Title:

Predicting treatment costs after stroke episode in Italy.

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ABSTRACT

OBJECTIVES: Given the pressure on healthcare budgets, assessing the cost of managing a disease has become a major research focus: this is especially true for stroke, being it responsible for more than 200,000 new episodes in Italy; yet collection of these data are labour intensive and difficult. Understanding the predictors of cost provides an efficient means of incorporating such information in the policy- and decision-making process.

METHODS: We present a prospective, incidence-based study of stroke patients admitted to 46 hospitals in Italy. Questionnaires were designed for socio-demographic information, stroke subtype, pre-stroke living arrangement and independence, disability levels, initial NIHSS, medical treatments and complications, during and after hospitalization. Informal care and production losses were also investigated. Patients were followed-up for a year after discharge.

RESULTS: 546 patients were consecutively enrolled in the study for the acute phase of stroke management. The Barthel Index was the strongest predictor of acute hospitalization cost in all models evaluated. Other major predictors were stroke subtype, hypertension, and the time between the stroke and the admission ("time to care").

CONCLUSIONS: Through the use of key patient characteristics and organizational data easy to collect at the time of the admission, multivariate regression models allows for prediction of the cost of stroke care, which may be helpful in the context of therapeutic decisions and budgetary planning purposes.

RATIONALE AND OBJECTIVES

As in most industrialized countries healthcare expenditure is threatening to exceed what they can reasonably afford, regulators are heightening their interests in understanding the cost of care, its determinants, and how may be modified by specific treatments. Cost of illness studies have become an important source of information for policy- and decision-makers, the principal aim of cost of illness studies being to evaluate the economic burden a specific illness imposes on society as a whole.[1]

As a debilitating disease with long-term consequences, stroke requires a significant social and economic burden to society: hospitalization for emergent therapy, diagnostic evaluation, initiation of secondary preventative measures, and planning of the next level of formal and informal care.[2] It is the second leading-cause of death in the world, and the first cause of disability in adult-old ages in developed countries: the incidence of stroke is prone to increase in spite of growing awareness whereabouts risk factors control, due to continuously rising proportion of the elderly population in this part of the world.[3] The most important risk factors are age, hypertension, presence of atrial fibrillation and other heart diseases, or lifestyle factors such as smoking, alcohol and diet.[4]

In Italy stroke is the third cause of death, after cancer and myocardial infarction, and it is responsible for 10-12% of all deaths every year: stroke incidence ranges from 250 to 300 on 100,000 inhabitants, and it is supposed to rise due to increasing proportion of elderly people.[5] It is estimated that 155,000 Italians suffer from first-ever stroke each year, and that another 39,000 from recurrent stroke; the most frequent is ischemic stroke (80%), while intra-cerebral and subarachnoid hemorrhages are less present (17% and 3% respectively). There are currently around 900,000 cases of stroke in the country with the growth perspective of 1,000,000 cases in 2008.[6]

Despite the strong economic relevance of cerebral vascular disease, published data on stroke management costs in Italy are still limited; few data are available on first-ever stroke in acute phase, but the economic impact of a disease is related also with the chronic phase of survivors.[7] Furthermore, empirical evidence demonstrates that productivity losses account for a large portion of the overall cost, independently of the type of stroke considered.[8,9,10]

Studies of the economic burden of stroke typically use a prevalence-based approach to estimating the cost of stroke in a given year, and often focus solely on the direct costs of care; these studies are helpful in

identifying the costs of stroke at a given point in time, however retrospective analysis based on hospital discharges and stroke registries adopted in the above studies are likely to present misallocation of costs; prevalence-based studies have been used to estimate the cost of treating stroke in Canada, Netherlands, UK, USA, New Zealand and Sweden.[11]

Incidence-based studies estimate costs over a period of time beginning with initial event; this approach provides a better estimate of the costs to society, or to a particular payer, managing the patient from an event onward, and it is deemed appropriate if the goal is to better understand the potential economic impact of a given treatment that reduces the incidence of the disease or improves health outcomes.

