

Acute Phase Predictors of 6-Month Functional Outcome in Italian Stroke Patients Eligible for In-Hospital Rehabilitation

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on behalf of the Italian Study Group on Implementation of Stroke Care (ISC Study)

Purpose: The aim of the study was to assess early poststroke prognostic factors in patients admitted for postacute phase rehabilitation.

Methods: A 1-yr multicenter prospective project was conducted in four Italian regions on 352 patients who were hospitalized after a first stroke and were eligible for postacute rehabilitation. Clinical data were collected in the stroke or acute care units (acute phase), then in rehabilitation units (postacute phase), and, subsequently, after a 6-mo poststroke period (follow-up). Clinical outcome measures were represented using the Barthel Index and the modified Rankin Scale. Univariate and multivariate analyses were performed to identify the most important prognostic index.

Results: Modified Rankin Scale score, minor neurologic impairment, and early out-of-bed mobilization (within 2 days after the stroke) proved to be important factors related to a better recovery according to Barthel Index (power of prediction = 37%). Similarly, age, premorbid modified Rankin Scale score, and early out-of-bed mobilization were seen to be significant factors in achieving better overall participation and activity according to the modified Rankin Scale (power of prediction = 48%). Barthel Index at admission and certain co-morbidities were also significant prognostic factors correlated with a better outcome.

Conclusions: According to the Barthel Index and modified Rankin Scale, early mobilization is an early predictor of favorable outcome.

Key Words: Stroke Recovery, Stroke Care, Prognostic Factors, Predictors, Outcome

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CME Objectives: Upon completion of this article, the reader should be able to: (1) Incorporate prognostic factors of good clinical outcomes after stroke in developing treatment plans for patients admitted to rehabilitation; (2) Identify acute phase indicators associated with favorable 6-mo outcome after stroke; and (3) Recognize the cut-off for early mobilization linked to better outcome in stroke survivors admitted to rehabilitation.

Level: Advanced

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The assessment of early prognostic factors of recovery after stroke is a fundamental step in patient management, to assess appropriate treatment and the best settings for rehabilitation.

According to a recent Cochrane review,¹ a wide variety of factors influence stroke prognosis: epidemiologic factors (age, sex, and socioeconomic status); stroke characteristics (ischemic or hemorrhagic, size and location, pathogenesis); neurologic deficits (sensory loss and poor trunk control are associated with poor outcome); co-morbidities and complications after stroke therapies; functional scores at hospital admission (National Institutes of Health Stroke Scale [NIHSS] score, modified Rankin

Scale [mRS] score, etc); and type of immediate care (organized and specialized treatment in a stroke unit is associated with improved patient survival and favorable recovery).

Previous studies identified early predictors for recovery in patients admitted to hospital after stroke: a NIHSS score of 6 or less within the first 24 hrs is a predictor of good recovery at 3 mos,² whereas a score of 16 or higher is associated with a high probability of death or severe disability; age of 65 yrs increases the likelihood of death within 2 mos after the stroke or prolongation of hospitalization³; hemorrhagic stroke is associated with higher morbidity and mortality than ischemic stroke.⁴

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Pre-existing functional impairment may also be predictive of a negative outcome and can reduce patients' response to thrombolysis and survival.⁵

Myint et al.⁶ developed a clinical prognostic tool combining age, sex, type of stroke, clinical presentation of stroke, and patients' prestroke disability, as a predictor of acute stroke mortality and length of stay in hospital.

Other authors⁷⁻⁹ considered that different prognostic factors during the rehabilitation phase such as young age, a Mini Mental State Examination of 24 or higher at admission, premorbid Rankin Score 0 to 1, and early inpatient rehabilitation (within 2 weeks after stroke) are considered positive predictors, whereas dysphagia, aphasia, urinary incontinence, disability at rehabilitation unit admission, cognitive impairment, trunk control deficits, and living alone are related to poor functional gain.

Some recent trials^{10,11} studying the effect of early out-of-bed mobilization after stroke, which is recommended in various guidelines, found that there is no advantage to exposing stroke survivors to very early mobilization (within 24 hrs after the stroke) but did demonstrate that patient mobilization within the first 48 hrs prevents immobility-related complications and accelerates functional recovery in the first 3 mos after stroke.

Nevertheless, several of these studies focus on early prognostic indicators assessed in stroke units or acute care units, without making a distinction between severe stroke patients and those who are eligible for rehabilitation care or for an early home discharge. When prognostic indicators are collected in the rehabilitation phase, data concerning the acute phase are often missing. We have decided to focus our study on the predictive factors of that population among stroke survivors who are admitted to rehabilitation, because, to our knowledge, no other study in the literature has explored this type of patients from this point of view. In daily clinical practice, simple prognostic indicators in stroke patients eligible for rehabilitation could be extremely helpful for clinicians to predict recovery and assess the best postacute rehabilitation treatment.

The aims of the study were to define the most important acute phase prognostic indicators for patients admitted for rehabilitation and to explore their correlation with participation at 6 mos after stroke, focusing in particular on their independence in basic-activities of daily living.

METHODS

This study analyzed data from a larger multicenter prospective project (ISC study), involving four Italian regions. The four regions followed the same guidelines for patient admission to rehabilitation after stroke, so the access to rehabilitation facilities was regulated by homogenous criteria.

