Identification of Stroke Etiology May Contribute to Improve the Outcome in Dedicated Units

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Background: The purpose of our study is to investigate whether stroke unit (SU) care and the utilization of Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria may contribute to reduce death and disability in hospitalized patients after a first-ever ischemic stroke (IS). *Methods:* Data included in the present study were derived from our previous study on the incidence and outcome of cerebrovascular diseases in the district of Udine, performed from April 1, 2007, to March 31, 2009. *Results:* We identified 429 hospitalized first-ever IS cases, 297 of 429 (69.2%) patients were admitted to a dedicated SU and 132 of 429 (30.8%) to a general medical ward. According to the TOAST criteria, 101 of 132 first-ever ISs (76.5%) admitted to general medical wards were of undetermined (UND) etiology, whereas in only 105 of 297 (35.4%) patients admitted to the SU, the diagnosis remained UND. Multivariable analysis after propensity score matching showed that compared with general medical wards, SU care was associated with a reduced probability of being dead or highly disabled ($P = .025$) at the end of follow-up. Moreover, patients with an UND diagnosis had a worse 6-month case fatality ($P < .0001$) and also higher risk of being dead or highly disabled ($P < .0001$). *Conclusions:* Our study provides real-world evidence that accurate etiologic subtype classification of ISs according to TOAST criteria and SU care as opposed to general medical ward management are associated with reduction of the proportion of poor outcomes in first-ever IS patients. **Key Words:** Ischemic stroke—TOAST criteria—ischemic stroke subtypes—vascular events—stroke unit care—medical ward.
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Introduction

Many literature data[1-7] showed that stroke unit (SU) care is associated with long-term reductions in death, disability, and institutionalized long-term care in ischemic stroke (IS) patients. American Heart Association/American Stroke Association Guidelines[8] recommend that patients with an acute stroke should be hospitalized in a comprehensive and specialized SU with dedicated beds and staff.

Other studies[9,10] showed that the benefits of the treatment in an SU depend on the presence of a multidisciplinary team specialized in stroke management. Overall, these factors showed a 46% decrease in the risk of death for patients hospitalized in SUs with respect to patients hospitalized in general medical wards.[11]

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Previous investigations identified several ways in which SUs can contribute to reduce case fatality and disability, but they did not evaluate if a complete diagnostic investigation of the etiology of IS[12] may contribute to the improved prognosis.

The purpose of our study is to investigate the contribution of etiopathologic diagnosis in determining the better outcome of patients admitted to SUs with respect to patients admitted to general medical wards.

Methods

Data included in the present study were derived from our previous study on the incidence and outcome of cerebrovascular diseases in the district of Udine, performed from April 1, 2007, to March 31, 2009.[13,14] Being an observational study, diagnostic procedures and clinical management of patients were not carried out according to a specific protocol but according to the practice of the treating physicians. The local Ethics Committee approved the study.

Study Population

For the purpose of the present single-hospital–based study, we considered only hospitalized patients who were resident in the town of Udine and in the 8 neighboring municipalities of Campoformido, Martignacco, Pagnacco, Pasian di Prato, Pavia di Udine, Pradamano, Pozzuolo del Friuli, and e Tavagnacco. This population counts 153,312 residents (data based on the 2001 census data; 80,349 women and 72,963 men). All those residents are served by a single general hospital, the Santa Maria della Misericordia University Hospital. Almost all stroke and transient ischemic attack (TIA) patients refer to the Santa Maria della Misericordia University Hospital. The University Hospital has an emergency department, an SU, and 3 general medical wards also admitting acute stroke patients.

The ward-admitting decisions regarding acute IS patients were not carried out according to a specific protocol but according to the practice of the emergency department and to the accessibility of ward beds.

Case Ascertainment and Inclusion and Exclusion Criteria

All methodologic data have been extensively reported in the parental population-based study on the incidence and outcome of cerebrovascular diseases in the district of Udine.[13,14] We report here only data referring to patients older than 18 years, who had a first-ever IS, and were admitted to our Santa Maria della Misericordia University Hospital during the study period.

