Direct thrombectomy for stroke in the presence of absolute exclusion criteria for thrombolysis

Abstract

Background Intravenous thrombolysis (IVT)-ineligible patients undergoing direct thrombectomy tended to have poorer

functional outcome as compared with IVT-eligible patients undergoing bridging therapy. We aimed to assess radiological

and functional outcomes in large vessel occlusion-related stroke patients receiving direct thrombectomy in the presence of

absolute exclusion criteria for IVT vs relative exclusion criteria for IVT and vs non-exclusion criteria for IVT.

Methods A cohort study on prospectively collected data from 2282 patients enrolled in the Italian Registry of Endovascular

Treatment in Acute Stroke cohort for treatment with direct thrombectomy (n=486, absolute exclusion criteria for IVT alone;

n=384, absolute in combination with relative exclusion criteria for IVT; n=777, relative exclusion criteria for IVT alone;

n=635, non-exclusion criteria for IVT).

Results After adjustment for unbalanced variables (model 1), ORs for 3-month death was higher in the presence of absolute

exclusion criteria for IVT alone (vs relative exclusion criteria for IVT alone) (1.595, 95% CI 1.042–2.440) and in the presence of absolute exclusion criteria for IVT alone (vs non-exclusion criteria for IVT) (1.235, 95% CI 1.014–1.504). After

adjustment for predefned variables (model 2: age, sex, pre-stroke mRS≤1, NIHSS, occlusion in the anterior circulation,

onset-to-groin time, and procedure time), ORs for 3-month death was higher in the presence of absolute exclusion criteria

for IVT alone (vs relative exclusion criteria for IVT alone) (1.235, 95% CI 1.014–1.504) and in the presence of absolute

exclusion criteria for IVT alone (vs non-exclusion criteria for IVT) (1.246, 95% CI 1.039–1.495). No signifcant diference

was found between the groups as regards any type of intracerebral hemorrhage and parenchymal hematoma within 24 h,

successful and complete recanalization after procedure, and modifed Rankin Scale score 0–2 at 3 months. After adjustment

for predefned variables of model 2, ORs for death were higher in the presence of recent administration of IV heparin (OR:

2.077), platelet count<100,000/mm3

(OR: 4.798), bacterial endocarditis (OR: 15.069), neoplasm with increased hemorrhagic risk (OR: 6.046), and severe liver disease (OR: 6.124).

Electronic supplementary material The online version of this

article (https://doi.org/10.1007/s00415-020-10098-w) contains

supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

Conclusions Radiological outcomes were similar after direct thrombectomy in patients with absolute, relative, and nonexclusion criteria for IVT, while an increase of fatal outcome was observed in the presence of some absolute exclusion

criterion for IVT.

Keywords Stroke · Thrombectomy · Thrombolysis · Outcome

Introduction

Mechanical thrombectomy for ischemic stroke with large vessel occlusion (LVO) substantially reduces disability with fve

randomized clinical trials (RCTs) leading to guideline changes

worldwide [1–5]. Direct thrombectomy is recommended

within 6 h in the presence of contraindications to intravenous

thrombolysis (IVT) listed in the current summary of product

characteristics (SPC) of Actilyse and up to 16–24 h of last time

known well in patients selected according to the clinical and

radiological criteria of DEFUSE-3 and DAWN trials [6–8].

The experience accumulated over the years by centers performing IVT suggests that the use of Actilyse is efective and

sufciently safe for ischemic stroke regardless of the presence

of some contraindications listed in the SPC of the drug. Therefore, the current guidelines re-classifed the contraindications

to the use of Actilyse into “absolute” or “relative exclusion

criteria” for IVT [9]. Among three RCTs (i.e., MR CLEAN,

ESCAPE, and REVASCAT) [1, 2, 5] including a total of 188

patients (108 direct mechanical thrombectomy vs 80 controls)

who were ineligible for IVT, only a MR CLEAN sub-analysis

listed the specifc contraindications for Actilyse; however, data

on outcome were not reported [10].

A recent meta-analysis reported that IVT-ineligible patients

treated with direct mechanical thrombectomy tended to have

lower rates of functional independence and had higher odds

for fatal outcome, as compared with IVT-eligible patients

treated with bridging therapy [11]. However, IVT-ineligible

patients are inherently diferent from IVT-eligible patients,

as suggested by of-label thrombolysis studies that reported

a higher rate of sICH [12-14] and a higher rate of poor functional outcome and/or death [13, 15] in some absolute exclusion criterion for IVT.