In Italy, patients with stroke may be admitted to rehabilitation facilities only in the case of severe disability (Rankin Scale score modified from 3 to 5), or if they require medical care for any clinical instability, or if changes in their functional status are expected with the help of rehabilitation. These are the main criteria for admission to in-hospital rehabilitation (referring to the State - Regional Authorities Conference¹² and to Stroke Care Document¹³).

The study was approved by the local ethics committee of the national coordinating center, on February 14, 2012, Code 47/2012/O/Oss.

Between November 2012 and February 2013, patients in acute medical or neurological units who met the following inclusion criteria were recruited in the study: age of 18 yrs or older, residence in the same region as the hospital consulted, and first stroke. A diagnosis of clinical stroke was defined as an acute onset of neurological deficits lasting more than 24 hrs, with no apparent cause other than cerebrovascular accident. Stroke diagnosis was confirmed instrumentally by computed tomography scan or magnetic resonance imaging; all patients provided written informed consent. Patients with a diagnosis of transient ischemic attack and patients who died within the first 24 hrs from stroke onset were excluded.

In line with the aim of the study, the clinical data of patients receiving in-hospital rehabilitation after the acute phase were analyzed, and patients with other destinations at discharge from the acute care unit were excluded.

The mRS and Barthel Index (BI) were used to estimate patient outcome 6 mos after stroke.

The mRS¹⁴ is a commonly used scale for measuring overall functional independence in the daily activities of patients who have experienced a stroke or other causes of neurological disability.

The BI¹⁵ is considered a reliable disability scale for stroke patients and is used to measure performance in 10 common activities of daily living (8 related to personal care and 2 related to mobility). Each performance item is rated on this scale with a given number of points assigned to each level. A total score of 100 is the highest degree of functional independence in activities of daily living.

Baseline Assessment and Follow-up

Clinical assessments were performed by an expert physician for every center, specifically trained before the beginning of the study. The assessors did not participate to the data analysis.

The baseline assessment (T0) was collected within 72 hrs after hospital admission and consisted of the following: sociodemographic data (age and sex); functional status before stroke (mRS); admission to stroke unit or other units; type of stroke (ischemic/hemorrhagic), subtype of ischemic stroke according to the Oxfordshire Community Stroke Project (total anterior circulation infarct [TACI]/LACI/PACI/POCI*), and affected side (right or left hemiparesis); and admission NIHSS score, and admission BI score. The following risk factors and comorbidities were also assessed: hypertension, severe heart disease/heart failure, heart attack, valve disease, atrial fibrillation, vascular diseases such as atherosclerotic disease of the carotid artery, lower limb arteriopathy, previous TIA; metabolic syndrome such as diabetes, hyperlipidemia, and homocysteine elevation; and presence of urinary or fecal incontinence, dysphagia, or aphasia. All these factors or co-morbidities were clinically evaluated by physiatrists and reported as dichotomous terms (present/absent during the first week after stroke).

After the acute phase, a second assessment (T1) was carried out at discharge from the acute unit and included the following: potential complications in the early phase (fever >38°C, hyperglycemia, pneumonia, pulmonary embolism, deep vein thrombosis, urinary infection, heart failure, heart attack, hemodynamic instability, seizures); evaluation of the time elapsing before rehabilitation; time elapsing before out-of-bed mobilization of the patient in the acute phase (sitting out of bed within

the first few days in the acute ward); and the interval between stroke occurrence and admission to the rehabilitation unit (onset admission interval).

A prospective assessment was performed at 6-mo follow-up (T2): all patients were contacted by researchers 6 mos after the stroke, and the following data were collected: living at home (alone or with caregivers) and functional status (mRS¹⁶ and BI scores¹⁷). In the case of death, the date and the circumstances of death were obtained from a family member or hospital database.

Potential Predictors and Outcome Measures

The main purpose of this study was to identify early predictors of a favorable recovery at 6 mos after stroke in patients admitted to in-hospital rehabilitation, more specifically concerning daily activity independence and participation. We considered the outcome at 6 mos (dependent variables) to be favorable if the mRS score was 0 to 2^{18,19} and BI score was 75 or higher.²⁰

The following independent variables (predictors) were acute phase indicators, more specifically: age, sex, premorbid mRS score, NIHSS score at hospital admission, risk factors or co-morbidities, type of stroke (ischemic/hemorrhagic), subtype of ischemic stroke, affected side, admission to stroke unit or general ward, acute phase complications (0–1 complication vs. ≥ 2), presence of aphasia, dysphagia or incontinence in the acute phase, early rehabilitation (i.e., early assessment by a physiotherapist and early individual rehabilitation program according to the patient's clinical conditions or early assessment by a speech therapist for the assessment and treatment of dysphagia) in the acute ward (within 72 hrs vs. ≥ 72), and early out-of-bed mobilization by nursing staff (cut-off identified with statistical methods).

Statistical Analysis

Data were presented as medians and percentiles (interquartile range). Intergroup differences in demographic and clinical data were assessed using nonparametric (χ^2 and Mann-Whitney) tests. Multivariate analyses were performed using logistic binary regression models to identify multiple relationships between a variable of interest and two or more explicative variables. Inclusion of explicative variables in the models followed stepwise procedures (forward and backward), with specific motivations for each variable. Where appropriate, the individual variables included were reported with their odds ratio (OR), and the significance of each coefficient in the model was examined. Non-significant variables with a *P* value of greater than 0.05 were removed from the model in a step-by-step process, starting with the variables showing the highest probability levels. Each time a variable was excluded, the integrity of the model was checked using the Hosmer-Lemeshow test. The “IBM SPSS Version 23.0” and “MedCalc Version 16.8.0” software packages were used for the analyses.

