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Predictors of mortality in acute ischemic stroke treated with endovascular thrombectomy despite successful reperfusion: subgroup analysis of DIRECT-MT

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Title page

Predictors of mortality in acute ischemic stroke treated with endovascular thrombectomy despite successful reperfusion: subgroup analysis of DIRECT-MT

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Keywords: acute ischemic stroke; reperfusion; mortality; mechanical thrombectomy

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Abstract

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

Design: Subgroup analysis of a multicenter randomized clinical trial.

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

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 at baseline≥17, Alberta Stroke Program Early Computed Tomography Score (ASPECTS) <9, glucose level at hospital arrival≥130 mg/dl, location of internal carotid artery occlusion, embolization into a new territory, symptomatic 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 ≥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), and symptomatic ICH (OR, 11.70; 95% CI, 4.74 to 28.89; P<0.001) were significant independent predictors of 90-day mortality.

Conclusions: Symptomatic ICH is a strong predictor of 90-day mortality in acute ischemic stroke treated with mechanical thrombectomy despite successful reperfusion, as well as, severe neurologic deficits (NIHSS score≥17) and high glucose level (glucose level ≥130mg/dl) 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 multicenter randomized clinical trial data from 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 generalizability of the findings to other populations.

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Introduction

The overwhelming benefit of endovascular thrombectomy for acute ischemic 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 acute ischemic stroke. However, despite the rates of successful reperfusion (modified Thrombolysis in Cerebral Infarction(mTICI) 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]. But 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, multicenter, prospective, randomized, open-label trial, designed to determine whether endovascular thrombectomy alone would be noninferior to combined treatment with endovascular thrombectomy preceded by intravenous alteplase in patients who had acute ischemic stroke 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 acute ischemic stroke treated with endovascular thrombectomy despite successful reperfusion. Approval to conduct this study was obtained from the institutional review board.

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

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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 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 hemorrhage (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, intracranial atherosclerosis, ipsilateral extracranial internal carotid artery (ICA) obstruction 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, Alberta Stroke Program Early Computed Tomography Score and glucose level at hospital arrival we observed a nonlinear relationship, we determined the optimal cutoff value discriminating between mortality and survival using restricted cubic spline functions. Data are presented as numbers with percentages. Pearson chi-square test or Fisher exact test was used to compared baseline characteristics, angiographic outcomes, procedural complications and symptomatic between the mortality and survival groups in univariate analysis. Variables with $P \leq 0.05$ in the univariate analysis were included in the multivariable logistic regression model-building process, except symptomatic ICH, to evaluate association with 90-day mortality. Multivariable models were built basing on backwards selection. The retention criterion was set at $p \leq 0.05$. 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. All data were processed using the SAS software, version 9.2 (SAS Institute).

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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 acute ischemic stroke 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] versus 33.0% [37/112]; P<0.001). In successful reperfusion patients, procedural complications (vessel dissection, contrast extravasation, embolization into a new territory, femoral access complications) occurred in 73 patients (14.3%).

The shape of the relationship with age, NIHSS score at baseline, ASPECTS score and glucose level appeared to be nonlinear (online supplementary Figure I). We identified a value of 70 years for age, 17 for NIHSS score, 9 for ASPECT score and 130 mg/dl for glucose level as optimal cutoff value for discriminating deceased from survived patients. Baseline characteristics, angiographic outcomes, procedural complications and symptomatic ICH for study patients are summarized in table1.The mortality group had a significantly higher prevalence of age ≥70 years, diabetes mellitus, NIHSS score at baseline≥17, ASPECTS score < 9, glucose level at hospital arrival≥130 mg/dl, location of internal carotid artery occlusion, embolization into a new territory, symptomatic ICH than the survival group had. Inversely, prevalence of smoking was lower in mortality group. There was no difference was found for sex, hypertension, hypercholesterolemia, previous ischemic 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, anesthesia, extracranial stent placement, intracranial stent placement, vessel dissection, contrast extravasation, femoral access complications.

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In multivariable analysis (Table2), NIHSS score ≥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 at baseline≥17, and glucose level at hospital arrival≥130 mg/dl.

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 acute ischemic stroke 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, 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 indicates that it is difficult to reverse the outcome of stroke with severe neurological deficit (as indicated by a high NIHSS score) despite successful reperfusion. In our analysis of the DIRECT-MT data, we determined a NIHSS score cutoff value of 17, and NIHSS score ≥17 increased the risk of a mortality approximately threefold, whereas the increase estimated for glucose level was two.