The inclusion criteria for the present study were the following: (1) first-ever stroke according to the World Health Organization definition, admitted to the SU or the general medical wards, (2) ischemic type of stroke, and (3) patients resident in the town of Udine and in the 8 neighboring municipalities. Because this study regards the comparison between SU and general medical wards, TIA and stroke patients residing in the town of Udine and in the 8 neighboring municipalities not admitted to the hospital or admitted in other wards were also excluded.

Definitions

According to the World Health Organization, the definition of stroke was "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin."[15,16] Patients undergoing a thrombolysis were diagnosed as stroke patients even if symptoms completely resolved within 24 hours. Incident stroke was defined as a first-ever stroke, occurring within the study period and with no clinical history of stroke.

Stroke types were classified as IS, intracerebral hemorrhage, and subarachnoid hemorrhage. Stroke type was assigned according to clinical data, confirmed by brain imaging. Stroke cases that did not undergo imaging were classified as undetermined (UND).

High blood pressure was defined as systolic pressure of 140 mm Hg or more, diastolic pressure of 90 mm Hg or more, use of antihypertensive medication, and/or being told at least twice by a physician or other health professional that high blood pressure was the diagnosis. Hypertension was considered as treated if patients were using antihypertensive medication. Subjects with a new diagnosis of hypertension or hypertensive subjects not receiving drug therapy were considered as untreated.

Atrial fibrillation (AF) was diagnosed if a patient had AF documented in electrocardiographic (ECG) recording before stroke onset and/or during hospitalization. Diabetes mellitus was defined as history of diabetes that was confirmed in medical records, use of insulin/oral hypoglycemic agents, and/or random nonfasting blood glucose concentration of 11.1 mmol/L or more. Previous TIA was defined as an acute loss of focal cerebral or ocular function lasting less than 24 hours presumed, after adequate investigation, to be attributable to embolic or thrombotic vascular disease, occurred within 3 months before the IS.

Time-to-admission to the hospital was defined as the time from onset of symptoms to hospital arrival/admission.

Patients' Evaluation and Follow-up

The patients were assessed by a study neurologist within 24 hours if admitted to the SU or within 48 hours if admitted to general medical wards. All the participants signed an informed consent at the time of the interview. If

needed, the principal caregiver of the subject enrolled in the study signed up the informed consent on behalf of the patient.

The data gathering concerned event characteristics, demographic issues, risk factors, and diseases. The National Institutes of Health Stroke Scale (NIHSS) score and the modified Rankin Scale (mRS) score (prestroke and at 1 and 6 months from the ischemic event) were performed and scored by trained neurologists. The patients were asked to report any diagnosis and any use of prescription drugs. The hospital and outpatients records were reviewed by the researchers to obtain a confirmation of the self-reported diagnosis. In patients who were dysphasic or died before being assessed, information was obtained by the relatives, general practitioners, hospital records, and/or death certificates.

All patients were evaluated by study neurologists at 1 and 6 months from the index event, regarding 3 main outcomes: (1) death (Rankin score 6), (2) high-grade disability (Rankin score 3-5), and (3) death (Rankin score 6) or high-grade disability (Rankin score 3-5).

SU Care and General Medical Wards

SU is a multidisciplinary ward, located in the Department of Neurosciences, with 6 dedicated beds and a dedicated team, specialized in stroke management. In SU after stroke onset, continuous monitoring of blood pressure, heart rhythm, blood glucose, oxygen saturation, fluid balance, and neurologic status are provided to the patients. Thanks to an interdisciplinary co-operation among neurologists and neuroradiologists; in SU, it is possible to perform systemic or local thrombolysis. As soon as possible, patients are treated with physiotherapy and speech therapy, provided by a specialized medical and nursing team.

Subtypes of IS

One study neurologist (G.L.G.), not aware about treatment and ward of admission, reviewed the clinical history, neurologic examination, diagnostic investigations, and brain imaging studies of all the 429 recruited patients and assigned infarct subtype classifications by the use of Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.