Beyond substantial economic burden that stroke poses to society, it is well established that stroke has profound and wide-ranging effects on physical, mental and social domains of patients' lives. Therefore, a comprehensive assessment of health-related quality of life is essential to document the full impact of stoke. Since no existing measure covers all the domains required, the concurrent application of different, general and disease specific, rating scales is warranted for comprehensive assessment of health-related quality of life in patients with stroke; however, a recently published review on stroke cost of illness studies have found it remarkable that in the studies conducted in the last, almost four, decades little attention was paid to this kind of physical and psychological burden borne by the patient and family.[12]

As total cost of stroke and its components varies according to patient age, the presence of comorbidities, and several indicators of disease severity, including functional and neurological impairment and stroke subtype, the time between the stroke event and the admission in order to get the necessary care, likewise health-related quality of life measurements, the purpose of the current analyses was to estimate direct and productivity costs of stroke in Italy from a societal perspective over 1 year period, to distinguish the incidence of various costs components and subjects who bear them, and to seek combinations of these economic, clinical and social factors that predict the costs of managing stroke over the first year in the Italy.

METHODS

An observational, prospective, incidence-based, multi-centre cost of illness study was designed: observational, as one of the aims was capturing the actual clinical management of illness in Italy without intervening in the current practice of clinicians; prospective, meaning that the relevant events did not occur before the study initiation and that the process of data collection was done by following the patients; incidence-based implied that patients experiencing both first-ever and recurrent stroke were enrolled in the study. After the enrolment period, patients were followed up over a period of 1 year. Sample size was determined assuming the standard deviation of the present population being similar to the one estimated in a similar study: 600 cases was the number required to have a 95% confidence interval that the average social cost per patient has a precision of Euro 1,000.[6] In order to obtain a geographically representative sample, the national territory was divided in 5 macro-areas: North-East, North-West, Centre, South and Islands; in order to avoid any selection bias, the choice of centres was conducted including both highly specialized and not specialized centres across different geographical areas listed above (medicine, neurology and stroke unit wards). The number of patients to be enrolled in each macro area was assessed on the basis of resident population according to most recent available data from Italian National Institute for Statistics (ISTAT).

Patients were enrolled according to the following inclusion criteria:

- Diagnosis of stroke event (first-ever and recurrent) according to ICD-10 (Ischemic Stroke or Intracerebral Hemorrhage – TIAs are excluded) and supported by CT scan and/or MRI;
- Patients above 18 years of age;
- Patient's Informed Consent to participate.

Exclusion criteria include:

- Presence of Subarachnoid Hemorrhage;
- Sever pathologies with unfavourable 1-year prognosis (e.g. cancers, fatal renal, hepatic or respiratory insufficiency);
- Disabling and progressive neurological pathologies (e.g. multiple sclerosis, Parkinson's disease);
- Patients with dementia (diagnosed according to DSM-IV criteria);
- Presence of logistical factors that would not allow a completion of follow-up (e.g. non residents of the Region);

- Refusal, or withdrawal, of patient's Informed Consent to participate.

The patients were consecutively enrolled in each centre for a maximum of 16 units in a 3-month period. Direct, non-direct healthcare costs and productivity losses were assessed to calculate the annual economic burden of stroke event. Direct healthcare costs referred to the hospitalization in the acute phase, re-admissions, clinical consultations, tests, domiciliary care, drugs, rehabilitation sessions, other rehabilitation costs (i.e. appliances, aids). Direct costs which did not relate to the consumption of healthcare resources included costs of transportation to health providers, other out-of-pocket expenses and informal care, that is the time family members or volunteers spent to care for the patient. Patients' time off work (working days lost, permanent reduction or loss of working activity) was considered to measure productivity losses.

