Neurological Sciences (2019) 40:319–326
https://doi.org/10.1007/s10072-018-3644-3

ORIGINAL ARTICLE

# Management of acute ischemic stroke, thrombolysis rate, and predictors of clinical outcome

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Received: 9 March 2018 / Accepted: 9 November 2018 / Published online: 14 November 2018


## Abstract

**Background and aims** Monitoring the quality of acute ischemic stroke (AIS) management is increasingly important since patient outcome could be improved with better access to evidence-based treatments. In this scenario, the aim of our study was to identify thrombolysis rate, reasons for undertreatment, and factors associated with better outcome.

**Methods** From January to December 2016, individuals diagnosed with AIS at the Policlinic San Martino Hospital in Genoa, Italy, were prospectively included. Severity of stroke, site of occlusion, rate and time related in-hospital management of systemic thrombolysis, and mechanical thrombectomy were recorded. Safety and clinical outcomes were compared between different subgroups.

**Results** Of 459 AIS patients (57.3% females, mean age 78.1), 111 received i.v. thrombolysis (24.4%) and 50 received mechanical thrombectomy (10.9%). Apart from arrival behind the therapeutic window, which was the first limitation to thrombolysis, the main reason of undertreatment was minor stroke or stroke in rapid improvement. Baseline NIHSS $\geq 8$ was associated with unfavorable clinical outcome (mRS > 2) (OR 20.1; 95% CI, 1.1–387.4, $p = 0.047$). Age older than 80 years (OR 5.0; 95% CI, 1.4–64.1, $p = 0.01$), baseline NIHSS $\geq 7$ (OR 20.1; 95% CI, 1.1–387.4, $p = 0.047$), and symptomatic intracranial hemorrhage (OR 22.9; 95% CI, 2.0–254.2, $p = 0.01$) proved independently associated with mortality.

**Conclusions** i.v. thrombolysis and mechanical thrombectomy rate was higher than that of previous reports. Minor stroke or stroke in rapid improvement was a major reason for exclusion from thrombolysis of eligible patients. Higher NIHSS proved an independent predictor of unfavorable clinical outcome and death. Strategies to avoid in-hospital delays need to be enforced.

**Keywords** Stroke · Management · Clinical outcome · Thrombolysis

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s10072-018-3644-3) contains supplementary material, which is available to authorized users.

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## Introduction

Stroke is the second most common cause of death and a major cause of disability worldwide [1, 2]. Since proper therapy in the acute phase improves stroke prognosis, monitoring the quality of stroke care is crucial. Thrombolytic treatment improves functional outcome after acute ischemic stroke (AIS) and is a first-line treatment worldwide. However, only a minority of AIS patients currently receive thrombolysis because of late hospital arrival or presence of one or more exclusion criteria. In Italy, the Italian Stroke Organization (ISO) has critically reappraised the latter in 2016, resulting in updated stroke guidelines [3]. In this scenario, the aim of our study was to investigate the management of patients presenting to the emergency room (ER) of our hospital with suspect of AIS in order to (1) identify factors associated with possible underutilization of thrombolysis; (2) compare clinical and safety

outcome in different groups of patients; and (3) identify factors associated with poor clinical outcome and risk of death.

## Methods

We prospectively collected data from consecutive individuals suspected for AIS who were admitted between 1 January 2016 and 31 December 2016 to the ER of the Policlinic San Martino Hospital, a teaching University Hospital that serves a population of 300,000 inhabitants of Genoa, Italy. The review of medical records allowed us to select for our analysis only patients in which the diagnosis of AIS was confirmed. In these latter patients, the following data were recorded: age; gender; medical history and concomitant medications; modality of presentation (ambulance or private transportation); severity of stroke based on the National Institutes of Health Stroke Scale (NIHSS) score (baseline and after thrombolytic therapy); time from onset of symptoms to ER; time from onset of symptoms to first medical evaluation; door-to-CT (cerebral tomography) scan time; time from onset of symptoms to needle (STN); door-to-needle (DTN) time; time from onset of symptoms to groin puncture; time from onset of symptoms to end procedure; door-to-groin puncture time; site of artery occlusion; outcome of reperfusional treatment delivery based on the Thrombolysis in Cerebral Infarction (TICI) score; reason for not performing i.v. thrombolysis or mechanical thrombectomy; department and length of hospitalization; destination at discharge.