The subtype definitions were based on risk factors profiles, clinical features, and results of diagnostic tests, including neuroimaging studies (brain computed tomography [CT] or magnetic resonance imaging [MRI]), vascular imaging (carotid duplex, transcranial Doppler), ECG, echocardiography (transesophageal or transthoracic), and assessment of prothrombotic syndromes. According to Adams et al,[12] the "probable" diagnosis is made if the clinical findings, neuroimaging data, and results of diagnostic studies are consistent with 1 subtype and other etiologies have been excluded; otherwise, the "possible" diagnosis is made when the clinical findings and neuroimaging data suggest a specific subtype, but other studies are not done. In this study, ISs were classified using the degree of certainty of "probability" and not of "possibility."

The IS subtypes were classified, according to the original Trial of ORG 10172 in Acute Stroke Treatment[12] criteria, in 5 major categories: large-artery atherosclerosis, including large-artery thrombosis and artery-to-artery embolism; cardioembolism (CE); small-vessel occlusion; and stroke of other determined cause. Patients with definite stroke etiology were distinguished from strokes of UND cause (2 or more causes identified, negative evaluation, and incomplete evaluation [UND]). Stroke etiology was defined as "incomplete evaluation" when essential studies such as brain imaging (CT/MRI), angiographic evaluation (duplex imaging of extracranial arteries, CT angiography, magnetic resonance angiography, digital subtraction angiography for determination of atherosclerosis, or arteriopathy), echocardiography, and ECG were not performed.

Statistical Analyses

Characteristics of the study population were described using mean ± SD or median and range for continuous or ordinal variables and percentages for categorical variables. *T* test or Mann–Whitney test, as appropriate, were used to compare continuous variables. For categorical variables, cross-tabulations were generated, and a chi-square or Fisher exact test was used to compare distributions. The outcome measures were 3: (1) death (defined as Rankin score of 6), (2) dependency condition (defined as Rankin score between 3 and 5), and (3) death or dependency condition (defined as Rankin score > 2).

Description of our population addressed the following characteristics at admission: age, gender, time to admission, modified Rankin score, NIHSS score, AF, previous TIA, hypertension (treated or not), and diabetes mellitus. Standard multivariable logistic models were performed controlling for all the previously mentioned variables.[17] All the baseline characteristics (Table 1) were, therefore, included in the multivariable analysis to adjust for possible confounders, including preadmission disability status and NIHSS score at hospital entry (Supplemental Tables 1-3). Furthermore, because of the observational nature of our study, a propensity score matching was performed to test the effect of exposure to either etiopathologic diagnosis or SU care. Propensity score was calculated based on patients' baseline characteristics (Table 1), and matching was performed within the same propensity score radius. The probability of being unexposed to etiologic diagnosis or exposed to SU care was, therefore, used as a matching criterion when estimating the effect of the 2 exposures. Confidence intervals after matching were estimated using bootstrapping. Because

Table 1. *Distribution of baseline characteristics*

	Stroke unit (n = 297), *n* (%), mean ± SD, or median and range	Medical ward (n = 132), *n* (%), or mean ± SD, or median and range	*P*
Age (y)	74.74 (±12.36)	84.36 (±8.26)	<.0001
Female	147 (49.49%)	80 (60.61%)	.033
Time to admission (h)	2.5 (0-144)	2.6 (0-240)	.836
mRS prestroke	0 (0-5)	1 (0-5)	<.0001
	.67 (±1.18)	1.58 (±1.50)	
NIHSS	5 (0-39)	8 (0-46)	.033
	7.74 (±7.37)	10.10 (±9.14)	
tPA given	12 (4,04%)		
Atrial fibrillation	103 (34.68%)	58 (43.94%)	.068
Previous TIA	24 (8.08%)	14 (10.61%)	.396
Hypertension			.995
Absent	51 (17.41%)	23 (17.69%)	
Treated	202 (68.94%)	89 (68.46%)	
Not treated*	40 (13.65%)	18 (13.85%)	
Diabetes mellitus	57 (19.19%)	41 (31.06%)	.007

Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; TIA, transient ischemic attack.