Once a predictive model of outcomes (BI ≥ 75 vs. < 75 ; mRS 0–2 vs. 3–5) had been defined, an investigation was carried out to ascertain whether there was a cut-off point for “early out-of-bed mobilization” (the independent variable) that could predict each subject's belonging to one of the two categories. If a reference criterion was available, receiver-operating characteristic (ROC)

analyses provided a processing method for the construction of cut-off points. Having used a continuous variable such as “early out-of-bed mobilization,” in which sensitivity and specificity have the same statistical weight, the best cut-off point for obtaining a positive result from the test is the maximum value that can be obtained for both of these aspects of which the sum is the highest possible. This is necessary to identify a possible predictive value able to explain positive patient outcomes. With this procedure, the cut-off point determination is equivalent to the achievement of the minimum value of false negative and false positive, which can cause classification errors. The cut-off point obtained with this method has the characteristic of maximizing the potential for correct diagnosis and minimizing errors of classification. In the case in which *c* is the best cut-off point of the test results, Youden introduced the following index for the ROC curve: $J = \max[\text{sensitivity}(c) + \text{specificity}(c) - 1]$. Moreover, finding the best cut-off point is equivalent to measuring the *J* of the Youden Index. This index is an important synthesis of the ROC curve. From a graph point of view, the Youden Index is the greatest vertical distance between the ROC curve and the diagonal line. Receiver-operating characteristics describe the relationship between sensitivity and specificity for different cut-off points. Receiver-operating characteristic analyses provide an evaluation of the ability of the diagnostic instruments to discriminate between health and disease.

RESULTS

Between November 2012 and February 2013, 1030 patients were enrolled. Seventy-seven patients (7.5%) died in the first 2 wks after the stroke. Three hundred fifty-two patients were included in this study because they had been admitted to rehabilitation units after the acute phase, whereas 601 patients did not continue rehabilitation and were discharged to other destinations (Fig. 1). Patients admitted to rehabilitation units (*N* = 352) in the regions involved in the project did not differ at discharge from the acute ward in age, Trunk Control Test score, Motricity Index score, mRS score, and BI score.

Mean age was 75 yrs, patients were admitted to the rehabilitation units 11 days after stroke, and almost all of them had been independent before the stroke. Thirty-four percent of patients were admitted to a stroke unit, 66% to other units (neurology, intensive care unit, medical department, etc.). Most patients had ischemic stroke (78.4%). Twenty-five percent of the patients had two or more complications in the acute phase.

At 6-mo follow-up, 310 patients were reassessed: 247 were still living at home (79.7%), 63 were living in other settings (20.3%), and 42 died in the first 6 mos after the stroke. The 42 patients who died within 6 mos after the stroke had certain peculiar characteristics: older age (mean = 79.5), premorbid disability (mean mRS = 0.93 vs. 0.39), higher NIHSS score at admission (mean = 12.36 vs. 9.8), and lower BI score at admission (mean = 15.48 vs. 30.63).

The ROC curve shows a value of 48 hrs (early out-of-bed mobilization) as a cut-off between poor and good outcome (BI ≥ 75 and mRS 0–2) (Fig. 2).

Table 1 shows the statistical data of patients who completed follow-up (*n* = 310).

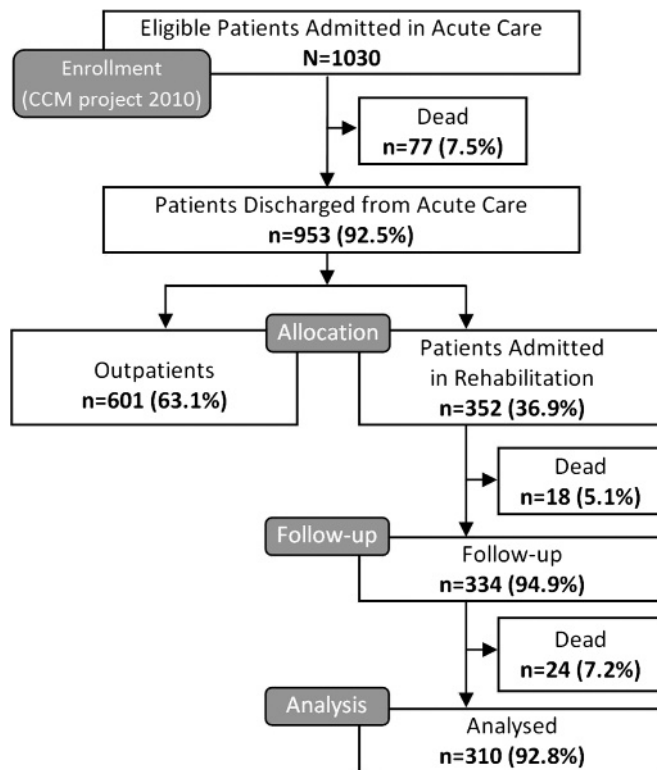


FIGURE 1. Study flowchart.

