




Original research

Mechanical thrombectomy for in-hospital stroke: data from the Italian Registry of Endovascular Treatment in Acute Stroke

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ABSTRACT

Background The benefit, safety, and time intervals of mechanical thrombectomy (MT) in patients with in-hospital stroke (IHS) are unclear. We sought to evaluate the outcomes and treatment times for IHS patients compared with out-of-hospital stroke (OHS) patients receiving MT.

Methods We analyzed data from the Italian Registry of Endovascular Treatment in Acute Stroke (IRETAS) between 2015 and 2019. We compared the functional outcomes (modified Rankin Scale (mRS) scores) at 3 months, recanalization rates, and symptomatic intracranial hemorrhage (sICH) after MT. Time intervals from stroke onset-to-imaging, onset-to-groin, and onset-to-end MT were recorded for both groups, as were door-to-imaging and door-to-groin for OHS. A multivariate analysis was performed.

Results Of 5619 patients, 406 (7.2%) had IHS. At 3 months, IHS patients had a lower rate of mRS 0–2 (39% vs 48%, $P<0.001$) and higher mortality (30.1% vs 19.6%, $P<0.001$). Recanalization rates and sICH were similar. Time intervals (min, median (IQR)) from stroke onset-to-imaging, onset-to-groin, and onset-to-end MT were favorable for IHS (60 (34–106) vs 123 (89–188.5); 150 (105–220) vs 220 (168–294); 227 (164–303) vs 293 (230–370); all $P<0.001$), whereas OHS had lower door-to-imaging and door-to-groin times compared with stroke onset-to-imaging and onset-to-groin for IHS (29 (20–44) vs 60 (34–106), $P<0.001$; 113 (84–151) vs 150 (105–220); $P<0.001$). After adjustment, IHS was associated with higher mortality (aOR 1.77, 95% CI 1.33 to 2.35, $P<0.001$) and a shift towards worse functional outcomes in the ordinal analysis (aOR 1.32, 95% CI 1.06 to 1.66, $P=0.015$).

Conclusion Despite favorable time intervals for MT, IHS patients had worse functional outcomes than OHS patients. Delays in IHS management were detected.

INTRODUCTION

Several randomized clinical trials have defined the impact and benefit of mechanical thrombectomy (MT) on the outcome of patients with acute ischemic stroke (AIS).¹ These data are representative of

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In-hospital stroke (IHS) is associated with poor clinical outcomes due to concomitant acute illnesses, comorbidities, and frequent contraindications to intravenous thrombolysis. Conversely, few data are available on the impact of mechanical thrombectomy (MT) in these patients, and the time intervals from stroke onset/acceptance in the emergency department to imaging and the endovascular procedure are unclear.

WHAT THIS STUDY ADDS

⇒ This study provides extensive data on IHS patients receiving MT and evaluates the benefit and safety of MT in this setting for a large sample. Detailed data regarding time intervals from stroke onset-to-imaging and MT are provided, while delays in acute stroke management are identified and quantified for IHS patients compared with out-of-hospital strokes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Knowledge of the potential benefit and time delays of MT may allow the implementation of specific stroke paths for managing IHS, favoring the improvement of the outcomes in these patients.

patients who directly access the emergency department (ED) from the community setting (out-of-hospital stroke, OHS) and follow a specific pathway for stroke treatments.

However, up to 17% of all strokes occur in hospitalized patients (in-hospital stroke (IHS)), which may not be included in specific protocols for AIS management.^{2–3} In addition, these patients differ from the general population because they carry concurrent acute medical conditions requiring a hospital stay and are more often ineligible to receive intravenous thrombolysis (IVT).^{4,5}

As a result, worse functional outcomes and higher mortality in patients with IHS have been reported.^{6,7} However, in the era of endovascular treatments (EVT), few data are available on the benefit of MT in this population. Because exclusion criteria for MT are narrower than those for IVT, the endovascular approach seems particularly suitable in these patients due to their higher susceptibility to intracranial large vessel occlusion (LVO), potentially representing a unique option for treatment.^{8,9}

To date, results regarding the benefit of MT in patients with IHS have been contradictory.^{10–14} Moreover, the time intervals from stroke recognition to imaging and reperfusion, as well as in-hospital delays, significantly differ among these studies, leading to variability in the functional outcomes. Finally, most of them derive from single-center experience with small samples, which are potentially inadequate to represent this population. Overall, the evidence appears inconsistent in defining the actual role of EVT in these patients. This work aims to clarify these points by evaluating the efficacy, safety and times of MT in a large cohort of patients with IHS compared with OHS, taken from the Italian Registry of Endovascular Treatment in Acute Stroke (IRETAS).