A single local stroke neurologist performed all data entries. Since our institution is a "hub" center in the regional thrombolysis organization, patients could be admitted even from "spoke" centers in order to perform thrombectomy.

Intravenous thrombolysis with a recombinant tissue plasminogen activator (rtPA) was administered less than 4.5 h after symptom onset at the standard dose of 0.9 mg/kg either at spoke or hub center. Thrombectomy was performed less than 6 h after symptom onset either with thromboaspiration or stent retriever.

### Outcome measures

Functional outcome was measured at 3 months by the modified Rankin Scale (mRS). Favorable outcome was defined as a mRS score $\leq 2$ on day 90. Safety outcomes were symptomatic intracranial hemorrhage (sICH) (defined as a neurological deterioration causing a 4-point or more worsening on the NIHSS score causally related to intracranial hemorrhage detected by CT at 36 h or less after the initiation of thrombolysis) and mortality rate at 3 months.

### Statistical analysis

For clinical and demographic data, descriptive statistics were used such as median (1st–3rd quartile), mean (± standard deviation), and frequencies (percentage). Associations between sex, patients aged below 80 years and above 80 years, and atrial fibrillation and other disease characteristics were analyzed by chi-square test for categorical variables (or Fisher's exact test when appropriate) and Student's $t$ test or Mann-Whitney $U$ test for continuous variables. Logistic regression models were used to assess the impact of the abovementioned variables on 90-day mortality and on functional outcome measured at 3 months. Only factors significantly associated with the outcome at univariate analysis were included in a multivariate model with a stepwise procedure.

$P$ values $< 0.05$ were considered statistically significant. All analyses were carried out using the SAS software version 9.3 (Institute Inc., Cary, NC, USA).

## Results

During the study period, 819 patients with suspect of AIS were admitted to the ER, and after the revision of the medical records, the diagnosis was confirmed in 459 subjects. Figure 1 and Table 1 summarize the characteristics of our confirmed stroke patients' population. In the other 359 cases, a diagnosis of hemorrhagic stroke, acute ischemic attack, or other stroke mimic was made.

Two hundred twenty-five patients (49% of total AIS stroke population) arrived within the therapeutic window and 111 of these were treated with i.v. thrombolysis. This represents 24.4% of the total AIS population ($n = 459$) and 49% of eligible (i.e., arrived within therapeutical window) patients ($n = 225$). Seventy-six patients with confirmed AIS (16%) had a wake up stroke, and for this reason, all but one were excluded from thrombolytic treatment. The single wake up stroke patient treated occurred after implementation in our hospital of a guideline-based protocol for this type of stroke. Among i.v. thrombolyzed patients, 47.4% achieved a favorable outcome (mRS $\leq 2$) at 3 months, 1.8% developed sICH, and 22% were dead at 3 months. Among the 225 patients who arrived to the ER within the therapeutic window, 150 (67%) underwent CT angiography. The latter revealed an occlusion of a proximal cerebral artery in 84 (56%) cases and were therefore eligible for thrombectomy. The latter were performed in 50 cases, leading to a thrombectomy rate of 10.9% of total AIS population and of 59.5% of all eligible patients. Of these 50 cases, 36 and 14 were rescue and primary treatments, respectively. Seven out of these 50 patients had a mild stroke (NIHSS $\leq 6$ on admission). Thrombectomy was performed in 47 cases in the anterior circulation and in 3 cases, in the posterior one. Recanalization, as indicated by TICI 2b/3, was obtained in 56% of patients. Sites of occlusion were the internal carotid