*Hypertension not treated comprehends both new diagnosis of hypertension and hypertension not receiving treatment.

patients were not randomized, an analysis to determine the magnitude of unmeasured confounding is also presented. Results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). Survival function was described using the Kaplan–Meier approach. Differences in survival rates were analyzed by the log-rank test. All analyses were conducted with STATA/SE 12.1. All 2-tailed statistical significance levels were set at P less than .05.

Results

A total of 429 patients were included in this study (Supplemental Fig 1); 297 of 429 (69.2%) were admitted to the SU, whereas 132 of 429 (30.8%) to the general medical wards. CT scan was performed in 427 included patients (99.5%) and MRI scan in 29 (6.8%). Baseline characteristics of the patients are reported in Table 1. Compared with patients treated in general medical wards, patients who received SU care were younger ($P < .0001$) and had lower mRS prestroke scores ($P < .0001$), NIHSS scores at admission ($P = .033$), and proportion of diabetes mellitus ($P = .007$). There were not statistically significant differences in the prevalence of AF, previous TIA, hypertension, and average time to admission to the hospital between groups.

Table 2 presents data on the TOAST distribution in the 2 groups of patients. Among the 132 first IS patients admitted to general medical wards, 101 (76.5%) were classified as UND, whereas only 105 of 297 patients (35.3%) admitted to the SU had an UND etiology ($P < .0001$).

Patients who were hospitalized in the SU showed a significantly better survival than patients hospitalized in the general medical wards (log-rank test $P < .0001$; Fig. 1). Survival rate for SU patients was 81.76% (95% CI, 76.87%-85.71%) at 6 months, whereas 59.23% (95% CI, 50.28%-67.11%) for general medical ward patients.

The proportion of patients who received SU care with dependency condition (mRS score 3-5) at the end of the follow-up was less than in the general medical wards, 27.6% for SU and 32.6% for controls, respectively ($P = .001$; Table 3).

Causes of Death

A total of 55 of 297 patients (18.51%) admitted to SU died 6 months after stroke, whereas 55 of 132 (41.66%) patients admitted to general medical ward died at the end of the follow-up. The causes of death are shown in Supplemental Table 4.

Compared with general medical ward group, in the SU group, there were significantly less cases of death because of stroke recurrence (6 patients [2.02%] and 15 patients [11.36%], respectively; $P < .0001$).

Outcome Measure of Death

The multivariable analysis (Table 4) showed that patients for whom a definite etiology of stroke could be achieved were less likely to be dead at 6 months than those with strokes of UND origin ($P < .0001$); furthermore, across the subtypes of stroke of UND etiology, we found that the largest part of the risk of mortality seemed

Table 2. *TOAST distribution among first ischemic stroke according to the ward of admission and according to mRS*

	Total, N = 429 (%)	Medical ward, n = 132 (%)	Stroke unit, n = 297 (%)	P*	mRS 0, n = 70 (%)	mRS 1, n = 68 (%)	mRS 2, n = 56 (%)	mRS 3, n = 56 (%)	mRS 4, n = 49 (%)	mRS 5, n = 20 (%)	mRS 6, n = 110 (%)	P†
TOAST determined	223 (51.98)	31 (23.48%)	192 (64.65%)	<.0001	52 (74.28)	44 (64.70)	34 (60.71)	40 (71.42)	23 (46.93)	7 (35.00)	23 (20.90)	<.0001
Large-artery disease	53 (12.35%)	12 (9.09%)	41 (13.80%)		11	8	5	11	7	4	7	
Cardioembolic	89 (20.75%)	12 (9.09%)	77 (25.93%)		21	19	11	10	12	3	13	
Lacunar	73 (17.02%)	6 (4.55%)	67 (22.56%)		19	14	18	16	3	0	3	
Other causes	8 (1.86%)	1 (.76%)	7 (2.36%)		1	3	0	3	1	0	0	
TOAST undetermined	206 (48.02%)	101 (76.52%)	105 (35.35%)		18 (25.72)	24 (35.30)	22 (39.29)	16 (28.58)	26 (53.07)	13 (65.00)	87 (79.09)	
Multiple causes	23 (5.36%)	8 (6.06%)	15 (5.05%)		3	4	5	2	3	1	5	
Negative evaluation	48 (11.19%)	5 (3.79%)	43 (14.48%)		10	14	8	2	5	2	7	
Incomplete evaluation	135 (31.47%)	88 (66.67%)	47 (15.82%)		5	6	9	12	18	10	75	

