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Original Article

Effectiveness of Thrombectomy in Stroke According to Baseline Prognostic Factors: Inverse Probability of Treatment Weighting Analysis of a Population-Based Registry

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Background and Purpose In real-world practice, the benefit of mechanical thrombectomy (MT) is uncertain in stroke patients with very favorable or poor prognostic profiles at baseline. We studied the effectiveness of MT versus medical treatment stratifying by different baseline prognostic factors.
Methods Retrospective analysis of 2,588 patients with an ischemic stroke due to large vessel occlusion nested in the population-based registry of stroke code activations in Catalonia from January 2017 to June 2019. The effect of MT on good functional outcome (modified Rankin Score ≤2) and survival at 3 months was studied using inverse probability of treatment weighting (IPTW) analysis in three pre-defined baseline prognostic groups: poor (if pre-stroke disability, age >85 years, National Institutes of Health Stroke Scale [NIHSS] >25, time from onset >6 hours, Alberta Stroke Program Early CT Score <6, proximal vertebrobasilar occlusion, supratherapeutic international normalized ratio >3), good (if NIHSS <6 or distal occlusion, in the absence of poor prognostic factors), or reference (not meeting other groups' criteria).
Results Patients receiving MT (n=1,996, 77%) were younger, had less pre-stroke disability, and received systemic thrombolysis less frequently. These differences were balanced after the IPTW stratified by prognosis. MT was associated with good functional outcome in the reference (odds ratio [OR], 2.9; 95% confidence interval [CI], 2.0 to 4.4), and especially in the poor baseline prognostic stratum (OR, 3.9; 95% CI, 2.6 to 5.9), but not in the good prognostic stratum. MT was associated with survival only in the poor prognostic stratum (OR, 2.6; 95% CI, 2.0 to 3.3).
Conclusions Despite their worse overall outcomes, the impact of thrombectomy over medical management was more substantial in patients with poorer baseline prognostic factors than patients with good prognostic factors.

Keywords Thrombectomy; Stroke; Prognosis; Outcome; Registries; Propensity score

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Introduction

After several randomized controlled trials (RCTs) failed to demonstrate the superiority of endovascular treatment of stroke over medical management,[1,2] the inclusion criteria of the next RCTs were narrowed, excluding patients with better natural history or poor prognostic factors at baseline, that could hamper the identification of the therapeutic effect of vessel revascularization. These RCTs demonstrated the efficacy of mechanical thrombectomy (MT) in patients with stroke due to large vessel occlusion in the anterior circulation.[3] However, in clinical practice, a substantial proportion of patients do not fulfill these inclusion criteria.[4] The Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN) trial and Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE-3) (DAWN NCT02142283; DEFUSE-3 NCT02586415) RCTs extended the evidence for MT to the late time window using advanced imaging,[5,6] but evidence for MT's utility in other patient subgroups or without advanced imaging selection is lacking. Non-randomized reports[7-9] and subgroup analysis of RCTs[10] suggest that the benefit of revascularization may be broader. Here, we estimated the efficacy of MT in patients with a vascular occlusion within a population-based registry of stroke codes characterized by a broader clinical spectrum than patients enrolled in RCTs. Since this is a non-randomized study, we used an inverse probability of treatment weighting (IPTW) analysis from a propensity score (PS) in order to obtain a well-balanced pseudo-population for baseline factors.

Methods

This observational study, conducted in accordance with STROBE guidelines (Supplementary Table 1), is based on the *Codi Ictus Catalunya* (CICAT) registry, a government-mandated, prospective, hospital-based dataset that includes all stroke code activa-

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tions in Catalonia. We used data from consecutive patients in whom the stroke code was activated directly by the emergency medical services from January 2017 to June 2019. The following variables were registered: demographic information, vascular risk factors, pre-stroke functional status (modified Rankin Scale [mRS]), National Institutes of Health Stroke Scale (NIHSS) at admission, the presence of large vessel occlusion on admission, site of occlusion (proximal occlusion was defined as an intracranial occlusion of the internal carotid, M1 portion of the middle cerebral artery, tandem occlusion, or basilar artery occlusion; distal occlusion was defined as an occlusion distal to M1 portion of the middle cerebral artery, or in the anterior or posterior cerebral artery), revascularization treatment (none, systemic thrombolysis alone, MT with or without thrombolysis), and time metrics including time from onset to imaging and time to revascularization treatment (systemic thrombolysis and MT).

