Complications of mechanical thrombectomy for acute ischemic stroke: Incidence, risk factors, and clinical relevance in the Italian Registry of Endovascular Treatment in acute stroke

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Giancarlo Salsano 1, Giovanni Pracucci 2, Nicola Mavilio 1, Valentina Saia 3, Monica Bandettini di Poggio 4, Laura Malfatto 1, Fabrizio Sallustio 5, Andrea Wlderk 5, Nicola Limbucci 6, Patrizia Nencini 6, Stefano Vallone 7, Andrea Zini 8, Guido Bigliardi 7, Mariano Velo 9, Isabella Francalanza 9, Paola Gennari 10, Rossana Tassi 10, Mauro Bergui 11, Paolo Cerrato 11, Giuseppe Carità 12, Cristiano Azzini 12, Roberto Gasparotti 13, Mauro Magoni 13, Salvatore Isceri 8, Christian Commodaro 14, Francesco Cordici 14, Roberto Menozzi 15, Lilia Latte 15, Mirco Cosottini 16, Michelangelo Mancuso 16, Alessio Comai 17, Enrica Franchini 17, Andrea Alexandre 18, Giacomo Della Marca 18, Edoardo Puglielli 19, Alfonsina Casalena 19, Francesco Causin 20, Claudio Baracchini 20, Luca Di Maggio 21, Andrea Naldi 21, Andrea Grazioli 22, Stefano Forlivesi 22, Luigi Chiumarulo 23, Marco Petruzzellis 23, Giuseppina Sanfilippo 24, Gianpaolo Toscano 24, Nicola Cavasin 25, Critelli Adriana 25, Maria Porzia Ganimede 26, Maria Pia Prontera 26, Giorgianni Andrea 27, Marco Mauri 27, William Auteri 28, Alfredo Petrone 28, Carlo Cirelli 29, Anne Falcou 29, Simona Corraine 30, Valeria Piras 30, Giuseppe Ganci 3, Tiziana Tassinari 3, Nunzio Paolo Nuzzi 31, Manuel Corato 31, Simona Sacco 32, Guido Squassina 13, Paolo Invernizzi 13, Ivan Gallesio 33, Delfina Ferrandi 33, Giovanni Dui 34, Gianluca Deiana 34, Pietro Amistà 35, Monia Russo 35, Francesco Pintus 36, Antonio Baule 36, Giuseppe Craparo 37, Marina Mannino 37, Lucio Castellan 1, Danilo Toni 38, Salvatore Mangiafico 6

1IRCCS San Martino Policlinic Hospital, Neuroradiology and Neurology, Genoa, Italy.

2Department of NEUROFARBA, Neuroscience Section, University of Florence, Florence, Italy.

3Neuroradiology Unit and Neurology and Stroke Unit, Santa Corona Hospital, Pietra Ligure, Italy.

4IRCCS San Martino Policlinic Hospital, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genova, Genoa, Italy.

5Imaging and Interventional Radiology and Stroke Unit, Policlinico Tor Vergata, Roma, Italy.

6Interventional Neurovascular Unit and Stroke Unit, Ospedale Careggi-University Hospital, Firenze, Italy.

7Neuroradiology and Neurology, Ospedale Civile S. Agostino-Estense, University Hospital, Modena, Italy.

8IRCCS Istituto delle Scienze Neurologiche di Bologna, Department of Neurology and Stroke Center and Neuroradiology, Maggiore Hospital, Bologna, Italy.

9Neuroradiology and Stroke Unit, Department of Clinical and Experimental Medicine, University of Messina, Policlinico G. Martino Messina, Italy.

10Neuroradiology and Neurology, 161157AOU Senese, Siena, Italy.

11Interventional Neuroradiology Unit and Stroke Unit, Città della Salute e della Scienza-Molinette, Torino, Italy.

12Neuroradiology and Neurology, Arcispedale S. Anna-University Hospital, Ferrara, Italy.