The aim of this study was to assess radiological and functional outcomes in LVO-related acute ischemic strokes treated

with direct mechanical thrombectomy in the presence of absolute exclusion criteria for IVT vs relative exclusion criteria for

IVT and vs non-exclusion criteria for IVT.

Methods

Study design, participants, and procedures

We conducted a cohort study on prospectively collected data

of patients enrolled in the Italian Registry of Endovascular

Treatment in Acute Stroke (IRETAS). The IRETAS is a multicenter, observational internet-based registry (Supplemental Table 1). Acute ischemic stroke patients with LVO who

received endovascular procedures between January 2011 and

December 2017 were included in the present study. 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.

Data collection

Data collection is provided in the Supplemental Data.

Inclusion and exclusion criteria

We included all patients aged 18 years and older who

received direct mechanical thrombectomy within 24 h from

known symptom onset or symptom recognition time (for

unwitnessed stroke) or awakening time (for wake-up stroke).

We identifed the presence of absolute and relative exclusion

criteria for IVT according to the current guidelines [9]. As

regards time window for treatment, we defned arbitrarily

the time between known symptom onset and endovascular

treatment hospital admission as absolute exclusion criterion for IVT if it was>4.5 h. Given that recruitment largely

preceded the evidence for mechanical thrombectomy in

unknown onset strokes [7, 8], the choice of type of endovascular procedure for these patients was at the discretion of

the neurologist and neuroradiologist. We defned arbitrarily

unwitnessed stroke and wake-up stroke as absolute exclusion criteria for IVT if the symptom recognition time or

awakening time were>4.5 h from endovascular treatment

hospital admission.

Outcome measures

The radiological outcome measures were (a) any type of

intracerebral hemorrhage (ICH) and (b) parenchymal hematoma (PH) within 24 h; (c) successful recanalization and d)

complete recanalization after procedure defned as thrombolysis in cerebral infarction (TICI) grading system 2b/3

and 3, respectively. The functional outcome measures were

(a) favorable functional outcome (mRS score 0–2) and (b)

death at 3 months.

Statistical analysis

We performed statistical analyses using SPSS 22.0 statistical package. Diferences between the cohorts were explored

using the Mann–Whitney U test for continuous variables.

Diferences between proportions were assessed by Fisher's

exact test or $\chi 2$

test, where appropriate. Continuous variables

were reported as median and interquartile range (IQR) values. Proportions were calculated for categorical variables,

dividing the number of events by the total number excluding

missing/unknown cases.

We estimated the association of the presence of absolute

exclusion criteria for IVT alone (vs relative exclusion criteria for IVT alone, vs non-exclusion criteria for IVT) and

the presence of relative exclusion criteria for IVT alone (vs

non-exclusion criteria for IVT) with outcome measures by

calculating the odds ratio (OR) with two-sided 95% confdence intervals (CI) after three adjustment models. Model 1

included group diferences in baseline characteristics (probability value<0.10), model 2 included age, sex, pre-stroke

mRS score<1, NIH Stroke Scale (NIHSS) score, symptom

onset-to-groin puncture time, LVO in the anterior circulation

and procedure time, model 3 included variables of model

2 plus occlusion site and Alberta Stroke Program Early

Computed Tomography (ASPECT) score≥6, type of procedure, additional intra-arterial (IA) fbrinolysis, and general

anesthesia. Careggi collateral score did not enter the models because the number of missing values was greater than

one-third of the entire cohort.

Standard protocol approvals, registrations,

and patient consents

The need for ethical approval or patient consent for participation in the IRETAS varied among participating hospitals.

Ethical approval and informed consent were obtained when

required.

Data availability statement

Anonymized data will be shared by request from any qualifed investigator.

Results

Among 2737 patients registered in the IRETAS cohort by 44

centers for treatment with direct mechanical thrombectomy

(Supplemental Table 2), 2282 patients were included in the

study. Flow diagram of patient inclusion and exclusion is

provided in the Supplemental Data. Characteristics of the

included and excluded patients are provided in Supplemental Table 3.

Characteristics of the patients with (n=870) and without (n=1412) absolute exclusion criteria for IVT are provided in Table 1. Absolute exclusion criteria for IVT are listed in Table 2, while relative exclusion criteria for IVT are listed in Supplement Table 4.

