation. However, there is no evidence that the administration of intravenous insulin improves functional outcomes or mortality rates in AIS.[18] Moreover, hyperglycaemic may also occur after mechanical thrombectomy, both in diabetic and non-diabetic patients, and recent study demonstrated that glucose levels within 24 hours after mechanical thrombectomy is able to predict adverse outcomes in AIS.[19] However, DIRECT-MT trial only collected the admission glucose level. Therefore,we could not evaluate the impact of the glucose levels within 24 hours after mechanical thrombectomy on stroke mortality.

Smoking is a well-known independent risk factor for stroke. Interestingly, previous studies have reported that smoking was associated with a lower risk of mortality,[20 21] calling smoking paradox in literature. Currently, the mechanism of the smoking paradox has not yet been explained, and its existence is controversial. Some researchers insisted that the smoking paradox was probably caused by unmeasured or residual confounding, younger age and other differences in baseline characteristics, not the biological effects of smoking.[22–24] Statistical methods such as multivariable regression or propensity score analysis may address most, but not all, of the confounding in risk analyses. Furthermore, previous studies and our study did not distinguish current smokers from ex-smokers and had no medical record of the quantity of smoking. Therefore, we could not assess the effects of smoking status and quantity on the outcome.

We further found symptomatic ICH resulted in significantly increased mortality. In our study, 5.3% cases with successful reperfusion developed symptomatic ICH, similarly to what is reported in randomized controlled trials (4.4%).[6] However, there was no difference in the incidence of symptomatic ICH between successful reperfusion with failed reperfusion patients. Interestingly, Neuberger *et al* published a report on risk factors of intracranial haemorrhage after endovascular thrombectomy of anterior circulation ischaemic stroke.[25] In their analysis, they found complete reperfusion (eTICI 3) were attributable to lower ICH rate in comparison with subtotal recanalisation (eTICI 2b, eTICI 2c) and had lower quantity of thrombectomy manoeuvres, which was a risk factor of haemorrhagic transformation.

Our analysis has several limitations. First, DIRECT-MT trial was designed in accordance with the 2015 American Heart Association/American Stroke Association guidelines.[26] All stent retriever devices approved by China Food and Drug Administration were allowed in the trial as a first line, and aspiration devices were allowed as a second option. Recently, newer generation devices such as aspiration catheters have been used as first-line devices for large vessel occlusion. Second, all patients in the DIRECT-MT trial were Chinese, which may limit the generalisability of the findings to other populations. In a pooled analysis of five thrombectomy trials, predominantly enrolled white patients, functional recovery was higher (46% vs 36.6%) despite a lower percentage of patients (71% vs more than 80%) with reperfusion.[6] It is possible that Chinese patients have more intracranial atherosclerotic lesions than white patients do.[27] Third, DIRECT-MT trial did not distinguish current smokers from ex-smokers and had no medical record of the quantity of smoking, which probably resulted in the smoking paradox, and DIRECT-MT trial did not collect the glucose level after thrombectomy, which is also a predictor of outcomes. Finally, we could not exclude overfitting in multivariate analyses, as well as a loss of power to identify independent predictors.

## CONCLUSIONS

In conclusion, symptomatic ICH and high post-thrombectomy NIHSS score (NIHSS score ≥11) are strong predictor of 90-day mortality in AIS treated with endovascular thrombectomy despite successful reperfusion, as well as high NIHSS score (NIHSS score ≥17) and glucose level (glucose level ≥130 mg/dL) at hospital arrival. However, further studies need to be performed to confirm the association between smoking and mortality.

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**Competing interests** None declared.

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this study was obtained from the institutional review board. Participants gave informed consent to participate in the study before taking part.

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