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ORIGINAL ARTICLE

Adherence to recommendations and clinical outcomes of patients hospitalized for stroke: the role of the admission ward—a real-life investigation from Italy

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Abstract

Objective To determine whether out-of-hospital healthcare and adverse outcomes are better in stroke patients admitted to a neurology ward compared with those admitted to general wards.

Methods Beneficiaries of the National Health Service from the Italian Lombardy Region who were discharged alive after hospital admission during the year 2009 for ischemic stroke (9776 patients) or intracerebral or subarachnoid hemorrhage (1102 patients) entered into the cohort and were followed until 2012. Exposure of interest was the ward type where inpatients were admitted (neuro vs. general wards). Outcomes were out-of-hospital healthcare (i.e., drug prescriptions, diagnostic procedures, and laboratory clinical evaluations) and adverse clinical outcomes (i.e., all-cause death and hospital readmission). Exposure-outcome associations were investigated. High-dimensional propensity score methodology was used for taking into account confounders. Mediation analysis was used to verify whether the association between ward type and clinical outcomes is mediated by out-of-hospital adherence to healthcare.

Results Better adherence to out-of-hospital healthcare received from patients discharged from neuro, rather than general, wards was observed being the proportions of adherent patients 42.4% and 39.5%, respectively. Compared with general wards, discharge from neuro was associated with reduced 3-year emergency admissions (from 50.1 to 47.5% among ischemic stroke patients) and reduced 3-year mortality (from 37.5 to 27.0% among hemorrhagic stroke patients). From 10 to 15% of outcome risk, reductions were mediated by better adherence to out-of-hospital healthcare.

Conclusions For patients with acute ischemic and hemorrhagic stroke, admission to neuro vs. general wards is associated with better out-of-hospital healthcare and long-term adverse outcomes.

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Keywords Healthcare utilization database · Intracerebral or subarachnoid hemorrhage · Ischemic stroke · Mortality · Neurology wards · Population-based cohort study

Introduction

Ischemic stroke (IS) and intracerebral or subarachnoid hemorrhage (ISH) are leading causes of non-communicable diseases, together affecting an estimated 25 million people and contributing to 6.5 million deaths globally each year [1]. In the first decade of the twenty-first century, a 30-day mortality following stroke ranged between 13 and 23% after IS and between 25 and 48% after ISH [2]. A 5-year mortality ranged between 40 and 61%, depending on stroke type [3, 4]. Improvements in stroke care have reduced post-stroke mortality [3–5], but still currently, stroke remains a leading cause of death [6].

It may be argued that stroke patients managed in neurology wards receive high-quality care because the focus is specifically addressed to patients who need special care which is provided by caregivers whose training emphasizes the unique aspects of the disease processes seen in those patients [7, 8]. We then performed a large population-based real-life study, investigating the cohort of patients admitted in hospital for IS or ISH. The hypothesis addressed by this study was that, after accounting for differences in clinical profiles and other features, admission in a neurological ward (neuro) would be associated with better healthcare (drug prescriptions, diagnostic procedures, and laboratory clinical evaluations) and reduced short-term and long-term adverse outcomes (i.e., mortality and hospital readmission) than admission to general ward.

Methods

Setting

The data used for this study were retrieved from the healthcare utilization databases of Lombardy, a region in Italy that accounts for about 16% (almost ten million) of its population. The Italian population is covered by the National Health Service (NHS), and in Lombardy, an automated system of databases has been created to collect a variety of information, including (1) an archive of residents who receive NHS assistance (the whole resident population), reporting demographic and administrative data; (2) a database on hospital discharge records including information on primary diagnosis and up to five co-existing conditions and procedures coded according to the International Classification of Diseases, Clinical Modification 9th revision (ICD-9 CM); (3) a drug prescription database providing information on outpatient drug prescriptions reimbursed by the NHS and coded according to the Anatomical Therapeutic Chemical (ATC) classification system; and (4) a database on diagnostic imaging and laboratory analyses performed by services accredited from the NHS. For each patient, we linked the above databases via a single identification code. In order to preserve privacy, each identification code was automatically converted into an anonymous code. The inverse process was prevented by deletion of the conversion table. Details of healthcare utilization databases of the Lombardy Region and of their use in the field of neurology have been reported elsewhere [9].

The ICD-9 CM and ATC codes used in the present study are reported in Supplementary Table S1.

Cohort selection and follow-up

The target population included Lombardy residents, aged 18 to 99 years, who were beneficiaries of the NHS. Of these, those who were hospitalized with a primary diagnosis of IS and ISH in the year 2009 were identified, and the first hospital admission via the emergency department in that year was defined as the index hospitalization. In order of allowing patients' characterization through their previous contacts with the NHS, cohort members who were beneficiaries of the NHS from less than 2 years before the index hospitalization were excluded. In addition, as we were interested to measure healthcare delivered and outcome occurred among stroke survivors living in the community, patients who died during the index hospitalization were also excluded. Finally, with the aim of reducing between individuals and between managements heterogeneity, patients who were admitted to a department of neurosurgery were excluded. The remaining patients were included into the final cohort whose members accumulated person-years of follow-up starting from the cohort entry (i.e., index hospital discharge) until the earliest date among outcome onset (see below), or death, emigration, or 3 years after the index hospitalization.