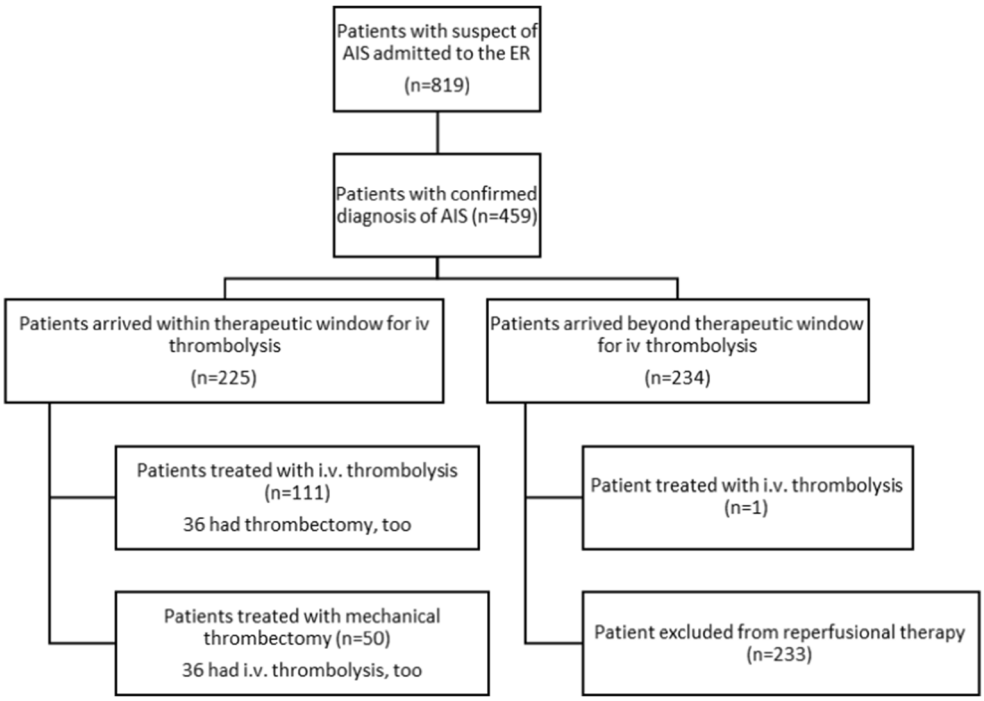


**Fig. 1** Study cohort selection flow diagram

artery (ICA) in 4 cases (3%), middle cerebral artery (MCA) M1 segment in 32 cases (21%), MCA-M2 segment in 7 cases (5%), "tandem" occlusion in 4 cases (3%), and vertebrobasilar (VB) in 3 cases (2%). In this population, 40% of patients achieved a favorable outcome (mRS $\leq 2$) at 3 months, the 2% developed sICH, and the 30% was dead at 3 months. Data related to reperfusional treatment are shown in Table 2.

Systemic thrombolysis and mechanical thrombectomy were not performed in 114/225 and in 34/84 eligible patients, respectively. Reasons are shown in Table 3. Minor and rapidly improving symptoms were the most frequent reason for i.v. treatment exclusion. Among patients affected by minor stroke ($n = 24$), 50% presented with dysarthria or aphasia, 42% with slight motor deficits, and 8% with ptosis or diplopia. Of the

**Table 1** Baseline characteristics of the 459 patients with confirmed diagnosis of acute ischemic stroke

| | |
|---|---|
| Age, years (mean ± SD) | 78.1 (± 11.9) |
| Female sex, *n* (%) | 263 (57.3%) |
| Mean NIHSS on admission (mean ± SD)* | 11.4 ± 6.1 |
| | *N* = 97 |
| Previous ischemic stroke, *n* (%) | 140 (30.5%) |
| Hypertension, *n* (%) | 282 (61.4%) |
| Atrial fibrillation, *n* (%) | 121 (26.4%) |
| Diabetes mellitus, *n* (%) | 89 (19.4%) |
| Antiplatelet treatment before stroke, *n* (%) | 194 (42.3%) |
| Ongoing anticoagulant therapy, *n* (%) | 70 (15.2%) |
| Admission to the ER by ambulance, *n* (%) | 344 (74.9%) |
| "Wake up stroke" | 76 (16.6%) |
| Patients treated with i.v. thrombolysis, *n* (% of total AIS patients) | 112 (24.4%) |
| Patients treated with mechanical thrombectomy, *n* (% of total AIS patients) | 50 (10.9%) |
| Arrival to ER within 4.5 h after symptom onset, excluding wake up stroke, *n* (%) | 225 (49.0%) |
| Admission to Stroke Unit, *n* (%) | 292 (63.6%) |
| Median hospitalization length, days (1st–3rd quartiles) | 8.9 (5–14) |
| Patients discharged home, *n* (%) | 230 (50.1%) |