The impact of MT was studied in three pre-defined baseline prognostic groups defined around some of the main inclusion criteria of the pivotal RCTs that demonstrated the efficacy of MT in stroke, selected primarily for being well-established prognostic factors in stroke (not necessarily for potential interactions with the effect of MT). Patients meeting these criteria were classified as the reference prognostic group (premorbid mRS ≤1, age ≤85 years, NIHSS ≤24 and ≥6, time from onset ≤6 hours, Alberta Stroke Program Early CT Score [ASPECTS] ≥6,[11] proximal vascular occlusion in the anterior territory); patients not meeting at least one of the standard inclusion criteria were classified into poor (premorbid mRS >1, age >85 years, NIHSS ≥25, time from onset >6 hours, large infarct with ASPECTS <6, proximal occlusion in the vertebrobasilar territory, supratherapeutic international normalized ratio >3), and good (if NIHSS <6 or distal occlusion in the anterior or posterior territory in the absence of any of the poor-prognosis features) prognostic groups. The primary outcome measures were centrally evaluated 3 months after the stroke and included functional outcome and vital status (good functional outcome defined as mRS ≤2, survival as mRS <6). The univariate distribution of the primary outcome measures was reported in each prognostic group according to the treatment received. Symptomatic intracranial hemorrhage was defined according to the European Cooperative Acute Stroke Study II (ECASS II) criteria.[12] Successful recanalization following MT was defined as a grade 2b or 3 according to the modified thrombolysis in cerebral ischemia scale.[13] The ASPECTS score was not a mandatory variable in our registry but may have influenced treatment choice and was used for the study group assignment. For this reason, a sensitivity analysis for the primary outcomes was conducted after multiple data imputations for missing values, including ASPECTS.

This is a Real-World Evidence (RWE) analysis using the population-based CICAT registry, which satisfies all legal requirements mandated by the local law of personal data protection. The dataset was processed and analyzed according to local and European laws: Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016, on Data Protection and Spanish Organic Law 3/2018, of December 5, on Protection of Personal Data and guarantee of digital rights. The Ethical Committee at Hospital Clínic approved the study (registry code HCB/2019/0716). Informed consent was waived because of the retrospective nature of the study.

Statistical analyses

Continuous variables were described as mean±standard deviation or median with interquartile range (IQR), as appropriate. Categorical variables as absolute frequencies and percentages, or median with IQR for ordinal categorical variables. We used standardized differences, defined as differences between groups divided by pooled standard deviation, to assess heterogeneity between cohorts for baseline covariables.

To assess the impact of an intervention on the primary outcomes in the absence of randomization, we used an IPTW analysis on PS suitable for multiple confounders in observational studies. The purpose of IPTW analysis is the creation of pseudo-populations with low associations between treatment, confounders and indication bias. This methodological approach produces groups in which the treatment assignment is independent of measured baseline covariates by weighting subjects by the inverse probability of treatment received.[14,15] The estimation of the IPTW was performed calculating the PS from a logistic regression model to receive MT according to the variables described in Table 1 and stabilized by the proportion of MT or medical treatment. IPTW-weighted logistic regression models were used to estimate the odds ratio (OR) and their 95% confidence interval (CI) of good functional outcome and survival at 3 months. These analyses were made for each prognosis stratum and included age, pre-stroke mRS, systemic thrombolysis, NIHSS score, and occlusion site. We checked for the adequate balance of baseline covariates after IPTW analyses in each prognostic stratum by calculating standardized differences, and a difference greater than ±0.20 represented a meaningful imbalance.[16] In this analysis, the maximum standardized difference was 0.145, corresponding to baseline mRS for poor prognosis.

The primary analysis did not include the ASPECT scale in IPTW calculation due to a high proportion of missing data (1,324 patients, 1,016 [49%] treated with MT, and 308 [48%] with medical management alone). A sensitivity analysis was

Table 1. Baseline characteristics of the treatment groups

Characteristic	Mechanical thrombectomy	
	No (n=592)	Yes (n=1,996)
Age (yr)	75.0±13.3	71.0±13.6
Women	301 (51)	965 (48)
Pre-stroke mRS		
≤1	416 (71)	1,682 (84)
>1	176 (29)	314 (16)
Systemic thrombolysis	423 (71)	917 (46)
Hypertension	398 (67)	1,222 (61)
Diabetes mellitus	131 (22)	384 (19)
Dyslipidemia	258 (44)	851 (43)
Atrial fibrillation	165 (28)	561 (28)
Coronary heart disease	100 (17)	280 (14)
Previous stroke/TIA	70 (12)	208 (10)
Smoking habit	60 (10)	283 (14)
NIHSS at admission	14 (7–20)	17 (11–21)
Delay to imaging (min)	158 (93–251)	162 (80–310)
ASPECTS	8 (6–10)	9 (8–10)
Occlusion site		
M2, ACA, PCA	232 (39)	350 (18)
M1	196 (33)	1,009 (51)
TICA/Tandem	154 (26)	516 (26)
VB	10 (2)	121 (6)