Baseline, healthcare, and outcome data

Baseline data included age at index hospitalization, gender, the ward of discharge (neuro vs. general), co-medications (blood-pressure-lowering agents, lipid-lowering agents, antiplatelet, oral anticoagulant, antiarrhythmics, and antidiabetic agents), and comorbidities (stroke, ischemic heart disease, heart failure, hypertension, arrhythmia, cancer, diabetes, chronic obstructive pulmonary disease) recorded in the 2-year period before index hospitalization. Clinical status was further assessed through the so-called Multisource

Comorbidity Score, a new comorbidity index obtained from both inpatients diagnostic information and outpatients drug prescriptions, recently validated in the Italian setting [10].

Selected diagnostic procedures received from each cohort member during the index hospital stay (i.e., computerized axial tomography—CAT—of head, magnetic resonance imaging—MRI—of brain, electrocardiogram, arteriography of cerebral arteries, diagnostic ultrasound of head and neck, diagnostic ultrasound of heart) were recorded.

During the 6-month period after cohort entry, we recorded the following information: (i) prescription of selected drugs (blood-pressure-lowering agents, lipid-lowering drugs, antiplatelet, oral anticoagulant, antiarrhythmics, and antidiabetic medicaments), (ii) exposure to diagnostic procedures (i.e., carotid Doppler ultrasonography, neuroimaging—CAT, MRI—or cerebral angiography), and (iii) laboratory clinical evaluation (i.e., lipid profile). An overall adherence score was developed by counting the number of different healthcare services (drug prescription, diagnostic procedure, and laboratory clinical evaluation) used at least once from the cohort members. The score had values of zero, 1, and 2 according to whether none, only one, or at least two health services were used within a 6-month period after discharge, respectively.

Three outcomes were considered: all-cause mortality, hospital readmission with main diagnosis of stroke, and hospital admission for any cause provided that it occurred via emergency department.

Data analysis

As cohort members admitted in neuro and those admitted in general wards might be different for clinical profile and other relevant characteristics, and because of the limited information available from healthcare database as ours, we decided of adopting a 1:1 high-dimensional propensity score (HDPS) matching design to account for both measured and residual confounders [11]. Exposure propensity scores were derived through the HDPS algorithm, an automated technique that identifies and prioritizes covariates that may serve as proxies for unmeasured confounders in large electronic healthcare databases [11]. Shortly, the predicted probability of being admitted to neuro (i.e., the propensity score of interest) was estimated for each cohort member through a logistic regression model which includes as covariates the abovementioned baseline data, plus all the possible causes of hospital discharge experienced by, and all the drug prescribed to, cohort members in the 2-year period prior to the index hospital admission. The 200 most predictive covariates were selected. Groups were 1:1 matched on their propensity score using a nearest neighbor matching algorithm without replacement [12].

T test, chi-square test, and its version for the trend were used when appropriate to test differences in demographic, clinical, and healthcare between cohort members discharged from neuro and from general wards.

The Kaplan-Meier estimators of cohort members' cumulative proportions experiencing a given outcome after 30 days, 1 year, and 3 years after index discharge were calculated according to whether cohort members were discharged from neuro or general wards, and time-to-event comparisons were made by using the log-rank test. The probability of experiencing a specific outcome from the index discharge until any particular time was subsequently estimated through the cause-specific cumulative incidence function [13], a method which takes into account for competing nature of the considered outcomes (e.g., the occurrence of hospital readmission for stroke likely affects the subsequent probability of death). With this approach, a subject was assumed of experiencing the outcome only once, and the overall incidence at a given time was decomposed into a sum of the individual cumulative incidence functions for each type of outcome.

Mediation analysis was performed according to VanderWeele and Vansteelandt [14] with out-of-hospital adherence to healthcare as a potential mediator of the observed exposure-outcome association. In other words, we sought to address whether differences in the outcome risk experienced by patients cared in neuro and general wards may be partially (or entirely) mediated by differences in healthcare adherence received within 6 months after the index discharge.

Finally, to evaluate if the benefit associated with neurology ward is affected by stroke unit, since many neurology wards included stroke units within them, all the statistically significant analyses were repeated excluding patients discharged from a neurology ward with stroke unit.

All analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC). For all hypotheses tested, two-tailed p values less than 0.05 were considered significant.

Data availability The data that support the findings of this study are available from Lombardy Region but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Lombardy Region.

Results

Patients

Thirteen thousand and seventy beneficiaries of NHS from Lombardy aged 18 to 99 years were admitted in hospital with diagnosis of stroke during the year 2009. Among these, 356 patients were excluded because they were admitted at a neurosurgery department and other 78 because they were beneficiaries of the NHS from less than 2 years. Among the remaining 12,636 patients, 10,633 and 2003 had diagnosis of IS and ISH, respectively. Among the IS patients, 5769 ones were admitted in neuro and 413 of them (7.2%) died during the hospital stay. The corresponding figures for general wards were 4864 patients of whom 444 (9.1%) died. Among the ISH patients, 887 ones were admitted in neuro and 323 of them (36.4%) died during the hospital stay. The corresponding figures for general wards were 1116 patients of whom 578 (51.8%) died. Finally, the 10,878 patients who survived the index hospital admission were included into the final cohort.