13Neuroradiology Unit and Stroke Unit, Spedali Civili, Brescia, Italy.

14Department of Neuroradiology, Neurology and Stroke Unit, Cesena-Forlì, AUSL Romagna Azienda Ospedaliera, Cesena, Italy.

15Neuroradiology Unit and Stroke Unit, Ospedale Universitario, Parma, Italy.

16Department of Translational Research and New Technologies in Medicine and Surgery, 9310University of Pisa, Pisa, Italy.

17Radiology Unit and Stroke Unit, Ospedale Centrale, Bolzano, Italy.

18Institute of Neuroradiology and Neurology, A. Gemelli University Polyclinic, IRCCS and Foundation, Sacred Heart Catholic University, Rome, Italy.

19Ospedale Civile Mazzini, Teramo, Italy.

20Stroke Unit and Neurosonology Laboratory, Department of Neuroscience, University of Padua School of Medicine, Padua, Italy.

21Neuroradiology and Neurology, 18698Ospedale San Giovanni Bosco, Torino, Italy.

22UOC Neuroradiologia, DAI Patologia e Diagnostica, Azienda Ospedaliera Universitaria Integrata, Verona, Italy.

23Interventional Neuroradiology Unit and Stroke Unit, Policlinico, Bari, Italy.

24Diagnostic and Interventional Neuroradiology Unit and Stroke Unit, IRCCS Mondino Foundation San Matteo Hospital, Pavia, Italy.

25Neuroradiology Unit and Neurology Unit, Ospedale dell'Angelo, USSL3 Serenissima, Mestre, Italy.

26Interventional Radiology Unit and Stroke Unit, Ospedale SS. Annunziata, Taranto, Italy.

27Neuroradiology Unit and Stroke Unit, Ospedale Universitario Circolo, ASST Sette Laghi, Varese, Italy.

28Interventional Neuroradiology Unit and Neurology Unit, Azienda Ospedaliera Annunziata, Cosenza, Italy.

29Department of Human Neurosciences, Interventional Neuroradiology and Neurology, Università degli Studi di Roma Sapienza, Roma, Lazio, Italy.

30Neuroscience Department, Azienda Ospedaliera G. Brotzu, Cagliari, Sardinia, Italy.

31IRCCS Humanitas Clinical and Research Center, Rozzano, Milano, Italy.

32Department of Clinical Scieces and Biotechnology, Presidio Ospedaliero SS. Filippo e Nicola, Avezzano, Italy.

33Department of Radiology and Neuroradiological Unit, Department of Neurology, Azienda ospedaliera "SS Antonio e Biagio e C. Arrigo," Alessandria, Italy.

34Radiology and Interventional Radiology Unit and Neurology Unit, 97998Ospedale San Francesco, Nuoro, Italy.

35Department of Neuroradiology and Neurology, Hospital of Rovigo, Rovigo, Italy.

36Unit of Neuroradiology and Stroke Unit, Santissima Annunziata Hospital, Sassari, Italy.

37Department of Neuroradiology and Neurology, AOOR Villa Sofia-V. Cervello, Palermo, Italy.

38Emergency Department Stroke Unit, Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy.

Corresponding author(s):

Giancarlo Salsano, IRCCS San Martino Policlinic Hospital, Largo Rosanna Benzi, 10, 16132 Genova, Italy. Email: giancarlo.salsano@yahoo.it

Abstract

Background

There are limited data concerning procedure-related complications of endovascular thrombectomy for large vessel occlusion strokes.

Aims

We evaluated the cumulative incidence, the clinical relevance in terms of increased disability and mortality, and risk factors for complications.

Methods

From January 2011 to December 2017, 4799 patients were enrolled by 36 centers in the Italian Registry of Endovascular Stroke Treatment. Data on demographic and procedural characteristics, complications, and clinical outcome at three months were prospectively collected.