Values are presented as mean±standard deviation, number (%), or median (interquartile range). Standard difference was considered acceptable if not greater than ±0.20.
mRS, modified Rankin Scale; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; M2, second segment of the middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; M1, first segment of the middle cerebral artery; TICA, terminal internal carotid artery; VB, vertebro-basilar.

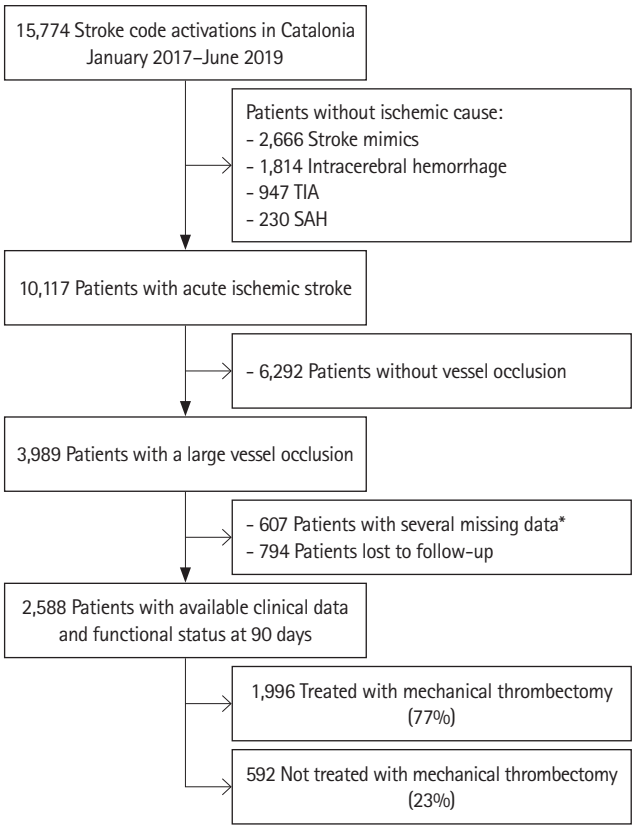

Figure 1. Study selection process. The flow-diagram shows the patients included in the analysis. TIA, transient ischemic attack; SAH, subarachnoid hemorrhage. *Missing values were vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary heart disease, previous stroke/TIA, smoking habit variables) in 401 patients, delay to imaging in 214, and occlusion site in 503.

made, including the ASPECTS scale with missing data imputation to the previously described logistic regression model. We used the expectation-maximization algorithm,[17] which relies on the flexible and reasonable missing at random assumption using age, sex, delay to radiological evaluation, NIHSS, mRS, comorbidities as hypertension, diabetes, dyslipidemia, atrial fibrillation, coronary heart disease, presence of a previous stroke, actual smoke, and presence of distal occlusion.

We calculated the number needed to treat (NNT) for saving a patient from poor outcomes. NTT was estimated according to logistic regression models used in the primary analysis adapting the calculation proposed by Bender and Blettner[18] and Bender et al.[19] to present context by means:

$$NNT = \frac{1}{(OR - 1) \times P_0} + \frac{OR}{(OR - 1) \times (1 - P_0)}$$

Where OR was estimated from IPTW-weighted logistic regression models and P_0 was the proportion of non-event.

In all statistical analyses, we applied a two-sided type I error of 5%. SPSS version 25 (IBM Co., Armonk, NY, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) were used for the analysis.

Results

Characteristics of the cohort

From 15,774 stroke code activations during the study period, 10,117 had an ischemic stroke, and 3,989 had a vessel occlusion identified on initial imaging. After excluding patients with missing information, the analysis included 2,588 patients (Figure 1). Patients excluded from the analysis were younger and received systemic thrombolysis in a lower proportion than those included, but the other variables showed similar distribution according to the standard difference values (Supplementary Table 2).