METHODS

We performed a retrospective cohort study of IRETAS, a multi-center, observational registry that includes patients treated with MT for AIS since 2011 in the national territory. The details of the structure, organization, and purpose of the registry have been described previously.¹⁵ To date, 61 centers have joined the program and accepted its rules, including the consecutive registration of all patients with AIS receiving EVT. However, only centers with at least 80% data completeness were used for analysis to reduce selection bias. Ethical approval was not required for this retrospective study. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies were followed.

Study design

We retrospectively included patients ≥ 18 years old with AIS due to LVO receiving EVT, with or without previous IVT, between January 2015 and December 2019. The eligibility criteria for MT were according to national guidelines.¹⁶ OHS was defined as AIS that occurred in the community setting (direct admission to the ED), while IHS was AIS experienced by patients while hospitalized, independent of the cause of admission. In the selected period, a total of 9805 endovascular procedures were registered. Of them, 387 were intra-arterial thrombolysis and were excluded because they were outside the scope of this study. We only included patients directly admitted to hub centers. We excluded patients initially admitted to spoke centers ($n=3799$) to reduce potential bias represented by different door in-door out times in spoke centers as well as the possible different transportation times to hub centers, both of which may vary across the country. Additional information regarding MT-treated IHS patients from spoke centers is provided separately (online supplemental material, table A).

Population characteristics

Demographic, clinical, and radiological characteristics of patients including sex, age, pre-admission disability (modified Rankin Scale (mRS)), vascular risk factors, medications, National Institutes of Health Stroke Scale (NIHSS) at admission, Alberta Stroke Program Early CT score (ASPECTS), and site of vessel occlusion were recorded. The etiology of strokes

were categorized as atherothrombotic, cardioembolic, arterial dissection, intra-/periprocedural (if it occurred because of surgical or radiological therapeutic interventions), hypercoagulability state (due to coagulation disorders or induced by comorbid illness such as active neoplasms), or other or undetermined (negative assessments after complete or incomplete investigation, or in presence of two or more stroke contributors). The definition of the stroke etiology was left to the expert vascular neurologist of each single center and was determined at 3 months.

For reperfusion therapies, the following features were collected: IVT administration or contraindication (as defined by national guidelines), type of EVT (thrombus aspiration, stent retriever, or combined) and anesthesia during the procedure (general, none, or conscious sedation), and complications related to MT (subarachnoid hemorrhage, arterial dissection, distal embolism, retroperitoneal/puncture site growing hematoma).¹⁷

Time intervals from symptoms onset to cranial imaging, groin puncture, and end of EVT were registered. The clinical onset was considered the first recognition of stroke symptoms or the last time the patient was known to be well both for OHS and IHS. However, to directly compare the management time of AIS inside the hospitals between the two groups, door-to-imaging, door-to-groin, and door-to-end of EVT for OHS were also calculated and compared with time intervals of IHS patients, who were already hospitalized.

Outcomes

The primary outcome was the proportion of patients with favorable functional outcomes at 3 months (defined as mRS score 0–2) and 3-month mortality. The secondary endpoints were: good or complete recanalization rate after EVT (defined as Thrombolysis In Cerebral Infarction (TICI) 2b or 3), proportion of patients with symptomatic intracranial hemorrhage (sICH) (according to the European Co-operative Acute Stroke Study-II (ECASS-II) criteria),¹⁷ and onset-to-imaging and onset-to-groin times.

Statistical analyses

Data are reported as absolute numbers, percentages, and median (IQR). Differences in baseline characteristics in the cohorts were calculated using χ^2 tests for categorical variables, and the Mann-Whitney U test for continuous variables. The association between IHS and functional outcomes (mRS 0–2 and mortality at 3 months) was assessed with two multivariable logistic regression models. An ordinal regression model was built to evaluate the association between IHS and the mRS scale, taking the whole range of the scale into account as the dependent variable. We included in the model only those variables found to be predictive in the univariate analysis (data not shown) and we took into account the collinearity between variables and missing data. We also considered the importance of each variable in the ‘goodness of fit’ of the model. Therefore, variables with a high number missing or with little contribution to the ‘goodness of fit’ of the model were not considered. After selection, the following independent variables were included: age, sex, pre-stroke mRS, NIHSS at admission, coronary artery disease, history of malignancy, posterior circulation stroke, combined treatment IVT+MT, and onset-to-end of EVT.