Results

The complications cumulative incidence was 201 per 1000 patients undergoing endovascular thrombectomy. Ongoing antiplatelet therapy ($p < 0.01$; OR 1.82, 95% CI: 1.21–2.73) and large vessel occlusion site (carotid-T, $p < 0.03$; OR 3.05, 95% CI: 1.13–8.19; M2-segment-MCA, $p < 0.01$; OR 4.54, 95% CI: 1.66–12.44) were associated with a higher risk of subarachnoid hemorrhage/arterial perforation. Thrombectomy alone ($p < 0.01$; OR 0.50, 95% CI: 0.31–0.83) and younger age ($p < 0.04$; OR 0.98, 95% CI: 0.97–0.99) revealed a lower risk of developing

dissection. M2-segment-MCA occlusion ($p < 0.01$; OR 0.35, 95% CI: 0.19–0.64) and hypertension ($p < 0.04$; OR 0.77, 95% CI: 0.6–0.98) were less related to clot embolization. Higher NIHSS at onset ($p < 0.01$; OR 1.04, 95% CI: 1.02–1.06), longer groin-to-reperfusion time ($p < 0.01$; OR 1.05, 95% CI: 1.02–1.07), diabetes ($p < 0.01$; OR 1.67, 95% CI: 1.25–2.23), and LVO site (carotid-T, $p < 0.01$; OR 1.96, 95% CI: 1.26–3.05; M2-segment-MCA, $p < 0.02$; OR 1.62, 95% CI: 1.08–2.42) were associated with a higher risk of developing symptomatic intracerebral hemorrhage compared to no/asymptomatic intracerebral hemorrhage. The subgroup of patients treated with thrombectomy alone presented a lower risk of symptomatic intracerebral hemorrhage ($p < 0.01$; OR 0.70; 95% CI: 0.55–0.90). Subarachnoid hemorrhage/arterial perforation and symptomatic intracerebral hemorrhage after endovascular thrombectomy worsen both functional independence and mortality at three-month follow-up ($p < 0.01$). Distal embolization is associated with neurological deterioration ($p < 0.01$), while arterial dissection did not affect clinical outcome at follow-up.

Conclusions

Complications globally considered are not uncommon and may result in poor clinical outcome. Early recognition of risk factors might help to prevent complications and manage them appropriately in order to maximize endovascular thrombectomy benefits.

Introduction

Randomized controlled trials (RCTs) on acute ischemic strokes due to large vessel occlusion (LVO) demonstrated the overwhelming superiority of endovascular therapy plus intravenous thrombolysis (IVT) compared to best medical therapy in terms of functional outcome (Suppl. 7–15). However, most trials (ESCAPE, EXTEND IA, SWIFT PRIME, REVASCAT, THRACE, PISTE, THERAPY (Supplemental reference 8–15)) were stopped early after an interim review analysis for efficacy, and because of that, there is limited knowledge regarding complications of endovascular thrombectomy (ET) in the treatment of acute ischemic stroke, although it is considered the standard of care. In this context, only few studies have focused on procedural complications as primary endpoint resulting in incomplete and inconsistent data collection (Suppl. Table 1).

Aims

The aim of this study is to evaluate the cumulative incidence and the clinical relevance in terms of increased disability and mortality of procedural-related complications for endovascular therapy. Moreover, risk factors for all the observed complications have been identified.

Materials and methods

Study design, participants, and procedures

We conducted a cohort study on patient's data collected prospectively in the IRETAS (Italian Registry of Endovascular Stroke Treatment in Acute Stroke) a multicenter, observational

internet-based registry (Suppl. Table 2). Patients with acute ischemic stroke showing LVO and treated with bridging therapy (ET + IVT) or with thrombectomy alone (direct thrombectomy) between January 2011 and December 2017 were analyzed. To date, 56 centers (Suppl. Table 3) are giving their contribution to IRETAS. However, only records gathered by centers with at least 80% of completed data were considered suitable for statistical analysis. This center-based selection was adopted to avoid selection bias.1 Hence, a total of 36 Italian centers out of 56 met these parameters and were included in the present study. Moreover, participating centers joined registry at different times. All participating centers were required to accept the rules of the IRETAS, including consecutive registration of all stroke patients receiving endovascular procedures, irrespective of whether treatment was according to guidelines. STROBE criteria for observational studies were fulfilled.2