Abbreviations: mRS, modified Rankin Scale; TIA, transient ischemic attack; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.
*Pearson chi-square: TOAST determined vs undetermined by hospital ward.
†Pearson chi-square: TOAST determined vs undetermined by mRS score.

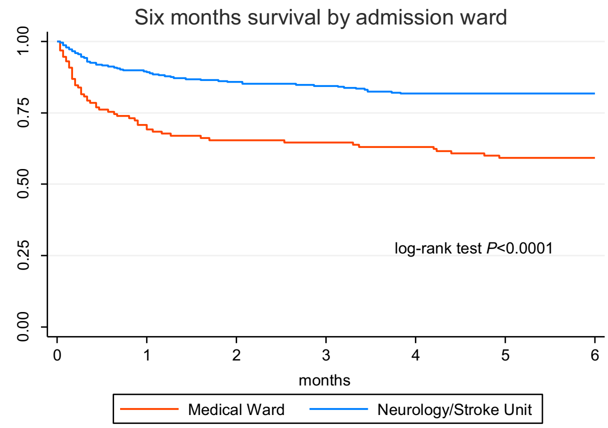

Figure 1. *Survival curves for patients admitted to stroke unit and to medical ward.*

to be attributable to stroke of incomplete evaluation (OR, 5.36; 95% CI, 2.37-12.14, $P < .0001$; Table 4).

After propensity score matching, the lack of an etiologic diagnosis was found to have an effect of 1.31 (95% CI, 1.21-1.44, $P < .0001$; Table 5). UND etiology for incomplete evaluation was associated with a higher risk of 6-month mortality of 1.46 (95% CI, 1.33-1.64, $P < .0001$; Table 6).

Considering the presence of an unmeasured confounder with 1.5 relative risk association with this outcome, and simulating several prevalences in exposed and unexposed to etiologic diagnosis, this 31% increase in risk could range between 12% and 36% (percentage of bias being between 17.4 and −4.0%).

Outcome Measure of Dependency Condition (Rankin Score 3-5)

The multivariable model (Table 4) showed that at 6 months, the dependency condition of patients treated in general medical wards was significantly higher than of patients treated in the SU ($P = .005$).

After propensity score matching, the effect of hospital care was associated with dependency condition with a distinct trend (OR, .83; 95% CI, .71-1.01, $P = .078$; Table 5). Etiologic diagnosis showed no effect on reducing dependency ($P = .969$).

Considering the general underestimation of the importance of autonomy compared with survival and, therefore, assuming the presence of an unmeasured confounder with 1.7 relative risk association with dependency outcome, this 17% decrease in risk could range between 23% and 12% (percentage of bias being between 23.1 and −5.2%).

Outcome Measure of Death or Dependency Condition (Rankin Score 3-6)

SU care was also associated with a reduction in the likelihood of 6-month death or disability ($P = .009$; Table 4).