In the whole study cohort, 1,996 patients received MT and

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592 medical management alone. Successful recanalization was achieved in 83% of patients treated with MT. Patients receiving MT were more likely to belong to the reference and poor category groups, were younger, had less pre-stroke disability, received systemic thrombolysis less frequently, and had better ASPECTS scores (Table 1). The pre-defined prognostic groups according to baseline characteristics included 976 patients (38%) in the reference group, 1,191 patients (46%) in the poor prognosis group, and 421 patients (16%) in the good prognosis group. The description of the prognostic factors determining group assignment is detailed in Supplementary Table 3.

Clinical outcome distributions without IPTW adjustment

The functional status at 3 months in the study cohort according to the treatment received in each prognostic group without IPTW adjustment are summarized in Figure 2. Any hemorrhage in follow-up imaging was more frequently found in patients treated with MT compared to those treated with only medical treatment in all prognosis subgroups (Table 2).

Primary outcome results: IPTW analysis

The standard differences of the clinical and radiological variables at baseline between patients who received MT and those who received medical treatment alone were adequately balanced after IPTW in the whole cohort (Figure 3) and stratified by prognostic groups (Supplementary Table 4). In the IPTW logistic regression model, MT was related to good outcomes in the subgroups of reference (OR, 2.94; 95% CI, 1.96 to 4.35; $P<0.0001$) and poor prognosis (OR, 3.85; 95% CI, 2.56 to 5.88;

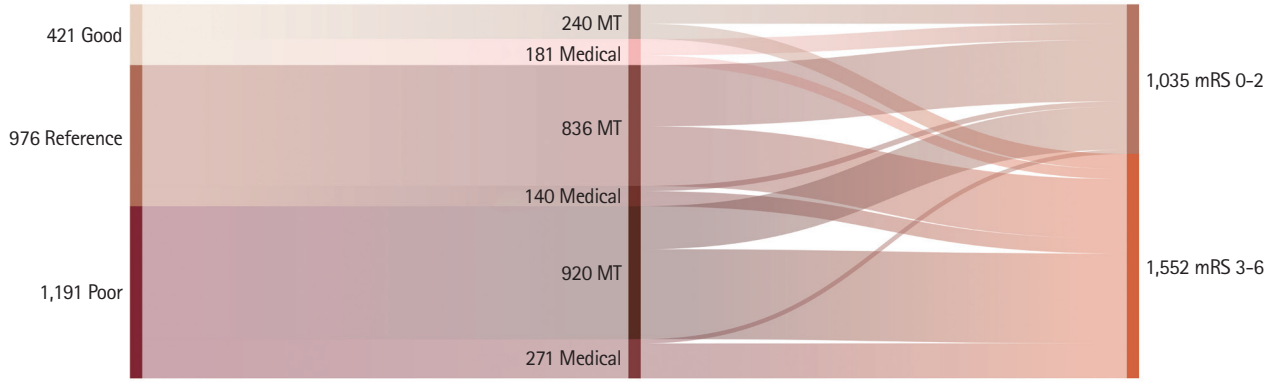

Figure 2. Primary outcome measures without inverse probability of treatment weighting adjustment. The Sankey diagram showing the treatment and outcomes in each baseline prognostic category. MT, mechanical thrombectomy; mRS, modified Rankin Scale.

Table 2. Clinical course, radiological outcomes, and safety outcome measures

Outcome	Whole cohort		Good prognostic group		Reference prognostic group		Poor prognostic group	
	Medical (n=592)	MT (n=1,996)	Medical (n=181)	MT (n=240)	Medical (n=140)	MT (n=836)	Medical (n=271)	MT (n=920)
TICI 2b/3		1,658 (83)		198 (83)		700 (84)		760 (83)
Hemorrhagic transformation	82 (14)	450 (23)	25 (14)	51 (21)	24 (17)	208 (25)	33 (12.18)	191 (21)
HI1	15 (3.8)	151 (9.4)	2 (1.5)	22 (11)	2 (2.2)	70 (10)	11 (6.63)	59 (8.0)
HI2	20 (5.0)	126 (7.8)	8 (5.8)	8 (4.2)	6 (6.5)	64 (9.3)	6 (3.61)	54 (7.4)
PH1	17 (4.3)	65 (4.0)	5 (3.6)	8 (4.2)	8 (8.6)	29 (4.2)	4 (2.41)	28 (3.8)
PH2	16 (4.0)	60 (3.7)	8 (5.8)	3 (1.6)	3 (3.2)	28 (4.1)	5 (3.01)	29 (4.0)
rPH	14 (3.5)	48 (3.0)	2 (1.5)	10 (5.2)	5 (5.4)	17 (2.5)	7 (4.22)	21 (2.9)
NIHSS at 24–36 hr	11 (4–20)	8 (3–18)	3 (1–9)	5 (1–12)	16 (6–20.5)	8 (3–16)	17 (8–21)	11 (3–20)