Statistical analysis

We performed all statistical analyses using Statistical Package for Social Sciences software version 21.0. The categorical variables were reported as frequency and percentage, while the continuous variables as mean and standard deviation. Differences between the cohorts were explored using the Mann–Whitney U test for continuous variables. Differences between proportions were assessed by Fisher exact test or $\chi 2$ test, where appropriate. No attempt to replace missing values was made. Multivariable binary logistic regression analyses were performed to identify the independent predictive factors for each complication, including all variables with a value of $p < 0.1$ at univariable analysis. The following variables were evaluated as potential risk factors for complications: age, sex, arterial hypertension, diabetes mellitus, smoking, atrial fibrillation, previous cardiovascular event, antiplatelet therapy, anticoagulation therapy, direct thrombectomy, NIHSS at onset, site of vascular occlusion, time from arterial puncture to revascularization (groin-to-reperfusion), type of anesthesia, and success in revascularization (TICI score). Hosmer–Lemeshow goodness-of-fit statistics has been employed to assess model calibration. A value of $p < 0.05$ was considered significant.

Results

During the study period, a total of 4799 acute ischemic stroke patients underwent ET and were registered in IRETAS by 36 Italian centers. Baseline patient characteristics as well as clinical and procedural parameters are listed in Table 1.

The cumulative incidence of procedure-related complications over the study period was 201 per 1000 patients undergoing endovascular therapy. Cumulative incidence and incidence rates for all specific complications are listed in Table 2.

A total of 4516 out of 4799 patients were monitored for 90 days after ET, and the follow-up was 94.1% complete (5.9% of patients were lost at follow-up).

In the subgroup of patients treated with direct thrombectomy, 2209 out of 2361 patients (93.5%) completed three months' follow-up with 6.5% of patients lost.

Procedure-related complications clinical relevance and risk factors

Subarachnoid hemorrhage/arterial perforation was associated with poor functional outcomes ($p < 0.01$) and higher mortality (mRS = 6, $p < 0.01$; Table 3) at three-month follow-up. At univariable analysis, NIHSS at onset, site of LVO, antiplatelet therapy, TICI ≤ 2 a, and general anesthesia were associated with subarachnoid hemorrhage/arterial perforation and were included in multivariable analysis (Suppl. Table 4). On Figure 1(a), factors associated with a higher risk of subarachnoid hemorrhage/arterial perforation at multivariable analysis are reported.

Arterial dissection was not associated with lower mRS ($p = 0.94$) or higher mortality at three-month follow-up ($p = 0.37$) (Table 3). Univariable and multivariable risk factors' analysis for dissection is reported in Suppl. Table 5 and in Figure 1(b).

Embolization to new arterial territory or distal embolization in target territory was related to worse functional outcomes ($p < 0.01$) but not to increased mortality ($p = 0.15$) at three-month follow-up (Table 3). At univariable analysis, higher NIHSS, site of LVO, atrial fibrillation, hypertension, TICI ≤ 2 a, and groin-to-reperfusion time were associated with embolization and were included in the multivariable analysis (Suppl. Table 6). Panel c of Figure 1 shows that hypertension and M2-segment-MCA occlusion were related to lower risk of clot embolization at multivariable analysis.

sICH was related to poor functional outcome and increased mortality at three-month follow-up ($p < 0.01$; Table 3). At univariable analysis, higher NIHSS, site of LVO, diabetes, groin-to-reperfusion time, hypertension, antiplatelet therapy, smoking, and TICI ≤ 2 a were associated with sICH and were included in multivariable analysis (Suppl. Tables 7 and 8).

Higher NIHSS, diabetes, antiplatelet therapy, occlusion of carotid-T, TICI ≤ 2 a, and groin-to-reperfusion time were related to sICH at multivariable analysis. The subgroup of patients treated with direct thrombectomy showed a lower risk of sICH (Figure 1(d)).