Table 1 shows their baseline characteristics according to the ward of discharge before and after HDPS-matching. Compared with IS patients discharged from general wards, those from neuro were in average younger and more likely men, and exhibited better clinical profile (i.e., suffered from less comorbidities and took fewer medicines). Conversely, there were fewer differences for ISH patients, being those discharged from neuro in average older and more likely treated with antihypertensive, lipid-lowering agents, and antiplatelet with respect to those on general wards. There was no evidence that demographic, clinical, and therapeutic baseline features differed between HDPS-matched cohort members according to the ward of discharge, neither for IS nor for ISH.

Healthcare exposure

Table 2 shows that, during the index hospital stay, both IS and ISH patients discharged from neuro more frequently had an MRI of brain or an ultrasound examination of head and neck and less frequently had a brain CAT scan than those admitted in other wards did. ISH patients from neuro less frequently were evaluated with arteriography of cerebral arteries. Of interest, the average lengths of hospital stay (SD) in neuro and general wards were, respectively, 10.0 days (6.3) and 10.7 days (7.3) for IS patients ($p < 0.001$) and 14.3 days (8.9) and 19.6 days (19.1) for ISH patients ($p < 0.001$).

As far as out-of-hospital healthcare is concerned (Table 3), there was no clear evidence that the use individual health services during the 6-month period after the index discharge differed depending on the ward type, if not because patients from neuro were more frequently treated with oral anticoagulant, had more controls of lipid profile (IS patients) and with MRI, CAT, and cerebral angiography (ISH patients), than those admitted in other wards. It is, however, noteworthy that there was a statistical evidence of better overall adherence score among patients who were discharged from neuro.

Outcomes

The proportions of patients who experienced the considered outcomes are reported in Table 4. There was evidence that, compared with IS patients discharged from general wards, those on neuro had 20%, 11%, and 8% reduced risk of the 30-day, 1-year, and 3-year all-cause emergency admissions. As far as ISH patients are concerned, those discharged from neuro had 29%, 29%, and 32% reduced risk of 1-year all-cause emergency admission and 1-year and 3-year mortality, respectively.

Figure 1 shows that the cumulative 1-year and 3-year incidences of adverse outcome (mortality, all-cause emergency admissions, or stroke readmissions) of IS patients were 28.7% and 48.5% for admissions in neuro vs. 30.2% and 50.8% for admission in a general ward. The corresponding figures for ISH patients were 32.6% and 53.8% vs. 42.8% and 57.5%.

Mediation analysis showed that 10% and 15% of the reduced risk of long-term composite outcome among IS and ISH patients were, respectively, mediated by better adherence to out-of-hospital healthcare.

Neurology ward without stroke unit

Adherence score and outcomes were compared again after the exclusion of patients discharged from a neurology ward with stroke unit. Supplementary Tables S2 and S3 show that (i) both the adherence to recommendations and the clinical outcomes were better among IS patients who were discharged from neuro and, (ii) albeit not significant, the same results were observed among ISH patients.

Discussion

Consistently with registry-based European multicountry studies [15, 16], as well as with population-based Italian investigations [17–20], results of the present study confirm the well-known poor prognosis of stroke patients, being 30-day, 1-year, and 3-year mortality rates 3%, 15%, and 27%. In addition, not only mortality but also other clinically relevant outcomes such as all-cause emergency admissions and stroke readmissions make worrying the prognosis of stroke patients, being the cumulative risk of occurring any one of these outcomes higher than 50% after 3 years after discharge. As a novel and original message, our findings clearly showed that, after accounting for differences in demographic, therapeutic, and clinical profile of the included patients, admission in a neurology ward was associated with reduced short-term and long-term adverse outcomes, than in general ward, being the outcome reduction more pronounced for ISH patients (10.2% and 3.9% at 1 year and 3 years, respectively) than for IS one (1.5% and 2.3%). The importance of treatment in a stroke unit is well known. Indeed, the mortality reduction for stroke patients admitted in stroke units was highlighted both from an Italian observational study [21] and from a meta-analysis of clinical trials [22]. Moreover, both the stroke unit and neurology ward were associated with a lower

Table 1 Baseline characteristics of original and HDPS-matched cohort members admitted for ischemic stroke and intracerebral or subarachnoid hemorrhage according to whether they were discharged from neurology or general wards. Lombardy, 2009–2012