Values are presented as number (%) or median (interquartile range).
MT, mechanical thrombectomy; TICI, thrombolysis in cerebral ischemia; HI1, hemorrhagic infarction type 1 (small petechiae along the margins of the infarct); HI2, hemorrhagic infarction type 2 (confluent petechiae within the infarcted area but no space-occupying effect); PH1, parenchymal hematoma (blood clots in ≤30% of the infarcted area with some slight space-occupying effect); PH2, parenchymal hematoma (blood clots in >30% of the infarcted area with a substantial space-occupying effect); rPH, remote parenchymal hematoma; NIHSS, National Institutes of Health Stroke Scale.

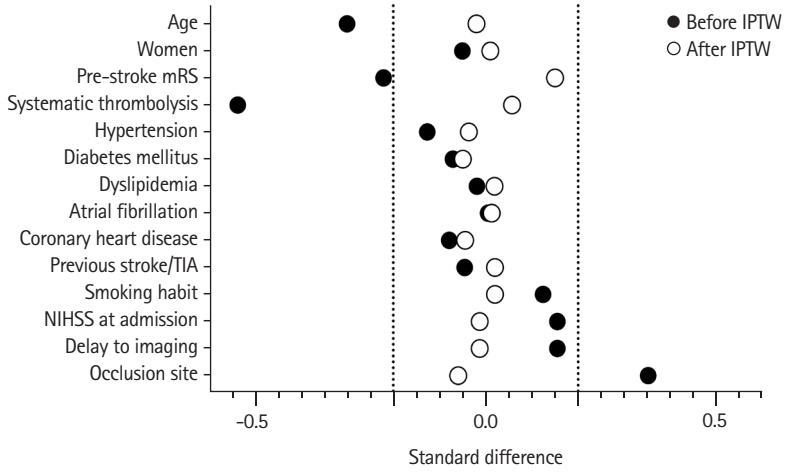

Figure 3. Standardized differences before and after inverse probability of treatment weighting (IPTW). Standardized differences between mechanical thrombectomy and medical treatment before and after IPTW. mRS, modified Rankin Scale; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale.

Table 3. Main and sensitivity analysis for outcome by logistic regression models with IPTW

Primary outcome variables	Percent (%)	Main analysis			Sensitivity analysis		
		Logistic regression analyses (IPTW)			Logistic regression analyses (IPTW) including ASPECTS (imputed values)		
		OR (95% CI)	*P*	NNT (95% CI)	OR (95% CI)	*P*	NNT (95% CI)
Whole cohort							
Good outcome	40	2.44 (1.96–2.94)	<0.0001	5 (4 to 7)	1.82 (1.52–2.22)	<0.0001	7 (5 to 10)
Survival	79	2.04 (1.67–2.5)	<0.0001	11 (9 to 14)	1.33 (1.08–1.67)	0.009	23 (14 to 85)
Good prognostic group							
Good outcome	59	1.23 (0.85–1.79)	0.270	21 (–41 to ∞ to 7)	1.28 (0.88–1.89)	0.207	18 (–41 to ∞ to 7)
Survival	90	0.69 (0.35–1.37)	0.293	26 (–34 to ∞ to 8)	0.65 (0.33–1.28)	0.218	22 (–34 to ∞ to 7)
Reference prognostic group							
Good outcome	47	2.94 (1.96–4.35)	<0.0001	4 (3 to 7)	2.78 (1.89–4.17)	<0.0001	5 (3 to 7)
Survival	84	1.32 (0.83–2.08)	0.243	31 (–37 to ∞ to 12)	1.11 (0.68–1.82)	0.679	75 (–18 to ∞ to 14)
Poor prognostic group							
Good outcome	28	3.85 (2.56–5.88)	<0.0001	4 (2 to 5)	1.89 (1.35–2.7)	0.0002	8 (4 to 16)
Survival	70	2.56 (1.96–3.33)	<0.001	7 (6 to 9)	1.27 (0.94–1.69)	0.121	22 (–80 to ∞ to 9)

IPTW, inverse probability of treatment weighting; ASPECTS, Alberta Stroke Program Early CT Score; OR, odd ratio; CI, confidence interval; NNT, number needed to treat.