Arterial access site complications requiring surgical repair were related to increased mortality at 90 days' follow-up (Table 3). Univariable and multivariable risk factors analysis are shown in Suppl. Table 9.

Discussion

Procedure-related complications may occur during or after endovascular treatment with a wide range of intracranial or extracranial events. A better knowledge of endovascular adverse events is fundamental to prevent and manage them appropriately in order to maximize the benefits of the endovascular technique, avoiding iatrogenic additional damages. However, data on the frequency of endovascular complications and on their clinical impact are limited in the literature due to underpowered studies. In the current multicenter study, we have

exclusively focused on cumulative incidence providing our estimate on risk factors and clinical relevance of complications. ET complications are rare when taken individually, but globally, they account for 10–20% of patients. Most RCT and non-RCT publications have mainly focused on the efficacy of ET resulting in fragmented data collection regarding procedural adverse events. Patients deriving from 9 RCTs (2027) and 34 non-RCT studies (8003) were reviewed (Suppl. Table 1). Among 2027 patients treated with endovascular therapy plus IVT included in RCTs (Suppl. reference 7–15), 838 patients (41%) had data on subarachnoid hemorrhage/arterial perforation reporting 36 cases (1.8%). Similarly, between 8003 patients analyzed in non-RCT studies (Suppl. reference 16–49), only 2223 patients (27.8%) had data on subarachnoid hemorrhage/arterial perforation registering 100 adverse events (4.5%) (Figure 2(a)). In our study, we found 135 subarachnoid hemorrhage/arterial perforation with an incidence rate of 2.81%. In these patients, there was a statistically significant correlation of subarachnoid hemorrhage/arterial perforation with unsuccessful revascularization results (TICI ≤ 2 a) and worse clinical outcome at 90-day follow-up. In literature, subarachnoid hemorrhage is described as common and often benign complication compared to arterial perforation that is a dramatic even.3 In the IRETAS, subarachnoid hemorrhage caused by arterial perforation4 or resulting from stretching of the arterioles and venules in the subarachnoid spaces during the stent-retriever withdrawing5 are considered in the same way. M2-segment-MCA and carotid-T occlusion were associated with higher risk of subarachnoid hemorrhage as compared to M1-segment-MCA, posterior circulation, or tandem occlusion. This may be due to different causes: carotid-T occlusion may be more technically demanding, requiring more frequent blind navigation in partially overlapping anatomies (choroidal artery may overlap to pcom-PCA or siphon in postero–anterior, MCA, and ACA in lateral projections), and it may cause larger infarctions; according to Mokin et al.,6 subarachnoid hemorrhage is more frequently common in distal occlusion sites and during difficult crossing of the thrombus with a microcatheter or microwire.

Arterial dissection is often an asymptomatic complication7 with an incidence ranging from 0.6 to 3.9% in RCT studies (Suppl. reference 7–15) and from 1 to 7% in non-RCT studies (Suppl. reference 16–49). Only 16 (2%) dissections were recorded in 777 RCTs patients (38%) while 118 (3%) dissections were identified in 4006 non-RCT patients (50.0%) (Figure 2(b)). We report 81 dissections with an incidence rate for dissection of 1.69%. There was a statistically significant correlation of dissection with unfavorable revascularization results (TICI ≤ 2 a) without worsening the clinical outcome at three months according to Simonetti et al. (Suppl. reference 17).

RCT studies showed 44 embolization to new arterial territory/distal embolization in target territory (5.6%) in 777 patients (38%) while non-RCT studies counted 113 embolization (4.1%) in 2667 patients (33.3%) (Figure 2(c)). We reported 365 clot embolization with an incidence rate of 7.61%. Distal embolization may reduce the functional independence at 90 days because the disrupted clots can migrate in a previously unaffected area or block the collateral flow to the potentially salvageable tissue. Distal site occlusion such as M2-segment-MCA showed a lower risk of migration, possible due to clot characteristics that are shorter in length compared to proximal LVO.8

Moreover, gender, hypertension, age, diabetes mellitus, smoking habit, atrial fibrillation, prior cerebrovascular event, and onset NIHSS were not associated with higher rate of subarachnoid hemorrhage, clot embolization, and dissection.

