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Neurorehabilitation and its impact on functional status in patients who have suffered a stroke[☆]

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KEYWORDS

Elderly;
Dependency;
Disability;
Stroke;
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Abstract Stroke represents the main cause of functional dependence and in the Portuguese adult population.

Objective: to analyse the impact of rehabilitation on functional state and basic activities of daily life (ABVD), 8 weeks following a stroke, in a population of elderly people in north-western Portugal.

Methodology: Observational, longitudinal and retrospective study. The patients were grouped into 3 groups according to the rehabilitation treatment received: Non-rehabilitation (NR), light rehabilitation (RL) and intense rehabilitation (RI).

Sociodemographic data, clinical variables (on stroke), hospital stay, rehabilitative treatment, and functional status (Barthel Index) were collected.

Results: 350 patients, with a mean age of 75.83 (± 8.02) years. The hospital stay was longer in the group of RL (19.7 (± 8.69)), RI (17.67 (± 10.05)) and of those who did not undergo rehabilitation (10.97 (± 6.96)), ($p = .001$).

A significant increase ($p < .001$) was observed in the Barthel index scores from admission to 8 weeks after the stroke.

Age ($p = .003$) and hospital stay ($p = .013$) were shown as risk factors for functional dependence. Similarly, taking as a reference the patients who did not undergo rehabilitation, the subjects who underwent light rehabilitation (OR (95% CI): 6.37 (1.74–23.25), $p = .005$) and intensive rehabilitation (OR (95% CI): 2.28 (1.08–4.82, $p = .030$), had a significantly higher risk of presenting functional dependence

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Conclusion: undergoing intensive rehabilitation improves functional state and ABVD compared to light rehabilitation, 8 weeks following a stroke in elderly patients.
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PALABRAS CLAVE

Anciano;
Dependencia;
Discapacidad;
Ictus;
Neurorrehabilitación

Neurorrehabilitación y su impacto en el estado funcional en pacientes que han sufrido un ictus

Resumen El ictus representa la principal causa de dependencia funcional y en la población adulta Portuguesa.

Objetivo: Aanalizar el impacto de la rehabilitación en el estado funcional y en las actividades básicas de la vida diaria (ABVD), tras 8 semanas de sufrir un ictus, en una población de ancianos del noroeste de Portugal.

Metodología: Estudio observacional, longitudinal y retrospectivo. Los pacientes fueron agrupados en 3 grupos de acuerdo con el tratamiento rehabilitador recibido: No rehabilitación (NR), rehabilitación ligera (RL) y rehabilitación intensa (RI).

Se recogieron datos sociodemográficos, variables clínicas (sobre el ictus), estancia hospitalaria, tratamiento rehabilitador, y estado funcional (Índice Barthel).

Resultados: 350 pacientes con edad media de 75,83 ($\pm 8,02$) años. La estancia hospitalaria fue mayor en el grupo de RL (19,7($\pm 8,69$)), RI (17,67($\pm 10,05$)) y del que no realizó rehabilitación (10,97($\pm 6,96$)), ($p = 0,001$).

Se observó un aumento significativo ($p < 0,001$) en las puntuaciones del índice de Barthel desde el ingreso hasta las 8 semanas tras el ictus

La edad ($p = 0,003$) y la estancia hospitalaria ($p = 0,013$) se presentaron como factores de riesgo de presentar dependencia funcional. De igual manera, teniendo como referencia a los pacientes que no se sometieron a rehabilitación, aquellos sujetos que realizaron rehabilitación ligera (OR (IC 95%): 6,37 (1,74–23,25), $p = 0,005$) y rehabilitación intensa (OR (IC 95%): 2,28 (1,08–4,82, $p = 0,030$), tuvieron un riesgo significativamente mayor de presentar dependencia funcional

Conclusión: la realización de una rehabilitación intensa mejora el estado funcional y las ABVD con respecto a la rehabilitación ligera, a las 8 semanas de sufrir un ictus en pacientes ancianos.