P<0.0001), but not in the good prognostic category (OR, 1.23; 95% CI, 0.85 to 1.79; *P*=0.27). MT was associated with survival only in the poor prognosis category (OR, 2.56; 95% CI, 1.96 to 3.33; *P*<0.001), more details are shown in Table 3 and Figure 4. Consequently, the NNT for good outcome was 4 (95% CI, 3 to 7) in the reference prognosis group, 4 (95% CI, 2 to 5) in the poor prognosis group, and not interpretable because the CI does not include the NNT value in the good prognosis group (21; 95% CI, –41 to ∞ to 7).

Sensitivity analysis

The sensitivity analyses after multiple data imputations confirmed the associations between MT and functional outcome. MT remained associated with good outcomes in the reference and poor baseline prognosis category groups. MT was associated with survival in the whole cohort of the sensitive analysis but did not reach signification when assessed for each prognostic category (Table 3 and Figure 4).

Discussion

This sizeable and representative population-based registry confirmed the benefit from MT in terms of functional outcome and survival in real-life practice, mainly in patients with non-

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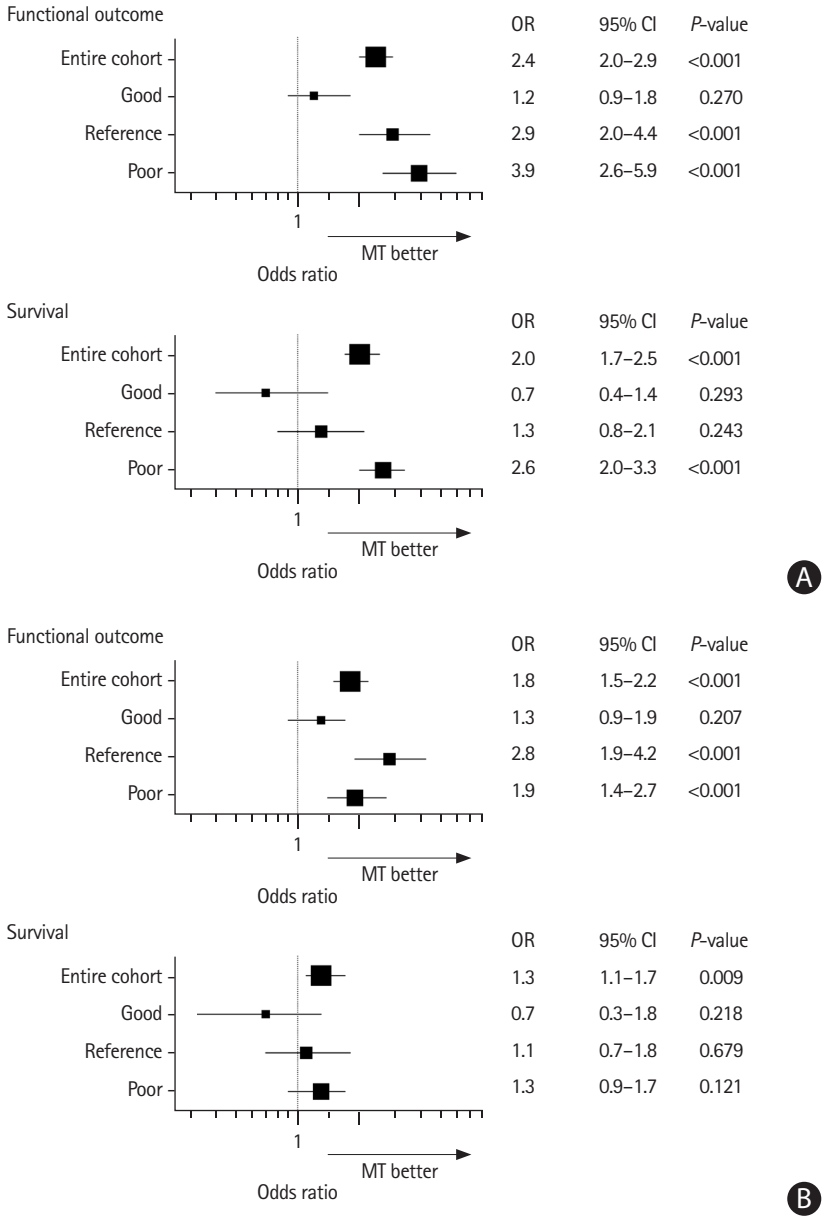