After propensity score matching, the effect of hospital care on death or dependency condition was found to be

Table 3. *Disability status and mortality among ischemic stroke patients at 6 months follow-up*

	Stroke unit, n = 297 (n, %)	Medical ward, n = 132 (n, %)	P*
Independent (mRS score 0-2)	160 (53.88)	34 (25.76)	.001
0	64 (21.55)	6 (4.55)	
1	56 (18.86)	12 (9.09)	
2	40 (13.47)	16 (12.12)	
High disability (mRS score 3-5)	82 (27.60)	43 (32.58)	
3	38 (12.79)	18 (13.64)	
4	32 (10.77)	17 (12.88)	
5	12 (4.04)	8 (6.06)	
Mortality (mRS score 6)			
6	55 (18.52)	55 (41.66)	

Abbreviation: mRS, modified Rankin Scale.
*Pearson chi-square: independence vs high disability by hospital ward.

to .84 (95% CI, .71-.98, $P = .025$). Remarkably, the effect of missed etiologic diagnosis was 1.24 (95% CI 1.13-1.38, $P < .0001$; Table 5). UND etiology for incomplete evaluation was associated with a higher risk of 6-month death or dependency condition of 1.46 (95% CI, 1.32-1.63, $P < .0001$; Table 6).

Considering the presence of an unmeasured confounder with 1.6 relative risk association with this outcome, this 24% increase in risk could range between 3% and 30% (percentage of bias being between 20.3 and −4.6%).

Discussion

In our study, we highlighted the important role of both SU care treatment and of a definite etiologic diagnosis of stroke according to TOAST criteria for IS patient mortality and functional outcome. In particular, we observed that the determined etiologic classification of stroke according to TOAST criteria was positively associated with the outcome of 6-month case fatality and with a reduced probability of being dead or highly disabled at the end of follow-up. Moreover, SU care also had a significantly positive impact on the composite outcome of mortality. These findings suggest that 6-month case fatality and death or disability outcome may depend on these factors.

Several studies demonstrated high mortality in patients with stroke of UND etiology.[18,19] The data from the Rochester Epidemiology Project indicate that stroke of unknown cause is an independent determinant of poor outcome, but Petty et al[19] classified IS in 4 categories based on the National Institute of Neurological Diseases

Table 4. *Multivariate analysis: association between outcome and type of diagnosis by care setting*

	Etiology, stroke of undetermined vs determined etiology, odds ratio (95% CI)	P	Hospital care, stroke unit vs medical wards, odds ratio (95% CI)	P
6-Month case mortality		<.0001	.98 (.45-2.13)	.961
	3.84 (1.88-7.86)			
	Incomplete evaluation: 5.36 (2.37-12.14)	<.0001		
	Negative evaluation: 1.94 (.60-6.33)	.271		
	Multiple causes: 3.30 (.87-12.49)	.078		
6-Month high disability (Rankin 3-5)		.538	**.31 (.14-.71)**	**.005**
	.81 (.41-1.60)			
	Incomplete evaluation: 1.59 (.62-4.09)	.339		
	Negative evaluation: .51 (.18-1.45)	.209		
	Multiple causes: .44 (.10-1.99)	.289		
Death or disability		.517	**.37 (.17-.78)**	**.009**
	1.22 (.67-2.24)			
	Incomplete evaluation: 2.61 (1.11-6.16)	.028		
	Negative evaluation: .68 (.28-1.69)	.409		
	Multiple causes: .83 (.25-2.83)	.771		

Abbreviation: CI, confidence interval.
Bold values represent statistically significant data.

Table 5. *Multivariate analysis after propensity score matching: association between outcome and type of diagnosis by care setting*

	Etiology, stroke of undetermined vs determined etiology, odds ratio (95% CI)	*P*	Hospital care, stroke unit vs medical wards, odds ratio (95% CI)	*P*
6-Month case mortality	**1.31 (1.21-1.44)**	<.0001	.93 (.80-1.02)	.212
6-Month high disability (Rankin 3-5)	.99 (.88-1.43)	.969	**.83 (.71-1.01)**	.078
Death or disability	**1.24 (1.13-1.38)**	**<.0001**	**.84 (.71-.98)**	**.025**

and Stroke Data Bank criteria and did not classify stroke according to the TOAST criteria. Nam et al[18] showed that the risk of long-term mortality in patients with an incomplete evaluation (4.8% of the patients) was second highest after CE (HR 2.53, 95% CI, 1.63-3.91, and HR 2.84, 95% CI, 2.01-4.02, respectively). In describing these results, 3 main issues are to be considered.[19] The first relates to a methodologic aspect regarding the classification of ISs, which was not fully respectful of Adams et al criteria.[12] In addition, differently from our study, Nam and colleagues did not consider the setting of care (medical ward or SU). Finally, they did not make a direct comparison between ISs of UND and determined etiology.[20]