	Original cohort			HDPS-matched cohort		
Ischemic stroke						
	Neurology ($n = 5356$)	General ($n = 4420$)	p value[c]	Neurology ($n = 3688$)	General ($n = 3688$)	p value[c]
Men	2866 (53.5%)	1936 (43.8%)	< 0.001	1736 (47.1%)	1719 (46.6%)	0.692
Age: mean (SD)	71.4 (13.3)	76.8 (11.4)	< 0.001	75.4 (11.2)	75.5 (11.5)	0.937
Comorbidities[a]						
Previous stroke	298 (5.6%)	298 (6.7%)	0.015	225 (6.1%)	222 (6.0%)	0.884
Ischemic heart disease	181 (3.4%)	194 (4.4%)	0.010	140 (3.8%)	133 (3.6%)	0.666
Heart failure	217 (4.1%)	401 (9.1%)	< 0.001	194 (5.3%)	192 (5.2%)	0.917
Hypertension	2145 (40.1%)	1860 (42.1%)	0.042	1522 (41.3%)	1522 (41.3%)	1.000
Arrhythmia	892 (16.7%)	949 (21.5%)	< 0.001	730 (19.8%)	722 (19.6%)	0.815
Cancer	258 (4.8%)	262 (5.9%)	0.015	179 (4.9%)	188 (5.1%)	0.630
Diabetes	767 (14.3%)	755 (17.1%)	< 0.001	592 (16.1%)	584 (15.8%)	0.799
COPD	189 (3.5%)	261 (5.9%)	< 0.001	161 (4.4%)	158 (4.3%)	0.864
Medications[b]						
Blood-pressure-lowering agents	3821 (71.3%)	3521 (79.7%)	< 0.001	2848 (77.2%)	2851 (77.3%)	0.934
Lipid-lowering agents	1591 (29.7%)	1336 (30.2%)	0.575	1118 (30.3%)	1110 (30.1%)	0.839
Antiplatelet	2799 (52.3%)	2546 (57.6%)	< 0.001	2077 (56.3%)	2039 (55.3%)	0.373
Oral anticoagulants	506 (9.5%)	500 (11.3%)	0.003	382 (10.4%)	387 (10.5%)	0.849
Antiarrhythmics	377 (7.0%)	315 (7.1%)	0.866	261 (7.1%)	259 (7.0%)	0.928
Antidiabetic agents	986 (18.4%)	932 (21.1%)	0.001	750 (20.3%)	737 (20.0%)	0.706
Multisource comorbidity score						
0	3547 (66.2%)	2384 (53.9%)	< 0.001	2239 (60.7%)	2219 (60.2%)	0.991
1	1006 (18.8%)	1128 (25.5%)		816 (22.1%)	882 (23.9%)	
2	489 (9.1%)	478 (10.8%)		387 (10.5%)	323 (8.8%)	
3	170 (3.2%)	222 (5.0%)		136 (3.7%)	145 (3.9%)	
4	144 (2.7%)	208 (4.7%)		110 (3.0%)	119 (3.2%)	
Intracerebral or subarachnoid hemorrhage						
	Neurology ($n = 564$)	General ($n = 538$)	p value[c]	Neurology ($n = 341$)	General ($n = 341$)	p value[c]
Men	289 (51.2%)	248 (46.1%)	0.088	174 (51.0%)	178 (52.2%)	0.759
Age: mean (SD)	72.4 (13.3)	71.3 (15.3)	0.182	71.4 (14.4)	71.6 (14.8)	0.852
Comorbidities[a]						
Previous ischemic stroke	49 (8.7%)	46 (8.6%)	0.935	25 (7.3%)	22 (6.5%)	0.650
Ischemic heart disease	12 (2.1%)	13 (2.4%)	0.748	4 (1.2%)	4 (1.2%)	1.000
Heart failure	25 (4.4%)	23 (4.3%)	0.898	11 (3.2%)	8 (2.4%)	0.485
Hypertension	245 (43.4%)	193 (35.9%)	0.010	129 (37.8%)	134 (39.3%)	0.694
Arrhythmia	70 (12.4%)	66 (12.3%)	0.942	38 (11.1%)	39 (11.4%)	0.904
Cancer	35 (6.2%)	42 (7.8%)	0.297	13 (3.8%)	15 (4.4%)	0.700
Diabetes	64 (11.4%)	51 (9.5%)	0.311	28 (8.2%)	31 (9.1%)	0.683
COPD	19 (3.4%)	18 (3.4%)	0.983	11 (3.2%)	10 (2.9%)	0.825
Medications[b]						
Blood-pressure-lowering agents	393 (69.7%)	351 (65.2%)	0.116	214 (62.8%)	220 (64.5%)	0.633
Lipid-lowering agents	125 (22.2%)	96 (17.8%)	0.074	60 (17.6%)	60 (17.6%)	1.000
Antiplatelet	210 (37.2%)	191 (35.5%)	0.550	122 (35.8%)	118 (34.6%)	0.748
Oral anticoagulant	65 (11.5%)	56 (10.4%)	0.554	30 (8.8%)	36 (10.6%)	0.437
Antiarrhythmics	42 (7.5%)	32 (6.0%)	0.320	17 (5.0%)	23 (6.7%)	0.328
Antidiabetic agents	91 (16.1%)	80 (14.9%)	0.562	44 (12.9%)	48 (14.1%)	0.654
Multisource comorbidity score						
0	358 (63.5%)	352 (65.4%)	0.705	248 (72.7%)	237 (69.5%)	0.930

Table 1 (continued)

	Original cohort		HDPS-matched cohort	
1	109 (19.3%)	90 (16.7%)	54 (15.9%)	64 (18.8%)
2	53 (9.4%)	59 (11.0%)	23 (6.7%)	28 (8.2%)
3	21 (3.7%)	16 (3.0%)	7 (2.1%)	9 (2.6%)
4	23 (4.1%)	21 (3.9%)	9 (2.6%)	3 (0.9%)

HDPS high-dimensional propensity score, *SD* standard deviation, *COPD* chronic obstructive pulmonary disease

[a] According to hospital admission in the 3 years before the current one

[b] According to drugs dispensed in the 3 years before the current one

[c] Differences between the two groups were tested using *T* test (age), chi-square statistics, or its version for the trend (multisource comorbidity score)

intrahospital mortality rate [23]. We add to the available knowledge that not only stroke units but also neurology wards, although to a lesser extent, are in average effective in preventing clinical outcomes until 3 years after index discharge. It is noteworthy that 35 out of 42 neurology wards included stroke unit within them at the time of the study.