At 6-mo follow-up, 113 patients had a mRS score 0–2 (independent-mild disability) and 197 patients had a score 3–5 (moderate to severe disability).

Considering the BI score at follow-up, 150 patients had a BI score of 75 or higher (independent-mild dependence) and 160 patients had a score of less than 75 (moderate to severe dependence).

Table 1 shows the distribution of the different variables in univariate analysis for the mRS score (favorable activity/participation, 0–2) and for the BI (good functioning if BI score ≥ 75) at 6 mos; the distribution is similar for BI and mRS for the following variables: younger age, being independent before stroke (premorbid mRS 0), lower NIHSS score at hospital admission, clinical syndrome, no aphasia, no dysphagia, and no

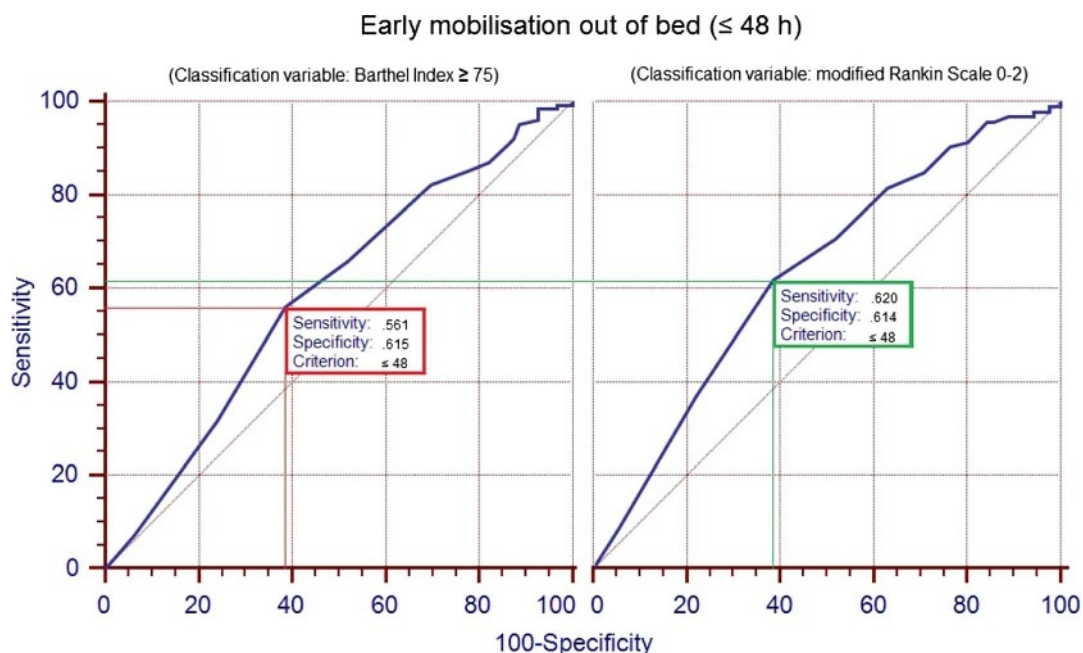


FIGURE 2. Early out-of-bed mobilization using classification variables: (BI ≥ 75 and mRS 0–2).

TABLE 1. Sociodemographic and clinical variables of the patients ($n = 310$) at T0 and univariate analysis for BI cut-off and for mRS cut-off at T2