*NIHSS* National Institutes of Health Stroke Scale

*NIHSS score was available only for part of the patients who underwent thrombolysis. The number of patients for whom it was available is specified in the cell

**Table 2** Main data related to reperfusional treatment (i.v. and/or endovascular). Please note that some patients received both treatments (see text for further details)

| | i.v. thrombolysis $N = 112$ | Mechanical thrombectomy $N = 50$ |
|---|---|---|
| Age, years (mean ± SD) | 75.5 (± 13.4) | 74.3 (± 11.2) |
| Median NIHSS score on admission (1st–3rd quartiles)* | 11 (7–16) | 13 (10–17) |
| | $N = 96$ | $N = 46$ |
| Median door-to-CT time, min (1st–3rd quartiles)* | 13 (10–34) | |
| | $N = 73$ | |
| Median door-to-needle time, min (1st–3rd quartiles)* | 78 (60–104.5) | |
| | $N = 100$ | |
| Median symptoms-to-needle time, min (1st–3rd quartiles)* | 140 (120–180) | |
| | $N = 103$ | |
| Median time from door to groin puncture, min (1st–3rd quartiles)* | | 172 (135–210) |
| | | $N = 45$ |
| Median time from symptoms to groin puncture, min (1st–3rd quartiles)* | | 225 (210–279) |
| | | $N = 46$ |
| Median time from symptoms to end procedure, min (1st–3rd quartiles)* | | 330 (300–360) |
| | | $N = 46$ |
| mRS ≤ 2 at 90 days* | 47.4% | 40% |
| | ($N = 108$) | $N = 48$ |
| sICH | 1.8% | 2% |
| Mortality rate at 90 days* | 22% | 30% |
| | ($N = 108$) | $N = 48$ |

*NIHSS* National Institutes of Health Stroke Scale, *CT* computed tomography, *sICH* symptomatic intracranial hemorrhage

*In some cases, this variable was not recorded and could not be computed based on available records. The number of patients for whom it was available is specified in the cell

114 non i.v. thrombolyzed patients, 13 received primary thrombectomy while among the 34 patients who did not performed mechanical thrombectomy, 24 received i.v. thrombolysis.

The subgroup of AIS patients whom was not performed neither i.v. nor endovascular thrombolysis counted 331 subjects. Among these patients, 38.7% achieved a favorable outcome (mRS ≤ 2) at 3 months and 19.6% was dead at 3 months. Data about NIHSS at baseline or sICH were not available in this population.

Compared with men, women were older ($p < 0.0001$), more often affected by atrial fibrillation ($p$ 0.04) and less often functionally independent at 90 days ($p < 0.0001$). Rates of thrombolysis administration (both systemic and endovascular) were not significantly different ($p = 0.43$ and $p = 0.17$, respectively). Further details about sex and outcome differences are present in online Table 1.

Comparing patients aged below and above 80 years, in the latter ones, the 90-day clinical outcome was worse ($p < 0.0001$), mortality rate was higher ($p < 0.0001$), and they had less chance to be discharged home ($p$ 0.0003). Twenty percent of patients aged over 80 years were treated with i.v. thrombolysis. Rates of thrombolysis administration (both systemic and endovascular) were significantly lower in patients aged above 80 years ($p = 0.01$ and $p = 0.04$, respectively) (for further details, see online Table 2).