Absolute exclusion criteria for IVT alone were reported in 486 (21%) patients, absolute in combination with relative exclusion criteria for IVT in 384 (17%) patients, relative exclusion criteria for IVT alone in 777 (34%) patients, and non-exclusion criteria for IVT in 635 (28%) patients.

Characteristics of the patients with absolute exclusion criteria for IVT alone, relative exclusion criteria for IVT alone, and non-exclusion criteria are provided in Table 3

Associations of the presence of absolute exclusion criteria for IVT alone (vs relative exclusion criteria for IVT alone, vs non-exclusion criteria for IVT) and presence of relative exclusion criteria for IVT alone (vs non-exclusion criteria for IVT) with outcome measures after three adjustment models are provide in Table 4. ORs for death was higher in the presence of absolute exclusion criteria for IVT alone (vs relative exclusion criteria for IVT alone) in model 1 (OR: 1.595, 95% CI 1.042–2.440) and in model 2 (OR: 1.485, 95% CI 1.060–2.080). ORs for death was higher in the presence of absolute exclusion criteria for IVT alone (vs non-exclusion criteria for IVT) in model 1 (OR: 1.235, 95% CI 1.014–1.504) and in model 2 (OR: 1.246, 95% CI 1.039–1.495). We found no signifcant diference between

the groups as regards any type of ICH and PH within 24 h,

successful and complete recanalization after procedure, and

favorable functional outcome at 3 months.

In the unadjusted ordinal logistic regression and after

adjustment for pre-defned variables of model 2 (age, sex,

pre-stroke mRS≤1, NIHSS score, LVO in the anterior circulation, symptom onset-to-groin puncture time, and procedure

time), beneft of successful recanalization (vs unsuccessful

recanalization) on 3-month mRS (from 0 to 6) was similar

in patients with absolute exclusion criteria for IVT alone

(OR: 0.327, 95% CI 0.223–0.481; adjusted OR: 0.411, 95%

CI 0.256–0.659), relative exclusion criteria for IVT alone

(OR: 0.273, 95% CI 0.202–0.369; adjusted OR: 0.256, 95%

CI 0.180–0.364), and non-exclusion criteria for IVT (OR:

0.305, 95% CI 0.214–0.434; adjusted OR: 0.341, 95% CI

0.226–0.514) (Supplemental Table 5). In patients with successful recanalization, we found no signifcant diference

on 3-month favorable functional outcome between the presence of absolute exclusion criteria for IVT alone and relative

exclusion criteria for IVT alone (reference) (OR: 0.672, 95%

CI 0.289–1.564, p=0.356), between the presence of absolute exclusion criteria for IVT alone and non-exclusion criteria for IVT (reference) (OR: 0.586, 95% CI 0.245–1.403,

p=0.230), and between the presence of relative exclusion

criteria for IVT alone and non-exclusion criteria for IVT

(reference) (OR: 0.948, 95% CI 0.478–1.881, p=0.878),

Table 1 Demographics and clinical characteristics of the patients with and without absolute exclusion criteria for IVT

Data are n (%) or median (IQR). Numbers within square brackets indicate number of missing values

	Absolute exclusion criteria for IVT		p value
	Yes (n=870)	No (n=1412)	
Demographics			
Age (years), median (IQR)	74 (63–80)	73 (61–79)	0.033
Male sex, n (%)	428 (49.2)	731 (51.8)	0.245
Years			
2016–2017, n (%)	500 (57.5)	700 (49.6)	<0.001
Medical history			
Hypertension, n (%)	488 (61.9) [82]	722 (64.5) [293]	0.247
Diabetes mellitus, n (%)	157 (19.9) [82]	215 (19.2) [293]	0.725
Hyperlipidemia, n (%)	174 (22.1) [82]	312 (27.9) [293]	0.005
Smoke habit, n (%)	126 (16) [82]	229 (20.5) [293]	0.014
Previous stroke/transient ischemic attack, n (%)	51 (6.5) [82]	89 (8) [293]	0.247
Atrial fbrillation, n (%)	414 (52.5) [82]	314 (28.1) [293]	<0.001
Coronary heart disease, n (%)	100 (12.7) [82]	121 (10.8) [293]	0.217
Congestive heart failure, n (%)	94 (11.9) [82]	85 (7.6) [293]	0.002
Antiplatelet treatment, n (%)	191 (22)	430 (30.5)	<0.001
Oral anticoagulant treatment, n (%)	371 (42.6)	79 (5.6)	<0.001
Statin treatment, n (%)	128 (14.7)	199 (14.1)	0.712
Baseline data			
Pre-stroke mRS score≤1, n (%)	602 (80.3) [120]	1037 (84.9) [190]	0.009
NIHSS score, median (IQR)	18 (14–22) [48]	18 (13–21) [94]	0.090
ASPECT score≥6, n (%)	626 (96) [218]	1050 (95.6) [314]	0.806
Occlusion site			<0.001
Tandem, n (%)	80 (9.2) [5]	219 (15.6) [12]	