The associations between variables and outcomes are presented as odds ratios (ORs) and 95% confidence intervals (95% CIs). We considered P values < 0.05 to be statistically significant. Statistical analyses were performed using IBM SPSS version 28.

RESULTS

Baseline characteristics

In accordance with the inclusion criteria, we extracted the data of 5619 MTs from the Registry. Of them, 406 (7.2%) were undertaken in patients with IHS. The baseline features of IHS and OHS patients treated with MT are reported in table 1. Age, sex, and NIHSS at admission did not differ between the two groups. IHS patients had a higher pre-stroke mRS >2 (13.4% vs 4.2%, P<0.001) and a more severe vascular profile including recent stroke (17.1% vs 3.1%, P<0.001), extracranial internal carotid artery stenosis (7.9% vs 3.6%, P<0.001), atrial fibrillation (39.4% vs 34%, P=0.036), congestive heart failure (13.9% vs 6.9%, P<0.001), and coronary artery disease (17.6% vs 10.4%, P<0.001); a history of malignancy was significantly higher in this group (11.3% vs 5.2%, P<0.001). In addition, they were more likely to be taking anticoagulants (27.6% vs 14.2%, P<0.001), antiplatelets (37.2% vs 24.9%, P<0.001), and statins (18% vs 13.1%, P=0.006) compared with OHS patients. In IHS patients, stroke etiology was more frequently related to hypercoagulable states or occurred as a consequence of surgical or radiological therapeutic interventions (3.6% vs 1.3%, P=0.002, and 7.6% vs 0.1%, P<0.001, respectively). The ASPECTS and the site of arterial occlusion for the anterior circulation did not differ between the two groups, while a higher proportion of posterior circulation stroke for IHS was noted (14.2% vs 9.8%, P=0.005).

Treatments, safety, time intervals, and clinical outcomes

IVT was more likely to be contraindicated in IHS patients (79.2% vs 38.8%, P<0.001). Differences between groups regarding IVT contraindication are detailed in the online supplemental material, table B, with recent major surgery, the use of anticoagulants, and stroke in the past 3 months the most represented. Regarding the endovascular procedure, MT was less likely to be performed by only using stent retrievers in IHS patients (14.2% vs 18.9%, P=0.03), whereas recanalization rates and safety measures were similar between groups, including sICH.

The stroke onset-to-imaging time (min, median (IQR)) was significantly shorter in the IHS group (60 (34–106) vs 123 (89–188.5), P<0.001) as well as onset-to-groin puncture and onset-to-end of EVT (150 (105–220) vs 220 (168–294), P<0.001, and 227 (165–303) vs 293 (230–370), P<0.001, respectively). However, when considering the in-hospital management times, door-to-imaging, door-to-groin, and door-to-end of EVT for OHS were significantly shorter compared with stroke onset-to-imaging, onset-to-groin, and onset-to-end of EVT for IHS patients (29 (20–44) vs 60 (34–106), P<0.001; 113 (84–151) vs 150 (105–220), P<0.001; and 181 (139–237) vs 227 (165–303), P<0.001, respectively).

At 3 months, a lower proportion of mRS 0–2 outcome (39% vs 48%, P<0.001) and a higher mortality were found in IHS patients (30.1% vs 19.6%, P<0.001). These findings did not change when excluding patients with mRS pre-stroke >2 from the analysis (42.3% vs 50.4%, P=0.007, and 28.3% vs 17.5%, P<0.001, respectively). The details on EVT, time intervals, and clinical outcomes are provided in table 2 and figure 1.

In the multivariate analysis, IHS patients had 1.77 (95% CI 1.33 to 2.35, P<0.001) times the odds of being dead at 3 months. In the shift analysis, the adjusted OR for a one-point shift toward a worse outcome in mRS for IHS was 1.32 (95% CI 1.06 to 1.66, P=0.015). The results of the whole multivariate analysis are provided in the online supplemental material, table C.