Based on our results, for the first time, our study provides evidence that treatment in an SU reduces mortality of IS patients, thanks to a valid etiologic classification of ISs according to the TOAST criteria. In the SU, 35.35% of patients remained without a definite diagnosis, compared with 76.52% of ISs admitted in medical wards ($P < .0001$; Table 2). For both types of admission, the main cause of stroke of UND etiology was incomplete evaluation (66.67% for general medical wards and 15.82% for SU). Our opinion is that these benefits can be explained through more effective treatment of underlying causes of stroke, in addition to the prevention and treatment of complications, in particular infections, the better nursing care, the early mobilization, and more effective rehabilitation procedures,[6] and may not depend only on the lack of single diagnostic evaluations.

Differently from us, Paradowski and Maciejak[21] found no significant differences in TOAST classification among 279 IS patients treated in neurologic or internal medicine wards. Their rates of UND stroke were lower than ours, both for patients admitted in the neurologic and medical ward (15.1% versus 17.2%). However, in this study, ISs were classified into 5 subtypes only on the basis of CT scan and clinical symptoms. Cardiodiagnostic and ultrasound examinations were not performed and used for classification.

Through a dichotomization of the subtypes of IS into determined and UND, multivariate analysis showed that patients, who did not receive a diagnosis of stroke of determined etiology, were characterized by a worse 6-month case fatality ($P < .0001$; Table 4). The effect of a lacking diagnosis on 6-month case mortality outcome was also confirmed after propensity score matching analysis ($P < .0001$; Tables 5 and 6). Additionally, we used multivariable analysis to investigate which category of stroke of UND etiology (multiple causes, negative evaluation and incomplete evaluation) had the highest risk of 6-month mortality. A striking result of our study is that, when the diagnosis of an UND stroke was because of an incomplete evaluation, it was significantly associated with a high risk of 6-month mortality. The patients with an UND stroke for incomplete evaluation were nearly 6 times more likely to be dead at 6 months after the stroke than the patients with a stroke of any determined etiology (large-artery atherosclerosis, CE, SAO, or stroke of other determined cause; $P < .0001$; Table 4). The different OR underlines the importance of the role of a dedicated team. In fact, in an SU, the specialized and multidisciplinary diagnostic approach and the comprehensive and fast diagnostic workup allow to perform a valid and complete etiologic subtype

Table 6. *Multivariate analysis after propensity score matching: association between outcome and incomplete evaluation*

	Incomplete evaluation vs complete evaluation*; Odds ratio (95% CI)	*P*	Incomplete evaluation vs multiple causes or negative evaluation†; Odds ratio (95% CI)	*P*
6-Month case mortality	**1.46 (1.33-1.64)**	**<.0001**	**1.36 (1.13-1.61)**	**.001**
6-Month high disability (Rankin 3-5)	1.08 (.44-1.30)	.398	1.02 (.85-1.26)	.827
Death or disability	**1.46 (1.32-1.63)**	**<.0001**	**1.28 (1.10-1.53)**	**.005**

*Complete evaluation includes determined etiology, multiple causes, and negative evaluation (propensity score analysis performed on all patients: n = 429 classified as complete evaluation: n = 294; incomplete evaluation: n = 135).

†OR calculated only within the undetermined TOAST etiology group (propensity score analysis performed only within undetermined etiology: n = 206 classified as incomplete evaluation: n = 135; multiple causes or negative evaluation: n = 71).

classification of ISs according to TOAST criteria and, as a consequence, a better therapeutic management.[22] These characteristics cannot be matched in general medical wards because of the lack of specialization and of a more limited access to diagnostic investigations (carotid ultrasound, CT or MRI, and echocardiography). As a result, we found more cases of death because of stroke recurrence among patients treated in general medical ward ($P < .0001$). A possible explanation for the increased risk of stroke recurrence could be that an incomplete evaluation may deprive patients of useful specific exams and prevents the instauration of correct therapies. A complete and fast diagnostic workup is effective for the prevention of secondary strokes. In addition, it reduces the duration of hospitalization[23] and the possible complications because of the permanence of an elderly and often disabled patient in the hospital setting.