Intra-cranial internal carotid artery, n (%) 165 (19.1) [5] 274 (19.6) [12]

M1-segment middle cerebral artery, n (%) 386 (44.6) [5] 563 (40.2) [12]

M2-segment middle cerebral artery, n (%) 95 (11) [5] 122 (8.7) [12]

Vertebro-basilar arteries, n (%) 139 (16.1) [5] 222 (15.9) [12]

Good collateral circulation, n (%) 262 (73) [511] 360 (68.8) [889] 0.201

Relative exclusion criteria for IVT, n (%) 384 (44.1) 777 (55) <0.001

Non-exclusion criteria for IVT, n (%) – 635 (45) NA

Symptom onset-to-groin puncture time (min), median (IQR) 250 (185–341) 230 (171–300) <0.001

Type of procedure 0.576

Aspiration alone, n (%) 252 (40.4) [247] 387 (37.9) [391]

Stent retriever alone, n (%) 268 (43) [247] 462 (45.2) [391]

Combination of aspiration and stent retriever, n (%) 103 (16.5) [247] 172 (16.8) [391]

Additional IA fbrinolysis, n (%) 69 (7.9) 172 (12.2) 0.001

General anesthesia, n (%) 328 (45.1) [142] 613 (50) [186] 0.035

Procedure time (min), median (IQR) 70 (45–105) [16] 75 (50–110) [42] 0.016

Radiological outcome measures

Any ICH, n (%) 191 (23.1) [43] 320 (24.2) [90] 0.567

PH, n (%) 75 (9.1) [43] 123 (9.3) [90] 0.878

Successful reperfusion (TICI 2b/3), n (%) 624 (72) [10] 1055 (75.6) [17] 0.112

Complete reperfusion (TICI 3), n (%) 488 (56.7) [10] 795 (57) [17] 0.930

Functional outcome measures

3-Month mRS score 0–2, n (%) 316 (38.3) [46] 567 (43.2) [99] 0.027

3-Month death, n (%) 227 (27.5) [46] 262 (20) [99] <0.001

after adjustment for pre-defned variables of \model 2 (age,

sex, pre-stroke mRS≤1, NIHSS score, LVO in the anterior

circulation, symptom onset-to-groin puncture time, and procedure time).

The causes of death in the entire cohort were sICH in

98 (20%) patients, unsuccessful recanalization in 132 (27%)

patients, systemic causes (i.e., sepsis, acute renal failure,

status epilepticus, advanced cancer, pulmonary embolism,

acute myocardial infarction, intestinal infarction, extra-cranial hemorrhage, or hematological disease) in 66 (13.5%)

patients, and unknown or unavailable causes in 193 (39.5%)

patients (Supplemental Table 6). After adjustment for diferences in baseline characteristics variables between groups of

patients with and without absolute exclusion criteria for IVT,

ORs for death related to symptomatic ICH (sICH, 0.711,

95% CI 0.337–1.498), death related to index stroke with

unsuccessful recanalization (0.969, 95% CI 0.523–1.796),

and death related to unknown or unavailable causes (0.831,

95% CI 0.474–1.454) were not diferent between the groups,

while OR for death related to systemic causes (2.294, 95%

CI 1.058–4.973) was higher in patients with absolute exclusion criteria for IVT (Supplemental Table 6).