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

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or mortality in acute ischemic stroke patients with large vessel occlusion after endovascular thrombectomy[14, 15]. In previous studies and present study, hyperglycemia was defined in accordance with the absolute glucose concentration, failing to distinguish between poor management of diabetes and a physiologic stress response to acute stroke. Recently, a novel index of stress hyperglycemia ratio (SHR, the admission random blood glucose divided by the glycosylated hemoglobin level) was proved to be a better predictor of poor outcome or mortality than absolute hyperglycemia in patients treated with endovascular thrombectomy[16, 17]. But we did not collect hemoglobin 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 acute ischemic stroke[18].

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[19, 20], 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[21-23]. 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]. But there was no difference in the incidence of symptomatic ICH between successful reperfusion with failed reperfusion patients. Interestingly, Möhlenbruch et al. published a report on risk factors of intracranial hemorrhage after endovascular thrombectomy of anterior circulation

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ischemic stroke[24]. In their analysis, they found complete reperfusion (eTICI 3) were attributable to lower ICH rate in comparison to subtotal recanalization (eTICI 2b, eTICI 2c), and had lower quantity of thrombectomy maneuvers, which was a risk factor of hemorrhagic transformation.

Our analysis has several limitations. First, DIRECT-MT trial was designed in accordance with the 2015 American Heart Association/American Stroke Association guidelines[25]. 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. In addition, all patients in the DIRECT-MT trial were Chinese, which may limit the generalizability of the findings to other populations. Moreover, 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. 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 is a strong predictor of 90-day mortality in acute ischemic stroke treated with endovascular thrombectomy despite successful reperfusion, as well as, a severe neurological deficit (NIHSS score≥17) and high glucose level (glucose level ≥130mg/dl) at hospital arrival. However, further studies need to be performed to confirm the association between smoking and mortality.

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Author Contributions

ZY, LYZ and JML contributed to conception and design of the study. HL, JBH, JC and SSY drafted the manuscript or tables or figures. PFY, YWZ, PFX and XXZ contributed to comments on the draft manuscript and revised the report. Site investigators contributed to data acquisition not analysis. HC, GL, WJD, CML, LY, LF, YP and SL coordinated the study. XFY conducted the statistical analysis.

Ethics Approval

This trial was approved by Ethics Committee (EC) of Shanghai Changhai Hospital (ID: CHEC2018-003) on Jan 15,2018.

Conflict of Interest Statement

None declared.

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Data sharing statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table1 Baseline characteristics, angiographic outcomes, procedural details and complications in mortality and survival at 90 days.

项目	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
Hypercholesterolemia	1(1.28)	18(4.17)	0.3611
Previous ischemic 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 at baseline≥17	60(76.92)	214(49.54)	<0.0001
ASPECT score < 9	47(61.04)	201(46.74)	0.0208

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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)	
M2middle cerebral artery segment	6(7.69)	42(9.72)	
Cause of stroke			
Cardioembolic	39(50.00)	189(43.75)	0.1399
Intracranial atherosclerosis	10(12.82)	32(7.41)	
Ipsilateral extracranial	4(5.13)	44(10.19)	
Undetermined	25(32.05)	167(38.66)	
Anesthesia			
Local anesthesia	27(35.06)	158(37.26)	0.2423
Sedation	18(23.38)	129(30.42)	
General anesthesia	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
Embolization 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

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

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Table 2. Independent predictors of 90-day mortality.

	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Smoking	0.38(0.17-0.83)	0.015	0.30(0.13-0.70)	0.005
NIHSS score	3.14(1.77-5.55)	<0.001	3.08 (1.70-5.60)	<0.001
Glucose level	2.54(1.51-4.27)	<0.001	2.62(1.52-4.52)	<0.001
Symptomatic ICH	Not include	-	11.70(4.74-28.89)	<0.001