Variables	(T0 = Admission) All	(T2 = 6 Months After Stroke)			
		BI < 75 BI ≥ 75 n (%), Median (IQR)	P	mRS 3–5 mRS 0–2	P
Subject, n	310	160 (51.6) 150 (48.4)		197 (63.5) 113 (36.5)	
Age, yr	75.0 (65.0–81.0)	78 (72.0–83.0) 72 (61.0–77.0)	<0.0001 ^a	77.0 (68.0–83.0) 73.0 (58.0–77.0)	<0.0001 ^a
OAI, d	11.0 (7.0–15.0)	11.0 (7.5–15.5) 10.0 (7.0–14.0)	0.1900 ^a	11.0 (8.0–16.3) 10.0 (7.0–13.0)	0.0308 ^a
Premorbid Rankin score	0.0 (0.0–0.0)	0.0 (0.0–1.0) 0.0 (0.0–0.0)	<0.0001 ^a		
BI score	25.0 (5.0–50.0)			15.0 (0.0–35.0) 45.0 (28.6–70.0)	<0.0001 ^a
NIHSS score	8.0 (4.8–14.0)	11.0 (6.0–16.0) 6.0 (4.0–11.0)	<0.0001 ^a	10.0 (6.0–16.0) 6.0 (4.0–11.0)	<0.0001 ^a
Sex, male	155 (50.0)	72 (45.0) 83 (55.3)	0.0694 ^b	96 (48.7) 59 (52.2)	0.5558 ^b
Stroke unit, admission	207 (66.8)	104 (65.0) 103 (68.7)	0.4934 ^b	131 (66.5) 76 (67.3)	0.8914 ^b
Stroke Type			0.9857 ^b		0.7863 ^b
Hemorrhagic	66 (21.3)	34 (21.2) 32 (21.3)		41 (20.8) 25 (22.1)	
Ischemic	244 (78.7)	126 (78.8) 118 (78.7)		156 (79.2) 88 (77.9)	
Clinical syndromes			<0.0001 ^b		<0.0001 ^b
TACI	65 (26.6)	49 (38.9) 16 (13.6)		56 (35.9) 9 (10.2)	
PACI	107 (43.9)	49 (38.9) 58 (49.2)		64 (41.0) 43 (48.9)	
LACI	27 (11.1)	13 (10.3) 14 (11.9)		14 (9.0) 13 (14.8)	
POCI	45 (18.4)	15 (11.9) 30 (25.4)		22 (14.1) 23 (26.1)	
Affected Side			0.1710 ^b		0.0110 ^b
Right	153 (49.4)	85 (53.1) 68 (45.3)		108 (54.8) 45 (39.8)	
Left	157 (50.6)	75 (46.9) 82 (54.7)		89 (45.2) 68 (60.2)	
Aphasia	106 (34.2)	64 (40.0) 42 (28.0)	0.0263 ^b	80 (40.6) 26 (23.0)	0.0020 ^b
Dysphagia	156 (50.3)	98 (61.3) 58 (38.7)	<.0001 ^b	114 (57.9) 42 (37.2)	<0.0001 ^b
Presence of Incontinence	164 (52.9)	118 (73.8) 46 (30.7)	<0.0001 ^b	136 (69.0) 28 (24.8)	<0.0001 ^b
Complications in acute phase, (≤1)	242 (78.1)	111 (69.4) 131 (87.3)	<0.0001 ^b	143 (72.6) 99 (87.6)	0.0020 ^b
Risk factors					
Hypertension	187 (60.3)	98 (61.3) 89 (59.3)	0.7300 ^b	126 (64.0) 61 (54.0)	0.0845 ^b
Severe heart disease	46 (14.8)	25 (15.6) 21 (14.0)	0.6880 ^b	35 (17.8) 11 (9.7)	0.0559 ^b
Atrial fibrillation	39 (12.6)	22 (13.8) 17 (11.3)	0.5210 ^b	26 (13.2) 13 (11.5)	0.6657 ^b

(Continued on next page)

TABLE 1. (Continued)

Variables	(T0 = Admission) All	(T2 = 6 Months After Stroke)			
		BI < 75 BI ≥ 75 n (%), Median (IQR)	P	mRS 3–5 mRS 0–2	P
Vascular diseases	22 (7.1)	14 (8.8) 8 (5.3)	0.2420 ^b	18 (9.1) 4 (3.5)	0.0651 ^b
Metabolic diseases	150 (48.4)	83 (51.9) 67 (44.7)	0.2040 ^b	105 (53.3) 45 (39.8)	0.0225 ^b
Early mobilization (≤48 hr)	106 (34.2)	37 (23.1) 69 (46.0)	<0.0001 ^b	49 (24.9) 57 (50.4)	<0.0001 ^b
Early rehabilitation (≤72 hr)	178 (57.4)	91 (56.9) 87 (58.0)	0.8413 ^b	109 (55.3) 69 (61.1)	0.3267 ^b

^aMann–Whitney test.

^bχ² test.

IQR, interquartile range; OAI, onset admission interval (time elapsing before admission to rehabilitation unit); metabolic diseases (diabetes, hyperlipidemia, homocysteinemia); vascular diseases (atherosclerotic disease of the carotid artery, previous TIA, lower limb arteriopathy); severe heart disease (heart failure, heart attack, valve disease).

incontinence at admission to the acute care unit, having 0 to 1 complication in acute phase. When considering out-of-bed mobilization in the acute phase, the outcome was better (BI ≥75 and mRS 0–2) if patients achieved sitting out-of-bed within 2 days after the stroke (Table 1).

No difference was found between males and females, between different risk factors, between patients admitted to a stroke unit or other unit, or between the type (ischemic or hemorrhagic) of stroke.

Multivariate analysis and logistic regression (Tables 2 and 3) showed strong common predictors for favorable outcome (mRS 0–2 and BI ≥75) at 6 mos after the stroke, such as younger age, absence of TACI syndrome, absence of incontinence, and early out-of-bed mobilization (within 48 hrs).

A lower NIHSS score at admission is correlated with a better outcome in performing activities of daily living (BI score ≥75 at 6 mos).

When considering early rehabilitation, patients who began rehabilitation with physiotherapists 72 hrs after stroke had a better outcome 6 mos later (BI score ≥75).

Higher BI score at admission, left hemiplegia, absence of hypertension, and early out-of-bed mobilization are independent predictors of a favorable mRS score (0–2) at 6 mos.

In addition, an analysis with binary logistic regression was performed, to detect significant differences between the two groups of patients: stroke survivors with early mobilization (within 48 hrs of the acute event) compared with patients with

TABLE 2. Multivariable binary logistic regression summarizing the characteristics of the predictive model using the BI (≥75) 6 months after stroke (n = 310)

	Coefficients		OR (95% CI)	P
Intercept	5.974			<0.0001
Age (for 1-yr increase)	-0.055	0.946	(0.9220–0.971)	<0.0001
Premorbid Rankin score (for 1-point increase)	-0.637	0.529	(0.345–0.810)	0.0034
NIHSS score (for 1-point increase)	-0.070	0.932	(0.892–0.974)	0.0018
TACI syndrome	-1.226	0.293	(0.137–0.628)	0.0016
Presence of incontinence	-1.475	0.229	(0.126–0.414)	<0.0001
Early mobilization (≤48 hr)	0.834	2.303	(1.212–4.379)	0.0109
Early rehabilitation (≤72 hr)	-0.709	0.492	(0.267–0.907)	0.0230
Nagelkerke R ² = 0.445	T _{jur} R ² = 0.350			
Area under the ROC curve = 0.841, 95% CI = 0.796–0.880				
Classification table (cut-off value P = 0.50)				
Actual Group	Predicted Group		Percent Correct	
	BI < 75	BI ≥ 75		
BI ≥ 75	39	111	74.00%	
BI < 75	126	34	78.75%	
Percent of cases classified correctly			76.45%	

CI, confidence interval.