In the entire cohort, association of single absolute exclusion criterion for IVT with intracerebral bleedings, recanalization, and functional outcomes are provided in Supplemental Tables 7, 8, and 9. After adjustment for pre-defned

variables of model 2 (age, sex, pre-stroke mRS≤1, NIHSS

score, LVO in the anterior circulation, symptom onsetto-groin puncture time, and procedure time), OR for PH

was higher in patients with platelet count<100,000/mm3

(OR: 3.201, 95% CI 1.149–8.916; p=0.026) (Supplemental Table 7), OR for successful recanalization was lower

in patients with ulcer disease of the gastrointestinal tract

in the last 3 months (OR: 0.283, 95% CI 0.083–0.959;

p = 0.043) (Supplemental Table 8), and OR for favorable functional outcome was lower in patients with neoplasm with increased hemorrhagic risk (OR: 0.292, 95%

CI 0.138–0.616; p=0.001) (Supplemental Table 9). ORs

for death were higher in patients with administration

of IV heparin in the previous 48 h with partial thromboplastin time (aPTT) (OR: 2.077, 95% CI 1.176–3.668;

p=0.012), platelet count<100,000/mm3

(OR: 4.798, 95%

CI 1.905–12.086; p=0.001), bacterial endocarditis or pericarditis (OR: 15.069, 95% CI 2.244–101.179; p =0.005),

neoplasm with increased hemorrhagic risk (OR: 6.046, 95%

CI: 3.338–10.950; p<0.001), and severe liver disease (OR:

6.124, 95% CI 1.077–34.922; p = 0.041) (Supplemental

Table 9).

Additional results in the subgroups of the entire cohort

are provided in Supplement Data.

Discussion

Our study showed that the presence of absolute exclusion

criteria for IVT alone (vs relative absolute exclusion for

IVT alone and vs non-exclusion criteria for IVT) in patients

treated with direct mechanical thrombectomy did not afect

the radiological outcome measures; ORs for death was

higher in patients with absolute exclusion criteria for IVT

alone after adjustment for unbalanced variables (model 1)

and predefned variables (model 2), whereas no diference

was observed on 3-month functional outcome among the

groups. Among the groups, efect of successful recanalization on 3-month mRS was similar, and no signifcant diference on 3-month functional favorable outcome in patients

with successful recanalization. As to causes of death, ORs

for death related to symptomatic ICH or unsuccessful recanalization were similar among patients with and without

absolute exclusion criteria for IVT, while OR for systemic

causes of death, mainly related to complications of the conditions reported as absolute exclusion criteria for IVT, was

higher in this group of patients.

About 62% of patients of the entire cohort have relative

exclusion criteria for IVT alone (34%) patients or non-exclusion criteria for IVT (28%), and hence were candidates to

IVT. Although our data come from patients having exclusively LVO-related stroke, they are in line with a recent

study that reported a gap between eligibility to IVT (defned

Table 2 Absolute exclusion criteria for IVT

Data are n (%) or median (IQR)

a

The “symptom onset>4.5 h” group included strokes with known

symptom onset>4.5 h from endovascular treatment hospital admission, unknown onset strokes and wake-up strokes with symptom recognition time or awakening time>4.5 h from endovascular treatment

hospital admission

N (%)

Oral anticoagulant with INR>1.7 or DOAC 343 (15)

Symptom onset>4.5 ha 323 (14.3)

Recent administration of IV heparin 94 (4.1)

Neoplasm with increased hemorrhagic risk 69 (3)

current or recent severe bleeding 33 (1.4)

Platelet count<100,000/mm3 26 (1.1)

Known hemorrhagic diathesis 17 (0.7)

Ulcer disease of the gastrointestinal tract (<3 months) 15 (0.7)

Traumatic external heart massage or puncture of noncompressible blood vessel (<10 days)

12 (0.5)

Severe liver disease 10 (0.4)

Intracranial hemorrhage on brain CT 8 (0.4)

Bacterial endocarditis 7 (0.3)

Suspicion of subarachnoid hemorrhage despite normal

CT

4 (0.2)

Acute pancreatitis 3 (0.1)

Hemorrhagic retinopathy 3 (0.1)

Table 3 Demographics and clinical characteristics of the patients with absolute exclusion criteria for IVT alone, relative exclusion criteria for

IVT alone, and non-exclusion criteria for IVT alone

	Absolute exclusion criteria for IVT alone (n=486)	Relative exclusion criteria for IVT alone (n=777)	Non-exclusion criteria for IVT alone (n=635)	*p value	**p value	***p value
Demographics						
Age (years), median (IQR)	72 (61–79)	72 (62–79)	72 (61–80)	0.999	0.814	0.630
Male sex, n (%)	236 (48.6)	407 (52.4)	324 (51)	0.203	0.434	0.784
Years						