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

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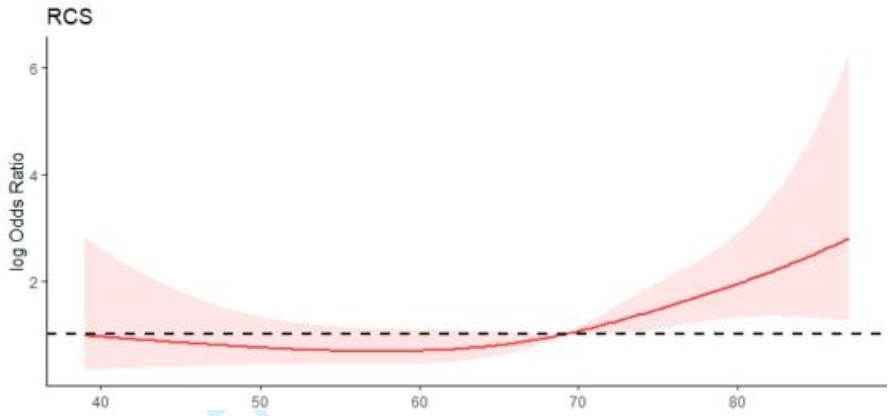
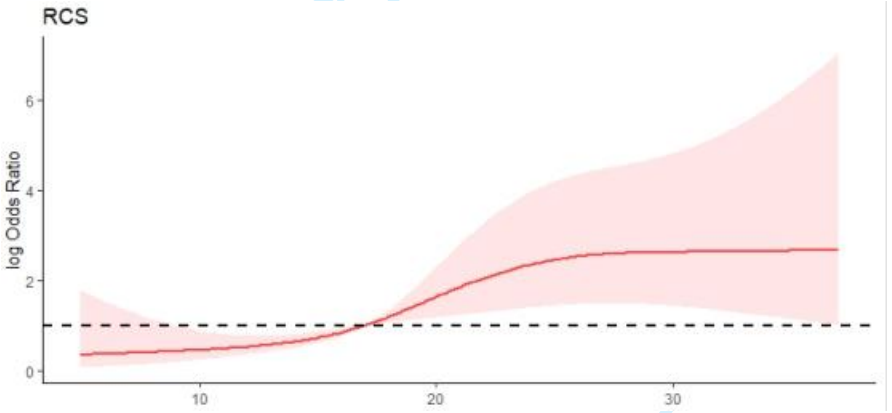