Certainly, procedure-related complications are iatrogenic injuries; however, adverse events should be considered as multi-factorial phenomena. Arterial stiffness,9 atherosclerosis,10 and thrombus properties11 are not predictable factors that may be associated with higher procedural complications rate. Moreover, arterial stiffness and atherosclerosis are closely related to gender, hypertension, age, diabetes mellitus, smoking habit, atrial fibrillation, prior cerebrovascular event, and stroke severity. This may explain why other studies included baseline characteristics for the patients into risk factors analysis.12–14

Intracranial hemorrhage is a common and serious complication of ET occurring intra-operatively or post-procedure, generally within 72 h. It can be classified in symptomatic and asymptomatic.15 Several criteria for the definition of ICH exist, so the rates of total sICH ranged from 3.6 to 9.3% of cases for RCT studies and from 3 to 34.9% of cases for non-RCT studies, depending upon the patient selection and definition applied.16–18 Moreover, only few non-RCT studies reported sICH rate of patients treated with direct thrombectomy while data from RCTs are lacking. From review of literature, only 15 studies with a total of 1585 patients (19.8%) treated with direct thrombectomy reported data on sICH with 99 (6.2%) hemorrhagic events (Figure 2(d)). Following ECASS II criteria, in our report, 170 patients submitted to direct thrombectomy developed an sICH with an incidence rate of 7.20%. Patients treated with direct thrombectomy were less affected by clinically relevant intraparenchymal hemorrhage, so IVT seems to be the main risk factor for developing sICH, but there are still no trial supporting a higher rate of sICH in patients treated with combined IVT and ET compared with IVT alone.

Higher NIHSS at onset, ongoing antiplatelet therapy, diabetes, and longer groin-to-reperfusion time were associated with higher risk of sICH, according to literature.19 We also discovered that carotid-T occlusion was significantly associated with a higher risk of developing sICH, likely due to a large ischemic core volume with subsequent reperfusion damage of the cerebral infarct tissue.20 Type of anesthesia did not affect complications rate of subarachnoid hemorrhage, clot embolization, dissection, and sICH.

This paper presents some limitations. We reviewed prospectively collected data that are self-reported by authors on an internet-based registry, without a centralized control of data quality, including the angiographic pre- and post-procedural results. There may be between-center inhomogeneity due to the lack of a common protocol of intervention. However, these are limitations shared with other similar registries, and our data represent the real-world experience of ET in a large number of Italian centers with medium-to-high volume of activity.

Declaration of conflicting interests

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Complication	*n*, %	Incidence per 1000 ET
Subarachnoid hemorrhage/arterial perforation	135 (2.9)	28.1
Dissection	81 (1.7)	16.9
Clot embolization	365 (7.6)	76.1
Access site	30 (0.6)	6.3
sICH	353 (7.4%)	73.6
		Cumulative incidence
		201
Subgroup of patient treated with ET without IVT		
Complication	*n*, %	Incidence per 1000 ET
sICH	170 (7.2)	72.0

sICH: symptomatic intracerebral hemorrhage; ET: endovascular thrombectomy; IVT: intravenous thrombolysis.

Inclusion and Exclusion Criteria and outcomes are provided in the online-only Data Supplement.