Our paper tried to understand the reasons for the higher effectiveness of treating stroke in a neuro ward. As it is well known that medicines and diagnostic and screening investigations play an important role in secondary prevention of stroke [24–27], and because we observed that patients who were discharged from neuro also had better adherence to recommended secondary preventive healthcare, we can speculate that long-term benefits of neuro admission might be due to better transferring of information between hospitals and primary care [28–30]. These conclusions, however, must be considered speculative. In fact, likely because available information did not entirely capture outpatient healthcare, only 10 to 15% of the outcome risk reductions associated with inpatient care in neurology wards seem to be mediated by better adherence to outpatient healthcare. However, whatever the reason for the benefits on clinical outcomes associated with admission to neurology is, our findings suggest that endorsing policy addressed to specialized wards should be recommended. From this point of view, it may be interesting to observe that almost the entire group of stroke unit in Italy (185 over 191) have been realized and managed by neurologists and in neurological wards.

At least two other results of our study deserve to be mentioned. One, the length of stay was shorter in neuro wards, a finding for which there are several possible explanations. One possibility is that patients with more severe neurologic damage are more likely admitted in general divisions, than in neuro ones. Alternatively, hospital stay may have been withdrawn earlier from neuro wards in order to entrust community services to continue and maintain cares. The observation that, after accounting for between-group differences in baseline characteristics, patients discharged from neuro exhibited better adherence with out-of-hospital healthcare plays at the favor of such a hypothesis. Because our database did not include detailed enough data for ascertaining the reason, the question still remains open. However, irrespectively from its reasons, because the length of stay is known to be as the most predictor of inpatient costs [31], our findings suggest that not only the patients but also the health care system could benefit from the admission of stroke patients in neuro wards.

Two, almost one in ten IS patients and almost one in five ISH patients discharged from a neuro ward, and even more than one in four discharged from an unskilled general ward, did not receive not even one of the drug prescriptions,

Table 2 Diagnostic procedures received during the index hospital stay by HDPS-matched cohort members admitted for ischemic stroke and intracerebral or subarachnoid hemorrhage according whether they were discharged from neurology or general wards. Lombardy, 2009–2012

	Ischemic stroke			Intracerebral or subarachnoid hemorrhage		
	Neurology ($n = 3688$)	General ($n = 3688$)	p value[a]	Neurology ($n = 341$)	General ($n = 341$)	p value[a]
CAT of head	2502 (67.8%)	2885 (78.2%)	< 0.001	241 (70.7%)	232 (68.0%)	0.455
MRI of brain	856 (23.2%)	521 (14.1%)	< 0.001	58 (17.0%)	39 (11.4%)	0.037
Electrocardiogram	708 (19.2%)	774 (21.0%)	0.055	58 (17.0%)	57 (16.7%)	0.919
Arteriography of cerebral arteries	45 (1.2%)	46 (1.3%)	0.916	9 (2.6%)	27 (7.9%)	0.002
Ultrasound of head and neck	1686 (45.7%)	1093 (29.6%)	< 0.001	26 (7.6%)	17 (5.0%)	0.156
Ultrasound of heart	958 (26.0%)	1027 (27.9%)	0.070	26 (7.6%)	36 (10.6%)	0.183

HDPS high-dimensional propensity score, *MRI* magnetic resonance imaging, *CAT* computerized axial tomography

[a] Differences between the two groups were tested using chi-square statistics

Table 3 Out-of-hospital healthcare received after the index discharge by HDPS-matched cohort members admitted for ischemic stroke and intracerebral or subarachnoid hemorrhage according whether they were discharged from neurology or other wards. Lombardy, 2009–2012

	Ischemic stroke			Intracerebral or subarachnoid hemorrhage		
	Neurology ($n = 3688$)	General ($n = 3688$)	p value[a]	Neurology ($n = 341$)	General ($n = 341$)	p value[a]
Medications						
Antiplatelet	2503 (67.9%)	2521 (68.4%)	0.653	59 (17.3%)	52 (15.3%)	0.468
Lipid-lowering agents	1387 (37.6%)	1401 (38.0%)	0.737	55 (16.1%)	55 (16.1%)	1.000
Oral anticoagulants	560 (15.2%)	453 (12.3%)	< 0.001	7 (2.1%)	13 (3.8%)	0.173
Antihypertensive	2706 (73.4%)	2713 (73.6%)	0.854	215 (63.1%)	200 (58.7%)	0.239
Antidiabetic agents	682 (18.5%)	677 (18.4%)	0.881	38 (11.1%)	34 (10.0%)	0.618
Antiarrhythmics	255 (6.9%)	236 (6.4%)	0.375	13 (3.8%)	18 (5.3%)	0.358
Diagnostic imaging						
Carotid Doppler ultrasound	579 (15.7%)	545 (14.8%)	0.271	25 (7.3%)	26 (7.6%)	0.884
MRI, CAT of head, cerebral angiography	315 (8.5%)	336 (9.1%)	0.389	117 (34.3%)	78 (22.9%)	0.001
Laboratory tests						
Lipid profile	1193 (32.4%)	1111 (30.1%)	0.039	79 (23.2%)	75 (22.0%)	0.330
Adherence score						
0	322 (8.7%)	347 (9.4%)	0.031	64 (18.8%)	92 (27.0%)	0.006
1	1790 (48.5%)	1857 (50.4%)		143 (41.9%)	141 (41.3%)	
2	1576 (42.7%)	1484 (40.2%)		134 (39.3%)	108 (31.7%)	