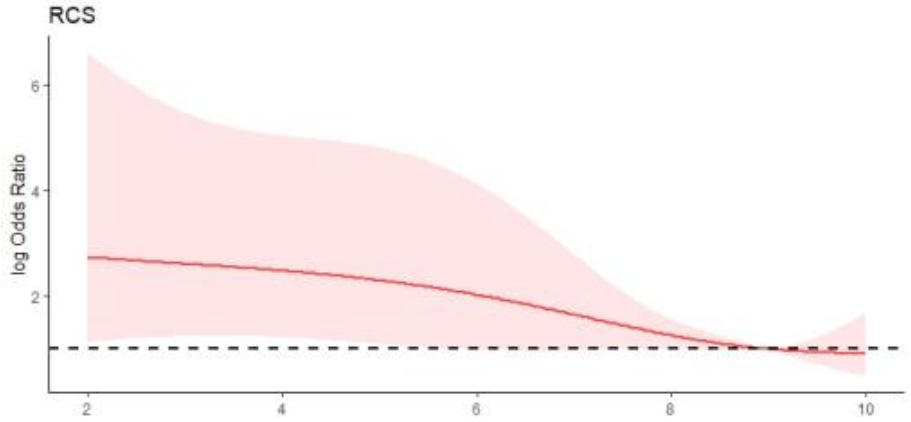
Age

B



NIHSS score at baseline

C



ASPECT score

D

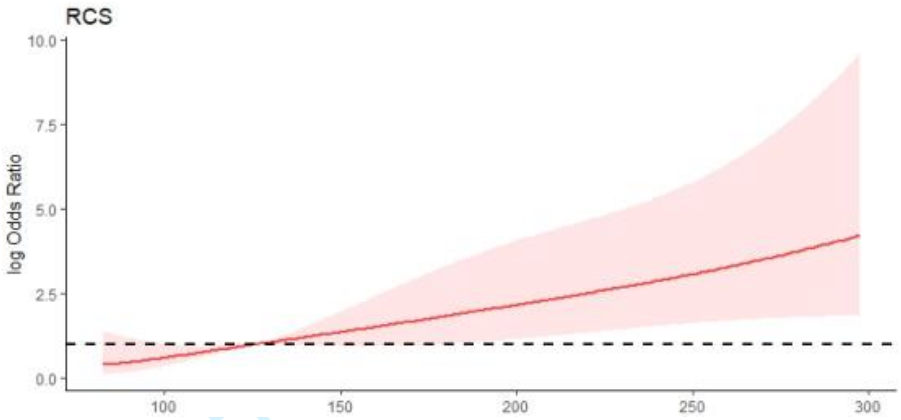


Figure I. Shape of association of 90-day mortality with age (A), National Institutes of Health Stroke Scale (NIHSS) score at baseline (B), Alberta Stroke Program Early Computed Tomography Score (ASPECTS) (C) and glucose level (D). The optimal cutoff value for discriminating deceased from survivor patients was 70 years for age, 17 for NIHSS score, 9 for ASPECT score and 130 mg/dl for glucose level.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1-2
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1-2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3-4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	3-4
	4b	Settings and locations where the data were collected	3-4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3-4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	3-4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	3-4
Sample size	7a	How sample size was determined	3-4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	3-4
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	3-4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	3-4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	3-4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	3-4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	3-4

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		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	3-4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	3-4
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	3-4
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	5-6
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5-6
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	5-6
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	5-6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	5-6
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	8-10
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Predictors of mortality in acute ischemic stroke treated with endovascular thrombectomy despite successful reperfusion: subgroup analysis of a multicenter randomized clinical Trial

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Surgery
Keywords:	Stroke < NEUROLOGY, Neurology < INTERNAL MEDICINE, NEUROSURGERY

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Title page

Predictors of mortality in acute ischemic stroke treated with endovascular thrombectomy despite successful reperfusion: subgroup analysis of a multicenter randomized clinical Trial

Hao Li1†, Jinbo Huang1†, Jie Cao2†, Shisheng Ye1, Hai Chen1, Geng Liao1, Weijie Du1, Chaomao Li1, Li Yuan1, Ling Fang1, Pengfei Yang3, Yongwei Zhang4, Pengfei Xing4, Xiaoxi Zhang3, Xiaofei Ye5, Ya Peng2, Sheng Liu6, Liyong Zhang7*, Zhi Yang1*, Jianmin Liu3, on behalf of the direct-mt investigators

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Number of Tables: 2; Supplemental material:1; Word count: 3616.

Keywords: acute ischemic stroke; reperfusion; mortality; mechanical thrombectomy

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Abstract

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

Design: Subgroup analysis of a multicenter randomized clinical trial.

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

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±6h) ⩾11, Alberta Stroke Program Early Computed Tomography Score (ASPECTS) <9, glucose level at hospital arrival≥130 mg/dl, location of internal carotid artery occlusion, embolization into a new territory, symptomatic 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±6h) ⩾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 ischemic 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 multicenter randomized clinical trial data from DIRECT-MT.

The large sample size provides robustness and strong statistical power for the reported

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outcomes.

All patients in the DIRECT-MT trial were Chinese, which may limit the generalizability of the findings to other populations.

Introduction

The overwhelming benefit of endovascular thrombectomy for acute ischemic 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 acute ischemic stroke. However, despite the rates of successful reperfusion (modified Thrombolysis in Cerebral Infarction(mTICI) 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]. But 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, multicenter, prospective, randomized, open-label trial, designed to determine whether endovascular thrombectomy alone would be noninferior to combined treatment with endovascular thrombectomy preceded by intravenous alteplase in patients who had acute ischemic stroke 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 acute ischemic stroke treated with endovascular thrombectomy despite successful reperfusion. Approval to conduct this study was obtained from the institutional review board.

Methods

Patients Selection

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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 ± 6h) 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 hemorrhage (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 ± 6h), Alberta Stroke Program Early Computed Tomography Score and glucose level at hospital arrival we observed a nonlinear relationship, we determined the optimal cutoff value discriminating between mortality and survival using restricted cubic spline functions. Data are presented as numbers with percentages. Pearson chi-square test or Fisher 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 $P \leq 0.05$ in the univariate analysis were included in the multivariable logistic regression model-building process, except symptomatic ICH and NIHSS score after thrombectomy (24

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±6h), 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 ± 6h) 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 $p \leq 0.05$. All data were processed using the SAS software, version 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 acute ischemic stroke 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] versus 33.0% [37/112]; P<0.001). In successful reperfusion patients, procedural complications (vessel dissection, contrast extravasation, embolization into a new territory, 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 ± 6h), ASPECTS score and glucose level appeared to be nonlinear (online supplementary Figure I). We identified a value of 70 years for age, 17 for NIHSS score on admission, 11 for NIHSS score after thrombectomy (24 ± 6h), 9 for ASPECT score and 130 mg/dl for glucose level as optimal cutoff value for discriminating deceased from survived patients. Baseline characteristics, angiographic outcomes, procedural complications, NIHSS score after thrombectomy (24 ± 6h) and symptomatic ICH for study patients are summarized in table1.The mortality group had