Five questionnaires were *ad hoc* designed in order to gather data on patients and caregivers to be administered at different times: during the acute phase (admission and discharge) – T0, at 3 months – T3, at 6 months – T6, at 12 months – T12, and a drop-out questionnaires; all questionnaires were filled out during patient's recurrent control visit in the hospital centres by the physician in charge.

T0 questionnaire was aimed at gathering data on patients' socio-demographic characteristics, clinical variables (e.g. type of stroke, comorbidities, subtypes of cerebral infarction – according to Bamford classification)[13,14], and patients' disability, as well as on quality of life. T0 questionnaire included data on resource consumption while in hospital (eg. physician visits, laboratory and imaging exams, rehabilitation and surgical procedures). T3, T6 and T12 questionnaires aimed at collecting data on the direct healthcare and non-healthcare expenditures, as well as productivity losses: gathered data referred to consumption of healthcare resources on both in-patient and out-patient basis, to non-healthcare resources and to productivity losses due to mortality and morbidity correlated with stroke. Furthermore, data on patients' disability level and quality of life were gathered at the end of each observation period. Drop-out questionnaire were filled in if the patient was transferred to another hospital, died or it was lost to the follow-up for any reason.

Alongside with mortality rates, National Institute for Health Stroke Scale (NIHSS), Barthel Index (BI), Modified Rankin Scale (MRS), and EuroQol (EQ-5D) were used in order to collect data on patients' outcomes.[15] NIHSS is a quantitative measure assessing neurological outcome and the degree of recovery for stoke patients, through 11 items: level of consciousness, gaze, visual fields, facial palsy, motor strength,

ataxia (wobbliness), sensation, language, dysarthria (slurred speech), and extinction or inattention (5 stroke severity levels were defined: very mild [NIHSS 0 to 9], mild [NIHSS 10 to 12], moderate [NIHSS 13 to 15], severe [NIHSS 16 to 19], very severe [NIHSS >= 20]).[16,17] NIHSS was administered at admission.

BI is composed of 10 items with varying weights; it classifies the damage of the stoke event through the patient's abilities of autonomously executing daily life activities (for example: personal toiletry, taking a bath, eating, going up the stairs and dressing) before and after the occurrence. The personal result is described through a score within the range of 0 - no autonomy at all, and 100 - complete autonomy (4 disability levels were defined: independence in basic activities of daily living - ADL [BI 100], mild dependence in ADL [BI 75 to 95], moderate dependence in ADL [BI 50 to 70], strong dependence in ADL [BI 0 to 45]).[12,18] BI was administered twice at admission, referring to the disability level before the occurrence and immediately after respectively, at discharge, and at follow-ups – T3, T6 and T12.

MRS is a disease-specific scale that has been widely used in stroke patients to define clinically discrete patient disability categories. MRS defines 6 levels of disability and one for death; 0 (no symptoms), 1 (no significant disability, despite symptoms, able to perform all usual duties and activities), 2 (slight disability, unable to perform all previous activities but able to look after own affairs without assistance), 3 (moderate disability; requires some help, but able to walk without assistance), 4 (moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance), 5 (severe disability, bedridden, incontinent, and requires constant nursing care and attention).[19,20] MRS was administered at discharge (or day 14), and at follow-ups.

EQ-5D instrument comprises a 5-domain health self-classification system (mobility, self-care, daily activities, pain, and anxiety/depression), with 3 degrees of severity (no problem, some problems, major problems) and a visual analogue scale (VAS), described as a "feeling thermometer" rated from 0 to 100, anchored by worst and best imaginable health state. The EQ-5D allows calculating a preference-based summary index based on time trade-off techniques in which the value 0 represents death and 1 represents perfect health.[14] EQ-5D was administered at discharge (or day 14), and at follow-ups.