HDPS high-dimensional propensity score, *MRI* magnetic resonance imaging, *CAT* computerized axial tomography

[a] Differences between the two groups were tested using chi-square statistics or its version for the trend (adherence score)

diagnostic procedures, and screening investigations recommended for stroke secondary prevention [24–27]. The lack of universal access to common drugs and basic medical equipment, as well as the lack of post-stroke follow-up programs of secondary stroke prevention [32], even in a country with universal access to essential health care services such as Italy, is another element of concern that health authorities should address.

The present study has several elements of strength. First, the investigation was based on a very large unselected population, which was made possible because in Italy, a cost-free healthcare system involves virtually all citizens. Second, health database

Table 4 Short-term (30 days) until long-term (3 years) outcomes experienced by HDPS-matched cohort members admitted for ischemic stroke and intracerebral or subarachnoid hemorrhage according whether they were discharged from neurology or general wards. Lombardy, 2009–2012

	Ischemic stroke			Intracerebral or subarachnoid hemorrhage		
Outcomes	Neurology ($n = 3688$)	General ($n = 3688$)	p value[a]	Neurology ($n = 341$)	General ($n = 341$)	p value[a]
All-cause deaths						
30 days	119 (3.2%)	121 (3.3%)	0.898	21 (6.2%)	23 (6.7%)	0.757
1 year	544 (14.8%)	528 (14.3%)	0.589	56 (16.4%)	77 (22.6%)	0.050
3 years	1008 (27.4%)	1012 (27.5%)	0.944	92 (27.0%)	127 (37.5%)	0.005
Readmissions for stroke						
30 days	35 (1.0%)	48 (1.3%)	0.151	3 (0.9%)	4 (1.2%)	0.704
1 year	199 (5.8%)	212 (6.2%)	0.534	15 (4.9%)	24 (8.1%)	0.118
3 years	351 (11.0%)	370 (11.5%)	0.476	41 (14.5%)	32 (11.3%)	0.476
All-cause emergency admissions						
30 days	171 (4.7%)	213 (5.8%)	0.030	21 (6.4%)	19 (5.7%)	0.764
1 year	913 (26.2%)	1015 (28.8%)	0.013	70 (22.3%)	93 (30.3%)	0.032
3 years	1611 (47.5%)	1731 (50.1%)	0.013	126 (41.7%)	137 (46.1%)	0.171