TABLE 3. Multivariable binary logistic regression summarizing the characteristics of the predictive model using the mRS (0–2) 6 months after stroke ($n = 310$)

	Coefficients	OR (95% CI)		P
Intercept	2.300			0.0133
Age (for 1-yr increase)	-0.050	0.951	(0.928–0.975)	0.0001
BI score (for 1-point increase)	0.031	1.032	(1.018–1.046)	<0.0001
Ischemic clinical syndrome (TACI)	-1.290	0.275	(0.108–0.703)	0.0070
Affected side (left)	0.954	2.60	(1.405–4.794)	0.0023
Presence of incontinence	-0.837	0.433	(0.225–0.833)	0.0122
Risk factors (hypertension)	-0.949	0.387	(0.196–0.765)	0.0064
Early mobilization (≤ 48 hr)	0.836	2.306	(1.126–4.723)	0.0223
Nagelkerke $R^2 = 0.478$		Tjur $R^2 = 0.384$		
Area under the ROC curve = 0.863, 95% CI = 0.820–0.899				
Classification table (cut-off value $P = 0.50$)				
Actual Group	Predicted Group		Percent Correct	
	mRS (3–5)	mRS (0–2)		
mRS score (0–2)	38	75	66.37%	
mRS score (3–5)	167	30	84.77%	
Percent of cases classified correctly			78.06%	

CI, confidence interval.

later mobilization (after 48 hrs from the acute event). The analysis highlighted that the presence of incontinence, dysphagia, and aphasia in the first week after stroke are unfavorable factors for early mobilization, whereas hypertension does not seem to be a limiting factor.

DISCUSSION

The aim of this multicenter prospective observational study was to identify early poststroke factors related to positive outcome in stroke patients admitted to rehabilitation hospitals. Whereas other studies^{2,3,5–11} only focused on clinical observations during acute stroke management or during in-hospital rehabilitation, including patients with a broad spectrum of disabilities, this study defined the early predictors of favorable outcome immediately after the acute phase. This approach, to our knowledge, has not been sufficiently reported in literature to date, especially in rehabilitation studies, and therefore provides a complementary perspective for giving valuable information to patients and their relatives, when prognosis is advocated in acute stroke management.

The patients included in our study were homogeneous at discharge from the acute ward, which confirms that the criteria for admission to rehabilitation units were similar in the four regions involved in the project.

Data analysis showed that 7.5 % of patients died in the first few days after the stroke; these patients were characterized by worse clinical conditions, older age, and poorer functional status at hospital admission. This percentage is probably underestimated, if we consider previous articles^{21,22} in which the rate of death after first ischemic stroke ranged from 16% to 23%, whereas intracerebral hemorrhage mortality is higher (35%–52% in the first few months, of which half in the first 2 days²³). We believe that the low death rate observed in our

research is due to the study protocol used, because the ethics committee approved the enrolment of patients able to give their consent in the first 48 hrs after stroke. Patients with severe clinical conditions and higher risk of death at admission were not able to give their consent and therefore could not be enrolled in the study.

In literature, there is an ongoing debate regarding the parameters defining clinical outcome, although most neurological and rehabilitation studies still use the Rankin Scale and BI or their respective modified versions.^{18,19,24} The BI is more frequently used in rehabilitation studies and explores the domain of activities^{24–28} defined by the International Classification of Functioning. For the BI, the cut-off level assessing positive patient outcome is discussed in several articles.^{18,29–32} Some of these authors chose a BI cut-off that we consider to be excessively restrictive to define a good outcome, such as Granger et al.,²⁹ who indicated a BI score of 60 as a pivotal score where patients move from dependency to assisted independence; therefore, in line with other authors,²⁰ we used a BI score of 75 or higher to define a satisfying outcome regarding the performance of activities of daily living.

Functional status at 6 mos is very important: other authors have found that a good BI score 6 mos after stroke is a powerful predictor of long-term survival; more specifically, 5-yr survival probability is 0.85 for patients in BI-class 95–100, 0.72 in BI-class 65–90, and 0.50 if BI is less than 60.³¹

With regard to the activity field explored with the mRS, some authors³² considered the mRS as a global evaluation assessing both general independence in activities of daily living and participation; this is especially true for neurological studies, whereas in rehabilitation papers, the mRS is considered a tool for measuring activity performance and not participation. We also decided to use the mRS because we believe that it should be considered as a global functional health index that

also describes participation (more than BI) and because it is one of the most frequently used indexes in stroke research. There is greater agreement concerning the cut-off level for the mRS: almost all authors consider a favorable outcome as having an mRS score of between 0 and 2.^{24,31,33}

Among the various clinical factors correlated with good outcome, we found that early out-of-bed mobilization (within 48 hrs from the acute event) seems to favorably influence both outcome parameters. These results are in line with previous studies^{10,11,34,35} that highlighted the importance of a global and multidisciplinary clinical approach from the very first hours of the acute phase.