The economic value of illness was estimated by identifying the cost-generating components and by attributing an appropriate monetary value to them. Prevalence-based approaches require a top-down analysis, thus allocating portions of a known total expenditure to each of several disease categories;

incidence-based methods instead are well know as bottom-up approaches, directly involving patients and caregivers: besides providing more reliable information whereabouts cost of stroke event, also allow the researchers to find the cost drivers predicting the services consumption patterns.[21,22] Bottom up approach can be divided into two steps: identifying and measuring the quantity of health inputs used, and the second step is to estimate the unit costs of the inputs used. The total costs are then calculated by multiplying unit costs per quantities.

Unit costs of resources were drawn from data available from the literature, and national/regional charges. Tariffs were used for laboratory and imaging tests, specialist visits and rehabilitation sessions; market values were used for pharmaceutical treatments and for the use of services provided by the private sector; national literature data available was used to evaluate daily resource consumption in medicine, neurology or stroke unit wards. Productivity losses were valued according to the human capital approach, which assigns monetary value (average annual wages corresponding to specific sectors/positions) to the inability to perform work as a result of premature death or morbidity associated with stroke. For caregivers and non-working patients, the replacement cost approach was applied (value estimates based on the corresponding market prices).

Statistical analysis

In order to evaluate costs of stroke management in relation to socio-demographic, clinical characteristics as well as disability level and health-related quality of life, bivariate analysis were performed applying different statistical tests according to the nature of the specific dependent variables. As is frequently the case with medical cost data, the distribution of the treatment cost is positively skewed.[23] The values were therefore logarithmically transformed to achieve a more normal distribution and permit use of standard parametric statistical tests. The equations were derived with the use of these log costs. Multiple variables were identified in order to perform multiple regression analysis with an objective of identifying the most relevant cost predictors. In the final model, using a stepwise backward procedure, associations were considered significant if $p<0.05$. Analyses were carried out with STATA version 9.0 (Stata Corp).

RESULTS

The following results concern the acute phase only, being the study ongoing at present.

A total of 546 patients met all eligibility criteria during the study period in 46 selected hospitals across Italy. The demographics and clinical status on presentation for the enrolled patients included in the analyses are summarized in Tables 1. Among this cohort, 96.3% stroke cases were living in their home before the stroke, either with family, or alone. The mean age for the admitted patients was 69.5 years, men (57.5%) being more frequent than women.

The mean length of stay (LOS) was 13.36+/-11.50 (SD) days; no statistically significant differences were registered in LOS for different intensity of care wards (medicine, neurology or stroke units). Direct healthcare costs for acute phase amounted to an average of Euro 5,463.7+/-4,283.7 (SD), as depicted in Table 2. The largest cost component of this total was the hospital cost (87.8%), followed by imaging (7.8%) and laboratory (1.8%) tests costs.

With the use of a multiple linear regression analysis, (log-transformed) stroke management costs in the acute phase was found to be predicted by a clinical history of hypertension, by the presence of lacunar syndromes (LACS), by physical disability at the admission (according to the Barthel Index), and by the “time to care” (time from stroke onset to hospitalization), as presented in Table 3. In particular, early functional disability as reflected by BI was the strongest predictor ($p<0.000$) of the stroke management costs in the acute phase: 10-point change in the BI causes an absolute change in the total cost of 4%. Stroke subtype is also a strong predictor of cost ($p<0.001$), having with a LACS stroke having 15% lower cost than the other subtypes. This finding indicates that stroke subtype carries prognostic implications beyond severity and dysfunction. Severity of neurological impairment as measured by NIHSS did not add predictive power beyond that already contributed by the BI. Thus, it appears that the relation between neurological impairment and cost is mediated by its association with other predictors. Another important cost predictor was hypertension ($p<0.01$), whose presence is associated with 14% increase in the cost of stroke management in the acute phase. The last, and less strong ($p<0.05$), determinant of cost was found to be “time to care”: 10-hours delay in the time to treatment would increase healthcare costs by 2%. Age, gender and the presence of comorbidities per se were not significant additional predictors of cost in the acute phase.