HDPS high-dimensional propensity score

[a] Differences between the two groups were tested using log-rank test

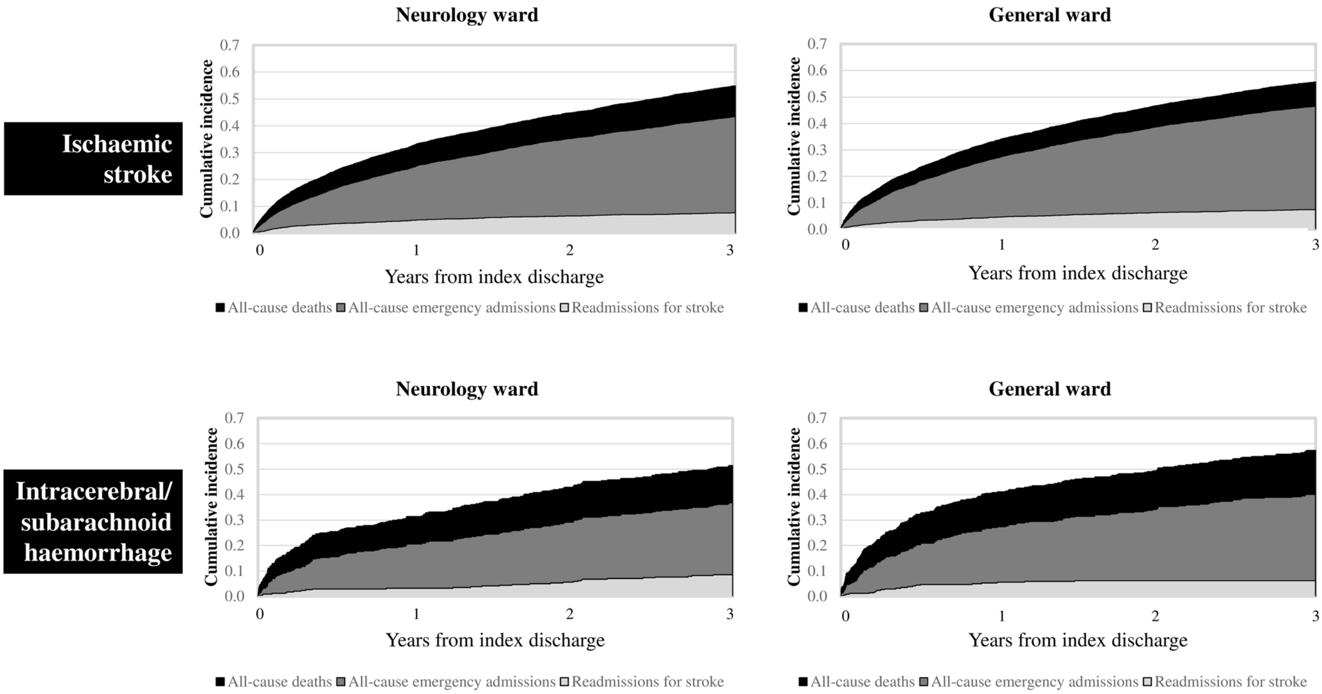

Fig. 1 Comparison of cumulative outcomes experienced by HDPS-matched cohort members admitted for ischemic stroke and intracerebral or subarachnoid hemorrhage according whether they were discharged from neurology or general wards. Lombardy, 2009–2012

provided highly accurate data, because health providers are required to report services in detail in order to obtain reimbursement, and incorrect reports have legal consequences.

Our study has also some limitations. One, because of privacy regulations, hospital records were not available for scrutiny, which means that differential diagnosis of stroke could not be checked. Owing to the lack of evidence from up-to-date studies performed in the healthcare system of the Lombardy Region, misclassification cannot be completely excluded in our setting. Moreover, the lack of clinical information useful for risk stratification and prognostication is one of the main cause of systematic uncertainty of our study. Two, drug treatment was derived from drug prescriptions, which requires, however, the assumption that drug prescription corresponds to drug consumption. There is, however, no guarantee that this is always the case, and indeed, it is likely that in a number of patients, the prescribed drugs are not assumed. This implies, however, that in the real world, the actual use of medicines may be even still less than the measured prevalence of drug users [33]. Three, we could not take into account the use of thrombolysis treatment because "hospital discharge data were found to be fairly insensitive in the reporting of thrombolysis," as reported by a recent Italian investigation [34]. Finally, the main limitation to be considered remains confounding. In fact, certain relevant clinical information might not have been completely captured, because it is either not fully or not directly measured in administrative data, and this may have led to residual confounding. Although high-dimensional propensity score methodology is attractive for efficiently addressing potential unmeasured confounding through proxy identification [35], the potential for some residual confounding remains.

In summary, our study suggests that inpatient cares of acute IS and ISH provided from neurology wards is more effective than those provided from unskilled general wards. Effectiveness concerns the short-term reduction of mortality and other clinical outcomes and benefits persist over time until 3 years after the index discharge likely mediated by better outpatients healthcare.

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Compliance with ethical standards

Conflict of interest Giovanni Corrao received research support from the European Community (EC), the Italian Agency of Drug (AIFA), and the Italian Ministry of Education, University and Research (MIUR). He took part in a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN, and BMS). He also received honoraria as member of Advisory Board from Roche.

Other authors declare that they have no conflict of interest to disclose.

Research involving human participants and/or animals/informed consent For this type of study, formal consent is not required.