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a significantly higher prevalence of age ≥70 years, diabetes mellitus, NIHSS score on admission ≥17, NIHSS score after thrombectomy (24±6h) ≥11, ASPECTS score < 9, glucose level at hospital arrival≥130 mg/dl, location of internal carotid artery occlusion, embolization into a new territory, symptomatic ICH than the survival group had. Inversely, prevalence of smoking was lower in mortality group. There was no difference was found for sex, hypertension, hypercholesterolemia, previous ischemic 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, anesthesia, extracranial stent placement, intracranial stent placement, vessel dissection, contrast extravasation, femoral access complications.

In the first multivariable analysis model (Table2), 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 acute ischemic stroke 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,

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intravenous thrombolysis was not associated with 90-day mortality in successful reperfusion patients. Other factors, such as age, proximal occlusion, 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 acute ischemic stroke 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 a NIHSS score cutoff value of 17 on admission and 11 at 24±6 hours after thrombectomy respectively, and NIHSS score higher than cutoff value increased the risk of a mortality approximately threefold and twelve 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 acute ischemic stroke patients with large vessel occlusion after endovascular thrombectomy[14, 15]. In previous studies and present study, hyperglycemia was defined in accordance with the absolute glucose concentration, failing to distinguish between poor management of diabetes and a physiologic stress response to acute stroke. Recently, a novel index of stress hyperglycemia ratio (SHR, the admission random blood glucose divided by the glycosylated hemoglobin level) was proved to be a better predictor of poor outcome or mortality than absolute hyperglycemia in patients treated with endovascular thrombectomy[16, 17]. But we did not collect hemoglobin 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

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outcomes or mortality rates in acute ischemic stroke[18]. Moreover, hyperglycemia 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 acute ischemic stroke[19]. But 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]. But there was no difference in the incidence of symptomatic ICH between successful reperfusion with failed reperfusion patients. Interestingly, Möhlenbruch et al. published a report on risk factors of intracranial hemorrhage after endovascular thrombectomy of anterior circulation ischemic stroke[25]. In their analysis, they found complete reperfusion (eTICI 3) were attributable to lower ICH rate in comparison to subtotal recanalization (eTICI 2b, eTICI 2c), and had lower quantity of thrombectomy maneuvers, which was a risk factor of hemorrhagic transformation.

Our analysis has several limitations. Firstly, DIRECT-MT trial was designed in

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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. Secondly, all patients in the DIRECT-MT trial were Chinese, which may limit the generalizability of the findings to other populations. In a pooled analysis of five thrombectomy trials, redominantly 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]. Thirdly, 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 acute ischemic stroke treated with endovascular thrombectomy despite successful reperfusion, as well as, high NIHSS score (NIHSS score≥17) and glucose level (glucose level ≥130mg/dl) at hospital arrival. However, further studies need to be performed to confirm the association between smoking and mortality.

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Author Contributions

ZY, LYZ and JML contributed to conception and design of the study. HL, JBH, JC and SSY drafted the manuscript or tables or figures. PFY, YWZ, PFX and XXZ contributed to comments on the draft manuscript and revised the report. Site investigators contributed to data acquisition not analysis. HC, GL, WJD, CML, LY, LF, YP and SL coordinated the study. XFY conducted the statistical analysis.

Ethics Approval

This trial was approved by Ethics Committee (EC) of Shanghai Changhai Hospital (ID: CHEC2018-003) on Jan 15,2018.

Conflict of Interest Statement

None declared.

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Data sharing statement： The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table1 Baseline characteristics, angiographic outcomes, procedural details and complications in mortality and survival at 90 days.