2016–2017, n (%) 288 (59.3) 389 (50.1) 311 (49) 0.001 0.001 0.708

Medical history

Hypertension, n (%) 260 (60.7) [60] 437 (65.4) [109] 285 (63.2) [184] 0.123 0.487 0.446

Diabetes mellitus, n (%) 89 (20.8) [60] 133 (19.9) [109] 82 (18.2) [184] 0.758 0.349 0.487

Hyperlipidemia, n (%) 105 (24.5) [60] 193 (28.9) [109] 119 (26.4) [184] 0.126 0.537 0.377

Smoke habit, n (%) 70 (16.4) [60] 136 (20.4) [109] 93 (20.6) [184] 0.113 0.118 0.940

Previous stroke/transient

ischemic attack, n (%)

22 (5.1) [60] 69 (10.3) [109] 20 (4.4) [184] 0.002 0.639 <0.001

Atrial fbrillation, n (%) 215 (50.2) [60] 183 (27.4) [109] 131 (29) [184] <0.001 <0.001 0.587

Coronary heart disease, n

(%)

58 (13.6) [60] 71 (10.6) [109] 50 (11.1) [184] 0.150 0.304 0.845

Congestive heart failure, n

(%)

47 (11) [60] 53 (7.9) [109] 32 (7.1) [184] 0.106 0.046 0.647

Antiplatelet treatment, n (%) 93 (19.1) 275 (35.4) 155 (24.4) <0.001 0.036 <0.001

Oral anticoagulant treatment,

n (%)

178 (36.6) 42 (5.4) 0 <0.001 <0.001 0.907

Statin treatment, n (%) 79 (16.3) 136 (17.5) 63 (9.9) 0.591 0.002 <0.001

Baseline data

Pre-stroke mRS score≤1,

n (%)

330 (80.9) [78] 578 (85.1) [98] 459 (84.5) [92] 0.076 0.140 0.810

NIHSS score, median (IQR) 17 (13–21) [23] 18 (13–22) [43] 17 (12–20) [51] 0.008 0.047 <0.001

ASPECT score≥6, n (%) 347 (95.1) [121] 575 (94.7) [170] 475 (96.1) [144] 0.882 0.221 0.137

Occlusion site 0.053 0.004 0.140

Tandem, n (%) 47 (9.7) [1] 115 (15) [9] 104 (16.5) [3]

Intra-cranial internal

carotid artery, n (%)

98 (20.2) [1] 136 (17.7) [9] 138 (21.8) [3]

M1-segment middle cerebral artery, n (%)

216 (44.5) [1] 314 (40.9) [9] 249 (39.4) [3]

M2-segment middle cerebral artery, n (%)

53 (10.9) [1] 76 (9.9) [9] 46 (7.6) [3]

Vertebro-basilar arteries,

n (%)

71 (14.6) [1] 127 (16.5) [9] 95 (15) [3]

Good collateral circulation,

n (%)

141 (75.4) [299] 217 (66) [448] 143 (73.7) [441] 0.029 0.725 0.078

Symptom onset-to-groin

puncture time (min),

median (IQR)

255 (185–350) 240 (180–320) 230 (170–296) 0.035 <0.001 0.005

Type of procedure 0.526 0.900 0.264

Aspiration alone, n (%) 139 (39.5) [134] 206 (36.4) [111] 181 (39.8) [180]

Stent retriever alone, n (%) 154 (43.8) [134] 269 (47.5) [111] 193 (42.4) [180]

Combination of aspiration

and stent retriever, n (%)

59 (16.8) [134] 91 (16.1) [111] 81 (17.8) [180]

Additional IA fbrinolysis,

n (%)

39 (8) 99 (12.7) 73 (11.5) 0.009 0.057 0.513

General anesthesia, n (%) 175 (44.3) [91] 359 (52.3) [90] 254 (47.1) [96] 0.014 0.425 0.084

by the absence of absolute exclusion criteria) and reality in ischemic stroke patients admitted to the Stroke Units of the Veneto region of Italy during a period of 12 weeks from September 18th to December 10th, 2017 [16]; only 46% of the potentially eligible patients were actually treated with IVT [16]. Therefore, most patients appear to be inappropriately deprived of bridging therapy in favor of direct thrombectomy.

Among the absolute exclusion criteria for IVT, patients with platelet count<100,000/mm3 had higher OR for PH, and patients with neoplasm with increased hemorrhagic risk had lower OR for favorable functional outcome; patients with recent administration of IV heparin, platelet count<100,000/mm3, bacterial endocarditis, neoplasm with increased hemorrhagic risk, and severe liver disease had higher ORs for death after adjustment for predefned predictors. To date, only a few observational studies assessed safety and efcacy of mechanical thrombectomy in the presence of a single absolute exclusion criterion for IVT [17–21]. Published data are in line with our results regarding thrombocytopenia [17, 18], active cancer, and [19, 20] recent administration of IV heparin [21]. The association between these absolute exclusion criteria for IVT

and increase of mortality was presumably related to an apparent poor pre-stroke health status such as the high frequency of

associated ongoing sepsis, recent surgery, myocardial infarction, renal disease, and other systemic complications. Also,

it is known that stroke is in itself a predictor of mortality in

patients with infective endocarditis [22] due to fatal complications such as meningitis and brain abscesses, while liver

disease is in itself associated with an increased risk of death

after ischemic stroke [23].

Our study has some limitations. First, the present study did

not randomize patients by treatment, but it is based on a retrospective analysis of prospectively collected data. Second, the

number of missing data for outcome measures and pre-defned

variables might have infuenced the fnal outcome. Third, reasons for the treatment were not recorded; it is likely that these

choices were infuenced by unmeasurable factors related to

individual physician's decision, which might have infuenced

our key fndings. In particular, we have not systematically

collected data of perfusion imaging for unwitnessed stroke,

wake-up-stroke, and stroke with known symptom onset>6 h.

Finally, we did not use data of collateral circulation because

they were missing in more than half of the patients included

in the analyses.

Nevertheless, to the best of our knowledge, this is the frst

study that systematically assessed whether there were diferences among absolute, relative, and non-exclusion criteria for

IVT on radiological and functional outcomes in the largest

large real word cohort of patients treated with direct mechanical thrombectomy that has not undergone restrictive selection

as regards age, pre-stroke mRS score, NIHSS score, site occlusion, ASPECT score, and time window for treatment.

Data are n (%) or median (IQR). Numbers within square brackets indicate number of missing values

*Absolute exclusion criteria for IVT alone vs relative exclusion criteria for IVT alone

**Absolute exclusion criteria for IVT alone vs non-exclusion criteria for IVT alone

***Relative exclusion criteria for IVT alone vs non-exclusion criteria for IVT alone

Table 3 (continued)

Absolute exclusion

criteria for IVT alone

(n=486)

Relative exclusion

criteria for IVT alone

(n=777)

Non-exclusion criteria

for IVT alone (n=635)

*p value **p value ***p value

Procedure time (min),

median (IQR)

70 (45–100) [11] 75 (50–110) [] 75 (50–108) [37] 0.005 0.045 0.430

Radiological outcome measures

Any ICH, n (%) 112 (24.3) [27] 187 (25.7) [50] 133 (22.4) [40] 0.631 0.463 0.156

PH, n (%) 44 (9.5) [27] 71 (9.8) [50] 52 (8.7) [40] 0.920 0.667 0.568

Successful reperfusion (TICI

2b/3), n (%)

365 (76) [6] 574 (74.5) [7] 481 (77) [10] 0.591 0.721 0.316

Complete reperfusion (TICI

3), n (%)

287 (59.8) [6] 424 (55.1) [7] 371 (59.4) [10] 0.113 0.902 0.115

Functional outcome measures

3-Month mRS score 0–2,

n (%)

196 (42.6) [26] 316 (43.2) [45] 251 (43.4) [56] 0.857 0.850 0.955

3-Month death, n (%) 115 (25) [26] 154 (21) [45] 108 (18.7) n[56] 0.118 0.015 0.297

Conclusion

Radiological outcomes were similar after direct thrombectomy in patients with absolute, relative, and non-exclusion

criteria for IVT, while an increase of fatal outcome was

observed in the presence of some current absolute exclusion

criterion for IVT. However, death related to sICH and unsuccessful recanalization was similar between the presence and

absence of absolute exclusion criteria for IVT, while patients

with absolute exclusion criteria for IVT had an increase of

death due to systemic causes, usually as complications of the

conditions classifed as absolute exclusion criteria for IVT.

Our data support the use of mechanical thrombectomy in

patients with absolute exclusion criterion for IVT. However,

future randomized trials are needed to confrm our fndings.

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