Parameter	Patients (4797)
Age (years), mean ± SD	69.02 ± 13.7
Gender, male *n* (%)	2434 (50.7)
NIHSS onset, *n* (%)	
<6	303 (6.3)
>6	4478 (93.3)
Missing	18 (0.4)
Atrial fibrillation, *n* (%)	1301 (27.1)
History of hypertension, *n* (%)	2623 (54.6)
Diabetes mellitus, *n* (%)	693 (14.4)
Smoke habit, *n* (%)	823 (17.3)
Prior cerebrovascular event, *n* (%)	208 (4.3)
Antiplatelet therapy, *n* (%)	1129 (23.5)
Oral Anticoagulant, *n* (%)	502 (10.5)
Treatment approach, *n* (%)	
Direct thrombectomy	2361 (49.2)
Bridging thrombectomy	2438 (50.8)
Occlusion site, *n* (%)	
ICA	524 (10.9)
Carotid-T	728 (15.2)
M1-segment-MCA	2070 (43.1)
M2-segment-MCA	546 (11.4)
Tandem occlusion	287 (6.0)
Posterior circulation	632 (13.2)
Missing	12 (0.2)
Anesthesia, *n* (%)	
Local	1093 (22.7)
Conscious sedation	1215 (25.3)
General	1736 (36.1)
Missing	755 (15.9)

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Missing	755 (15.9)

SD: deviation standard; MCA: middle cerebral artery; ICA: internal carotid artery; NIHSS: National Institutes of Health Stroke Scale; TICI: thrombolysis in cerebral ischemia.

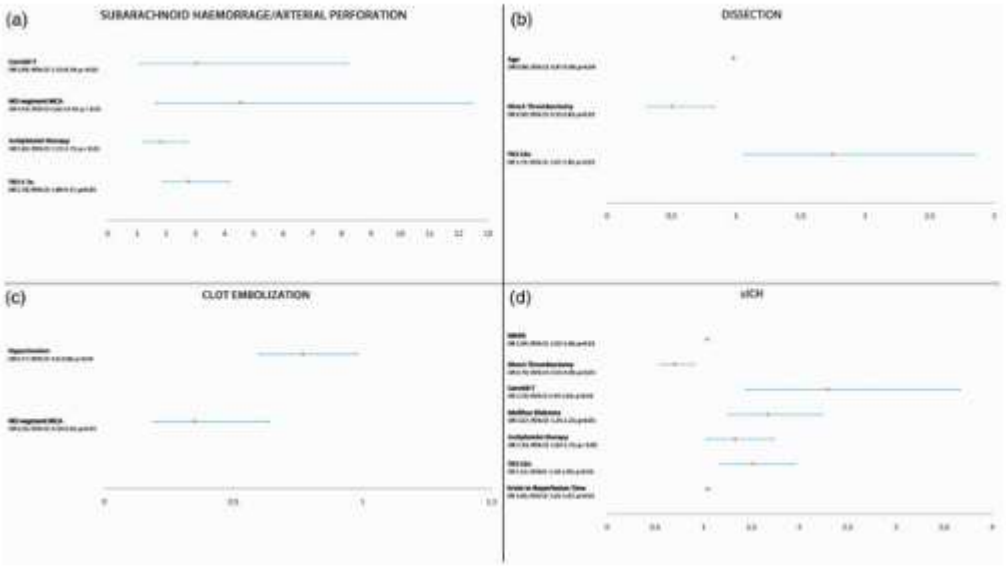

Figure 1. Risk factors for subarachnoid hemorrhage/arterial perforation (a), dissection (b), clot embolization (c), and sICH (d).