In addition, we suggest that admission to an organized stroke care is recommended for all patients with acute stroke. In our study, at the end of the follow-up period, 53.88% of patients admitted in the SU were independent (mRS score 0 to 2), compared with 25.76% of the patients admitted to general medical wards ($P = .001$; Table 3). After a multivariable analysis, we proved that long-term disability in patients with an acute stroke could be significantly benefited from an SU treatment ($P = .005$), and this association is independent from age and other characteristics, such as stroke severity and prestroke disability (Table 4; Supplemental Table 1).

The beneficial role of SU as a dedicated setting of care was also associated with the composite outcome of mortality and severe disability ($P = .009$). Multivariable analysis after propensity score not only confirmed that SU care was associated with a reduced probability of being dead or highly disabled ($P = .025$) at the end of follow-up but also showed that patients treated in an SU, compared with general medical wards, were less associated with dependency condition, although only with a distinct trend ($P = .078$; Tables 5 and 6). In our opinion, the lack of finding a significant association could be attributed to the difficulty of finding appropriate control matches and, thus, to the decreased size of the final sample. This is in line with several international studies, which also used combined outcome.[1,2,6] These benefits can be explained through the prevention and treatment of complications, in particular infections, the better nursing care, the early mobilization, and more effective rehabilitation procedures.[6,9]

In developed countries, stroke is the most common cause of acquired adult disability. Consequently, quality of health services and allocation of resources have become a topical subject.[24-26] The increasing age of the populations[26-28] and the limits of available resources are exacerbating this problem. Our finding of higher rate of dependency in the general medical ward category leads to the conclusion that dedicated acute stroke services should be used for all patients with acute stroke and not only in a limited group of patients, regardless of the etiology[29] and of age.[30] Unfortunately, in Italy, the spread of dedicated acute stroke services is still insufficient. In 2003, only 11% of stroke patients could be hospitalized in an SU, with a great heterogeneity between the different regions.[31] On one hand, semi-intensive units with early rehabilitation are both expensive and requiring extra resources, but on the other hand, it is recognized that this model is both superior to stroke care[5] and is cost-effective compared with the conventional care.[32] Our data on different disability outcomes confirms cost-effectiveness of SUs.

We are aware that our study has several limitations.

First of all, this study is not a randomized controlled trial. However, being the benefit of SUs already well established, no ethics committee would have approved a random assignment of patients to the 2 different types of wards. Moreover, in several circumstances in which it is not possible to carry out randomized trials, observational studies are considered a useful tool to understand the effects of a treatment or of different clinical services. In addition, if rigorously designed, this kind of analysis could estimate better than randomized trials the effects of interventions, particularly in everyday clinical practice.[33] Despite our efforts, we cannot exclude that our results could have been influenced by an incomplete adjustment for patients characteristics in selecting the model for the multivariable analysis.

Having considered these limitations, we believe, nevertheless, that the solidity of our results is supported by several factors. First, the importance of our rigorously designed single-hospital observational comparison study is that it provides "real-world" evidence of the effects of SU multidisciplinary diagnostic and treatment approach in everyday clinical practice. The exclusion of the neurologists involved in the study from the decision process regarding the choice of the type of ward of admission and the diagnostic and therapeutic management of patients permitted to control possible selection bias and any influence on the quality of stroke care because of the awareness of comparison in the team of treating neurologists.

Conclusions

Our study provides "real-world" evidence regarding the effectiveness of an accurate etiologic subtype classification of ISs, according to TOAST criteria and of comprehensive, specialized, and multidisciplinary therapeutic management in reducing poor outcomes for stroke patients.

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Supplementary Data

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