Variable	Mortality n=78	Survival n=432	P value

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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
Hypercholesterolemia	1(1.28)	18(4.17)	0.3611
Previous ischemic 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±6h) ⩾11	72(92.31)	197(45.60)	<0.0001
ASPECT score < 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)	
M2middle cerebral artery segment	6(7.69)	42(9.72)	
Cause of stroke			

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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)	
Anesthesia			
Local anesthesia	27(35.06)	158(37.26)	0.2423
Sedation	18(23.38)	129(30.42)	
General anesthesia	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
Embolization 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

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

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

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Smoking	0.38(0.17-0.83)	0.015	0.30(0.13-0.70)	0.005	0.450(0.202-1.003)	0.051
NIHSS score on admission≥17	3.14(1.77-5.55)	<0.001	3.08 (1.70-5.60)	<0.001	-	-
Glucose level	2.54(1.51-4.27)	<0.001	2.62(1.52-4.52)	<0.001	2.174(1.270-3.721)	0.005
Symptomatic ICH	Not include	-	11.70(4.74-28.89)	<0.001	Not include	-
NIHSS score after thrombectomy ≥11	Not include	-	Not include	-	12.04(5.09-28.46)	<0.001

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

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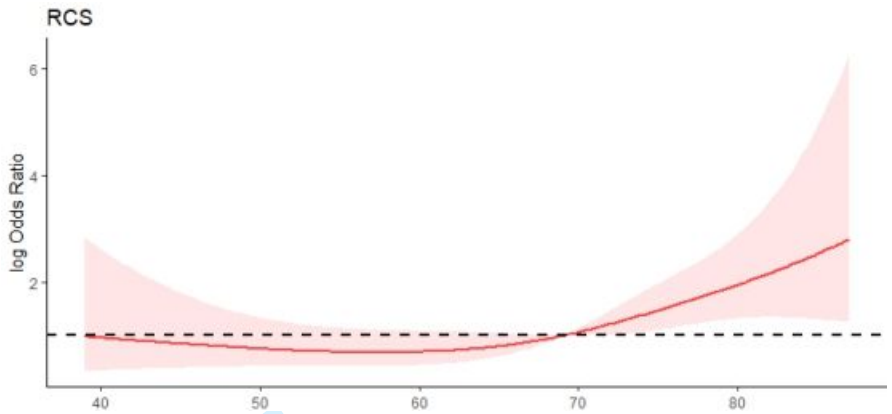
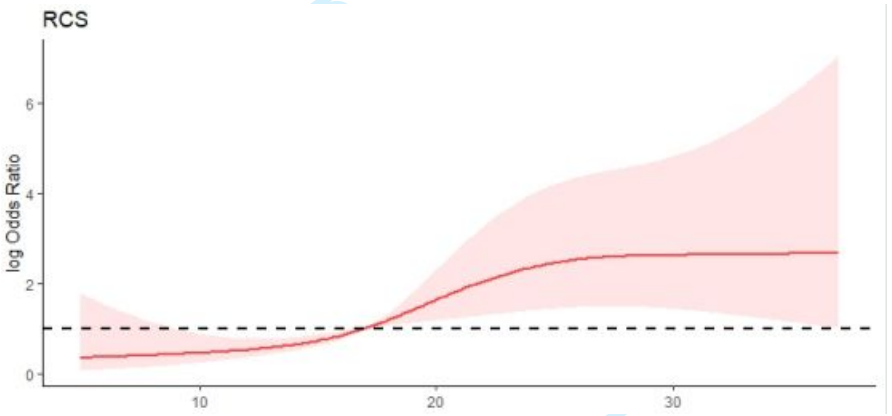
A