Compared with non-atrial fibrillation (AF) patients, those affected by AF were older ($p < 0.0001$) and had a prevalence of females ($p < 0.004$). The clinical outcome was more unfavorable ($p < 0.00005$), the mortality rate was higher ($p$ 0.005), and the probability to be discharged home was lower ($p$ 0.005). Successful reperfusion (TICI 2b/3) was achieved in 26.7% of AF patients and in 68.6% of non-AF patients ($p = 0.006$) (further details are shown in online Table 3). Incidentally, only 40% of AF patients were under oral anticoagulant therapy and 20% were not even receiving antiplatelet treatment. The rate of i.v. thrombolysis was significantly lower among AF patients ($p = 0.01$), while rate of mechanical thrombectomy was not significantly different among the two population ($p$ 0.91).

Factors associated with unfavorable clinical outcome (mRS > 2) in univariate analysis are listed in Table 4. Multivariate analysis showed that an NIHSS score higher than 8 was independently associated with negative clinical outcome while a TICI score 2b/3 had a strong protective effect.

Factors associated with mortality in univariate analysis are listed in Table 5. Multivariate analysis showed that age older than 80 years (OR 5.0; 95% CI, 1.4–64.1, $p$ value 0.01),

**Table 3** Reasons for ruling out alteplase or mechanical thrombectomy in patients with AIS

| | Reason for not administering i.v. thrombolysis ($N = 114$) | Reason for not performing mechanical thrombectomy ($N = 34$) |
|---|---|---|
| Minor stroke or stroke in rapid improvement | 37 (16.4%) | 5 (14.7%) |
| Ongoing anticoagulant therapy | 22 (9.7%) | – |
| Major surgery, severe trauma, or cerebral hemorrhage in the last 3 months | 17 (7.5%) | – |
| Severe comorbidities or advanced age (> 85 years) | 16 (7.1%) | 5 (14.7%) |
| Too severe stroke | 1 (0.4%) | 1 (2.9%) |
| Seizure at stroke onset | 7 (3%) | 1(2.9%) |
| "Early" CT ischemic change or absence of collateral circulation | 9 (4%) | 1 (2.9%) |
| Slow in-hospital management* | 4 (1.7%) | 2 (5.8%) |
| Too distal occlusion | – | 9 (26.5%) |
| Chronic carotid occlusion | | 3 (8.8%) |
| Unfavorable vascular anatomy | – | 2 (5.8%) |
| Spontaneous recanalization | – | 4 (11.7%) |
| Unknown reasons | 1 (0.4) | 1 (2.9%) |

*This entry includes patients who arrived within the therapeutic window but ended their diagnostic workup beyond the window. Reasons for this could not be understood, except in 1 patient who received initially a wrong diagnosis as acute ischemic attack, and in another 1 who arrived 4 h after symptoms onset

baseline NIHSS ≥ 7 (OR 20.1; 95% CI, 1.1–387.4, $p$ value 0.047), and sICH (OR 22.9; 95% CI, 2.0–254.2, $p$ value 0.01) were independently associated with mortality.

## Discussion

We observed that almost half of the patients affected by AIS arrived to the ER within the therapeutic window, and that 49% of these patients received i.v. thrombolysis, leading to i.v. thrombolysis rate of 24% among all AIS patients. This proportion is higher than that reported in similar, recent studies, in which 7.9% [4], 11% [5], and 14.6% [6] of AIS patients received i.v. thrombolysis. A combination of strategies might have played a role in this positive result, including being a high-volume hospital with a tertiary stroke center, holding frequent meetings with all involved specialists debating stroke protocol issues, adopting the recently revised (ISO)-SPREAD guidelines [3] and introducing a streamlined triage protocol for AIS patients ("stroke code").