DISCUSSION AND CONCLUSION

This is a comprehensive, incidence-based estimate of the total costs of stroke acute phase in Italy and, as such, provides unique information of relevance to future healthcare planning. The estimated present value of the total costs of the acute phase of stroke management (direct service use) for all first-ever-in-a-life and recurrent strokes occurring in Italy are estimated to be Euro 1.1 billion (USD 1.4 billion), amounting to 1% of total annual Italian healthcare expenditure.

Through the analysis of the data set, a multiple regression model has been developed that allows for prediction of overall acute phase stroke management costs, making use of key demographic and disease characteristics known at the time of patient presentation. The Barthel Index was the strongest predictor of cost in all models evaluated. In the final model, 10-point difference in the BI score (on a scale from 0 to 100) predicts a decrease in the total cost of about 4%. A diagnosis of lacunar syndromes was another significant predictor, as well as the presence or absence of hypertension. Comparison of specific findings across studies is difficult because of the vast differences in objectives, patient populations studied, parameters evaluated, measurement instruments used, and analytical approach. Broadly speaking, however, our findings are in line with previous reports on the determinants of stroke costs.[2,16] This is an encouraging finding in light of the fact that the Barthel Index is a well-researched instrument that is easy to administer and has been found to be reliable, valid, and sensitive.[24]

Although it is not surprising that disability (or stroke severity) at the admission is a major indicator of outcome and resource utilization, few studies have been able to demonstrate that the initial deficit could quantifiably predict these subsequent parameters. Other stroke measurement scales have been examined in this context, but rarely as early as on admission to the hospital.[2] For example, the NIHSS, Canadian Stroke Scale,[25] and Middle Cerebral Artery Neurological Scale, measured within 72 hours of stroke onset, were all found to correlate with long-term outcome, but short-term outcomes and need for acute rehabilitation were not addressed.[26,27]

Further investigation should be addressed on “time to care” variable: reducing the time spam between occurrence and delivery of care may lead to better outcomes and shorter LOS (eg. awareness campaign at population level, emergency community services). This variable is almost absent in all the major researches on stroke management, or being not significantly associated with costs;[8] nevertheless, our findings suggest

that a correlation between time to care and resources consumption in the acute phase does exist: 10-hours delay in the time to treatment would increase healthcare costs by 2%. While clinical variables, like stroke severity or the disability level at admission, could be poorly *a priori* controlled by healthcare actors in the short run, “time to care” variable could be improved in a proper way, and shortened as much as possible, both by investing in an efficient, skilled and targeted emergency community services, and by promoting campaigns aimed at raising people awareness on stroke early symptoms (not only for high risk persons), in order to activate the emergency service as timely as possible – this, together with and early diagnosis of clinical fundamental variables, could save lives and healthcare resources.

TABLES

Table 1: Sample characteristics (n=546).

SOCIO-DEMOGRAPHIC VARIABLES	N./ mean	%
Age	***n= 546***	*%*
Mean (SD)	69.5	*+/- 13*
Median	72.0	
Range	(19 - 96)	
< 45	28	*5.1%*
45 - 54	38	*7.0%*
55 - 64	96	*17.6%*
65 - 74	171	*31.3%*
75 - 84	169	*31.0%*
> 85	44	*8.1%*
Location		
North-West	152	*27.8%*
North-East	100	*18.3%*
Centre	101	*18.5%*
South	122	*22.3%*
Islands	71	*13.0%*
Gender		
Female	232	*42.5%*
Male	314	*57.5%*
Employment status		
Retired	369	*67.6%*
Employed	103	*18.9%*
Housewife	59	*10.8%*
Unemployed	6	*1.6%*
n.a.	9	*0.7%*
Living status		
Lives with family	446	*81.7%*
Lives by her/himself	80	*14.7%*
Other	9	*1.1%*
n.a.	11	*2.0%*
CLINICAL VARIABLES	N./ mean	*%*
Hypertension	383	*70.1%*
Diabetes	118	*21.6%*
Atrial Fibrilation	104	*19.0%*
Previous strokes	62	*11.4%*
Previous TIA	54	*9.9%*
Previous AMI	54	*9.9%*
Ischemic	458	*83.9%*
Hemorrhagic	80	*14.7%*
LACS – lacunar syndromes	169	*31.0%*
PACS – partial anterior circulation syndromes	173	*31.7%*
POCS – posterior circulation syndromes	77	*14.1%*
TACS – total anterior circulation syndromes	101	*18.5%*
NIHSS at admission	7.16	*+/- 6.5*
BI – Barthel Index at admission	52.29	*+/- 36.4*
BI – Barthel Index at discharge	67.48	*+/- 35.6*
Modified Rankin Scale at discharge	2.57	*+/- 1.6*
EQ-5D at discharge	0.46	*+/- 0.4*
Inhospital mortality	12	*2.2%*