References

1. Feigin VL, Norrving B, Mensah GA (2017) Global burden of stroke. Circ Res 120:439–448
2. Feigin VL, Lawes CMM, Bennett DA, Barker-Collo SL, Parag V (2009) Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 8:355–369
3. Koton S, Schneider AL, Rosamond WD et al (2014) Stroke incidence and mortality trends in US communities, 1987 to 2011. JAMA 312:259–268
4. Schmidt M, Jacobsen JB, Johnsen SP, Botker HE, Sorensen HT (2014) Eighteen-year trends in stroke mortality and the prognostic influence of comorbidity. Neurology 82:340–350
5. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, Kissela BM, Kittner SJ, Lichtman JH, Lisabeth LD, Schwamm LH, Smith EE, Towfighi A, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Quality of Care and Outcomes Research, Council on Functional Genomics and Translational Biology (2014) Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. Stroke 45:315–353
6. GBD 2015 Mortality and Causes of Death Collaborators (2016) Global, regional and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388:1459–1544
7. Diringer MN, Edwards DF (2001) Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage. Crit Care Med 29:635–640
8. Agostoni E, Carolei A, Micieli G, Provinciali L, Toni D, Vidale S (2018) The organisation of the acute ischemic stroke management: key notes of the Italian Neurological Society and of the Italian Stroke Organization. Neurol Sci 39:415–422
9. Corrao G, Rea F, Merlino L, Mazzola P, Annoni F, Annoni G (2017) Management, prognosis and predictors of unfavourable outcomes in patients newly hospitalized for transient ischemic attack: a real-world investigation from Italy. BMC Neurol 17:12
10. Corrao G, Rea F, Di Martino M et al (2017) Developing and validating a novel multisource comorbidity score from administrative data: a large population-based cohort study from Italy. BMJ Open 7: e019503
11. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA (2009) High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 20:512–522
12. Rassen JA, Glynn RJ, Brookhart MA, Schneeweiss S (2011) Covariate selection in high-dimensional propensity score analyses of treatment effects in small samples. Am J Epidemiol 173:1404–1413
13. Fine JP, Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496–509
14. Vanderweele TJ, Vansteelandt S (2010) Odds ratios for mediation analysis for a dichotomous outcome. Am J Epidemiol 172:1339–1348
15. Ayis SA, Coker B, Bhalla A, Wellwood I, Rudd AG, di Carlo A, Bejot Y, Ryglewicz D, Rastenyte D, Langhorne P, Dennis MS, McKevitt C, Wolfe CDA (2013) Variations in acute stroke care and the impact of organised care on survival from a European perspective: the European Registers of Stroke (EROS) investigators. J Neurol Neurosurg Psychiatry 84:604–612
16. Malmivaara A, A. Meretoja A, M. Peltola M.,M. Peltola, D. Numerato, R. Heijink, P. Engelfriet, S.H. Wild, É. Belicza, D. Bereczki, E. Medin, F. Goude, G. Boncoraglio, T. Tatlisumak, T. Seppälä, U. Häkkinen (2015) Comparing ischaemic stroke in six European countries. The EuroHOPE register study. Eur J Neurol 22:284–291
17. Santalucia P, Baviera M, Cortesi L, Tettamanti M, Marzona I, Nobili A, Riva E, Fortino I, Bortolotti A, Merlino L, Roncaglioni MC (2015) Epidemiologic trends in hospitalized ischemic stroke from 2002 to 2010: results from a large Italian population-based study. J Stroke Cerebrovasc Dis 24:1917–1923
18. Cesaroni G, Agabiti N, Forastiere F, Perucci CA (2009) Socioeconomic differences in stroke incidence and prognosis under a universal healthcare system. Stroke 40:2812–2819
19. Stuart M, Papini D, Benvenuti F, Nerattini M, Roccato E, Macellari V, Stanhope S, Macko R, Weinrich M (2010) Methodological issues in monitoring health services and outcomes for stroke survivors: a case study. Dis Health J 3:271–281
20. Finocchi C, Balestrino M, Malfatto L, Mancardi G, Serrati C, Gandolfo C (2018) National Institutes of Health Stroke Scale in patients with primary intracerebral hemorrhage. Neurol Sci 39: 1751–1755
21. Candelise L, Gattinoni M, Bersano A, Micieli G, Sterzi R, Morabito A, PROSIT Study Group (2007) Stroke-unit care for acute stroke patients: an observational follow-up study. Lancet 369:299–305
22. Sun Y, Paulus D, Eyssen M, Maervoet J, Saka O (2013) A systematic review and meta-analysis of acute stroke unit care: what's beyond the statistical significance? BMC Med Res Methodol 13:132
23. Nardetto L, Giometto B, Moretto G, Mantoan D, Saia M (2017) Hub-and-spoke stroke network in the Veneto region: a retrospective study investigating the effectiveness of the stroke pathway and trends over time. Neurol Sci 38:2117–2121
24. Hankey GJ (2014) Secondary stroke prevention. Lancet Neurol 13: 178–194
25. Chan DK, O'Rourke F, Shen Q et al (2011) Meta-analysis of the cardiovascular benefits of intensive lipid lowering with statins. Acta Neurol Scand 124:188–195
26. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease (2014) Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 45:2160–2236
27. Coutts SB, Wein TH, Lindsay MP, Buck B, Cote R, Ellis P, Foley N, Hill MD, Jaspers S, Jin AY, Kwiatkowski B, MacPhail C, McNamara-Morse D, McMurtry MS, Mysak T, Pipe A, Silver K, Smith EE, Gubitz G (2015) Canadian stroke best practice recommendations: secondary prevention of stroke guidelines, update 2014. Int J Stroke 10:282–291
28. Enthoven AC (2009) Integrated delivery systems: the cure for fragmentation. Am J Manag Care 15:S284–S290
29. Stange KC (2009) The problem of fragmentation and the need for integrative solutions. Ann Fam Med 7:100–103
30. Farrell TW, Tomoaia-Cotisel A, Scammon DL, Brunisholz K, Kim J, Day J, Gren LH, Wallace S, Gunning K, Tabler J, Magill MK (2015) Impact of an integrated transition management program in primary care on hospital readmissions. J Healthc Qual 37:81–92
31. Specogna AV, Turin TC, Patten SB, Hill MD (2017) Hospital treatment costs and length of stay associated with hypertension and multimorbidity after hemorrhagic stroke. BMC Neurol 17:158

32. Norrving B, Kissela B (2013) The global burden of stroke and need for a continuum of care. Neurology 80:S5–S12
33. Corrao G, Mancia G (2015) Generating evidence from computerized healthcare utilization databases. Hypertension 65:490–498
34. Baldereschi M, Balzi D, Di Fabrizio V et al (2018) Administrative data underestimate acute ischemic stroke events and thrombolysis treatments: data from a multicentre validation survey in Italy. PLoS One 13:e0193776
35. Patorno E, Glynn RJ, Hernández-Díaz S, Liu J, Schneeweiss S (2014) Studies with many covariates and few outcomes: selecting covariates and implementing propensity-score-based confounding adjustments. Epidemiology 25:268–278