Clinical outcome	Subarachnoid hemorrhage or arterial perforation, n (%)	No subarachnoid hemorrhage or arterial perforation, n (%)	p Value	Relative risk*	95% CI*
mRS 0–2 mRS 3–6	28 (1.4)	2006 (98.6)	<0.01	0.35	0.2–0.5
mRS 6 mRS 0–5	56 (6.5)	810 (93.5)	<0.01	3.42	2.4–4.8
	Dissection, n (%)	No dissection, n (%)	p value	Relative risk*	95% CI*
mRS 0–2 mRS 3–6	35 (1.7)	1999 (98.3)	0.94	1.02	0.6–1.6
mRS 6 mRS 0–5	11 (1.3)	855 (98.7)	0.37	0.70	0.4–1.3
	Embolization, n (%)	No embolization, n (%)	p Value	Relative risk*	95% CI*
mRS 0–2 mRS 3–6	107 (5.3)	1927 (94.7)	<0.01	0.44	0.4–0.7
mRS 6 mRS 0–5	76 (8.8)	790 (91.2)	0.15	1.20	0.9–1.5
	Access site complication, n (%)	No access site complication, n (%)	p Value	Relative risk*	95% CI*
mRS 0–2 mRS 3–6	7 (0.3)	2027 (99.7)	0.02	0.34	0.1–0.8
mRS 6 mRS 0–5	12 (1.4)	854 (98.6)	<0.01	2.81	1.4–5.8
	sICH, n (%)	No sICH, n (%)	p Value	Relative risk*	95% CI*
mRS 0–2 mRS 3–6	32 (1.6)	2002 (98.4)	<0.01	0.12	0.1–0.2
mRS 6 mRS 0–5	192 (22.2)	674 (77.8)	<0.01	5.03	4.1–6.1
	Subgroup of patient treated with MT without IVT				
	sICH, n (%)	No sICH, n (%)	p Value	Relative risk*	95% CI*
mRS 0–2 mRS 3–6	11 (1.2)	913 (98.8)	<0.01	0.11	0.1–0.2
mRS 6 mRS 0–5	88 (18.0)	401 (82.0)	<0.01	9.80	7.2–13.3

mRS: modified Rankin score; mRS 0–2: functional independence; mRS 3–6: poor outcome; mRs 6: dead; sICH: symptomatic intracerebral hemorrhage.
*Reference: mRS 0–2 for functional outcome mRS 6 for mortality.

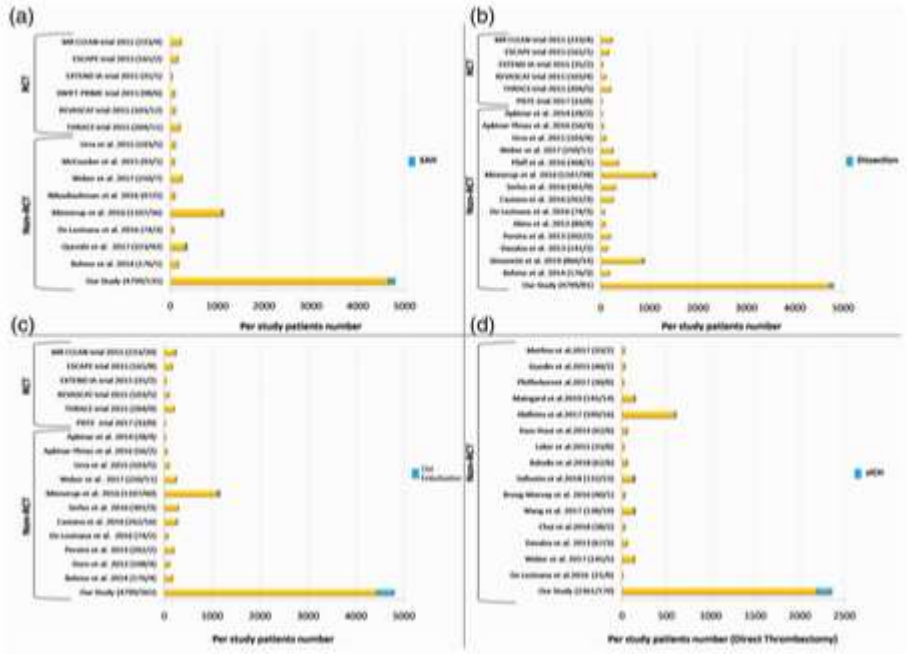

Figure 2. Per study patient numbers and complication rate deriving from the RCTs and non-RCTs studies for subarachnoid hemorrhage (a), dissection (b), and clot embolization (c). Panel d shows sICH rate in the group of patient treated with direct thrombectomy.