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Introduction

Stroke is presently one of the major causes worldwide of disability and death.¹ In Europe, 1.3 million people suffer from a first stroke every year, and the socioeconomic impact is high: estimated at approximately 45 billion Euros.² It is likely that these figures will rise since projections show that strokes will increase by 35% in Europe in 2050, mainly due to the ageing of the population.³ In Portugal this scenario is even worse, and it has become the primary cause of death.⁴ Although death from stroke has decreased over recent years, it continues to be a major health problem in the north of the country.^{5,6}

The decrease in mortality is partly due to advances in the treatment of stroke and the measures used during the last few years for early diagnosis and treatment of cerebrovascular disease.⁷ These advancements in the treatment of stroke are essentially based on early neurological care, admittance to stroke units, the application of fibrinolytic treatment in stroke and rehabilitation therapy. Of all of these,

rehabilitation therapy has the broadest therapeutic window: it may be applied both to ischaemic and haemorrhagic stroke, improve functional prognosis even several months after the stroke has occurred and reduce costs associated with the disease.⁸

Stroke is the most important cause of invalidity or disability in the adult. Six months after a stroke 26.1% of patients will have died, 41.5% are independent and 32.4% are dependent, with a global estimation among stroke survivors of 44% suffering from functional dependence.⁹

The approach to neurological dysfunctions should be initiated in the acute phase and be maintained, ensuring an appropriate transition to other resources in the patients with functional objectives when dysfunctions are prolonged over time and require medium to long-term treatment.^{10,11} This type of approach is a challenge for the patients with moderate/severe dysfunctions because due to their severity more time and more technical and human resources are required than would normally be administered to patients with mild dysfunctions.¹² This fact, combined with the fact that one of

the most recognized predictors of final post-stroke disability is the initial disability, means that many patients with moderate/severe stroke are considered "poor candidates" in terms of efficacy and cost to be included in rehabilitation programmes.¹¹ If added to this is the fact that there is a prevalence of patients who present with moderate to severe long term disability we may understand how stroke is a genuine problem for health and social structures.

After a stroke, recovery and return to a full life are the main aims of the survivors, their families and the health professionals who make every effort to provide the best possible care.^{10,12} This is achieved, among other means, with neurorrehabilitation.

Neurorrehabilitation has been defined as a combination of methods aimed at recovering lost or reduced neurological functions resulting from cerebral or medullar damage. In patients who have suffered a stroke the methods used in neurorrehabilitation take advantage of the cerebral plasticity to improve or normalize neurological and functional impairment.⁸ It is time-limited process, the aim of which is to prevent complications and reduce the neurological impairment to achieve the maximum functional capacity possible to facilitate personal autonomy and reintegration into family, social and working life. This rehabilitation must be begun early and in a coordinated fashion and maintained during the different phases of health care.¹³

The literature establishes that for stroke survivors there is an association between delay in initiating treatment and poorer functional evolution compared with an early start to treatment and a better prognosis. The processes of cerebral plasticity are optimized with rehabilitation programmes which begin in the early stages, the time dedicated daily to treatment and the prolongation in months of the rehabilitation.^{8,14}

The need for effective rehabilitation after a stroke is an essential element in care continuity and care which must be administered to these patients.¹⁰ The aim of this study is to analyse the impact of rehabilitation on functional status and basic activities of daily life (BADL), 8 weeks following a stroke in a population of elderly people in north-eastern Portugal.

Methodology

Observational, longitudinal and retrospective study, with a consecutive sample of patients admitted to hospital for acute stroke in a hospital in north-eastern Portugal (Braganza) between the years 2013 and 2017.

The study was approved by the Research Ethics Committee of the Local Unit of Saúde do Nordeste EPE (ULSNe) and developed in accordance with the principles expressed in the Declaration of Helsinki. The main researcher signed a document of confidentiality and was guaranteed data confidentiality and custody of the database.