The comparison between IHS coming from spoke centers compared with those directly admitted to hubs did not show differences in clinical outcomes, although time intervals were

Table 1 Demographic, clinical and radiological features of patients with in-hospital and out-of-hospital stroke treated with mechanical thrombectomy

	n=5619		P value
	Out-of-hospital stroke (n=5213)	In-hospital stroke (n=406)	
Demographic			
Age (median, IQR)	75.5 (64.9–82.2)	73.8 (65.1–80.5)	NS
Sex, female, n (%)	2707 (51.9%)	193 (47.5%)	NS
mRS pre-stroke 0–2, n (%)	4321 (95.8%)	335 (86.6%)	<0.001
NIHSS at admission, median (IQR)	16 (11–20)	17 (11–20.5)	NS
Last known well, n (%)	1377 (26.4%)	57 (14%)	<0.001
Medical history, n (%)			
Stroke/TIA (last 3 months)	148 (3.1%)	65 (17.1%)	<0.001
Atrial fibrillation	1602 (34%)	150 (39.4%)	0.036
Diabetes mellitus	801 (17%)	78 (20.5%)	NS
Hypertension	3110 (66.1%)	232 (60.9%)	0.039
Coronary artery disease	491 (10.4%)	67 (17.6%)	<0.001
Heart valve disease	278 (5.3%)	38 (9.4%)	<0.001
Congestive heart failure	325 (6.9%)	53 (13.9%)	<0.001
Smoker	777 (16.5%)	68 (17.8%)	NS
Dyslipidemia	1120 (23.8%)	90 (23.6%)	NS
Carotid stenosis (≥70%)	187 (3.6%)	32 (7.9%)	<0.001
Dementia	48 (1%)	4 (1%)	NS
History of malignancy	247 (5.2%)	43 (11.3%)	<0.001
Pre-stroke medications, n (%)			
All antiplatelets	1296 (24.9%)	151 (37.2%)	<0.001
Acetylsalicylic acid	1104 (21.2%)	134 (33%)	<0.001
Dipyridamole	6 (0.1%)	2 (0.5%)	NS
Clopidogrel	204 (3.9%)	39 (9.6%)	<0.001
Other antiplatelets	79 (1.5%)	10 (2.5%)	NS
All anticoagulants	740 (14.2%)	112 (27.6%)	<0.001
LMWH (anticoagulant dose)	46 (0.9%)	19 (4.7%)	<0.001
LMWH (prophylaxis)	89 (1.7%)	33 (8.1%)	<0.001
Oral anticoagulants	612 (11.7%)	62 (15.3%)	0.035
Antihypertensives	2285 (43.8%)	170 (41.9%)	NS
Statins	685 (13.1%)	73 (18%)	0.006
Stroke mechanism, n (%)			
Atherosclerotic	628 (19%)	50 (16.6%)	<0.001
Cardioembolic	1747 (53.1%)	171 (56.6%)	
Hypercoagulability	44 (1.3%)	11 (3.6%)*	
Dissection	110 (3.3%)	11 (3.6%)	
Intraprocedural	3 (0.1%)	23 (7.6%)†	
Not determined	732 (22.2%)	31 (10.3%)†	
Other	27 (0.8%)	5 (1.7%)	
Radiological, n (%)			
ASPECTS 6–10	4472 (97.3%)	339 (96.6%)	NS
Site of occlusion, n (%)			

Continued

Table 1 Continued

	n=5619		P value
	Out-of-hospital stroke (n=5213)	In-hospital stroke (n=406)	
Internal carotid artery	570 (11.2%)	54 (13.5%)	0.03
Carotid T	674 (13.2%)	46 (11.5%)	
Middle cerebral artery M1	2423 (47.6%)	179 (44.8%)	
Middle cerebral artery M2	650 (12.8%)	49 (12.3%)	
Tandem occlusion	273 (5.4%)	15 (3.8%)	
Posterior circulation	499 (9.8%)	57 (14.2%) [‡]	

Missing data: mRS pre-stroke (n=721), medical history (533), stroke mechanism (2019), ASPECTS (671), site of occlusion (130).
^{*}P=0.002.
[†]P<0.001.
[‡]P=0.005.
ASPECTS, Alberta Stroke Program Early CT Score; LMWH, low molecular weight heparin; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NS, not significant; TIA, transient ischemic attack.

significantly longer for the spoke group (online supplemental material, table A).

DISCUSSION

This study provides detailed data on functional outcomes and death at 3 months for a large cohort of patients with IHS treated with MT, and attempts to clarify questions about the latencies and delays from stroke onset to diagnosis and EVT in this population. Our data show that despite faster access to cranial imaging, groin puncture, and recanalization from clinical onset, patients with IHS have a worse outcome than community strokes. Nevertheless, delays in in-hospital management for IHS patients were detected.