Otherwise, early rehabilitation seems to be unfavorable, because patients who started rehabilitation within the first 72 hrs after stroke in our sample had an OR of 2.033 (1.103–3.745) for poor outcome at 6 mos (BI < 75). This point requires discussion.

A better functional and neurological status at hospital admission was found in patients who received early mobilization (≤ 48 hrs), by analyzing their characteristics.

To evaluate the goodness of fit of the binary logistic regression model to the early mobilization level (≤ 48 hrs coded as class 1), we have Nagelkerke ($R^2 = 0.424$). The independent variables remained in the model (in the first week of stroke) are the following: no incontinence (OR = 6.96, $P < 0.001$), hypertension (OR = 6.31, $P < 0.001$), no aphasia (OR = 2.54, $P = 0.01$), and no dysphagia (OR = 1.82, $P = 0.07$).

The “early mobilization” factor is a favorable predictor both for better BI score and better mRS at 6 mos after stroke. However, it could be due to the fact that patients with milder strokes tend to be easier to mobilize in the early poststroke period than those more severely affected. Thus, early mobilization factor may be a strong predictor, which prevails in multivariate analysis over other variables.

As stated in previous studies, focusing either on the acute phase alone or on the rehabilitation period alone, young age, patients without TACI syndrome, good continence, and early out-of-bed mobilization within 48 hrs are early independent predictors of a favorable outcome and can be used in the first days after stroke to predict good recovery for inpatients eligible for rehabilitation.

In our sample, there was no difference in outcome between patients admitted to a stroke unit versus a general ward: this is due perhaps to the characteristics of hospital care for stroke patients in the Emilia-Romagna region, which accounts for more than 75% of patients enrolled. Since 2007, a regional guideline has established the key points for stroke care from the emergency unit to the postacute phase in Emilia-Romagna, and the Italian National Health Service provides very high-quality care in the region's hospitals.

Finally, certain predictors are associated with just one of the two outcomes (BI or mRS score): minor neurological impairment (assessed with the NIHSS) in the acute phase is a favorable outcome predictor for BI alone, probably because it has an immediate impact on the improvement of basic-activities of daily living; hypertension and left hemiplegia are good outcome predictors the mRS alone. We could explain these findings by taking into account that hypertension represents a global factor that may implicate medical complications and more limitations in personal activities and participation; on the other hand, left hemiplegia is rarely

associated with aphasia, and this can have a huge impact on global outcome when measured with mRS.

The limit of this study is the lack of a connection with International Classification of Functioning core sets; it is still difficult to assess stroke patients with time-consuming core sets in the acute phase in Italy, where other evaluation tools are mandatory; other authors have reported a limited use of International Classification of Functioning core set for stroke in routine clinical assessment in their countries.³⁶ Moreover, studies in which International Classification of Functioning was used as a tool of assessment have reported some limitations due to the fact that qualifiers have to record the extent of the problem, but this does not satisfy the criteria for reliable measurement.³⁵

Another limit could be that the sample of stroke survivors observed in this study represents the clinical pathway of four Italian regions and not the whole country.

Another and last limit of this study may be the choice of investigation on stroke survivors admitted to in-hospital rehabilitation only. This decision derives from the fact that similar studies are lacking in this area. However, the study of this population may have an impact on generalization of our findings to a broader stroke population, but it should be considered when interpreting these results.

CONCLUSIONS

The four clinical factors influencing both outcome parameters (mRS and BI scores)—young age, patients without TACI syndrome (total anterior circulation infarction), good continence, and early out-of-bed mobilization within 48 hrs—can be considered strong acute phase indicators for recovery at 6 mos.

Early out-of-bed mobilization within 48 hrs after stroke may be a key component among predictors in acute stroke phase, because it summarizes other independent variables such as moderate neurological damage (better NIHSS score, no aphasia, no dysphagia, no incontinence) and mild disability (higher BI score).

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REFERENCES

1. Stroke unit trialists' collaboration: Organised inpatient (stroke unit) care for stroke. *Cochrane Database of Syst Rev* 2013;11
2. Adams HP Jr, Davis PH, Leira EC, et al: Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology* 1999;53:126–31
3. Kammersgaard LP, Jørgensen HS, Reith J, et al: Short- and long-term prognosis for very old stroke patients. The Copenhagen Stroke Study. *Age Ageing* 2004;33:149–54
4. Heuschmann PU, Wiedmann S, Wellwood I, et al: European Registers of Stroke: Three-month stroke outcome: the European Registers of Stroke (EROS) investigators. *Neurology* 2011;76:159–65
5. Karlinski M, Kobayashi A, Czlonkowska A, et al: Role of preexisting disability in patients treated with intravenous thrombolysis for ischemic stroke. *Stroke* 2014;45:770–5
6. Myint PK, Clark AB, Kwok CS, et al: The SOAR (Stroke subtype, Oxford Community Stroke Project classification, Age, prestroke modified Rankin) score strongly predicts early outcomes in acute stroke. *Int J Stroke* 2014;9:278–83
7. Massucci M, Perdon L, Agosti M, et al: Italian Cooperative Research (ICR2): Prognostic factors of activity limitation and discharge destination after stroke rehabilitation. *Am J Phys Med Rehabil* 2006;85:963–70
8. Denti L, Agosti M, Franceschini M: Outcome predictors of rehabilitation for first stroke in the elderly. *Eur J Phys Rehabil Med* 2008;44:3–11