In an attempt to increase thrombolysis utilization and consequently decrease stroke disability, this study identified reasons why patients did not receive thrombolysis. The largest barrier to thrombolysis continues to be late patient arrival to

**Table 4** Adjusted OR for functional dependency (mRS score of ≥ 3) predictors in stroke patients

| | OR (95% CI) | $p$ value | Multivariate | $p$ value |
|---|---|---|---|---|
| Age > 80 years | 3.5 (2.3–5.2) | < 0.0001 | | |
| Baseline NIHSS ≥ 8* | 5.0 (1.9–13) | 0.001 | 20.1 (1.1–387.4) | 0.047 |
| Female sex | 2.6 (1.8–3.8) | < 0.0001 | | |
| STN | 1.015 (1.0–1.0) | 0.003 | | |
| Atrial fibrillation | 2.2 (1.4–3.5) | 0.001 | | |
| TICI 2b/3 | 0.25 (0.1–0.9) | 0.036 | 0.1 (0.01–0.6) | 0.019 |
| Admission in Stroke Unit | 0.7 (0.5–1.0) | 0.076 | | |
| i.v. thrombolysis | 0.7 (0.4–1.1) | 0.091 | | |
| Mechanical thrombectomy | 1.0 (0.5–1.9) | 0.951 | | |
| Rescue therapy | 0.7 (0.4–1.5) | 0.419 | | |
| STE | 1.0 (1.0–1.0) | 0.528 | | |

*Dichotomized as per ROC curve

*NIHSS* National Institutes of Health Stroke Scale, *STN* time from symptoms to needle, *TICI* thrombolysis in cerebral infarction, *STE* time from symptoms to end procedure

**Table 5** Adjusted OR for mortality at 90 days in stroke patients

| | OR (95% CI) | *p* value | Multivariate | *p* value |
|---|---|---|---|---|
| Age > 80 years | 3.2 (1.9–5.3) | < 0.0001 | 5.0 (1.4–64.1) | 0.01 |
| Baseline NIHSS ≥ 7* | 8.1 (1.0–64.1) | 0.023 | 20.1 (1.1–387.4) | 0.047 |
| Atrial fibrillation | 2.0 (1.2–3.2) | 0.005 | | |
| sICH after rtPA | 15.8 (1.7–148.7) | 0.016 | 22.9 (2.0–256.2) | 0.01 |
| Admission in Stroke Unit | 1.0 (0.6–1.6) | 0.914 | | |
| Sex (F) | 1.3 (0.8–2.0) | 0.321 | | |
| Oral anticoagulant therapy (warfarin) | 1.3 (0.6–2.8) | 0.551 | | |
| New oral anticoagulant (NOAC) therapy | 1.9 (0.9–4.1) | 0.097 | | |
| i.v. thrombolysis | 1.1 (0.7–1.9) | 0.679 | | |
| Mechanical thrombectomy | 1.8 (0.9–3.4) | 0.093 | | |
| Rescue therapy | 1.3 (0.5–2.8) | 0.551 | | |

*Dichotomized as per ROC curve

*NIHSS* National Institutes of Health Stroke Scale, *sICH* symptomatic intracerebral hemorrhage, *NOAC* new oral anticoagulant