In the pre-EVT era, IHS has been associated with poor clinical outcomes compared with OHS. Both clinical and organizational elements are considered responsible for this discrepancy. Disadvantages for patients with IHS include multiple medical comorbidities, more severe clinical syndromes at stroke onset, ineligibility for IVT, and longer hospital stays with higher in-hospital mortality.⁵ Our data confirm that IHS patients present a more severe vascular profile and a higher burden of antithrombotic therapy. In this scenario, adequate primary and secondary stroke prevention appear crucial for these complex patients.¹⁸ IHS often occurs in patients with multiple comorbidities or those at high cardiovascular risk, particularly in the presence of cardiac diseases. Medical conditions such as fever, unstable blood pressure, leukocytosis, dehydration, hypercoagulability states and malignancy have been identified as risk factors for IHS.¹⁹ Discontinuation of antithrombotic agents is another leading cause for ischemic stroke in these patients. However, almost half of IHS have been reported to occur following cardiac or neurovascular procedures such as transcatheter aortic valve replacement, coronary artery bypass grafting, carotid stenting, endarterectomy, or cerebral angiography.²⁰ This finding is confirmed in our cohort where procedural or periprocedural stroke was much more represented in the IHS group. Regarding IVT, only a small proportion of IHS patients could receive it due to several contraindications. Considering the recommendations of recent guidelines regarding the utility of bridging therapy in case of LVO, the reduced eligibility for IVT may be a co-factor in the negative functional outcomes.²¹

Table 2 Details of stroke treatments, time intervals and outcomes of patients with in-hospital and out-of-hospital stroke treated with mechanical thrombectomy

	n=5619		P value
	Out-of-hospital stroke (n=5213)	In-hospital stroke (n=406)	
Treatments, n (%)			
IVT contraindications	1522 (38.8%)	248 (79.2%)	<0.001
Combined EVT+IVT	2539 (51.1%)	59 (15.2%)	<0.001
Endovascular treatment, n (%)			
Thrombectomy (stent retriever)	850 (18.9%)	51 (14.2%)*	<0.001
Thromboaspiration	2283 (50.7%)	171 (47.8%)	
Combined	1283 (28.5%)	116 (32.4%)	
Other	85 (1.9%)	20 (5.6%) [†]	
TICI 2b-3	4078 (80.4%)	303 (78.3%)	NS
Anesthesia, n (%)			
No anesthesia/sedation	2266 (54.9%)	164 (49.7%)	NS
General anesthesia	1858 (45.1%)	166 (50.3%)	
Safety, n (%)			
Subarachnoid hemorrhage	133 (2.6%)	15 (3.8%)	NS
Dissection	97 (1.9%)	5 (1.3%)	NS
Distal embolization	414 (8.1%)	24 (6%)	NS
Retroperitoneal/puncture site growing hematoma	33 (0.6%)	0 (0%)	NS
sICH	361 (7.6%)	26 (7%)	NS
Time intervals, min, median (IQR)			
Onset-to-imaging	123 (89–188.5)	60 (33.75–106)	<0.001
Onset-to-groin puncture	220 (168–294)	150 (105–220)	<0.001
Onset-to-end EVT	293 (230–370)	227 (164.5–303.5)	<0.001
Door-to-imaging	29 (20–44)	60 (33.75–106)	<0.001
Door-to-groin puncture	113 (84–151)	150 (105–220)	<0.001
Door-to-end EVT	181 (139–237)	227 (164.5–303.5)	<0.001
Imaging to groin puncture	84 (59–118)	81 (51.25–120)	NS
Procedure time	60 (40–90)	62 (39.5–94)	NS
Outcomes, n (%)			
3-month mRS 0–2	2373 (48.5%)	145 (39%)	<0.001
3-month mortality	958 (19.6%)	112 (30.1%)	<0.001

Missing data: IVT contraindications (n=1381), combined EVT+IVT (266), endovascular treatment (760), TICI (163), anesthesia (1165), safety (98), sICH (476), onset/door-to-imaging (730), onset/door-to-groin puncture (337), onset/door-to-end EVT (435), imaging-to-groin puncture (579), procedure time (350), outcomes (357). For IHS patients, door-to-imaging, groin, and end EVT correspond to onset-to-imaging, groin, and end EVT.
^{*}P=0.03.
[†]P<0.001.
EVT, endovascular treatment; IHS, in-hospital stroke; IVT, intravenous thrombolysis; mRS, modified Rankin scale; NS, not significant; sICH, symptomatic intracerebral hemorrhage; TICI, Thrombolysis In Cerebral Infarction.