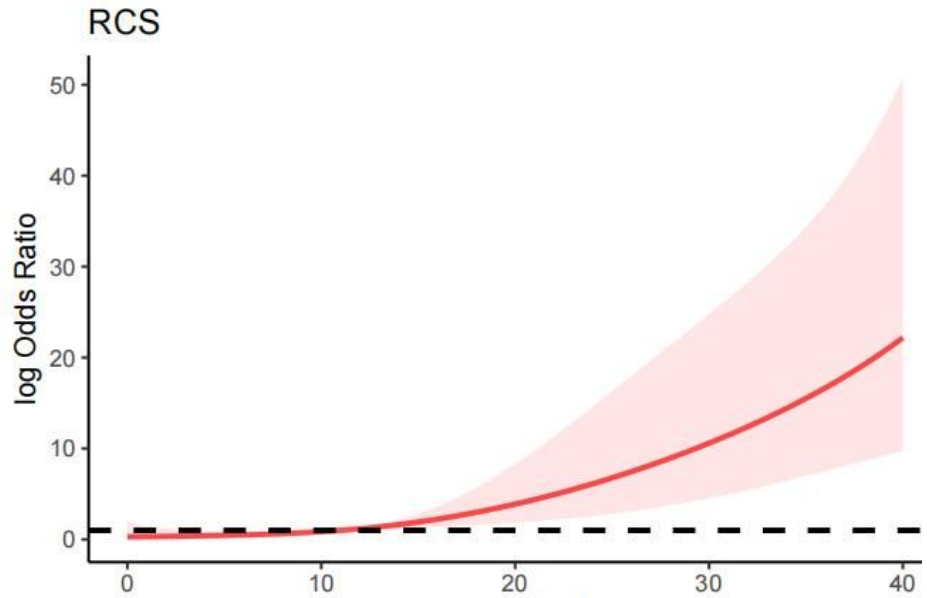
Age

B



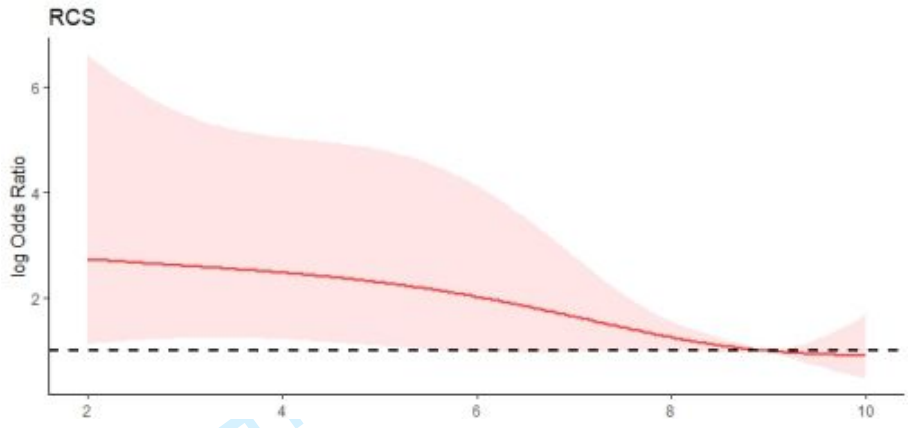
NIHSS score at baseline

C



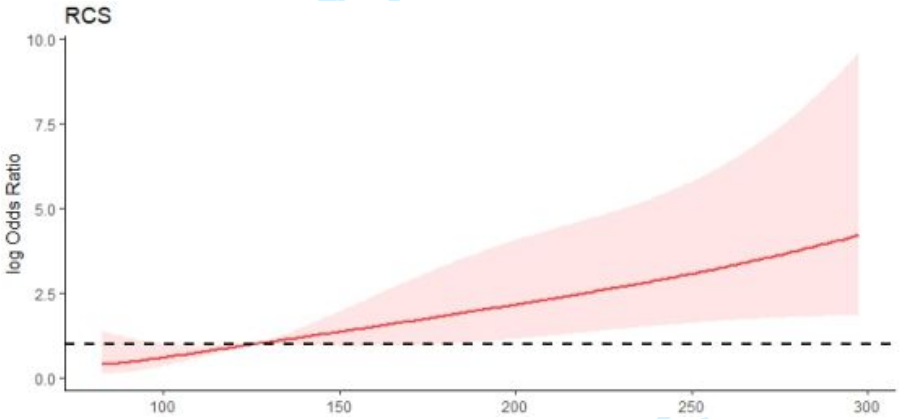
NIHSS score after thrombectomy (24±6h)

D



ASPECT score

E



Glucose level

Figure I. Shape of association of 90-day mortality with age (A), National Institutes of Health Stroke Scale (NIHSS) score at baseline (B), NIHSS score after thrombectomy (24 ± 6h) (C), Alberta Stroke Program Early Computed Tomography Score (ASPECTS) (D) and glucose level (E). The optimal cutoff value for discriminating deceased from survivor patients was 70 years for age, 17 for NIHSS score at baseline, 11 for NIHSS score after thrombectomy, 9 for ASPECT score and 130 mg/dl for glucose level.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1-2
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1-2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3-4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	3-4
	4b	Settings and locations where the data were collected	3-4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3-4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	3-4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	3-4
Sample size	7a	How sample size was determined	3-4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	3-4
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	3-4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	3-4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	3-4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	3-4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	3-4

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		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	3-4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	3-4
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	3-4
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA
	13b	For each group, losses and exclusions after randomisation, together with reasons	5-6
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5-6
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	5-6
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	5-6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	5-6
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	8-10
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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