9. Musicco M, Emberti L, Nappi G, et al: Early and long-term outcome of rehabilitation in stroke patients: the role of patient characteristics, time of initiation, and duration of interventions. *Arch Phys Med Rehabil* 2003;84:551–8
10. AVERT Trial Collaboration group, Bernhardt J, Langhorne P, Lindley RI, et al: Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet* 2015;386:46–55
11. Askim T, Bernhardt J, Salvesen O, et al: Physical activity early after stroke and its association to functional outcome 3 months later. *J Stroke Cerebrovasc Dis* 2014;23:e305–12
12. Guidelines for the definition of clinical pathways for stroke patients, Italian State-Region Authorities Conference Document, 2005
13. Guidelines for organization of integrated assistance to stroke patients-Stroke Care Program, Emilia-Romagna Region Document, 2007
14. Van Swieten JC, Koudstaal PJ, Visser MC, et al: Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604–7
15. Shah S, Vanclay F, Cooper B: Improving the sensitivity of the Barthel Index for stroke rehabilitation. *J Clin Epidemiol* 1989;42:703–9
16. Savio K, Pietra GL, Oddone E, et al: Reliability of the modified Rankin Scale applied by telephone. *Neurol Int* 2013;5:e2
17. Della Pietra GL, Savio K, Oddone E, et al: Validity and reliability of the Barthel Index administered by telephone. *Stroke* 2011;42:2077–9
18. Banks JL, Marotta CA: Outcomes validity and reliability of the modified Rankin Scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke* 2007;38:1091–6
19. Adams HP Jr, Leclerc JR, Bluhmki E, et al: Measuring outcomes as a function of baseline severity of ischemic stroke. *Cerebrovasc Dis* 2004;18:124–9
20. Uyttenboogaart M, Stewart RE, Vroomen PC, et al: Optimizing cutoff scores for the Barthel Index and the modified Rankin Scale for defining outcome in acute stroke trials. *Stroke* 2005;36:1984–7
21. Grysiewicz RA, Thomas K, Pandey DK: Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. *Neurol Clin* 2008;26:871–95
22. Feigin VL, Lawes CM, Bennet DA, et al: Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *Lancet Neurol* 2003;2:43–53
23. Zia E, Engstrom G, Svensson PJ, et al: Three-year survival and stroke recurrence rates in patients with primary intracerebral hemorrhage. *Stroke* 2009;40:3567–73
24. Sulter G, Steen C, De Keyser J: Use of the Barthel Index and modified Rankin Scale in acute stroke trials. *Stroke* 1999;30:1538–41
25. Salter K, Jutai JW, Teasell R, et al: Issues for selection of outcome measures in stroke rehabilitation: ICF activity. *Disabil Rehabil* 2005;27:315–40
26. Schepers VP, Ketelaar M, Van De Port IG, et al: Comparing contents of functional outcome measures in stroke rehabilitation using the International Classification of Functioning, Disability and Health. *Disabil Rehabil* 2007;29:221–30
27. Stucki G, Ewert T, Cieza A: Value and application of the ICF in rehabilitation medicine. *Disabil Rehabil* 2003;25:628–34
28. Granlund M, Eriksson L, Ylven R: Utility of International Classification of Functioning, Disability and Health's participation dimension in assigning ICF codes to items from extant rating instruments. *J Rehabil Med* 2004;36:130–7
29. Granger CV, Devis LS, Peters MC, et al: Stroke rehabilitation: analysis of repeated Barthel Index measures. *Arch Phys Med Rehabil* 1979;60:14–7
30. Kay R, Wong KS, Perez G, et al: Dichotomizing stroke outcomes based on self-reported dependency. *Neurology* 1997;49:1694–6
31. De Wit L, Putman K, Devos H, et al: Five-year mortality and related prognostic factors after inpatient stroke rehabilitation: a European multi-center study. *J Rehabil Med* 2012;44:547–52
32. De Haan R, Limburg M, Bossuyt P, et al: The clinical meaning of Rankin 'handicap' grades after stroke. *Stroke* 1995;26:2027–30
33. Langhorne P, Pollock A: for the Stroke Unit Trialists' Collaboration: What are the components of effective stroke unit care? *Age Ageing* 2002;31:365–71
34. Tam AK, Berbrayer D, Robinson LR: What should be the role of physiatrists in early acute care rehabilitation?: current literature, models of care, and thoughts for the future. *Am J Phys Med Rehabil* 2016;95:225–9
35. Berzina G, Paanalahti M, Lundgren-Nilsson Å, et al: Exploration of some personal factors with the International Classification of Functioning, Disability and Health core sets for stroke. *J Rehabil Med* 2013;45:609–15
36. Han KY, Kim HJ, Bang HJ: Feasibility of applying the extended ICF Core Set for Stroke to clinical settings in rehabilitation: a preliminary study. *Ann Rehabil Med* 2015;39:56–65