hospital mostly due to lack of recognition of signs and symptoms of stroke and consequent late presentation to ER. For this reason, a mediatic campaign (P.R.E.S.T.O. project) aimed to increase population's awareness on stroke has started in our district (Liguria) in October 2018. In order to reduce in-hospital delay, in 2015, we had modified our stroke activation protocol by introducing a prenotification sent to the emergency physician and neurologist by the paramedics from patients' home if AIS was suspected. In fact, it is widely recognized that the earlier the thrombolysis is administered, the better the outcome is [7]. Despite this, larger works have shown that only 18% have a DTN time of 60 min or less [8] and our results are consistent with this data. We are working systematically to reduce the time used in-hospital to treat AIS patients in order to maximize the number of patients treated within the so-called Golden Hour. For this reason, we recently made an amendment in our stroke protocol, such that rtPA bolus will be in the future administered on the CT table, thus avoiding wasting time in the transfer from the CT room to Stroke Unit. The impact of this initiative in reducing DNT time and functional outcome will hopefully be demonstrated in future investigations. Nevertheless, among modifiable issues, slowness in hospital management was a minor barrier to thrombolysis at our institution. Our study also confirms that among patients presenting within the treatment window, minor and rapidly improving symptoms are the primary reasons for i.v. treatment exclusion [9–11]. This withdrawal of therapy, however, is nowadays not recommended by the revised (ISO)-SPREAD guidelines, and therefore will be from now on discouraged at our hospital. There are evidence in fact that (a) many patients not given i.v. rtPA because of mild or rapidly improving symptoms experience early and marked progression with an increased risk of mortality and disability [12]; (b) i.v. rtPA in minor stroke has an excellent safety profile and can lead to excellent outcome [13]. The main reasons for exclusion from mechanical thrombectomy were distal occlusion, minor and rapidly improving symptoms, and severe comorbidities. According to American Heart Association/American Stroke Association Guidelines [14], in fact, causative occlusion of the ICA or proximal MCA, NIHSS score of ≥ 6, and prestroke mRS ≤ 1 are required criteria for mandatory endovascular therapy (class I; level of evidence A), while in cases having NIHSS < 6, the decision is left to a case-by-case analysis. In the future, making this decision will have to consider, among else, a symptomatic arterial occlusion can be a strong predictor of neurological deterioration and poor 3-month outcome even in acute mild stroke [15, 16]. Our study showed that older age, higher baseline NIHSS score, and atrial fibrillation are strongly associated with unfavorable clinical outcome and death, in agreement with previous reports [17–19]. The high rate of patients older than 80 years in our study is probably due to the particular demographic structure of Liguria, an Italian region with the oldest population. When affected by stroke, patients > 80 years old arrived to the ER with similar delay from onset compared to younger patients, but more frequently by use of emergency medical services. Therefore, they should theoretically have had a higher chance of being selected for i.v. thrombolysis. By contrast, both i.v. and endovascular thrombolysis rates were higher in patients < 80 years old compared to patients > 80 years old. This result, which suggests a less aggressive management of older patients, is consistent with data in the literature [20] despite evidence that i.v. rtPA is an effective treatment even for patients older than 80 [21, 22]. Nevertheless, the thrombolysis rate achieved in the elderly at our hospital proved higher than that previously reported [20]. When we dichotomized the score of NIHSS as per ROC curve, the value of ≥ 8 turned out to be the only independent predictor of poor clinical

outcome after adjustment for confounders (OR 20; 95% CI, 1.1–387, $p$ value 0.047). This might be hypothetically explained by the observation that these patients have more often a large artery occlusion [23]. Our study also provides evidence for a negative effect of AF on outcome after stroke. Compared with non-AF, patients with AF are less frequently independent ($p$ 0.0005) and have higher risk of death at 3 months ($p$ value 0.005). This is probably due to the association of AF and greater volumes of cerebral hypoperfused areas due to less developed collateral circulation, a combination leading to a higher final infarct volume [18]. In this scenario, the prevention of stroke related to AF should be a primary goal. By contrast, our results show that only part of AF patients were treated with anticoagulant before stroke. Thus, better implementation of guidelines concerning stroke prevention in AF patients is required. Our study also supports evidence of a worse functional outcome and higher mortality in women compared to men ($p < 0.0001$), probably due to their older age ($p < 0.0001$) and higher prevalence of cardioembolic stroke due to AF ($p$ 0.04), as it had been previously reported in larger series [24].

Positive aspects of our study include its prospective nature, the minimization of missing data, and the homogeneity of the data, all collected by a single local stroke neurologist. There are some potential limitations to our analysis. The first is the small size of the study population. For this reason, comparisons between small subgroups had only sufficient power to detect very large differences. Additionally, we did not have information on stroke severity (based on NIHSS score) in patients not treated with i.v. and/or endovascular thrombectomy, and this prevents from comparing clinical and safety outcomes between patients who did or did not receive reperfusional therapy.

**Acknowledgments** We thank Kristi Beshiri, Emanuele Giacheri, Simona Priora, and Angela Zuppa for their assistance in data collection.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** For this type of study, formal consent was not required.

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