Legend: n.a. - not answered

Table 2: In-hospital resource consumption and costs (n=546).

	Resources used per patient		Costs per patient (Euro)	
	Mean	St.dev	Mean	St.dev
LENGTH OF STAY	13.36	11.50	4,796.41	4121.90
General Ward	12.10	8.50		
Neorology	14.59	14.90		
Stroke Unit	12.57	7.70		
Drugs (posological units)	38.2	41.10	62.84	155.30
Drugs (pos. units per diem)	2.9	2.90		
Laboratory tests	36.5	28.00	100.47	111.10
Imaging	14.3	33.60	426.24	236.50
Specialist visits	1.3	1.50	21.03	25.10
Rehabilitation sessions	6.0	8.80	54.66	78.10
Disability aids	1.6	5.40	2.04	10.60
TOTAL COSTS			**5,463.7**	**4,283.7**

Table 3: Multivariate regression models estimating the effect of covariates on treatment cost

DEPENDENT VARIABLE Ln (TREATMENT COST)	INITIAL MODEL			FINAL MODEL (stepwise backward)		
Independent variables	*EXP(b)*	*t*	*p*	*EXP(b)*	*t*	*p*
Demographic						
Age (1 year increment)	0.999 -	0.67	0.506	(drop)		
Gender (female vs. male)	1.681	1.08	0.279	(drop)		
Clinical						
Hypertension (present vs. not)	1.131	2.44	0.015	1.139	2.71	0.007
Diabetes (present vs. not)	0.962 -	0.07	0.487	(drop)		
Atrial fibrillation (present vs. not)	1.007	0.12	0.904	(drop)		
Previous stroke	0.931 -	0.99	0.322	(drop)		
Previous TIA	1.154	1.86	0.063	(drop)		
Previous Acute MI	1.101	1.26	0.207	(drop)		
Stroke rating						
Ischemic	0.813 -	1.15	0.250	(drop)		
Hemorrhagic	0.812 -	1.09	0.274	(drop)		
LACS – lacunar syndromes	0.400 -	1.13	0.258	0.850 -	3.26	0.001
PACS – partial anterior circulation syndromes	1.065	0.09	0.392	(drop)		
POCS – posterior circulation syndromes	1.095	0.99	0.320	(drop)		
TACS – total anterior circulation syndromes	(drop)			(drop)		
NIHSS – National Institute for Health Stroke Scale	1.004	0.70	0.483	(drop)		
Disability level						
Barthel Index (admission)	0.996 -	4.47	0.000	0.996 -	6.36	0.000
Organizational						
Time to care (1 hour increment)	1.002	2.12	0.035	1.002	2.02	0.044
Constant	6,417.603	36.73	0.000	5,421.810	164.92	0.000
R-squared	0.151		**R-squared**	0.133		
Adj R-squared	0.120		**Adj R-squared**	0.126		
Number of obs	511		**Number of obs**	511		
F(18;492)	4.870		**F(4;506)**	19.370		
Prob > F	0.000		**Prob > F**	0.000		

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