Regarding organizational aspects, several systems-level factors have been associated with the poor prognosis of IHS patients, including difficulty in recognizing stroke symptoms, delayed alert to the neurologist, and reduced adherence to measures of stroke care quality during hospitalization.⁷ Combined with the absence of specific protocols for AIS management for IHS, this may translate into overcoming the time windows for reperfusion

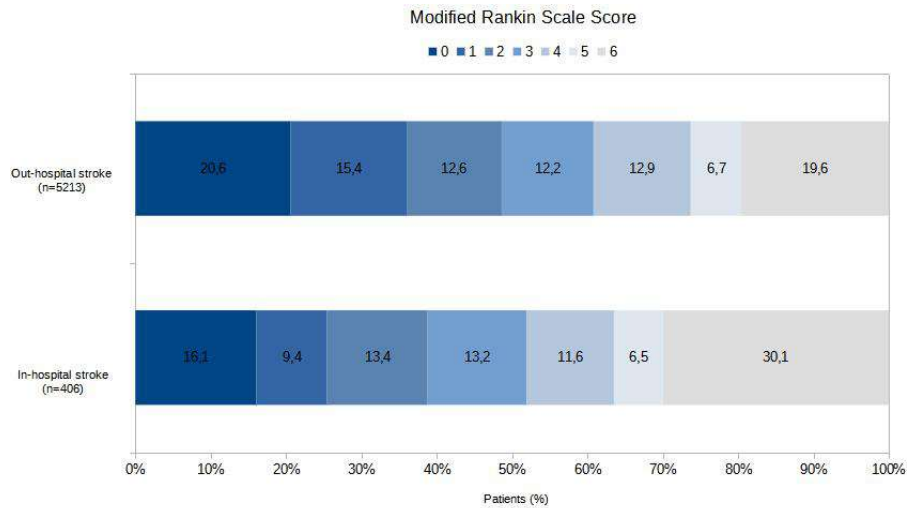


Figure 1 Distribution of functional scores at 3 months.

therapies.²² In this context, most of the available data refer to IHS patients who received IVT or who were not treated at all, while few studies specifically focused on EVT.²³

Preliminary evidence on the role of MT for LVO in patients with IHS is mostly derived from retrospective, observational, small sample size studies. Different authors have reported shorter time intervals from stroke symptoms onset to groin puncture and arterial recanalization for IHS patients compared with OHS, without differences in outcomes and death rate.^{12–14} However, these studies represent the experience of single high-volume stroke centers, with the availability of a neurovascular team and, in some cases, with the activation of a well-implemented acute stroke protocol. In contrast, the analysis of multicenter registry data demonstrated a significantly higher proportion of in-hospital death and lower independence at discharge for IHS patients after MT.¹⁰ In addition, significant in-hospital delays in managing AIS in hospitalized patients were documented.

Our data are relevant for clarifying these points. Considering symptom recognition or the last time known well as index time for stroke onset, the time intervals for brain imaging, groin puncture, and recanalization were favorable for patients with IHS, in line with previous single-center studies. However, despite the advantages in time intervals and similar recanalization rates, the functional outcomes remain poor for IHS patients. On the other hand, this study also evaluated the efficiency of the in-hospital system of stroke care by comparing the IHS times with OHS door-to-imaging, door-to-groin, and door-to-end of EVT. With these criteria, the median time to imaging and treatment was significantly longer for the IHS group. These findings are in line with those of a previous large-cohort study and indicate consistent in-hospital delays.¹⁰ However, overall, the in-hospital delays were offset by earlier identification of stroke and other efficiencies inherent with the patient having a stroke due to LVO in the hospital. The faster onset-to-imaging and onset-to-groin for IHS patients were mainly caused by the needlessness of transportation to the hospital, and this effect seems to overcome the absence of specific in-hospital stroke protocols outside the ED. At the same time, this advantage may be completely lost for IHS occurring in hospitals unable to offer EVT, which still requires patients to be transported to hub centers. Therefore, it seems that the poorer outcomes observed were attributable to IHS patients having more baseline comorbidities, more concurrent

acute illnesses, and more contraindications to IVT rather than hospital organizational deficiencies.

Sub-analysis of time intervals showed that the limiting factor was the transfer to the radiology room after stroke recognition while, after imaging, there were no differences between the two groups regarding transferring patients to the angiography suite and the procedure time. The faster door-to-imaging for OHS patients reflects the organizational capability of the ED in managing AIS through pre-specified and well-coded paths, which seem to be lacking for IHS. In our cohort, the diagnostic delay was estimated at approximately 30 min. This delay may further worsen the outcomes of IHS patients, emphasizing the need for specific inpatient systems of stroke care. Previous works demonstrated that dedicated and standardized protocols may reduce the treatment time for IHS patients, increasing the likelihood of offering reperfusion therapies.^{24–28} Periodic education on the recognition of stroke symptoms and the stroke alert process, the development of checklists for in-hospital stroke-code activation and rapid transportation to radiology, and the availability of a defined team to respond to stroke alerts are some of the interventions of proven effectiveness.^{5–20} However, IHS occurs in different contexts within hospitals, making it difficult to create a single model for its acute in-hospital management.^{29–30} On this basis, each institute should identify the determinants of its delays before establishing internal protocols.

In the multivariate analysis, IHS was an independent predictor of death at 3 months. This finding conflicts with that reported in the single-center experience where IHS was not associated with unfavorable outcomes compared with OHS.^{12–14} However, our data are representative of a broad population in the Italian national territory and are the expression of the outcomes on a large scale. Our data also showed that MT was technically feasible with similar recanalization rates to community strokes. Furthermore, MT was safe in terms of sICH or other procedure-related complications, even in critically ill patients with a higher antithrombotic therapy burden than OHS.

Limitations

This study presents some limitations, mostly related to its observational design. All data were retrospectively obtained from a multicenter prospective national registry, which is itself a potential source of bias. In addition, our findings may not be

representative of the whole national territory due to the voluntary participation of centers in the registry programs and rules. The study included only patients with IHS who received MT. Therefore, the results are applicable only for this specific population and are not generalizable for all IHS. Moreover, we do not know how many of the included centers adopted specific AIS protocols for IHS patients. For IHS, data relating to the reasons for hospitalization are not available, nor are further comorbidity data other than those presented. Neither central adjudication of the clinical nor radiological data were performed. Finally, our data refer to 3-month functional outcomes and do not provide information regarding in-hospital disability and mortality.

CONCLUSION

Overall, our data show that IHS is associated with worse functional outcomes and higher mortality despite faster access to the diagnostic and therapeutic process. Nonetheless, adherence to tailored stroke codes and training for in-hospital stroke management may reduce the delays associated with it, representing a significant step in the attempt to improve the outcomes of these patients.

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REFERENCES

- Ding D. Endovascular mechanical thrombectomy for acute ischemic stroke: a new standard of care. *J Stroke* 2015;17:123–6.
- Kimura K, Minematsu K, Yamaguchi T. Characteristics of in-hospital onset ischemic stroke. *Eur Neurol* 2006;55:155–9.
- Reich A. In-hospital stroke. *J Neurol Neuromedicine* 2017;2:22–6.
- Emmett ES, Douiri A, Marshall JJ, et al. A comparison of trends in stroke care and outcomes between in-hospital and community-onset stroke—the South London Stroke Register. *PLoS One* 2019;14:e0212396.
- Chen S, Singh R-J, Kamal N, et al. Improving care for acute in-hospital ischemic strokes—A narrative review. *Int J Stroke* 2018;13:905–12.
- Blacker DJ. In-hospital stroke. *Lancet Neurol* 2003;2:741–6.
- Cumblor E. In-hospital ischemic stroke. *Neurohospitalist* 2015;5:173–81.
- Vera R, Lago A, Fuentes B, et al. In-hospital stroke: a multi-centre prospective registry. *Eur J Neurol* 2011;18:170–6.
- Park HJ, Cho HJ, Kim Y-D, et al. Comparison of the characteristics for in-hospital and out-of-hospital ischaemic strokes. *Eur J Neurol* 2009;16:582–8.
- Akbik F, Xu H, Xian Y, et al. Trends in reperfusion therapy for in-hospital ischemic stroke in the endovascular therapy era. *JAMA Neurol* 2020;77:1486–95.
- Bulwa Z, Del Brutto VJ, Loggini A, et al. Mechanical thrombectomy for patients with in-hospital ischemic stroke: a case-control study. *J Stroke Cerebrovasc Dis* 2020;29:104692.
- Lu M-Y, Chen C-H, Yeh S-J, et al. Comparison between in-hospital stroke and community-onset stroke treated with endovascular thrombectomy. *PLoS One* 2019;14:e0214883.
- Yoo J, Song D, Lee K, et al. Comparison of outcomes after reperfusion therapy between in-hospital and out-of-hospital stroke patients. *Cerebrovasc Dis* 2015;40:28–34.