Figure 4. Primary outcome analysis. The forest plots illustrate the treatment effect in each group in terms of good functional outcome and survival in the main analysis (A) and in the sensitive analysis (B) after inverse probability of treatment weighting (IPTW) analysis. The sensitive IPTW analysis included the Alberta Stroke Program Early CT Score (ASPECTS) variable in the IPTW calculation after missing data imputation. OR, odds ratio; CI, confidence interval; MT, mechanical thrombectomy.

favorable prognostic factors at baseline. Consequently, it also suggested that the effect of MT was not homogenous in all patients with stroke and vessel occlusion, raising doubts on the efficacy of current revascularization techniques in patients with specific characteristics such as mild symptoms or distal occlusions. In contrast, patients with the poorest prognostic factors benefit substantially from MT.

The concerns about the external validity of the results generated in large RCTs addressing the efficacy of MT in large vessels occlusions are emphasized by the finding that in this multi-center registry reflecting clinical practice in Catalonia, more than half of the patients treated with MT did not meet the main inclusion/exclusion criteria used in most of the studies that confirmed the efficacy of MT versus best medical treatment. These results are reassuring when dealing with such patients and raise the question of whether the efficacy of MT in certain subgroups of patients may be best tested in studies like this, rather than in randomized clinical trials that are sometimes unpractical and whose results may not be generalized to all patients.

Although the severity of the symptoms did not significantly modify MT's effect in subgroup analyses of the thrombectomy RCTs,[3] as usual in most designs of RCTs, included patients are relatively homogeneous, which induces a selection bias. In the end, the vast majority of patients in those trials had moderate to severe strokes. Our registry has good internal validity and confirms the findings of observational reports describing decreased MT benefits in patients with milder strokes.[20-22] Overall, the evidence suggests that the risk of futile endovascular intervention is highest in patients with low NIHSS at baseline or distal occlusions. It is expected that the results of the ongoing Minor Stroke Therapy Evaluation RCT (NCT03796468) will shed light on the efficacy of MT in patients with mild strokes.

Inversely, patients included in the poor baseline prognostic stratum benefited as much as patients in the reference prognostic stratum. This is in line with recent observations describing few complications and potential benefits of thrombectomy in groups of patients with large infarctions,[7,10] or other poor prognostic factors such as poor collateral circulation[8] and older age.[23] At the same time, these results support the use of broad inclusion criteria in RCTs testing MT in stroke, as excluding patients with certain poor prognostic factors may paradoxically reduce the treatment's effect size.[24] Nevertheless, the overall clinical outcome is still poor in about two out of three patients of this subgroup of patients, meaning that they may benefit from better revascularization techniques, additional neuroprotectant strategies, or even improved imaging selection to identify extensive irreversible damage better. Although perfusion imaging is commonly used to select patients in the late time window in our population, technical parameters and operative criteria differed between centers, and quantitative data were not available in the registry.

The study has some limitations, primarily linked to its observational design, mainly the obvious prescription bias we tried to overcome with the IPTW statistical analysis technique. However, observational studies performed in large multicenter cohorts are vital to confirm the real-life clinical impact of the effect of interventions proved to be beneficial in clinical trials. The assessment of the baseline ischemic lesion using ASPECTS was optional in the registry and was available only in half of the patients, not allowing us to include it in the calculation of the IPTW. However, in the sensitivity analysis using missing imputation for patients without the ASPECTS value, the effect of MT on functional outcome and survival was similar to that of the main analysis, despite a reduced effect in the poor prognostic stratum (non-significant trend for survival), which reflects the prognostic value of ASPECTS. The evidence in favor of thrombectomy has gradually changed over time, and it could be argued that the definition of the groups in the study could be done differently. However, the objective of this analysis was not to study the effect of each specific prognostic factor, but to compare the impact of MT across different prognostic groups in a way that tries to minimize the influence of confounding factors. This is the main strength of the primary results of the study, stressing that the impact of MT is greater in patients with poorer overall prognosis.

Conclusions

This RWE analysis of a population-based registry reassures physicians considering MT for patients with poor prognostic indicators at baseline. Conversely, it suggests that extending the utility of MT to specific subgroups of patients with better natural history may require further research and technical advances.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2021.00962.

Disclosure

The authors have no financial conflicts of interest.