The participant patients fulfilled the following inclusion criteria: over 65 years of age who had suffered from an ischaemic or hemorrhagic stroke, and who had completed a functional assessment with the Barthel index on admittance, on discharge and 8 weeks following the stroke. Exclusion criteria were: patients with transitory ischaemic stroke and patients who had died before the 8 weeks had passed.

The flow diagram of participants is shown in Fig. 1. It shows the 538 patients who were hospitalised, after applying criteria of final sample participation, which was 350.

Patients were classified into 3 groups in accordance with the rehabilitation treatment received: No rehabilitation (NR), Light rehabilitation (LR) and Intense rehabilitation (IR). We considered "no rehabilitation" as those patients who did not receive any type of rehabilitation treatment from the health system; "light rehabilitation" as those patients who had 3 days or less per week of rehabilitation treatment and "Intense rehabilitation" as those patients who received 4 or more days of rehabilitation per week or on hospital discharge they went to centres considered to be of intensive rehabilitation.

Sociodemographic data were collected, such as age, sex, and clinical stroke type and subtype variables, laterality, hospital stay and rehabilitating treatment received. Functional status was assessed with the Barthel index.

Data collection was carried out by the main researchers. Data were collected from the patients' medical files and were computerized on a differentiated and anonymous basis to respect patient confidentiality and anonymity. The main researchers alone had access to these data.

Instruments of measurement

The types of ischaemic strokes were classified according to criteria of the *Oxford Community Stroke Project* (OCSP).¹⁵ In 1991, the *Oxfordshire Community Stroke Project* proposed a classification which enabled the location and size of the injury to be assessed, as well as offering early, fast and simple prognostic information on clinical outcome. The patients were classified as:

- TACS (total anterior circulation stroke). These include the combination or alteration in cortical functions (aphasia or dysphasia, dyscalculia or visual-spatial alteration), homonymous hemianopsia and motor or sensory impairment which includes at least two areas of the following: face, upper limb and lower limb.
- PACI (partial anterior circulation infarction). These meet with two of the three characteristics of the TACS or only one dysfunction of the higher brain functions.
- POCI (posterior circulation infarction). This is a focal neurological impairment which includes: ipsilateral paralysis of cranial walls with motor and/or contralateral sensory impairment, motor and/or bilateral sensory impairment, alteration of combined movements of the eyes, cerebellar dysfunction or an isolated alteration of the field of vision.
- LACI (lacunar infarction). These strokes present with a typical lacunar syndrome (pure motor or pure sensory stroke, hemiparesis-ataxia or dysarthria unsteady hand).

To assess functional status the Barthel index¹⁶ was used, which assesses the degree of dependence in BADL; scores range between 0 (greater dependence) and 100 (independence). Their overall results were grouped into categories of dependence: total dependence (score between 0 and 20); severe dependence (21–40 points); moderate dependence (41–60 points); slight dependence (61–90 points); independence (91–100 points).

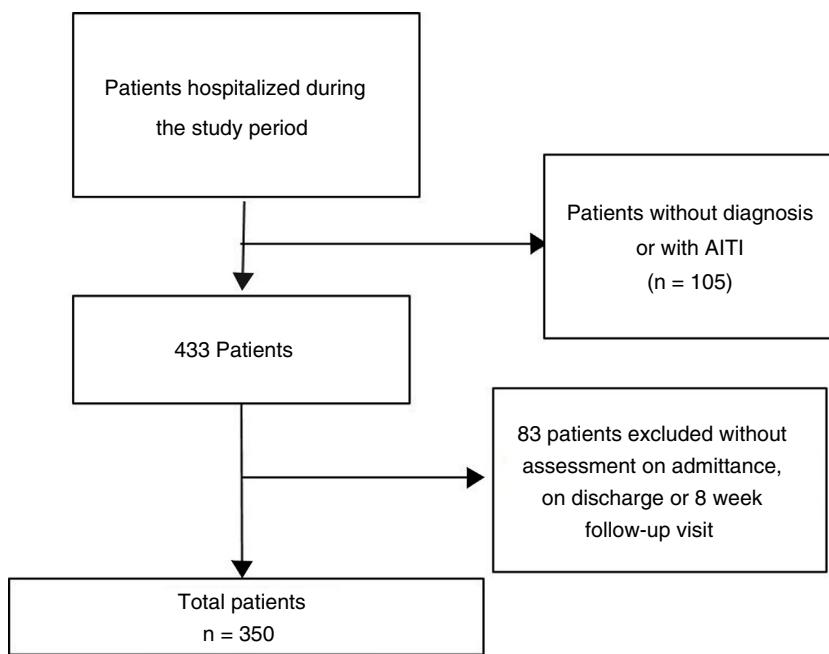


Figure 1 Flow diagram of the study.

Data analysis

A descriptive analysis of all collected variables was performed. Categorical variables were described using percentages and quantitative variables, using mean, and standard deviation (SD).

Relationships between variables was established. For this the Chi-square test was used for qualitative variables. To compare quantitative variables a normality test was performed (Kolmogorov Smirnov) and depending on whether normality was followed or not, parametric (ANOVA) and non parametric (Kruskal-Wallis) tests were used.

The odds ratio of different variables were also calculated using binary logistic regression. Firstly a univariate analysis was performed followed by multivariate analysis of the significant variables.

Data were analysed with the statistical programme SPSS for Windows v.22. For all statistical tests the threshold of significance was $p < .05$.

Results

A total of 350 patients were included, with a mean age of 75.83 (± 8.02) years. The main clinical characteristics according to post stroke rehabilitation carried out are shown in [Table 1](#). The length of hospital stay was longer in the group of patients who received light rehabilitation [19.76 (± 8.69)], followed by the group of Intense rehabilitation [17.67 (± 10.05)] and those who did not carry out rehabilitation [10.97 (± 6.96)], with significant differences existing between them ($p = .001$). Regarding the type of stroke, significant differences were observed in the proportion of TACS and LACI between the groups ($p < .05$). No statistically significant differences were found in the other analysed variables.

[Table 2](#) shows the status of functional dependence at hospital admittance, hospital discharge and 8 weeks after the stroke in accordance with the post stroke level of rehabilitation. Significant differences were found between the 3 rehabilitation groups received at the 3 moments of functional dependence assessment ($p < .001$), with the patients who received light rehabilitation in all cases being those with the lowest scores, followed by those of intense rehabilitation and no rehabilitation. In the intragroup analysis an improvement in the score of functional dependence was appreciated in the 3 groups of rehabilitation ($p < .001$), the highest being when the Barthel index was analysed 8 weeks after the stroke.

Functional status in performing BADL was analysed with the Barthel index at hospital admittance, hospital discharge and 8 weeks after the stroke in each of the groups of rehabilitation received ([Table 3](#)). A significant increase was observed ($p < .001$) in the scores of the Barthel index from admittance up until the 8 weeks after the stroke, with the exception of the item of bathing/showering in the group of light rehabilitation ($p = .368$).

Finally, univariate and bivariate analysis was performed with the baseline factors which could predict obtaining functional dependence 8 weeks after the stroke ([Table 4](#)). In the univariate analysis age (OR: 1.07; 95% CI: 1.02–1.12; $p = .003$) and mean hospital stay (OR: 1.06; 95% CI: 1.01–1.11; $p = .013$) were presented as risk factors for presenting with functional dependence. Similarly, taking as reference patients who had not undergone rehabilitation, the subjects who carried out light rehabilitation (OR: 6.37; 95% CI: 1.74–23.25; $p = .005$) and Intense rehabilitation (OR: 2.28; 95% CI: 1.08–4.82; $p = .030$) had a significantly higher risk of presenting with functional dependence. In the multivariate analysis similar results were obtained, with the exception of mean hospital stay, which did not present as a risk factor (OR: 1.04; 95% CI: .99–1.09; $p = .096$).

Table 1 Baseline characteristics of the study population.

	No rehabilitation (n = 141)	Light rehabilitation (n = 58)	Intense rehabilitation (n = 151)	p
Age (years)	75.02 (\pm 8.36)	78.05 (\pm 9.01)	75.74 (\pm 7.14)	.052
Sex (woman)	57 (40.4%)	24 (41.4%)	61 (40.4%)	.991
Hospital stay duration (days)	10.97 (\pm 6.96)	19.76 (\pm 8.69)	17.67 (\pm 10.05)	.001
Laterality				
Left hemisphere damage	68 (48.2%)	28 (48.3%)	68 (45.0%)	.837
Right hemisphere damage	59 (41.8%)	24 (41.4%)	75 (49.7%)	.333
Unknown (POCI included)	14 (10.0%)	6 (10.3%)	8 (5.3%)	.267
Classification of the stroke				
Haemorrhagic	19 (13.5%)	12 (20.7%)	30 (19.9%)	.275
POCI	24 (17.0%)	7 (12.1%)	16 (10.6%)	.260
TACS	12 (8.5%)	19 (32.8%)	34 (22.5%)	<.001
LACI	45 (31.9%)	8 (13.8%)	39 (25.8%)	.030
PACI	41 (29.1%)	12 (20.7%)	32 (21.2%)	.794
Ischaemic	122 (86.5%)	46 (79.3%)	121 (80.1%)	.275

LACI: Lacunar stroke; PACI: partial anterior circulation stroke; POCI: posterior circulation stroke; TACS: total anterior circulation stroke.
Data expressed as mean \pm standard deviation and frequencies (percentages).

Table 2 Evolution of the functional status according to the degree of post stroke rehabilitation.

	No rehabilitation (n = 141)	Light rehabilitation (n = 58)	Intense rehabilitation (n = 151)	p ^a
Barthel index on admittance	41.88 (\pm 29.71)	6.12 (\pm 14.33)	17.72 (\pm 20.30)	<.001
Barthel index on discharge	84.15 (\pm 25.41)	19.66 (\pm 18.70)	46.59 (\pm 27.56)	<.001
Barthel index 8 weeks after stroke	85.89 (\pm 25.28)	27.84 (\pm 27.32)	59.57 (\pm 31.42)	<.001
p ^b	<.001	<.001	<.001	

Data expressed as a mean (standard deviation).

^a Comparison between type of rehabilitation.

^b Comparison on admittance, on discharge and 8 weeks after stroke.

Discussion

The main findings of our study indicate that intense rehabilitation in patients who have suffered from a stroke prevents functional dependence, compared with those who have light rehabilitation.

The impairment of motor ability, with its subsequent loss of functional capacity is one of the main consequences of stroke.^{17,18} Recovery, together with the return to a full and significant life after the stroke is the main goal of survivors, their families and the health professionals in charge of providing them with the best care possible. Rehabilitation services are the primary mechanisms by which functional recovery is promoted and independence is achieved in patients with acute stroke.¹⁰ After hospital admittance and prior to hospital discharge, the patients undergo exhaustive assessment to evaluate the damage to their body and the functional impairment suffered after the stroke.¹⁹ As a result, health professionals are able to take a decision regarding the type of rehabilitation they should receive. However, in Portugal the range of rehabilitation services offered to the patients with stroke is broad and highly varied, with regard to type of care settings, duration, and intensity and in type of interventions administered, degree of participation of medical

specialists, nurses and other specific rehabilitation specialists. This lack of homogeneity leads to the creation of no common pattern to follow in post-stroke patient rehabilitation. This has been reflected in our study, since patients who had received light rehabilitation presented with a lower mean score in the Barthel index at hospital admittance and discharge than those who received Intense rehabilitation, and when assessed at 8 weeks their recovery was lower. This suggests that perhaps patients should have been given more intense and individualised rehabilitation earlier. The results of the clinical trial *A Very Early Rehabilitation Trial* (AVERT) suggest that early and intensive rehabilitation may improve functional recovery and accelerate the return of unaided ambulation.^{20,21} However, the question of what type of Intense rehabilitation should be carried out remains unresolved. Beyond the relevant results of the AVERT clinical trial, at present there are very few controlled and randomized studies that assess the efficacy and safety of the different rehabilitation techniques.^{22,23} These results are controversial due in part to their diversity and the small size of the samples included. In our study, our reference was the patients who did not have rehabilitation (since they were those who had functional independence on discharge). The patients who had light rehabilitation presented with a higher probability of functional dependence after 8 weeks

Table 3 Association between each activity /item of the Barthel index. On admittance, discharge and 8 weeks after stroke.

	Hospital Admittance	Hospital discharge	8 weeks after stroke	p
Feeding				
No rehabilitation	5.39 (3.64)	8.87 (2.42)	9.18 (2.36)	<.001
Light rehabilitation	.78 (2.05)	2.59 (2.99)	4.14 (3.98)	<.001
Intense rehabilitation	2.62 (2.93)	5.56 (3.19)	6.92 (3.64)	<.001
Bathing				
No rehabilitation	.28 (1.61)	2.66 (2.50)	3.23 (2.40)	<.001
Light rehabilitation	.00 (.00)	.09 (.66)	.00 (.00)	.368
Intense rehabilitation	.03 (.41)	.23 (1.05)	1.29 (2.20)	<.001
Washing				
No rehabilitation	.35 (1.29)	3.33 (2.36)	3.65 (2.23)	<.001
Light rehabilitation	.00 (.00)	.00 (.00)	.43 (1.42)	<.001
Intense rehabilitation	.10 (.70)	.46 (1.45)	1.52 (2.31)	<.001
Dressing				
No rehabilitation	3.76 (3.39)	7.77 (3.24)	8.16 (3.24)	<.001
Light rehabilitation	.52 (1.54)	1.03 (2.04)	1.64 (2.55)	<.001
Intense rehabilitation	1.29 (2.27)	3.48 (3.37)	5.03 (3.67)	<.001
Bowel control				
No rehabilitation	6.13 (4.11)	8.94 (2.85)	9.08 (2.71)	<.001
Light rehabilitation	.78 (2.26)	1.98 (3.37)	3.36 (4.33)	<.001
Intense rehabilitation	2.95 (3.71)	6.19 (3.95)	7.19 (3.89)	<.001
Urine control				
No rehabilitation	6.03 (4.16)	8.90 (2.81)	8.79 (2.92)	<.001
Light rehabilitation	.78 (2.26)	1.90 (3.22)	3.19 (4.36)	<.001
Intense rehabilitation	2.85 (3.63)	5.99 (3.96)	6.99 (3.96)	<.001
Use of bathroom				
No rehabilitation	3.76 (3.83)	8.76 (2.88)	8.69 (3.03)	<.001
Light rehabilitation	.34 (1.28)	1.29 (2.21)	2.16 (3.76)	<.001
Intense rehabilitation	1.19 (2.63)	4.37 (3.89)	5.86 (4.19)	<.001
Transference (bed-armchair)				
No rehabilitation	7.02 (4.85)	13.48 (3.04)	13.48 (3.38)	<.001
Light rehabilitation	1.47 (2.96)	6.21 (2.70)	6.21 (3.66)	<.001
Intense rehabilitation	3.44 (3.61)	9.07 (3.85)	10.07 (4.43)	<.001
Mobility				
No rehabilitation	6.67 (5.94)	13.58 (3.79)	13.72 (3.65)	<.001
Light rehabilitation	1.29 (3.45)	3.97 (4.66)	5.09 (5.17)	<.001
Intense rehabilitation	2.72 (4.27)	8.74 (5.36)	10.73 (5.33)	<.001
Going up and down stairs				
No rehabilitation	2.48 (3.31)	7.87 (3.39)	7.94 (3.33)	<.001
Light rehabilitation	.17 (.92)	.60 (1.64)	.95 (1.98)	<.001
Intense rehabilitation	.53 (1.65)	2.48 (3.26)	4.34 (3.82)	<.001

Kruskal-Wallis test.

than those who had intense rehabilitation. These results were similar both in the univariate analysis and the multivariate analysis. Furthermore, early initiation of intense rehabilitation after the stroke appears to have a greater importance than the type of rehabilitation made.^{24,25} Due to the study characteristics data regarding the period from the event to the start of rehabilitation are not available and for this reason we were unable to show them in our results.

Age is associated with a poorer prognosis after suffering from stroke, especially in the elderly over 85 years of age, where comorbidities are greater and their previous

functional status is further impaired than in younger patients.²⁶ In our study age was shown to be a risk factor of functional dependence 8 weeks after the stroke both in the univariate analysis (OR: 1.07; 95% CI: 1.02–1.12) and in the multivariate analysis (OR: 1.09; 95% CI: 1.04–1.15). Some studies^{27,28} demonstrate a lower recovery in older patients, leading in some cases to the indication to participate in specific rehabilitation programmes. However, other studies have been published in which justification for not carrying out a rehabilitation treatment was not found, since functional improvement after the stroke was proven,²⁹ with age

Table 4 Predictive baseline Factors of functional dependence 8 weeks after stroke (n=264).

Variable	Univariate analysis		Multivariate analysis	
	OR (IC 95%)	p	OR (IC 95%)	P
<i>Age</i>	1.07 (1.02–1.12)	.003	1.09 (1.04–1.15)	< .001
<i>Male sex</i>	.73 (.36–1.49)	.395	—	
<i>Mean hospital stay</i>	1.06 (1.01–1.11)	.013	1.04 (.99–1.09)	.096
<i>Type of stroke</i>				
Haemorrhagic	1.00 Ref		1.00 Ref	
Ischaemic	1.32 (.58–2.99)	.505	—	
POCI	.94 (.0–.94)	.918	—	
TACS	2.98 (.86–10.33)	.085	—	
LACI	.61 (.23–1.57)	.308	—	
PACI	2.42 (.75–7.76)	.135	—	
<i>Laterality</i>				
left	1.00 Ref		1.00 Ref	
right	1.37 (.65–2.86)	.401	—	
<i>Rehabilitation</i>				
No rehabilitation	1.00 Ref		1.00 Ref	
Light rehabilitation	6.37 (1.74–23.25)	.005	7.74 (1.91–31.30)	.004
Intense rehabilitation	2.28 (1.08–4.82)	.030	3.14 (1.35–7.31)	.008

LACI: Lacunar stroke; PACI: partial anterior circulation stroke; POCI: posterior circulation stroke; TACS: total anterior circulation stroke.

not being a determining factor for entry to the rehabilitation programmes after a stroke.³⁰ Due to the characteristics of our study, we are unaware of the reasons why some patients carried out light rehabilitation and others intense rehabilitation.

Our study had several limitations. Firstly, the study design was observational and therefore only involved association but not causality. Due to the retrospective characteristics of the study, several variables which could have impacted the final outcome were not collected, such as the time from the beginning of the stroke to rehabilitation and the type carried out, or the presence of comorbidities. Furthermore, one group was smaller than the others (141 vs. 58 vs. 151 patients respectively). Finally, only the functional status of patients was considered, not cognitive or language recovery.

To conclude, our findings suggest that in elderly patients carrying out intense rehabilitation improves the functional status and BADL, compared with light rehabilitation, 8 weeks after suffering from a stroke. We therefore believe it is essential to increase efforts made in the health systems so that neurorrehabilitation services are available to these patients, offering them appropriate rehabilitation therapy to improve their functional status after the stroke.

Financing

None.

Conflict of interests

S.R.M and F.L.E state that this study has been conducted within the context of a research visit in the Department of Nursing of the polytechnic Institute of Braganza.

The other authors have no conflict of interests to declare.

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