- 14 Caparros F, Ferrigno M, Decourcelle A, *et al.* In-hospital ischaemic stroke treated with intravenous thrombolysis or mechanical thrombectomy. *J Neurol* 2017;264:1804–10.
- 15 Mangiafico S, Pracucci G, Saia V, *et al.* The Italian Registry of Endovascular Treatment in Acute Stroke: rationale, design and baseline features of patients. *Neurol Sci* 2015;36:985–93.
- 16 SPREAD (Stroke Prevention and Educational Awareness Diffusion). Italian guidelines for stroke prevention and management, 8th ed. Available: <https://isa-aii.com> [Accessed 24 Oct 2022].
- 17 Toni D, Mangiafico S, Agostoni E, *et al.* Intravenous thrombolysis and intra-arterial interventions in acute ischemic stroke: Italian Stroke Organisation (ISO) – SPREAD guidelines. *Int J Stroke* 2015;10:1119–29.
- 18 Dawson J, Béjot Y, Christensen LM, *et al.* European Stroke Organisation (ESO) guideline on pharmacological interventions for long-term secondary prevention after ischaemic stroke or transient ischaemic attack. *Eur Stroke J* 2022;7:I–II.
- 19 Nadav L, Gur AY, Korczyn AD, *et al.* Stroke in hospitalized patients: are there special risk factors? *Cerebrovasc Dis* 2002;13:127–31.
- 20 Nough A, Amin-Hanjani S, Furie KL, *et al.* Identifying best practices to improve evaluation and management of in-hospital stroke: a scientific statement from the American Heart Association. *Stroke* 2022;53:e165–75.
- 21 Turc G, Tsvigoulis G, Audebert HJ, *et al.* European Stroke Organisation-European Society for Minimally Invasive Neurological Therapy expedited recommendation on indication for intravenous thrombolysis before mechanical thrombectomy in patients with acute ischaemic stroke and anterior circulation large vessel occlusion. *Eur Stroke J* 2022;7:I–XXVI.
- 22 Cumbler E, Wald H, Bhatt DL, *et al.* Quality of care and outcomes for in-hospital ischemic stroke: findings from the National Get With the Guidelines-Stroke. *Stroke* 2014;45:231–8.
- 23 Tsvigoulis G, Katsanos AH, Kadlecová P, *et al.* Intravenous thrombolysis for patients with in-hospital stroke onset: propensity-matched analysis from the Safe Implementation of Treatments in Stroke-East registry. *Eur J Neurol* 2017;24:1493–8.
- 24 Koge J, Matsumoto S, Nakahara I, *et al.* Improving treatment times for patients with in-hospital stroke using a standardized protocol. *J Neurol Sci* 2017;381:68–73.
- 25 Kassardjian CD, Willems JD, Skrabka K, *et al.* In-patient code stroke: a quality improvement strategy to overcome knowledge-to-action gaps in response time. *Stroke* 2017;48:2176–83.
- 26 Yoo J, Song D, Baek J-H, *et al.* Comprehensive code stroke program to reduce reperfusion delay for in-hospital stroke patients. *Int J Stroke* 2016;11:656–62.
- 27 Cumbler E, Anderson T, Neumann R, *et al.* Stroke alert program improves recognition and evaluation time of in-hospital ischemic stroke. *J Stroke Cerebrovasc Dis* 2010;19:494–6.
- 28 Nolan S, Naylor G, Burns M. Code gray -- an organized approach to inpatient stroke. *Crit Care Nurs Q* 2003;26:296–302.
- 29 Saltman AP, Silver FL, Fang J, *et al.* Care and outcomes of patients with in-hospital stroke. *JAMA Neurol* 2015;72:749–55.
- 30 Cadilhac DA, Kilkenny MF, Lannin NA, *et al.* Outcomes for patients with in-hospital stroke: a multicenter study from the Australian Stroke Clinical Registry (AUSCR). *J Stroke Cerebrovasc Dis* 2019;28:1302–10.