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Supplementary Table 1. STROBE statement—Checklist of items that should be included in reports of cohort studies

	Item no.	Recommendation	Page no.
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1, 5
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement) Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	10-12
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) If applicable, explain how loss to follow-up was addressed	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-13
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	13-14
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (e.g., average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	13
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	14-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of *PLoS Medicine* at http://www.plosmedicine.org/, *Annals of Internal Medicine* at http://www.annals.org/, and *Epidemiology* at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

*Give information separately for exposed and unexposed groups.

Supplementary Table 2. Baseline characteristics of the cohort included and excluded for the presence of missing data (except for ASPECTS) in the final analysis

Characteristic	Patients excluded (n=607)	Patients included (n=2,588)	Standard difference
Age (yr)	74.9±13.7	71.9±13.6	−0.221
Women	298 (49)	1,266 (49)	−0.004
Pre-stroke mRS			−0.192
≤1	438 (72)	2,098 (81)	
>1	169 (28)	490 (19)	
Systemic thrombolysis	221 (36)	1,340 (52)	0.313
Hypertension	130 (64)	1,620 (63)	−0.023
Diabetes mellitus	42 (21)	515 (20)	−0.017
Dyslipidemia	79 (39)	1,109 (43)	0.084
Atrial fibrillation	58 (28)	726 (28)	−0.008
Coronary heart disease	29 (14)	380 (15)	0.013
Previous stroke/TIA	13 (6)	278 (11)	0.156
Smoking habit	28 (14)	343 (13)	−0.014
NIHSS at admission	17 (17–19)	16 (16–17)	−0.013
Delay to imaging (min)	155 (138–194)	160 (153–169)	−0.132
ASPECTS	8 (8–9)	9 (9–10)	0.345
Occlusion site			0.068
M2, ACA, PCA	0 (0)	582 (22)	
M1	144 (27)	1,205 (47)	
TICA/Tandem	220 (42)	670 (26)	
VB	139 (26)	131 (5)	

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
ASPECTS, Alberta Stroke Program Early CT score; mRS, modified Rankin Scale; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; M2, second segment of the middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; M1, first segment of the middle cerebral artery; TICA, terminal internal carotid artery; VB, vertebro-basilar.

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Supplementary Table 3. Characterization of the factors determining the assignment of patients to poor or good prognosis categories

Variable	Poor prognostic group	Good prognostic group
Pre-stroke mRS >1	490 (41)	0 (0)
Age >85 years	334 (28)	0 (0)
Baseline NIHSS >25	85 (7)	0 (0)
Time from onset >6 hours	508 (43)	0 (0)
Vertebrobasilar occlusion	131 (11)	
Supratherapeutic INR	20 (1.7)	
Sum of poor prognostic factors		
0	0 (0)	421 (100)
1	837 (70)	0 (0)
2	331 (28)	0 (0)
3	22 (1.8)	0 (0)
4	1 (0.1)	0 (0)
Baseline NIHSS <6	72 (6.1)	135 (32)
Distal occlusion	229 (19)	353 (84)
Sum of good prognostic factors		
0	909 (76)	0 (0)
1	263 (22)	354 (84)
2	19 (1.6)	67 (16)

Values are presented as number (%).
mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; INR, international normalized ratio.

Supplementary Table 4. Standardized differences after IPTW in the whole cohort and in the pre-specified prognostic strata

Variable	Standard difference without IPTW	IPTW without stratification	IPTW stratified by prognostic groups		
			Good (n=421)	Reference (n=976)	Poor (n=1,191)
Age	−0.300	−0.020	0.039	0.035	−0.039
Women	−0.050	0.010	−0.034	−0.061	0.060
Pre-stroke mRS	−0.221	0.150	−0.120	0.028	0.145
Systemic thrombolysis	−0.536	0.057	−0.001	0.089	−0.036
Hypertension	−0.126	−0.036	−0.002	0.023	−0.083
Diabetes mellitus	−0.071	−0.049	0.014	−0.132	−0.015
Dyslipidemia	−0.019	0.019	−0.086	−0.039	−0.020
Atrial fibrillation	0.005	0.013	0.009	−0.043	−0.063
Coronary heart disease	−0.079	−0.044	0.081	−0.001	0.025
Previous stroke/TIA	−0.045	0.020	0.046	0.052	−0.002
Smoking habit	0.124	0.020	0.079	−0.029	0.103
NIHSS at admission	0.155	−0.013	0.013	−0.006	0.008
Delay to imaging	0.155	−0.013	0.013	−0.006	0.008
Occlusion site	0.352	−0.059	−0.066	0.141	0.003

IPTW, inverse probability of treatment weighting; mRS, modified Rankin Scale; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale.