

Stroke Rehabilitation Pathways:

how to build a stroke treatment policy.

Pedro Maciel Barbosa

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2. **From the healthcare system to individuals through stroke rehabilitation pathways. Outcomes, information, and satisfaction along 12 months prospective cohort in Portugal.**
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Throughout the work presented in this thesis, I have contributed to study design, data collection, data analysis and interpretation. I was also responsible for drafting the articles for publication and contributing to the final versions.

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List of abbreviations

CCA – Cost-consequence Analysis

COVID-19 – Coronavirus disease 2019

CT – Computerized Tomography

DAILYs – Disability-adjusted Life Years

ESAP – European Stroke Action Plan

ESO – European Stroke Organization

EU – European Union

GBD – *Global Burden of Diseases, Injuries, and Risk Factors Study*

GDP – Gross Domestic Product

HRQoL – Health-Related Quality of Life

ICD – International Classification of Diseases 11th Revision

LACI – Lacunar Cerebral Infarcts

MMSE – Mini-Mental State Examination

mRS – Modified Rankin Scale

NICE – National Institute for Health and Clinical Excellence

NHS – National Health Service

PACI – Partial Anterior Circulation Infarcts

PN – Patient Navigation

POCI – Posterior Circulation Infarcts

QALYs – Quality-adjusted Life Years

SU – Stroke Unit

TACI – Total Anterior Circulation Infarcts

TOAST – *Trial of Org 10172 in Acute Stroke Treatment*

WHO – World Health Organization

Abstract

Pedro Maciel Barbosa
THESIS SUPERVISOR: Professor Helena Szrek
CO-SUPERVISOR: Professor João Firmino Machado, Professor Vitor Tedim Cruz

Stroke Rehabilitation Pathways: how to build a stroke treatment policy.

Stroke impact defies worldwide health, social and economic policies, as a leading cause of mortality and disability globally. Despite considerable advances across the care pathway, post-stroke care is considered disorganized and fragmented even in the best health systems. Across Europe, stroke survivors face inconsistencies in the type and quality of therapies they have access to, and there is a lack of monitoring and evaluation systems.

Recovery from a stroke is an arduous journey which takes months or years of rehabilitation and is frequently incomplete. Robust evidence supports that stroke rehabilitation should be timely, intensive, multidisciplinary, with coordinated transfer across settings, and effectively interfaced with social and healthcare. The challenge is to bridge the gap between clinical guidelines, organizational models, and the actual provision of care, so that the stroke survivor has timely access to health services and, when needed, is easily guided from one service to another without obstacles, delays, or loss of information.

This thesis aims to contribute to the reflection and strategic planning of a new stroke care solution, considering as fundamental axes of its conceptualisation the integration of care, the care pathway of the stroke survivor and the economic evaluation.

The following paragraphs describe the specific objectives defined for this thesis, along with the corresponding methods and main results:

1) *To analyse the evolution of health-related quality of life over the first year after stroke, compare the results with population data, analyse the influence of different levels of stroke severity, and determine predictors of health-related quality of life.*

This study uses data from a one-year prospective cohort study of patients after their first-ever stroke. Patients were assessed four times, once in the first seven days after the stroke and 3, 6 and 12 months after hospital discharge. Individual data were obtained from interviews combined with data from clinical records. A generalised linear regression model was used to determine the independent predictors of health-related quality of life measured using the EQ-5D-3L and SF-6D instruments. The model included as explanatory variables age, gender, education, monthly income, type of residence, occupation, National Institute of Health Stroke Scale (NIHSS), Modified Rankin Scale

(mRS), Barthel Index (BI), Mini-Mental State Examination (MMSE), length of hospitalisation, access to, frequency of, and satisfaction with rehabilitation care.

Our findings demonstrate the negative effects of stroke on health-related quality of life with lower values in stroke survivors than in the general population, regardless of the type of stroke or severity. A decline in health-related quality of life was observed from baseline to the first three months in both indexes, with an increase from 3 months to 12 months. Higher health-related quality of life was associated with lower mRS, NIHSS, age, and length of stay, and with higher BI, MMSE, scholarly, occupation, and rehabilitation care.

2) To analyse the stroke care pathway from three perspectives: health system, health process and patient.

The second paper used the same methodology, sample, and data as the initial study, adding data on care delivery models and service utilisation by stroke survivors. Data at the health system and process level were extracted from patient interviews combined with data from institutional records. The pathway variable was defined by the sequences of different models of rehabilitation care over the first year after stroke.

The results of this study demonstrated the coexistence of nine alternative pathways and eight stroke rehabilitation settings in Portugal. A lack of agreement between clinical guidelines and actual care provision was identified. Regarding the referral model, most patients did not comply with the national standard. There were significant differences in outcomes between the main pathways, suggesting inefficiency and inequity, accompanied by an inadequate level of information and patient satisfaction.

3) To compare the cost-effectiveness of rehabilitation pathways during the first 12 months after stroke.

A decision tree model was used to assess the cost-effectiveness of the different pathways from both the stroke survivor and health care service perspectives (Portuguese National Health Service – NHS). The primary outcome of the study was cost per quality-adjusted life year (QALY), assuming a one-year analysis window. Benefits were calculated from utility data resulting from the assessment of health-related quality of life. Costs were determined based on individual stroke survivor data and regulatory and legal information sources. The benefits and costs of each of the invitation strategies were used to calculate incremental cost-effectiveness ratios (ICERs) and compared with a willingness-to-pay value of €20873 per QALY (i.e., the value of Portugal's gross domestic product per capita). The strategy with the highest ICER value, just below the willingness-to-pay threshold per QALY, was considered the most cost-effective option.

From the economic evaluation, we document that most pathways were not considered cost-effective, and cost analysis revealed a barrier to accessing rehabilitation care according to the pathway. Of the different options, this study defined pathway 3 (short-term unit for the first months followed by care in an outpatient community clinic) as the standard circuit of care for stroke rehabilitation. Pathway 3 was the most cost-effective,

both from stroke survivors and the health care service perspectives. Two other pathways were found to be cost-effective in the primary analysis, namely pathway 1 (rehabilitation inpatient centre in the first months followed by outpatient community clinic) from the survivor's perspective and pathway 7 (outpatient day hospital service in the first months followed by outpatient community clinic) from the health care service perspective. Sensitivity analysis showed that other routes if considered at minimal cost, would be cost-effective.

In conclusion, the results of this thesis show that recent government investments in improving emergency and acute stroke care are not being matched by updated health policies in the rehabilitation phase of stroke in Portugal, with the inherent loss of health gains for the patient. Opportunities for improvement were identified in the monitoring and information system, in the referral process between care models, in the translation of the best available evidence into clinical practice, and in the planning and organisation of the stroke survivor rehabilitation care network.

The literature considers that Portugal is one of the European countries with the greatest potential to reduce the incidence and prevalence of stroke in the coming years, which should motivate a challenge to build a stroke treatment policy based on quality improvement and respecting the necessary balance between financial sustainability and the best possible health outcomes.

Resumo

Pedro Maciel Barbosa
ORIENTADORA: Professor Helena Szrek
CO-ORIENTADOR: Professor João Firmino Machado, Professor Vítor Tedim Cruz

Percursos de Reabilitação: como construir uma política de tratamento do AVC.

O impacto do AVC pressiona as políticas de saúde, sociais e económicas mundiais, sendo uma das principais causas de mortalidade e incapacidade a nível global. Apesar dos avanços recentes, a prestação de cuidados ao sobrevivente de AVC é considerada fragmentada e desorganizada, mesmo nos melhores sistemas de saúde. Além disso, enfrenta inconsistências no tipo e na qualidade entre diferentes países europeus, onde se verifica uma carência de sistemas de monitorização e avaliação.

A recuperação de um AVC é um trajeto árduo que pode demorar meses ou anos, e é muitas vezes incompleto. No entanto, existe evidência robusta a suportar que a reabilitação do AVC deve ser atempada, intensiva, multidisciplinar, deve assegurar uma transferência coordenada entre níveis de cuidados e, deve garantir uma interface eficaz entre o setor social e de saúde. O desafio passa por promover a tradução da orientação clínica e do planeamento organizacional, no desenvolvimento de um circuito de cuidados onde o sobrevivente de AVC tenha acesso oportuno aos serviços de saúde e, quando necessário, seja facilmente guiado de um serviço para outro, sem obstáculos, atrasos ou perda de informações.

Esta tese pretende contribuir para a reflexão e o planeamento estratégico de uma nova solução de cuidados para o AVC, considerando como eixos fundamentais da sua conceptualização a integração de cuidados, o percurso de cuidados do sobrevivente do AVC e a avaliação económica.

Os parágrafos seguintes descrevem os objetivos específicos definidos para esta tese, bem como os respetivos métodos e principais resultados:

1) *Analisar a evolução da qualidade de vida relacionada com a saúde ao longo do primeiro ano após o AVC, comparar os resultados com os dados populacionais, analisar a influência dos diferentes níveis de severidade do AVC, e determinar os preditores da qualidade de vida relacionada com a saúde.*

Este estudo utiliza dados de um estudo de coorte prospetivo de um ano de doentes após o primeiro AVC. Foram avaliados quatro vezes, uma vez nos primeiros sete dias após o evento e após 3, 6 e 12 meses da alta hospitalar. Os dados individuais foram obtidos a partir de entrevistas combinados com dados de registos clínicos. Um modelo de regressão linear generalizado foi utilizado para determinar os preditores independentes da qualidade de vida relacionada com a saúde medidos através dos instrumentos EQ-

5D-3L e SF-6D. O modelo incluiu como variáveis explicativas a idade, o sexo, a escolaridade, o rendimento mensal, o tipo de residência, a ocupação profissional, a *National Institute of Health Stroke Scale (NIHSS)*, a *Modified Rankin Scale (mRS)*, o Índice de Barthel (IB), o *Mini-Mental State Examination (MMSE)*, o tempo de internamento, o acesso, frequência e satisfação com os cuidados de reabilitação.

Os nossos resultados demonstram os efeitos negativos do AVC na qualidade de vida relacionada com a saúde, com valores mais baixos nos sobreviventes de AVC do que na população em geral, independentemente do tipo de AVC ou da sua severidade. Foi observado um declínio na qualidade de vida relacionada com a saúde desde a avaliação inicial até aos primeiros três meses em ambos os instrumentos, com um aumento a partir dos 3 meses até aos 12 meses. Uma maior qualidade de vida relacionada com a saúde foi associada a um valor menor na escala mRS, na escala NIHSS, de idade e de tempo de internamento, a um valor maior no BI, no MMSE, a um nível superior de escolaridade, e á existência de ocupação profissional e acesso e frequência de cuidados de reabilitação.

2) *Analisar o percurso do tratamento do AVC sob três perspetivas: sistema de saúde, processo de saúde e paciente.*

O segundo estudo utilizou a mesma metodologia, amostra e dados do estudo inicial, adicionando dados relativos aos modelos de prestação de cuidados e utilização de serviços pelos sobreviventes de AVC. Os dados ao nível do sistema e do processo de saúde foram extraídos de entrevistas com doentes combinadas com dados de registos institucionais. A variável percurso foi definida através das sequências de diferentes modelos de cuidados de reabilitação ao longo do primeiro ano após o AVC.

Os resultados deste estudo demonstraram a coexistência de nove percursos alternativos e oito locais de prestação de reabilitação de AVC em Portugal. Foi identificada uma falta de conformidade entre as diretrizes de boas práticas e a real prestação de cuidados. No que respeita ao modelo de referenciação, grande parte dos doentes não cumpriu a norma nacional recomendada pela Direção Geral de Saúde. Verificaram-se diferenças significativas nos resultados entre os principais percursos, sugerindo ineficiência e iniquidade, acompanhado de um nível inadequado de informação e satisfação dos doentes.

3) *Comparar a custo-efetividade dos percursos de reabilitação durante os primeiros 12 meses após AVC.*

Foi utilizado um modelo de árvore de decisão para avaliar a relação de custo-efetividade dos diferentes percursos, tanto na perspetiva do sobrevivente de AVC, como do prestador que neste caso constituiu o Serviço Nacional de Saúde (SNS). Foi considerado como *outcome* primário do estudo o custo por *quality-adjusted life year* (QALY), assumindo uma janela temporal de análise de um ano. Os benefícios foram calculados a partir de dados de utilidade resultantes da avaliação da qualidade de vida relacionada com a saúde. Os custos foram determinados com base em dados individuais dos

sobreviventes de AVC e fontes de informação normativa e legal. Os benefícios e custos de cada uma das estratégias de convite foram utilizados para calcular rácios de custo-efetividade (*incremental cost-effectiveness ratios,* designados ICER) e comparados com um valor de disponibilidade a pagar de 20873€ por cada QALY (i.e., o valor do produto interno bruto *per capita* de Portugal). A estratégia que apresentou o valor de ICER mais elevado, imediatamente abaixo do patamar de disponibilidade a pagar por QALY, foi considerada como a opção mais custo-efetiva.

Da avaliação económica, documentamos que a maioria dos percursos não foi considerada custo-efetiva, e a análise de custos revelou constituir uma barreira no acesso aos cuidados de reabilitação de acordo com o percurso. Das diferentes opções, este estudo definiu o percurso 3 (unidade de convalescença nos primeiros meses seguido de cuidados em unidade convencionada) como o circuito padrão de cuidados para a reabilitação do AVC. O percurso 3 foi o mais rentável, tanto do ponto de vista do sobrevivente, como do SNS Dois outros circuitos foram considerados custo-efetivos na análise primária, nomeadamente o percurso 1 (centro de reabilitação nos primeiros meses seguido de cuidados em unidade convencionada), na perspetiva do sobrevivente, e o percurso 7 (serviço hospitalar ambulatório nos primeiros meses seguido de cuidados em unidade convencionada), na perspetiva do SNS. A análise de sensibilidade mostrou que outros percursos, se considerados a um custo mínimo, seriam custo-efetivos.

Em conclusão, os resultados desta tese demonstraram que os recentes investimentos governamentais na melhoria dos cuidados de emergência e de gestão do AVC agudo não estão a ser acompanhados pela respetiva atualização das políticas de saúde na fase de reabilitação do AVC em Portugal, com a inerente perda de ganhos em saúde para o doente. Identificaram-se oportunidades de melhoria ao nível do sistema de monitorização e informação, ao nível do processo de referenciação entre modelos de cuidados, na tradução da melhor evidência disponível para a prática clínica e no planeamento e organização da rede de prestação de cuidados de reabilitação do sobrevivente de AVC.

A literatura considera que Portugal é um dos países europeus com maior potencial para reduzir a incidência e prevalência do AVC nos próximos anos, o que deve motivar um desafio para a construção de uma política de tratamento do AVC baseada na melhoria da qualidade e respeitando o necessário equilíbrio entre a sustentabilidade financeira e os melhores resultados possíveis em saúde.

1
Introduction

The introduction is organized into three sections. First, we approach stroke in its definition, classification, and epidemiological evolution as a cause of mortality and disability. In the second section, we describe the phenomenon of care integration and its organizational translation into circuits and models of rehabilitation for stroke survivors. Finally, in the third section, we analyse the economic evaluations available for the treatment of stroke patients.

1.1 STROKE

1.1.1 DEFINITION AND CLASSIFICATION

In the International Classification of Diseases 11th Revision (ICD-11) of the World Health Organization (WHO), stroke is defined as an acute syndrome characterized by a focal or global deficit of brain function, with the sudden development of symptoms that persist for a period longer than 24 hours, confirmed by neuroimaging in the clinically relevant area. This neurological dysfunction can be caused by focal ischemic infarction in one or several sites of the brain, or by haemorrhage in the brain parenchyma, ventricular system, or subarachnoid region [1].

Faced with a comprehensive condition, stroke classification assumes a fundamental role in the stratification and differentiation of clinical care, and strategic planning of the healthcare model to be followed. *The Oxford Community Stroke Project classification developed by Bamford et al* suggested a descriptor of stroke subtypes, useful etiologically and in defining prognosis. According to this classification, stroke can be classified into two main categories: (i) Ischemic stroke and (ii) Hemorrhagic stroke. Four subcategories of ischemic events have been suggested based on the presented signs and symptoms: lacunar cerebral infarcts (LACI); total anterior circulation infarcts (TACI); partial anterior circulation infarcts (PACI); and posterior circulation infarcts (POCI). The classification is based on the clinical and anatomical features of the lesion. Although the work has been predominantly dedicated to ischemic injuries, the classification is also used for haemorrhagic events, according to the result of neuroimaging. About haemorrhagic stroke, this classification defines two subtypes, intracerebral haemorrhage and subarachnoid haemorrhage. [2].

An alternative system for the categorization of ischemic stroke subtypes based primarily on aetiology was developed for the *Trial of Org 10172 in Acute Stroke Treatment (TOAST)*. The TOAST classification defines five subtypes of ischemic stroke: 1) large vessel atherosclerosis, 2) cardioembolism, 3) small vessel occlusion (lacunar), 4) stroke of determined aetiology, and 5) stroke of undetermined aetiology [3].

A stroke survivor faces a complex and challenging recovery, which implies months or years of motor and cognitive rehabilitation [4]. There are far-reaching consequences in a person's life, including loss of memory and concentration, impaired communication and swallowing, impaired gait and movement control, social isolation and dementia, decreased productivity at work, and multiple functional limitations as simple as dressing and eating [5.6]. Stroke rehabilitation is often incomplete, compromising long-term *health-related quality of life* (HRQoL) [7]. In fact, after 15 years, two-thirds (63%) of survivors are living with a disability, nearly two out of five survivors (39%) have depression, and over a quarter (30%) manifest cognitive impairment. Furthermore, stroke patients are much more likely than other people to be living with another disease and to suffer a new cerebrovascular event [8].

1.1.2 EPIDEMIOLOGY AND BURDEN OF DISEASE

Stroke is one of the leading causes of death and disability worldwide which represents a high economic impact of post-stroke treatment and care. The latest results from the 2019 *Global Burden of Diseases, Injuries, and Risk Factors Study (GBD)* show that while age-standardized mortality rates and stroke prevalence have declined over time, the burden of disease per stroke remained high [9].

Globally, stroke was considered the second leading cause of death (5.5 million deaths), after ischemic heart disease. At the same time, it was the second most common cause of *disability-adjusted life years* (DALYs), accounting for 116.4 million DALYs in 2016, rising since 1990 with 95.3 million DALY.

The global number of deaths due to ischemic stroke (2.7 million) is slightly lower than the number of deaths due to haemorrhagic stroke (2.8 million deaths), as is the number of DALYs (51.9 vs 64.4 million). The world's highest stroke incidence rates were seen in East Asia, especially China, followed by Eastern Europe. Globally, data from 2019 indicate that women die less (2.6 vs 2.9 million deaths) and suffer fewer DALYs (50.8 vs 65.6 million) from strokes than men. The stroke age-specific incidence was similar between men and women younger than 55 years, but significantly higher for men in the 55-75 age group [10]. The age-standardized incidence rates worldwide are depicted in Figure 1.

As populations age, emergency care in the acute phase improves, and most “high and medium income” countries undergo the epidemiological transition from infectious diseases to non-communicable diseases as the predominant cause of morbidity, the

burden of stroke is expected to increase further [11]. Although globally the age-standardized incidence declined between 1990 and 2016, there were 80.1 million prevalent cases of stroke worldwide in 2016, of which 84.4% were ischemic, which corresponds to an increase of 7 % [10].

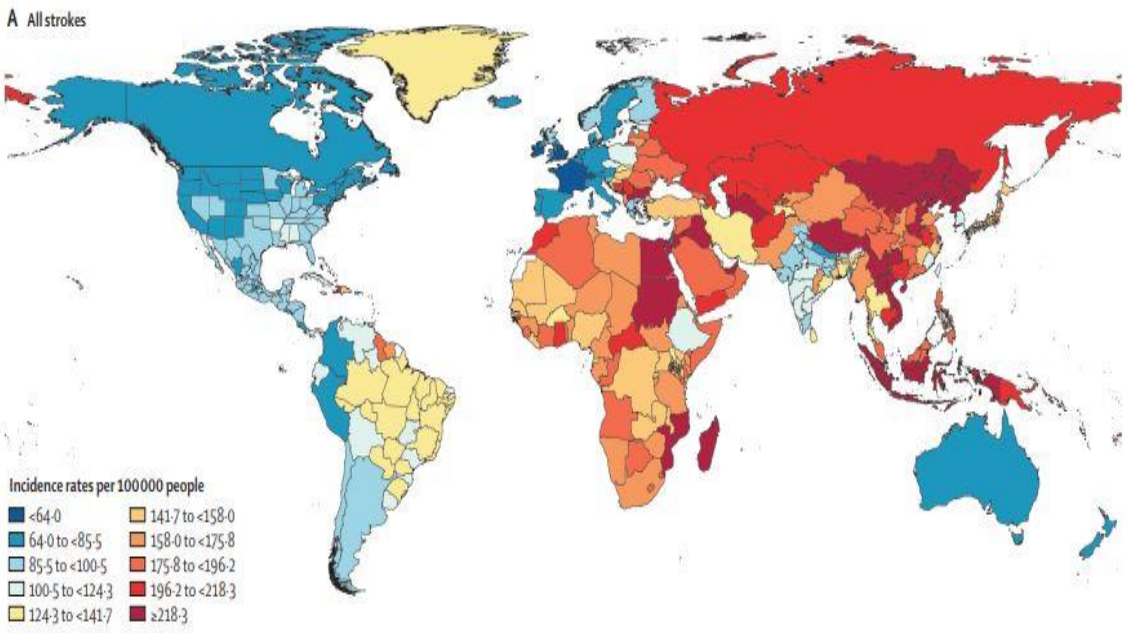


Figure 1. Age-standardised stroke incidence rates per 100000 people by stroke type and country, for both sexes, 2019. (Source: *Global Burden of Disease Study 2019* [11]).

Analysing European data, and in the European Union (EU), stroke is confirmed as the second most common cause of death and one of the main causes of disability in adults [12].

However, there are substantial differences in stroke burden across Europe, both in terms of mortality and DALYs. In 2017, there were an estimated 1.12 million incident stroke cases, 9.53 million prevalent stroke cases, 0.46 million stroke deaths, and 7.06 million DALYs lost. Strokes account for about 8% of all deaths, and there are wide variations in stroke mortality rates between countries. Rates are around three to four times higher than the EU average in Bulgaria, Romania and Latvia. And they are lowest in countries such as France, Luxembourg and Spain, with death rates around half the EU average. In terms of disability, stroke ranked first among neurological disorders in age-standardized DALYs in Central and Eastern Europe and second in Western Europe [10].

In 2047, population size is expected to be relatively stable, however, there will be 40,000 more incident stroke cases (3% increase) and 2.58 million more prevalent cases (27% increase) compared to 2019. A phenomenon similar to the global trend is due, in large part, to projected changes in the age structure of the European population and, in particular, to the increase in the number of residents aged ≥70 years, which reflects the ageing of the population [13]. Figure 2 demonstrates the estimated average annual percentage changes in the crude rates of stroke between 2018 and 2047.

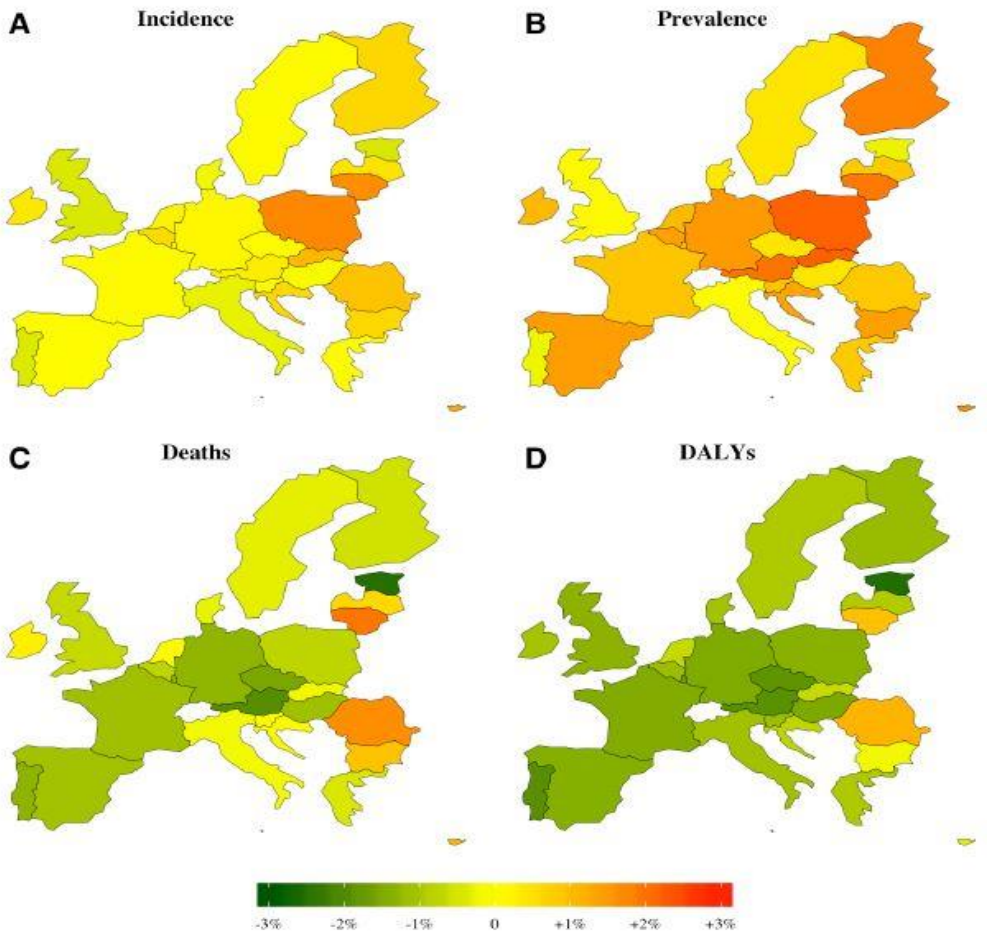


Figure 2. Projected average annual percentage change in the crude rates of incidence, prevalence, death, and disability-adjusted life years (DALYs) from 2018 to 2047.

(Source: *Burden of Stroke in Europe* [14]).

Portugal has stroke rates higher than the European Union average, positioning stroke as the main cause of death in recent decades [14]. In 2016, it accounted for 14,112 deaths, 27,447 new cases, and 187,018 DALYs lost. Every hour three Portuguese people suffer a stroke, one of which does not survive and at least another one has disabling sequelae [10]. As Portugal has been a country with tendentially higher stroke incidence rates in recent years, it has a greater capacity for improvement and sharp declines are projected. In fact, between 2018 and 2047, it is estimated that Portugal will register one of the biggest reductions in incidence (-1.57%) and prevalence (-1.3%) in Europe [13].

Given the magnitude of the disease burden, its economic costs challenge the sustainability of health systems [15]. Approximately 3 to 4% of total healthcare expenditures in Western countries are spent on stroke [16], and the American Heart Association projects that the global cost of stroke will increase from €98 billion in 2012 to €237 billion by 2030 [17]. In Europe, the socio-economic impact of stroke is high and increasing over time. The estimated annual total cost in the EU was €38 billion in 2012, €45 billion in 2015 and €60 billion in 2017 [18].

In 2017, stroke cost 32 European countries €60 billion, with healthcare accounting for €27 billion (45%), representing 1.7% of total healthcare expenditure. In social terms, across Europe approximately 43 million days were spent in nursing homes/residential homes due to stroke, representing a total cost to European welfare systems of €5 billion (8%). However, 47% (€29 billion) of the economic burden of stroke occurred in areas not directly related to health or social care. Productivity losses were valued at €13 billion (20%), split evenly between premature deaths and lost workdays. A total of 1.3 billion hours of informal care were provided to stroke survivors, costing Europe €16 billion (27%) [19].

Looking at European healthcare spending on stroke, out of a total of €27 billion, €16 billion (62%) was due to hospital admissions, followed by outpatient care (€4.7 billion, 18%), primary care (€3.3 billion, 13%), medication (€1.3 billion – 5%) and emergency care (€919 million, 3%). Stratifying the costs per citizen, it appears that the annual costs of stroke-related care in Europe were equivalent to €59 per person, ranging from €11 in Bulgaria to €140 in Finland [19]. Figure 3 shows the direct and non-direct healthcare costs of stroke per capita in 2015 in Europe.

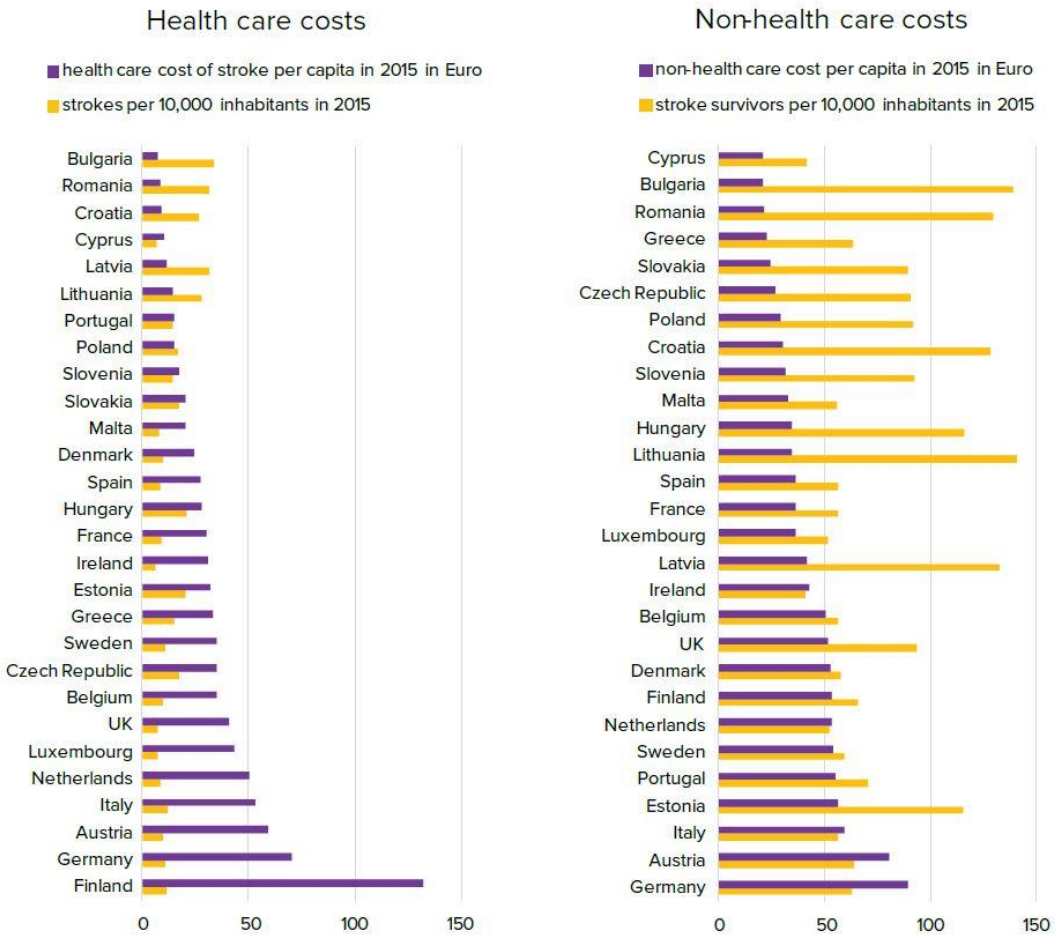


Figure 3. Health care and non-health care costs of stroke per capita in Europe and crude incidence and prevalence of stroke per 10,000 inhabitants in 2015. (Source: *The Burden of Stroke in Europe Report*, Stroke Alliance for Europe [47]).

The results of the sensitivity analysis showed that functional capacity losses had the greatest impact on total stroke costs (9% variation), followed by health resource costs. This item had the second greatest impact on total stroke costs (5% variation) [19].

In Portugal, stroke costs reached a total value of €783 million in 2017, which corresponds to 0.40% of gross domestic product. Of this amount, €257 million is spent on health care, which represents 1.53% of the global health budget and 33% of total stroke costs. In terms of social care, Portugal spent €15 million (2%), lost €207 million in lost productivity (26%), and €304 million in informal care (39%). In terms of health care, economic consumption breaks down as follows: €91 million (36%) were dedicated to inpatient hospital care, followed by outpatient care (€60 million, 24%), emergency care (€44 million, 17%), primary care (€37 million, 14%), and medication (€24 million – 9%) [19].

1.2 REHABILITATION OF THE STROKE SURVIVOR

1.2.1 CARE INTEGRATION

The EU currently lacks sustainable models of health and social care delivery. Current health systems face challenges for which they are not yet prepared, despite the concept of integrated care and citizen-centricity being part of the health lexicon for over two decades. This is because they were conceived in and for contexts very different from those we find today, namely about demographic changes, especially the tendency towards an ageing population and the increase in the burden of disease, strongly related to multiple morbidity [20], a characteristic of stroke.

The varied offer of health services, most of the time, does not take into account the needs of the person, leading them to a disconnected and complex path, with little or no linkage between settings, and without integration either between the different levels of health care or between these and social care [21]. Effectively, the existence of multiple care options and alternatives can be seen as positive from the perspective of person-centred care, where healthcare solutions are adapted to the needs of patients [22]. However, the fragmentation of configurations and pathways is not always synonymous with more developed health systems.

The process of care fragmentation through differentiation of care can have implications for all stakeholders [23]. The paying stakeholder loses coordination and effectiveness. The provider becomes solely responsible for his intervention linked to his organization's own culture [24]. The patient is disoriented throughout the health system, demonstrating low levels of information about the therapeutic options available, as well as the specificity of each level of intervention [25]. This explains the loss of access and quality, a scenario that usually leads to lower health gains and increased costs [26].

The need for the care of a stroke survivor is so complex and multidimensional that a multidisciplinary and long-term response is often mandatory. At the same time, stroke

recovery encompasses a whole spectrum of care, including rehabilitation and long-term care with the need for inpatient, outpatient, and community care [27], so its study and planning should take place in the form of integrated circuits, and not by delimited levels of intervention or individual provision of customized solutions.

It is important to overcome the major limitations of the current performance of health systems that result from sectorization and vertical organization [23], which led to a lack of coordination and discontinuity of health care [25]. The care integration process is essential to guarantee the sustainability of health systems. It is a multi-level, multimodal delivery and access-oriented strategy designed to address complex health needs by achieving better coordination of planning and financing processes across the continuum of care. It is not an end in itself, it is a means of optimizing system performance and obtaining quality outcomes for the stroke survivor [24].

1.2.2 STROKE CARE PATHWAY

In the care pathway for stroke survivors, the emergency phase, with intensive and acute care, was one of the phases of care that underwent the greatest advancement and development in recent decades. This improvement in care, however, may have led to an increase in the number of people who survive with sequelae, with major implications for health economics and the social burden of countries [29]. This increased burden of disease will soon severely affect the whole of Europe, with a particular impact on countries where inequalities in stroke care are greatest. Implementing coherent and understandable approaches to tackling stroke must become a priority for policymakers [28].

As with other non-communicable diseases such as cancer, specific stroke treatment pathways, standardized processes and based on the best available evidence, best care practices are needed [28]. However, many European countries still do not have a specific and comprehensive strategy to deal with stroke. To fill this gap, the European Stroke Action Plan (ESAP) 2018–2030 —a collaborative project of the European Stroke Organization (ESO) and the patient organization Stroke Alliance For Europe—was launched at the European Stroke Organization Conference and the European Parliament in May 2018. ESAP identified priorities for stroke treatment and research and set Europe-wide targets to be achieved by 2030: reduce the absolute number of strokes in Europe by 10%; treat at least 90% of all patients in specialized stroke units; and develop national stroke plans in all European countries [20].

Since the beginning of the COVID-19 pandemic, reduced or delayed access to rehabilitation care by stroke survivors has been reported in several European countries, due to the restriction of resources directed towards the provision of pandemic acute care, a phenomenon that has further delayed stroke treatment development processes [30].

To optimize autonomy, functional independence, participation and quality of life, rehabilitation is a powerful tool and one of the fundamental stages of the stroke care circuit [31]. Rehabilitation, in essence, represents a set of necessary interventions when a person has limitations in their daily physical, mental and social functioning, so its clinical role translates into a brutal impact on the lives of survivors, their families and communities while contributing to the sustainability of each country's health and social system [32].

However, in contrast to the acute phase of treatment, rehabilitation and later phases of stroke treatment have been neglected by health systems as well as in the research field [33]. The revolution in the recent past of emergency care with an impact on the stroke burden [34], deserves an equally effective response from the next step in the pathway of care at the level of rehabilitation, given the risk of losing the accumulated potential of transformation of the lives of its survivors. Although effective rehabilitation is considered a cost-effective strategy, it has not been prioritized in many countries and is still under-resourced in the total stroke management budget [35]. This situation probably stems from an installed perspective that considers rehabilitation a resource strategy, when preventive, promotional or curative interventions fail, or, as a specific service for disability, necessary only for some population targets [36].

The provision of post-stroke care is considered by the literature to be disorganized and fragmented even in the best health systems [37]. There is robust evidence to support that stroke rehabilitation should be timely, intensive, multidisciplinary, with coordinated transfer between settings and with an effective interface between social and community care [29]. However, the challenge of bridging the gap between clinical guidelines, organizational models, and care provision itself has failed.

There are no published standards of practice and universally accepted organizational models for a rehabilitation pathway in post-stroke patients in European countries, where different structures of health services and payment systems generally determine different pathways of care [38,39, 40]. Stroke survivors across Europe face inconsistencies in the type and quality of therapies they access. Generally, the different therapies and multidisciplinary treatments depend on where the patients live, with differences even within the same country [41]. Waiting times are too long for them to have their immediate rehabilitation needs assessed and therapies started, and the rehabilitation they have access to is not intensive enough. The intervention period is often short, and frequently it does not address such issues as relevant depression and cognitive impairment. Very few people receive follow-up assessments and long-term support is scarce [41,42].

Recent stroke study reports have pointed to the fact that stroke rehabilitation across Europe is not widely monitored or referenced in terms of health policies aimed at increasing the quality of care [41,43]. A minority of countries, such as Sweden and the UK, have well-established audit programs [43], but most countries either lack complete

stroke survivor care response tracking programs or have fragmented data collection systems for quality improvement [42].

When we analyse the patient-level data, the global perception of care reveals that current models of rehabilitation of stroke survivors do not respond to expectations. In fact, according to the literature, stroke patients consider that social and healthcare services do not meet all their needs. For example, in a UK study, 59% of patients reported unmet clinical needs [44]. On the other hand, many survivors express dissatisfaction with the quality of long-term support, its continuity, scope, and coordination [45].

Recent data show that stroke treatment services in Portugal are among the least developed in Europe [46], with scarce and outdated information on the context of stroke rehabilitation [43]. In 2019, Portugal comprised the ninth decile of the universal health coverage index of the Global Burden of Diseases study, with stroke treatment constituting the worst of the 23 health coverage indicators [46].

New care delivery scenarios must be designed to meet the targets set for 2030 by the Stroke Action Plan [18]. It is also imperative to bridge the gap between the rhetoric surrounding unsustainable health systems and investing in the transformative change that is required for the widespread adoption of integrated care models that promote effective navigation through complex health systems [47].

1.2.3 PRINCIPLES OF STROKE REHABILITATION

As most stroke patients survive, the greatest effect on their health status is usually caused by the long-term consequences for themselves and their families. Although there have been relevant medical developments in acute management recently, most post-stroke care continues to rely on rehabilitation interventions [29].

Stroke rehabilitation is heterogeneous due to its pathophysiological nature. The long-term effect of stroke is determined by the site and size of the initial injury, and the duration of subsequent recovery [27]. Recovery is a complex phenomenon that occurs by a combination of spontaneous processes dependent on stimulation and learning, which include distinct steps such as restoring the functionality of damaged neural tissue, reorganizing partially preserved neural pathways to relearn lost functions, and improving the gap between limited skills and the demands of the environment [48]. Although the results and the individual recovery patterns obtained are different, several cohort studies suggest that the recovery prognosis of bodily functions and activities is predictable in the first days after stroke [48,49].

Strategic principles underpin the stroke rehabilitation process, and some have been studied in randomized trials and systematic reviews [27]. Robust evidence supports the principle of multidisciplinary care as the basis for stroke rehabilitation [34, 50]. On the other hand, good rehabilitation outcomes seem to be strongly associated with high

motivation and involvement of survivors and their families. In this sense, the literature points out that the definition of goals that reproduce the specific rehabilitation objectives of an individual can improve the overall recovery result [51]. Third, task-specific and context-specific training are well-accepted principles in motor learning, which suggests that rehabilitation should target goals relevant to patients' needs, and should preferably take place as integrated into the community as possible [52]. Finally, different systematic reviews explore the impact of high-intensity therapy on recovery after stroke. Although there are no clear guidelines on the best levels of practice, the principle that intensive training is useful is widely accepted by the available evidence [53, 54]. The research on integrated care pathways is limited [55].

1.2.4 ORGANIZATIONAL MODELS OF STROKE REHABILITATION

The organization of stroke services is a current issue and deserves investment in terms of research and translation into practice [27]. This interest reflects an increased awareness of the public health implications of stroke [34]. Simultaneously, there is recognition that how services are organized has an important impact on the survivor's health outcome [56].

An integrated stroke rehabilitation care pathway should aim to meet the health needs of patients and caregivers effectively, efficiently, and equitably. The main goal is to respond to these needs through rapid functional diagnosis and prognosis, as well as early rehabilitation care and ongoing support. An integrated stroke rehabilitation service should provide these components in a coordinated and comprehensive manner, including a suite of services adaptable to most survivors [23]. The literature points to some organizational solutions that fulfil these assumptions, which are described below.

The Stroke Unit (SU) represent the solution with the greatest scientific maturity in the first phase after the stroke. In most developed countries, stroke patients are admitted to hospitals and there is robust evidence to indicate that this is probably the ideal model of care in an early stage [34, 57]. Admission must include a rapid assessment and diagnosis at an SU, where care is provided by a specialized multidisciplinary team. This team should be composed of doctors, nurses, physiotherapists, occupational therapists, speech therapists and social workers, whose work is coordinated through regular meetings [57]. Rehabilitation and discharge planning should start as early as possible and involve patients and families.

There is moderate-quality scientific evidence that patients who receive SU care are more likely to be alive, independent, and living in their own homes one year after the event. The apparent benefits were independent of the effect of the variables: age, gender, initial severity, or type of stroke. In survivors admitted to SUs, no increase in the length of hospital stay is observed, although this data presents some uncertainty [34]. Patients with different ages and severity of symptom profiles seem to benefit from this organizational model [58].

Care in units dedicated to stroke patients comprises different types of organization of hospital care, namely: i) stroke units that respond only in the acute phase and provide early discharge within seven days or so; ii) stroke units that accept patients after hemodynamic stabilization, usually after seven or more days, and focus on the long-term rehabilitation component; iii) stroke units that accept acutely ill patients but also provide rehabilitation for at least several weeks if needed [34].

Some studies include organizational models that, to a certain extent, involve the principles of an SU, such as mixed rehabilitation services where a multidisciplinary team provides a generic rehabilitation service, but not exclusively for people with stroke, and mobile stroke teams, where a multidisciplinary peripatetic team offers care in different hospital services [34].

While there is more consolidated evidence for comprehensive SUs (those that combine acute care and rehabilitation), there is some evidence of the effectiveness of single rehabilitation units [57], this is why the literature suggests different solutions depending on the setting of the hospital unit. Hospitals that receive fewer patients may plan to combine all care into one comprehensive unit. Meanwhile, hospitals with a higher number of stroke cases may need to consider providing some long-term rehabilitation in a separate stroke unit. In such circumstances, it is essential that these units are adequately staffed, and care is closely coordinated with other parts of the stroke service [23].

However, many important questions about stroke service delivery remain robustly unanswered. It is still unclear whether there are effective alternatives to hospital care and how care can best be provided after discharge [50]. The conventional approach to stroke care generally includes a period in the hospital with planned discharge when the patient has recovered sufficiently to return home with or without support. One of the main areas of concern for patients and their caregivers is the transition from being cared for in the hospital by a team of professionals to being at home under the responsibility of themselves and their caregivers, which often generates a feeling of abandonment [59].

Organizational models of rehabilitation for stroke survivors after hospital discharge find less support in the available literature [27]. However, two solutions are identified: i) early discharge teams with home support and ii) long-term rehabilitation units.

Supported early discharge services have been developed to attempt to improve the transition between the hospital and the community by accelerating home discharge and providing the rehabilitation team with the patient's home environment [60, 61]. Some arguments in favour of these services are summarized as a better partnership between patient and therapist, greater patient motivation by focusing the process on more realistic rehabilitation goals, provision of multidisciplinary rehabilitation in a more relevant context for the person, greater focus on self-directed activities and promoting a more realistic attitude towards future recovery. These services have been variously

referred to as 'early discharge services with home support', 'accelerated discharge schemes' and 'post-discharge support services [61].

This care solution appears to be most effective for a subgroup of patients with mild to moderate disability [50, 62]. The most recent systematic review of this organizational model argues that early discharge teams, equipped with appropriate resources and coordinated information within a multidisciplinary team applied to a selected group of stroke patients, can reduce long-term dependence and hospital admission, institutional care, as well as reducing the length of hospital stay. The results are inconclusive for services without the guarantee of a coordinated multidisciplinary team. No adverse impact was observed on the mental and subjective health status of patients or caregivers, nor hospital readmission [50]. However, the effective implementation of early discharge services with home support is complicated by the possible interaction with existing outpatient and community services, in addition to pressing the existence of many human resources. At present, these services are not widely available [27].

Another solution provided in the literature for post-discharge care is long-term rehabilitation units. This experience generally indicates a very uneven provision of ongoing support, rehabilitation, and post-stroke needs review. An important number of clinical trials have been carried out that address the issue of rehabilitation and long-term clinical support. Results show that stroke patients can achieve health gains with additional care, but the cost and full benefit of such services are unclear [23]. Indeed, the availability of physiotherapy, occupational therapy or a multidisciplinary rehabilitation team care for stroke patients living at home may prevent deterioration in activities of daily living, although the absolute effect was modest. No clear information has been found on the optimal intensity of this intervention [67].

In a study of caregivers and stroke patients, they were asked to identify the components of a good stroke service. The five most frequent comments were the desire to have: assistance in services for stroke patients; access to teams fully trained in the specific needs of stroke patients; availability of comprehensive information for patients and caregivers; support teams for the patient's transition from hospital to home; and a qualified contact available to answer questions and help with guidance within the delivery system [67].

1.2.5 REHABILITATION OF STROKE IN PORTUGAL

Concerning Portugal, the country has a health system based on a public National Health Service (NHS), universal and progressively free of charge, which includes various models of care for stroke survivors. The fragmentation of care options is accompanied by multiple possible pathways, which are not accompanied by the corresponding National Stroke Plan.

In fact, in Portugal, care for stroke survivors depends mainly on care structures under the supervision of the Ministry of Health, which is responsible for health services, and the Ministry of Labour and Social Solidarity, which is responsible for social care and benefits, such as pensions, unemployment and invalidity. In the case of a stroke patient, the care network becomes even wider and can be made up of several entities: the NHS (hospitals, rehabilitation units of various types, primary health centres), Social Security (financial support and social support care for patients and families), Private Institutions of Social Solidarity, non-profit organizations that directly provide most of the formal social care services to patients and families, *Misericórdias* (social solidarity organizations that operate according to catholic principles with a role to the community), religious entities (moral, financial and material support), City Councils and Parish Councils (expected to provide, for example, technical support and formal care), Firefighters (offer transport services based on cooperation agreements with the Ministry of Health), and other private rehabilitation clinics and service providers relevant to the patient (e.g., gyms) [68].

At the level of specific rehabilitation care, it is important to define two distinct phases: i) the intra-hospital phase, and ii) the post-hospital phase.

At the in-hospital rehabilitation stage, four different solutions can be identified: stroke units intended strictly for the acute phase, stroke units that guarantee the acute phase and part of the sub-acute phase; mixed rehabilitation inpatient units where a multidisciplinary team provides a non-exclusive rehabilitation service for people with stroke; and general inpatient units that guarantee mobile rehabilitation [69].

In global terms, 35 SUs were identified in Portugal in 2021 [70]. Data collected revealed that, in 2019, among the approximately 25,000 patients hospitalized annually for ischemic or haemorrhagic stroke, around 50% are treated in an SU, a percentage that has progressively increased over the years. Of 25,105 patients admitted for stroke in public hospitals, 12,996 were admitted to SU: 9,841 for ischemic stroke, of which 2,467 were treated with thrombolytic drugs, and 2,057 underwent endovascular thrombectomy treatment [71].

According to the technical definition in Portugal, the stroke unit must be made up of a multidisciplinary team of medical resources from various specialities, which must include neurology and internal medicine, must ensure a coordinator who must be an internist or a neurologist, must provide 24-hour stroke diagnosis and therapy, and of multiplanar computerized tomography (CT) equipment, with the protocol for Angio CT scan and magnetic resonance imaging, must include an allocation of between 7 to 9 beds and must ensure the availability of ultrasound equipment that allows performing a cardiac Doppler echo, of the neck and transcranial vessels [72, 73].

In Portugal, in terms of the post-hospital rehabilitation stage, eight rehabilitation care settings are identified as follows: Convalescence Unit (Short-term Unit), Medium Duration and Rehabilitation Units (Medium-term Unit), Long-term and Maintenance Units; (Long-term Unit), Regional Specialized Rehabilitation Centres (Rehabilitation

Centres), Integrated Continuing Home Care Teams (Home-based), Physical Medicine and Hospital Rehabilitation with outpatient care (Hospital), Conventional Rehabilitation clinic (Community clinic), and Private Clinic.

The Short-term, Medium-term, Long-term, and Home-based units are included in the National Network of Integrated Continuing Care and are regulated by Law No. 101/2006 [74]. Hospital services and Specialized Regional Rehabilitation Centres are regulated by the National Referral Network for Physical Medicine and Rehabilitation [75]. Community and Private clinics are regulated by Law No. 500/99 [76].

In terms of the process of referral and definition of rehabilitation care, the National Standard for Clinical Guidance indicates that in cases of a mild stroke, the patient is referred, preferably, to outpatient hospital treatment or a rehabilitation centre around the residence. In moderate stroke, in patients aged less than 75 years and in patients with severe stroke aged less than 55 years and good physical resistance, there is an indication for specialized hospitalization, which guarantees the execution of an intensive rehabilitation therapeutic plan. After the initial phase of rehabilitation, this can be completed in a hospital outpatient clinic or an outpatient rehabilitation centre in the area of residence. In moderate stroke, in patients over 75 years of age and patients with severe stroke over 55 years of age, there is an indication for initial hospitalization in medium-term integrated continuing care and rehabilitation units or short-term units, with a less intensive rehabilitation program. If these patients have a favourable functional and clinical evolution, have acquired the physical capacity to comply with an intensive rehabilitation therapeutic plan (> 3 h) or need more specific or differentiated interventions, they are referred for specialized hospitalization [77].

Of the eight available settings, four are administered by the Ministry of Health (Short-Term, Home-based, Hospital, Regional Rehabilitation Centre), and two are simultaneously part of the Ministry of Health and Ministry of Labour and Social Solidarity (Medium and Long-term). In addition, Private and Community clinics, which, being private, have an agreement with the Ministry of Health [74, 75, 76].

In three configurations, the NHS assumes the dual role of funder and provider (Home-based, Hospital, Regional Rehabilitation Centre), while in the Short-, Medium- and Long-term Unit settings and community clinic the NHS finances, but care is provided by a social or private partner. In private clinics, the funder and provider are private [74, 75, 76].

Among the seven options financed by the NHS, five are completely free for the patient and in two the payment varies according to the per capita income of the patient's household (Medium- and Long-term). In the private sector, the patient fully covers payment [74, 75, 76].

Regarding the rehabilitation process, the data show that the period of each configuration varies between a maximum period of care of 30 days in the Short-term units and unlimited time in the Community and Private clinics [74, 75, 76].

In terms of frequency, intensity and quality of care, there is no normative publication on the subject, nor follow-up reports, monitoring or evaluation of stroke survivor rehabilitation results in any of the eight care models. There are only legal norms regarding the organization and equipment of spaces and clinical responsibility.

Access to multidisciplinary care is heterogeneous across settings according to the normative definition. According to the National Network of Integrated Continuing Care, the Short-term and Home-based settings do not guarantee occupational and speech therapy or a rehabilitation specialist doctor, and the Medium and Long-term units do not guarantee speech therapy. Hospital services and Regional Rehabilitation Centres according to the definition ensure complete multidisciplinary teams. There are no monitoring and/or evaluation reports on these strategic principles [74, 75, 76].

Regarding early discharge teams with home support, one study sought to assess the impact of this solution within the NHS. Although the implementation of this organizational solution was considered easy and adequate, no differences were found in the results between the group exposed to the care of the early discharge team and the control group. However, it should be noted that this organisational model was exclusively funded for research purposes, so there is no evidence that this model is implemented anywhere in the country [78].

1.3 ECONOMIC EVALUATION OF THE STROKE REHABILITATION OF THE STROKE SURVIVOR

Stroke rehabilitation is complex, as it entails several patients' sociodemographic and clinical profiles and alternative settings and levels of care. The intervention occurs within a complex system where variations in stroke care between settings exist [83]. Since rehabilitation services play a significant role in stroke care and because they need a lot of resources, policymakers must consider any potential trade-offs between all pertinent costs and benefits [84], for optimal quality and outcomes.

Several systematic reviews to identify the economic evaluation evidence in stroke research have been conducted [85-88], with only one dedicated to rehabilitation services [89], and one on pathways of rehabilitation care. The importance of economic modelling stroke management derives mainly from the facts that stroke is a condition yielding one of the highest rates of mortality and disability in developed countries, and that it is costly for individuals, healthcare systems and society [90].

One review points out that the published cost-effectiveness analyses of stroke management are generally well-designed, nonetheless, certain improvements may be proposed. Systematic efforts should be made to consider resource use data, provided directly by patients and carers in economic models of stroke management. Furthermore, the use of reliable, local, epidemiological data about mortality, disability, quality-of-life

rates, and tariffs is considered essential when adapting cost-effectiveness models to different populations, which often differ in their environment, genetic background, and epidemiological history [88].

In economic evaluations, a generic outcome, quality-adjusted life years (QALYs), is often used, which incorporates both a measure of mortality and morbidity by weighting a year of life by the quality of life experienced by the patient. One of the most recent reviews in economic evaluations of stroke rehabilitation highlights that complex interventions such as stroke rehabilitation have widespread effects, which may not be represented by the changes in a single outcome [90]. Although a cost-utility analysis, which uses QALYs to infer health benefits, is the economic analysis preferred by decision-makers such as the National Institute for Health and Clinical Excellence (NICE), it may not capture all the broader health benefits that are associated with complex interventions or be sensitive to changes in health states [86]. A generic outcome has advantages in allowing comparisons to be drawn between interventions for different disease conditions, however, the use of such a single outcome such as HRQoL is limited in representing the multiple and wide-reaching consequences of stroke rehabilitation. That study supports a move away from conventional economic evaluation and decision-making, based purely on cost-effectiveness, toward multicriteria decision analysis frameworks. The approach advocated is a planned and full cost-consequence analysis (CCA), which tabulates all the costs and benefits separately [91].

Regarding the economic analysis of the different models of stroke care, the European Brain Council Value of Treatment Initiative examined published literature and reports from national agencies and organizations, to design policy recommendations based on the cost-effectiveness data. One of the recent highlights was the fact that full implementation of guideline-based comprehensive stroke services was associated with a 9.8% absolute reduction in risk of death or dependency with an incremental cost-effectiveness ratio of £5227 for comprehensive stroke care versus the usual standard of care assessed across countries [92]. In parallel, the largest US clinical trial on this topic, the COMPASS study (Comprehensive Post-Acute Stroke Services), was designed to implement an evidence-based and policy-supported comprehensive transitional care intervention focused on discharge from the acute care setting to home. It was determined that this transitional care intervention could reduce hospital-level resource costs and may be more feasible [93]. These data follow a previous review that demonstrated that integrated stroke services can reduce costs, sustaining the advantage of an integrated and organised care itinerary for stroke patients. Future research is recommended to focus on the moderately and severely affected patients, adopting a societal costing perspective, and including long-term costs and effects [94].

When analysing the economic evaluation of post-stroke rehabilitation care pathways, gaps are found in the literature. A recent study, although not addressing pathways from a care delivery perspective, sought to analyse the level of evidence on the cost-effectiveness of delivered patient navigation (PN) for stroke survivors. PN is a promising approach for managing pathways through health care systems and for improving patient

outcomes, which could be adapted to stroke rehab. The study recognises that its aftercare is performed by numerous different healthcare service providers, resulting in a high need for coordination. Nevertheless, this review reveals a large gap in knowledge regarding the cost-effectiveness of PN for stroke survivors, affirming that no conclusive statement about the cost-effectiveness can be made [95]. Beyond this review, only one study econometrically evaluated an integrated care pathway for post-stroke patients, without comparing alternatives, focused only on patients residing at home in the community, and on intervention from the primary care team. In a 6-month analysis, the management of post-stroke patients in the community using a pathway of care showed fewer costs per QALY compared to current conventional care and was considered very cost-effective [96].

In contrast, there is plenty of literature evaluating the cost-effectiveness of individual models of care such as early supported discharge services [97, 98], home rehabilitation [99, 100], stroke units [101], and stroke services [102].

Concerning early supported discharge services costing data are currently available from seven trials, which estimated total costs up to three months, six months or one year. Estimated costs ranged from 23% less to 15% greater in comparison to controls. These estimates were reported to be stable in sensitivity analyses. This updated analysis demonstrates that patients receiving early supported discharge services were more likely to be independent and living at home six months after stroke than those who received conventional services, however, most of the evidence appears to be for people with moderate disability [54]. Two cost-effectiveness studies confirm early supported discharge is both an effective and a cost-effective strategy with the main gains in years of life saved [97,98]. The latest evidence found that rural services were associated with higher costs per patient, suggesting additional resources and costs for rural services to meet evidence-based criteria [97].

In terms of home-based rehabilitation, it may be an option for individuals for whom ongoing rehabilitation is unavailable or inaccessible. In addition, increased pressure on hospitals and inpatient centres has meant that new rehabilitation approaches outside the setting ought to be considered [99]. The results of different studies have demonstrated that home-based rehabilitation is a cost-effective means of providing ongoing care, compared to centre-based rehabilitation [99, 100]. Evidence from these studies suggests that a shift from a centre-based to a home-based approach to stroke rehabilitation is likely to be good value for money. Further research should be conducted to assess the generalisability of these findings to local settings [100].

Some economic evaluations have also measured the effectiveness of the SU. The debate has concerned whether the perceived effort and cost of focusing the care of people hospitalised with stroke within specially organised units would be matched by tangible benefits for the people receiving that care. SU appear to improve outcomes, but in cost terms, length of stay is likely to dominate any individual component of acute patient care and rehabilitation [38]. In one analysis, stroke unit care was not associated with an

increase in total health and social care costs, but these conclusions were sensitive to some variation in cost estimates [101]. Another study, that estimated the cost-effectiveness of the SU compared with conventional care, showed a ratio much lower than the threshold, which confirms the cost-effectiveness of this model of care [102]. The updated network meta-analysis about SU care for stroke, although recognizing moderate-quality evidence that stroke patients who receive organised inpatient care are more likely to be alive, independent, and living at home one year after the stroke, advocates for more research to elucidate the cost implications of stroke units [38].

Alternatively, economic evaluations provide essential evidence to inform the return on investment and potential benefits of innovative or alternate models of stroke care [91]. Mobile stroke units are one example. This innovation of bringing specialized stroke-trained staff and portable computed tomography scanning equipment directly to the patient to enable prehospital imaging and treatment decisions has emerging cost-effectiveness data that indicate the additional costs can be offset by greater health benefits [103]. Telehealth is another financially debated innovation despite its potential to provide greater access to stroke specialists and guideline-based care. A review found telestroke was either cost-saving or a cost-effective intervention in 5 of the 8 studies and using a simulation model illustrated the cost savings and incremental health benefits that might be possible [104]. The COVID-19 pandemic has underscored the need for greater telehealth use across the continuum of stroke care. Economic evaluations to guide policy are emerging for the telepractice treatment for aphasia [105] and other forms of telerehabilitation [106].

There is obvious potential for stroke care policy change given recent studies of stroke care, costs, and outcomes. The attention to service delivery and quality of care persists; however, an important opportunity for policy leaders to address is adequate financing to optimize care quality and outcomes and requirements for measuring in policy decision-making. An international forum is required to create a methodological agreement for calculating the costs and effectiveness of stroke care, like the suggestions made by the International Consortium for Health Outcomes Measurement in 2016 for a common set of outcome measures [107].

2
Goals

To achieve the ambitious targets set for 2030 by the European Stroke Action Plan, European health policymakers need to recognize the need for, and support the development of, coherent, homogeneous, effective, and organized care pathways for the treatment of stroke [28].

With this investigation, we seek to contribute to the reflection and strategic planning of a new care solution for stroke, targeting three structural aspects: i) the integration of care, ii) the stroke survivor's pathways, and iii) cost-effectiveness evidence.

2.1 SPECIFIC OBJECTIVES

1. To analyze health-related quality of life evolution over the first year after stroke.
2. To determine the main predictors of health-related quality of life during the first year after stroke.
3. To identify the rehabilitation pathways during the first year after stroke, in Portugal.
4. To describe the rehabilitation pathways in terms of settings of care, health outcomes and the patient's level of information and satisfaction.
5. To evaluate the cost-effectiveness of post-stroke rehabilitation pathways from societal and provider perspectives.

3
Participants and Methods

The papers included in this thesis are based on data from a unique sample setting that ensured patient-level data in different study designs, which will be described herein.

3.1 PARTICIPANTS

This research uses data from a single-centre prospective cohort study that followed first-time stroke survivors across different clinical settings and institutions during the first 12 months.

All stroke patients were diagnosed at the emergency department of a public hospital in the northern region of Portugal (Pedro Hispano, Matosinhos). Patients were flagged by an automated digital search query (n=592) and then assessed for eligibility based on the following criteria: a) clinical confirmation stroke diagnosis; b) first episode of stroke; c) absence of global aphasia; d) written informed consent from the patient and primary carer. The study sample was restricted to patients able to respond to the HRQoL questionnaires by themselves. Of the 592 patients screened at the initial recruitment, 132 did not fulfil the inclusion criteria.

The final sample consists of 460 individuals and their primary carers. Patients were interviewed up to four times, during the following time points: i) in-hospital over the first seven days after stroke, ii) 3 months after hospital discharge, iii) 6 months after hospital discharge and iv) 12 months after hospital discharge, following their pathways of rehabilitation care. Data were collected from September 2018 to December 2020.

This thesis relates to the unique data representing a large sample of stroke patients identified since the acute event and followed through a chronic phase, with a wide range of age, stroke subtypes, degrees of severity and rehabilitation data collected over one year. In brief, the mean age was 74.4 years (SD = 12.9), and 52.7% were women. Approximately 85% of stroke patients were aged above 60 years. A total of 32 patients (8.3%) had TACS (Total Anterior Circulation Stroke), 144 (36.4%) had PACS (Partial Anterior Classification Stroke), 73 (18.5%) had POCS (Posterior Circulation Stroke), 90 (23.6%) had LACS (Lacunar Stroke), and 51 (13.2%) had Hemorrhagic Stroke. Most of the patients were married (52.7%), had attended elementary school (49.0%), were retired (69.2%) and had an individual monthly income below 1000€. Stroke disability upon first

assessment was 3 (Modified Rankin Scale) in 81.5%, and severity showed an average of 11.7 (National Institutes of Health Stroke Scale). The sample functional state was 60.2 on the Barthel Index baseline and the Mini-Mental State Examination mean was 24.2.

To reduce drop-out rates and losses to follow-up over the 12 months of data collection, participants were contacted one week before each assessment time point and reminded one day before each visit by telephone. Before each assessment time point, clinical records were reviewed and patients who died since the last interview were not included in the following follow-ups. In addition, if a participant did not answer telephone calls on three different days, they were considered lost to follow-up. Of the final cohort of 460 patients, 418 (89%) were followed up over 12 months.

Patients included in the study sample were informed and invited to participate by a healthcare professional who was not part of the research team. The study was analyzed and approved by the Ethics Committee of the *Unidade Local de Saúde de Matosinhos* (nº 57/14/RS).

3.2 DATA COLLECTION

The data collection used a combination of data sources: i) self-reported outcome measure instruments, ii) face-to-face interviews, iii) hospital data records, and iv) information available in legal documents and institutional reports. Regarding the face-to-face interviews, the interviewer was the same throughout the study and followed a standard operating procedure. The structured interview procedure was tested with eight stroke survivors not included in the sample, which allowed for testing and standardisation.

The care pathway variable was defined through the sequences of different rehabilitation settings for each patient over the first year post-stroke. At each data collection time point, patients were asked about where the rehabilitation plan had taken place since the last assessment, thus constructing an itinerary of care steps between the first week and 3-, 6- and 12 months post-stroke.

The research data were organized into three levels: system, process, and patient.

At the healthcare system level, the rehabilitation care pathway was described. For each rehabilitation setting six variables were determined: 1) sector, 2) model of care, 3) nature of the provider, 4) source of funding, 5) patient co-payment, 6) time from admission to discharge.

At the care process level, six variables were collected: 1) assessment at admission, 2) discharge plan, 3) patient involvement in defining rehabilitation goals, 4) multidisciplinary team availability, 5) frequency, 6) length of rehabilitation sessions, 7) Door to neurologic examination time, 8) length of hospital stay, and 9) Consecutive weeks of rehabilitation [11].

Patient data were organized into five groups: 1) pre-stroke sociodemographic characteristics, 2) outcome measures, 3) level of information, 4) level of satisfaction, and 5) cost.

Outcome measures included the Portuguese versions of the following instruments: 1) stroke severity - National Institutes of Health Stroke Scale (NHISS Scale) that is a systematic tool that provides a quantitative measure of stroke-related neurological deficit [18], 2) functional status - Barthel Index (BI) which is an instrument that assesses the subject's level of independence for performing ten basic life activities [19], 3) neurological disability - Modified Rankin Scale (mRS) that consists in a commonly used scale for measuring the degree of neurologic disability in stroke patients [20], 4) neurocognitive function – Mini-Mental State Examination (MMSE) which is a questionnaire that is used extensively in clinical and research settings to measure cognitive impairment [21], 5) Health-Related Quality of Life - EQ-5D-3L and SF-6D [22] which are two different instruments widely used in the literature to measure HRQoL. Information and satisfaction levels were measured by a 10-point numerical rating scale [23-25], where zero represents the lowest level and ten represents the highest.

At hospital discharge, each patient assessed their information level in eight dimensions: 1) diagnosis, 2) functional prognosis, 3) daily care training, 4) medication plan, 5) contact professional, 6) rehabilitation care costs, and 7) rehabilitation care model.

In each rehabilitation setting, each patient assessed their level of satisfaction in six dimensions: 1) referral process, 2) clinical information, 3) rehabilitation outcomes, 4) intensity of rehabilitation care, 5) family involvement and 6) self-involvement.

Costs were calculated assuming the following 2 independent payer perspectives: i) the healthcare service perspective, which includes only the costs and effects for the NHS part; ii) the individual perspective, which includes the cost and the effects for the individual with stroke. Both individual and healthcare service perspective costs include 2 main domains – health and social costs. Health costs comprise health intervention costs and individual transport costs. Social costs include social service costs (e.g. formal caregiver, day centre, nursing home), technical aid costs (e.g. walker, crutches, tripod, adjustable bed, recliner chair, wheelchair, shower chair, house adaptation for reduced mobility), and individual and informal caregiver productivity losses.

3.3 PREDICTORS OF HEALTH-RELATED QUALITY OF LIFE

In Paper 1, the cohort HRQoL results were compared with the general Portuguese population norms according to two different instruments - EQ-5D-3L and SF-6D. The assessment of potential predictors of HRQoL was made at 3- and 12-month follow-ups to allow an understanding of changes in HRQoL over time. It was performed through generalized linear models with a linear response. The final models were adjusted for all included variables and were initially applied to the complete sample and repeated by

severity level on a second moment. The predictors were grouped into pre-stroke characteristics, clinical characteristics, and healthcare characteristics. This study followed the STROBE Guidelines for observational studies.

3.4 REHABILITATION PATHWAYS

Paper 2 identified and characterized the rehabilitation care pathways using a three-level descriptive analysis - system, process, and patient to provide a comprehensive picture of the post-acute stroke care pathway in Portugal. Outcomes were assessed and compared between settings of care and pathways. For the setting assessment, the time of entry into each setting was considered the moment of evaluation. For the pathway assessment, the 12-month follow-up time point was considered the evaluation moment. Finally, to expand the broadness of the analysis, we sought to assess the level of information and patient satisfaction in the different care settings. This manuscript conforms to the STROBE Guidelines.

3.5 ECONOMIC EVALUATION

In Paper 3, we assessed the pathways' cost-effectiveness, from the societal and provider perspectives. A decision tree model was used to analyze the cost-effectiveness, considering patient-level data retrieved from our previous cohort study. The cost per quality-adjusted life year, the cost per pathway, and the cost per patient were considered as outcomes. The benefits for the first year were taken from utility data that was established in the same year. Therefore, discounts over time were not included in the decision model. Costs were determined based on the following assumptions: i) provider, which comprises NHS expenses when providing health care to post-stroke patients; ii) societal, which covers provider costs as well as patient and primary carer expenditures and productivity losses. There was no adjustment for inflation or purchasing power because all the costs were established in the reference year and received from Portuguese data sources. In the sensitivity analysis, the range values were the lowest and highest benefit and cost values observed for each patient along a particular pathway. Portuguese gross domestic product (GDP) per capita in 2021 was used as the external willingness-to-pay level when calculating the incremental cost-effectiveness ratio.

4
Papers

4.1 PAPER 1

Barbosa PM, Ferreira LN, Cruz VT, Silva A, Szrek H. Healthcare, Clinical Factors and Rehabilitation Predicting Quality of Life in First-time Stroke Patients: A 12-month Longitudinal Study. J Stroke Cerebrovasc Dis. 2022;31(4):106300.

Healthcare, Clinical Factors and Rehabilitation Predicting Quality of Life in First-time Stroke Patients: A 12-month Longitudinal Study

Pedro Maciel Barbosa,[a,b] Lara Noronha Ferreira,[c,d,e] Vitor Tedim Cruz,[b,f] Augusta Silva,[g] and Helena Szrek,[h]

Objectives: One of the long-term rehabilitation goals in stroke survivors is to achieve the best health-related quality of life (HRQoL). This study analyzes the evolution of HRQoL one-year post-stroke to establish the main pre-stroke, clinical, health care and rehabilitation predictors. *Materials and methods:* This study uses patient-level data from a one-year single-center prospective cohort study of first stroke patients, assessed at baseline, 3, 6 and 12 months. A generalized linear model with a linear response determined independent predictors of HRQol with EQ-5D-3L and SF-6D. The model included age, gender, scholarity, monthly income, residence, occupation, National Institute of Health Stroke Scale (NIHSS), Modified Rankin Scale (mRS), Barthel Index (BI), Mini-Mental State Examination (MMSE), length of stay, door-to-neurological examination time, access, frequency, and satisfaction with rehabilitation care. *Results:* A total of 391 acute stroke patients, with a mean disability of 3.7 and severity of 11.7 participated. A decline of HRQoL was observed from baseline to the first three months in both indexes, with an increase in HRQoL at 3 months until 12 months. Scores were significantly lower compared to corresponding population norms throughout follow-up, mostly affected by stroke severity, disability, rehabilitation access and frequency. Higher HRQoL was associated with lower mRS, NIHSS, age, length of stay, and with higher BI, MMSE, scholarity, occupation, and rehabilitation care. *Conclusion:* Clinical measures and rehabilitation care were the strongest HRQoL predictors of stroke survivors regardless of severity levels. These findings may contribute to the development of future health policies that focus on post-stroke recovery.

Key Words: Stroke—Health-related Quality of Life—Predictors—Rehabilitation—Health-Care—EQ-5D-3L—SF-6D

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Introduction

Stroke is considered the most important cause of long-term morbidity and disability in Europe.[1,2] The incidence and prevalence of stroke in Portugal is above the European average, and has been the leading cause of death over the last decades.[3]

As the population ages and acute stroke care improves, the prevalence of chronic stroke increase[4] and corresponding economic burden of stroke become greater.[5] This is forcing health systems to address the efficiency and effectiveness of stroke treatment to achieve the best health-related quality of life (HRQoL).

Recovery from a stroke is an arduous journey. It takes months or years of motor and cognitive rehabilitation and is frequently incomplete,[6] compromising long-term

From the [a]Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal; [b]Hospital Pedro Hispano, Unidade Local de Saúde, EPE; [c]Universidade do Algarve – ESGHT, Portugal; [d]Centre for Health Studies and Research of the University of Coimbra/Centre for Innovative Biomedicine and Biotechnology, Portugal; [e]Research Centre for Tourism, Sustainability and Well-Being (CinTurs), Portugal; [f]EPIUnit, Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal; [g]Center for Rehabilitation Research, Área Científica de Fisioterapia, Escola Superior de Saúde do Politécnico do Porto; and [h]Centre for Economics and Finance, University of Porto.

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Corresponding author. E-mail: pmb@ess.ipp.pt.

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HRQoL.[7] There are broader consequences including memory and concentration loss, aphasia, gait and movement impairment, social isolation, dementia, decreased job productivity and multiple functional disabilities (e.g dressing and eating).[8,9]

Because of the multiple dimensions that are chronically affected by stroke, there is a growing consensus that self-reported HRQoL is a key measure to understand the impact of the disease in post-stroke survivors.[8,10,11] After acute clinical stabilization, the main long-term rehabilitation goal in stroke survivors is to achieve HRQoL scores that are as high as possible.[12] Therefore, identifying variables that have the largest impact on stroke-specific HRQoL can contribute to the design of rehabilitation interventions,[13] however HRQoL is not routinely measured in clinical practice.[9]

Previous studies have identified predictors of HRQoL after stroke, however, consistent results are conditioned by substantial methodological differences. Some of the factors that differ across studies include: exclusion of care and rehabilitation data; heterogeneity of stroke severity with low representation of severe stroke; the use of different HRQoL instruments; the cross-sectional designs; and the timing of HRQoL measurement.[9,11,12,14,15]

The main goal of this study was to determine pre-stroke, clinical, health care and rehabilitation predictors of patients' HRQoL over first year post-stroke. The study also aims to analyze HRQoL evolution, compare the results with HRQoL norms of the general population and analyze the influence of different stroke severity levels.

Methods

Study design

This study uses data from a one-year single-center prospective cohort study of 391 acute first-time stroke patients (Figure 1) and their primary caregivers. Patients were interviewed up to four times, once in the first seven days after stroke (baseline), and during three follow-up home visits at 3, 6 and 12 months after discharge. Data was collected from September 2017 to November 2019. This study follows the Strobe Guidelines for observational studies.

Upon admission to a large public hospital in the North of Portugal (Pedro Hispano, Matosinhos) all stroke cases that entered the emergency department were flagged via an automatic digital search query (n=523). These were then screened for eligibility based on the following criteria: a) diagnosis of stroke confirmed by clinicians and supported by neuroimaging; b) first episode of stroke; c) not globally aphasic; d) patient and primary caregiver provided written informed consent. Participants were informed and invited to participate in the study by a health professional from the department who was not part of the research team. The study was described to the potential participants and informed consent was obtained. Patients were made aware that their participation would not affect the care they received. The study was reviewed and approved by the Ethics Committee of the Local Health Unit of Matosinhos (No. 57/14/RS).

The study sample was restricted to patients who were able to respond to the HRQoL questionnaires by themselves. Data (pre-stroke sociodemographic characteristics and MMSE) was obtained from face-to-face interviews with patients or their primary caregivers and combined with hospital data (clinical and health care characteristics) extracted from their medical records. The interviewer followed a data collection guideline to standardize the procedure.

To decrease drop-out rates, participants were contacted by a member of the research team by phone one week before each interview and reminded one day before the visit. Before each follow-up, medical records were reviewed and individuals who died within this period were removed from the sample (24 cases, 6.8%). If a subject did not answer phone calls on 3 different days, the participant was considered lost to follow-up to follow-up (18 cases, 5.1%) (Figure 1).

Outcome measures

In this study we have used longitudinal data organized into three categories: pre-stroke; clinical; and health care characteristics. Pre-stroke characteristics address the weight of socio-economic determinants and cognitive reserve on stroke,[16] clinical characteristics integrate the biological dimension of the disease in brain functioning,[17] and health care characteristics include the influence of rehabilitation care after hospital discharge.[18]

Patients assessment included HRQoL - EuroQol 5D (EQ-5D-3L) and Short Form 6 Health Survey Instrument (SF-6D), pre-stroke sociodemographic characteristics (sex, age, marital status, scholarity, patient monthly net income value, occupation and residence), clinical characteristics (stroke severity - NIHSS, daily life functioning - Barthel Index, neurological disability - mRS, neurocognitive function – MMSE, stroke aetiology, stroke subtype) and health care characteristics (length of hospital stay, stroke emergency fast track care – door to neurological examination time, rehabilitation care, consecutive rehabilitation care – number of weeks of rehabilitation without interruption and satisfaction with rehabilitation care measured by a 10-point numeric rating scale (NRS) commonly used to estimate different dimensions in stroke rehabilitation.[19,20] The classification of ischemic stroke was based on the OXFORD classification.[21,22]

Post-stroke HRQoL was assessed with the Portuguese versions of the EQ-5D-3L,[23] and the SF-6D.[24] EQ-5D-3L and SF-6D have been validated in many countries and have shown to be credible instruments in measuring post-stroke HRQoL.[25] In the current study, HRQoL at baseline and at follow-up was used to assess health status on the

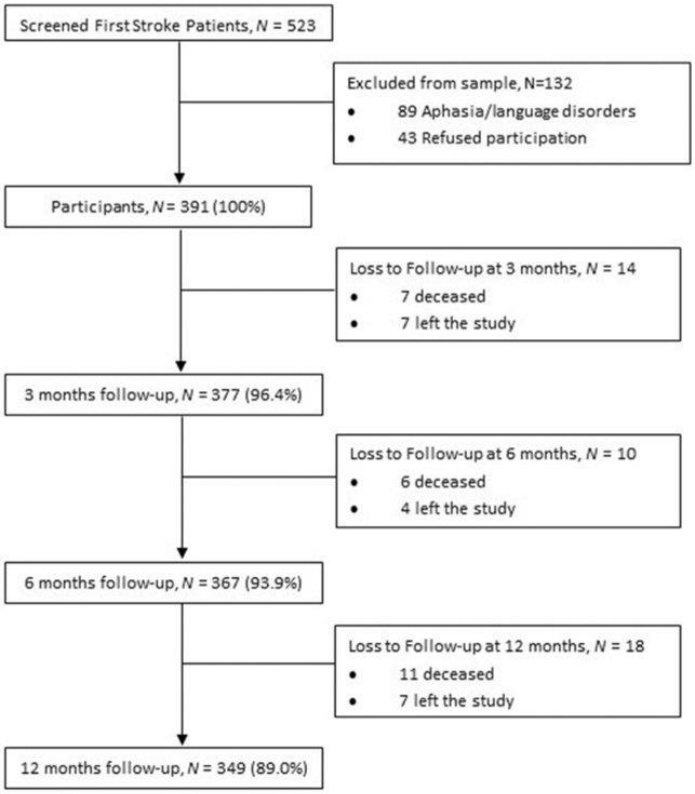


Fig. 1. *Flow diagram of sample screening and participants.*

day of the interview. Higher scores on the EQ-5D-3L or SF-6D indicate a higher HRQoL.

The EQ-5D is a measure that describes the respondent's health status through five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). In this study the version of the EQ-5D with three levels in each dimension, the EQ-5D-3L, was used.[26] The SF-6D is an econometric preference-based index derived from a selection of 11 items from the SF-36v2,[27] which are combined into six dimensions of health (physical functioning, role limitations, social functioning, pain, mental health and, vitality). The EQ-5D-3L and the SF-6D indices were calculated using the Portuguese value sets.[23,28] Both instruments are widely used in the literature to measure HRQoL.[6,15] By including both as dependent measures in our study, we are not only able to compare our results to more studies and can also have a better understanding of how the independent variables influence HRQoL, when measured by different instruments and, therefore, by different dimensions.

Clinical outcome measures included the Portuguese versions of: National Institute of Health Stroke Scale (NIHSS), a systematic tool that provides a quantitative measure of stroke-related neurological deficit;[29] Barthel Index (BI), an instrument that assesses the subject's level of independence for performing ten basic life activities;[30] Modified Rankin Scale (mRS), a commonly used scale for measuring the degree of neurologic disability in stroke patients;[31] and Mini Mental State Examination (MMSE), a questionnaire that is used extensively in clinical and research settings to measure cognitive impairment.[32]

Statistical analysis

The software IBM SPSS Statistics was used. Taking the multiple comparisons into account, a Bonferroni correction method was applied, and the significance level was fixed at 0.002.

We provide summary statistics for all key variables. The HRQoL results were compared with the general Portuguese population norms.[28,33] The difference between observed mean SF-6D index scores and mean EQ-5D index scores and the corresponding normative scores (expected mean) was tested using the one-sample t-test

for each time point: baseline, 3, 6 and 12 months of follow-up.

The frequency and mean differences in HRQoL were compared through the chi-square test, the student's t-test or the One-way ANOVA. The Pearson correlation coefficient was calculated to evaluate linear associations between continuous variables. The assessment of potential predictors (as exposures) of HRQoL was conducted at 3- and 12-months follow-up (as outcomes) to understand changes in HRQoL over time. This was performed through a generalized linear model with a linear response, obtaining regression coefficients (β) and respective 95% confidence intervals (CI). The final models were adjusted for all included variables, and were initially applied to the total sample, and repeated by severity level. The variables included in the model were all variables that showed an association with HRQoL. Among these, pre-stroke and clinical variables were used only from the baseline data, to avoid multicollinearity as they are highly correlated over time, whereas health care variables were used both from the baseline (fast track emergency care and length of hospital stay) and follow-up (rehabilitation care, consecutive and satisfaction) data according to the nature of the measure. Assumptions of linear regression were tested. The values of the residuals were independent since the Durbin-Watson statistics was close to 2 (1.981) and the variance of residuals was constant. The mean of residuals was zero and followed a normal distribution. Cook's distance was under 1, suggesting individual cases were not unduly influencing the model. For the remaining variables, the Variance Inflation Factor (VIF) was between 1.0 and 3.6, indicating no multicollinearity in the final model. The Adjusted R-square was 0.658, showing a good fit of the model.

Results

From the 523 patients screened at recruitment, 132 did not fulfil inclusion criteria. The final cohort consisted of 391 patients, and 349 (89%) were followed up to 12 months (Figure 1).

Mean age was 74.4 years (SD = 12.9), and 52.7% were women. Approximately 85% of stroke patients were aged above 60 years. A total of 32 patients (8.3%) had TACS (Total Anterior Circulation Stroke), 144 (36.4%) had PACS (Partial Anterior Classification Stroke), 73 (18.5%) had POCS (Posterior Circulation Stroke), 90 (23.6%) had LACS (Lacunar Stroke), and 51 (13.2%) had Hemorrhagic Stroke. Most of the patients were married (52.7%), had attended elementary school (49.0%), were retired (69.2%) and had an individual monthly income below 1000€. (64.5%) (Table 1).

Stroke disability upon first assessment was ≥3 (mRS) in 81.5% (n=319) of patients, and severity showed an average of 11.7 (NIHSS Scale). The sample functional state was 60.2 on the Barthel Index baseline and the MMSE mean was 24.2. Clinical characteristics are shown in Table 2.

HRQoL scores were significantly lower than the corresponding population norms at all four follow-up points (Appendix S1). Larger significant differences were found with the EQ-5D-3L index score in comparison with the expected mean for the general Portuguese population (Appendix S1).

Of the 391 patients, 55.5% (n=217) were admitted to the hospital via emergency fast track care and the mean hospital inpatient stay was 43 days (SD=16 days). The number of patients with access to rehabilitation care decreased from 96.7% at 3 months to 72.4% at 12 months. At 3 months, 85% had consecutive weeks of rehabilitation care, which decreased to 41.5% at 12 months. Average satisfaction with rehabilitation decreased from 7.5/10 at baseline to 4.9/10 at 12 months (Table 3).

The characteristics associated with HRQoL are presented in Appendices S2, S3 and S4. All sociodemographic variables (age, sex, scholarity, occupation, residence, and patient monthly income) show significant correlations with both dependent variables at at all time-points of the study. Similarly, significant associations are found for the clinical factors including mRS scale, NIHSS scale, BI scale

Table 1. *Pre-stroke characteristics.*

	n=391 *n* (%)
Age (years)	74.4 (12.9)
20-40	4 (0.9)
41-60	56 (14.2)
61-80	177 (45.3)
81-100	155 (39.6)
Sex	
Male	185 (47.3)
Female	206 (52.7)
Marital status	
Married/Civil Union	206 (52.7)
Divorced	138 (35.4)
Widowed	28 (7.1)
Single	19 (4.8)
Scholarity*	
Elementary School	192 (49.0)
Middle School	125 (31.9)
High School	75 (19.1)
Current Residence	
Home	323 (82.6)
Institutionalized	68 (17.4)
Occupation	
Retired	271 (69.2)
Employed	109 (27.9)
Unemployed	11 (2.8)
Patient monthly income (€)	
≤1000	252 (64.5)
>1000	139 (35.5)

*scholarity defined as 'elementary school' (equal or less than 6y), 'middle school' (7-9y) and 'high school' (≥10y)

Table 2. *Baseline clinical characteristics.*

	n=391
Subtype of stroke OXFORD, n (%)	
PACS	144 (36.4)
LACS	90 (23.6)
POCS	73 (18.5)
TACS	32 (8.3)
Haemorrhagic	51 (13.2)
NHISS Scale, mean (sd)	11.7 (8.5)
NHISS Scale, n (%)	
Mild (1-4)	63 (16.0)
Moderate (5-14)	151 (38.5)
Severe (15-24)	108 (27.6)
Very Severe (≥ 25)	70 (17.9)
mRS Scale, mode	3
mRS Scale, n (%)	
No symptoms at all (0)	0 (0)
No significant disability (1)	7 (1.7)
Slight disability (2)	66 (16.8)
Moderate disability (3)	156 (39.9)
Moderately severe disability (4)	98 (25.1)
Severe disability (5)	65 (16.5)
Mini Mental State Examination, mean (sd)	24.2 (3.1)
Barthel Index, mean (sd)	60.2 (29.5)
Slight dependency (91-99)	30 (7.7)
Moderate Dependency (61-90)	179 (45.8)
Severe Dependency (21-60)	143 (36.5)
Total Dependency (0-20)	39 (9.9)

sd, standard deviation

and MMSE Scale throughout. Health care factors including fast track path emergency care have significant associations at the 3-month and 6month follow-up, while the other variables (shorter length of hospital stay, access, frequency, and satisfaction with rehabilitation care) show significant correlations with both dependent variables at all time-points.

Figures 2 shows the evolution of reported HRQoL, evaluated through the EQ-5D-3L index and SF-6D index for the four categories of severity. A decline of HRQoL was observed from baseline to the first three months in both indexes in all categories, with an increase afterwards, where the highest values of HRQoL were achieved after 12 months. For mild strokes, the HRQoL showed a continuous improvement after baseline.

After multivariate analysis (Table 4), clinical characteristics including mRS, NIHSS, Barthel index and MMSE baseline scores were the strongest predictors of HRQoL at the 3-month and 12-month follow-up points. All categories of disability (moderate to severe disability) (mRS) were inversely associated with higher HRQoL, as evaluated by the SF6D and EQ-5D-3L, at both tthe 3 and 12-months (SF-6D β=-0.195; 95%CI: -0.255; -0.067; EQ-5D-3L β=-0.382; 95%CI: -0.524; -0.239). High severity (NIHSS) of stroke also proved to be inversely associated with HRQoL throughout follow-up, both through the SF-6D (β=-0.195; 95%CI: -0.255; -0.067) and the EQ-5D-3L indexes (β=-0.275; 95%CI: -0.342; -0.105). Increases in the Barthel index score were associated with higher HRQoL at both 3 and 12 months for both SF-6D (β=0.268; 95%CI: 0.190; 0.273) and EQ-5D-3L (β=-0.255; 95%CI: 0.233; 0.287). An increase in cognitive function assessed by MMSE was a moderate predictor of higher HRQoL at 3 and 12 months with the SF-6D (β=0.087; 95%CI: 0.047; 0.168) and EQ-5D-3L (β=-0.069; 95%CI: 0.029; 0.090).

In terms of health care variables, hospital stays under 15 days predicted higher HRQoL at 3 months for SF-6D (β=0.016; 95%CI: 0.003; 0.064) and during the first year for EQ-5D (β=0.011; 95%CI: 0.000; 0.024), while improved access, frequency and satisfaction with rehabilitation care were associated with better values of HRQoL at both 3 and 12 months follow-up for both indexes, SF-6D and EQ-5D-3L, showing a positive influence of rehabilitation care on stroke HRQoL (Table 4).

Statistically significant pre-stroke characteristics were: lower age, which was associated with higher HRQoL at 12 months by both the SF-6D (β=0.018; 95%CI: 0.010; 0.026) and EQ-5D-3L indexes (β=0.024; 95%CI: 0.017; 0.039); higher level of education was associated with higher HRQoL at 3 and 12 months, evaluated using both indexes; and, compared to retired patients, employed patients had a mean increase of 0.023 points (95%CI: 0.004; 0.042) on the SF-6D scale at 3 months (Table 4).

Gender monthly income, residence, and fast trask emergency care were no longer statistically significant after controlling for other factors in multivariate regression, and hence were not considered to be predictors of HRQoL in these patients.

After the initial analysis, we have also estimated regression models to determine the HRQoL predictors stratified by severity level. For this purpose, we assumed the NIHSS scale categories presented in Table 2. The results showed that predictors were consistent across severity levels (see supplementary material for more detailed information Appendices S5 and S6). We found that the weight of health-care characteristics is larger in higher severity groups, and that socio-demographic characteristics such as age, education, and occupation have greater predictive value for mild to moderate strokes.

Discussion

This is the first study to prospectively examine the determinants of HRQoL after stroke across a 1-year period in Portugal. Our results highlight the negative impact of stroke on HRQoL through both SF-6D and EQ-5D-3L indexes

Longitudinal analysis revealed that HRQoL is significantly lower in stroke survivors than in the general population, regardless of the type of stroke or severity.

Table 3. *Health care characteristics.*

	n=391
Fast Path Emergency Care (Door to neurological examination time), n (%)	
Yes	217 (55.5)
No	174 (44.4)
Length of hospital stay (days), mean (sd)	41 (16.7)
Median	38
Minimum	10
Maximum	138
≤ 15 week	108 (27.6)
≥ 15 week	283 (72.4)
In rehabilitation care, n (%)	
At 3 months follow-up	378 (96.7)
At 12 months follow-up	283 (72.4)
Consecutive rehabilitation (weeks), mean (sd)	
At 3 months follow-up	10.2 (0.8)
At 12 months follow-up	19.9 (6.4)
Satisfaction level with rehabilitation care, mean (sd)*	
At 3 months follow-up	7.5 (0.9)
At 12 months follow-up	4.9 (1.3)

sd, standard deviation

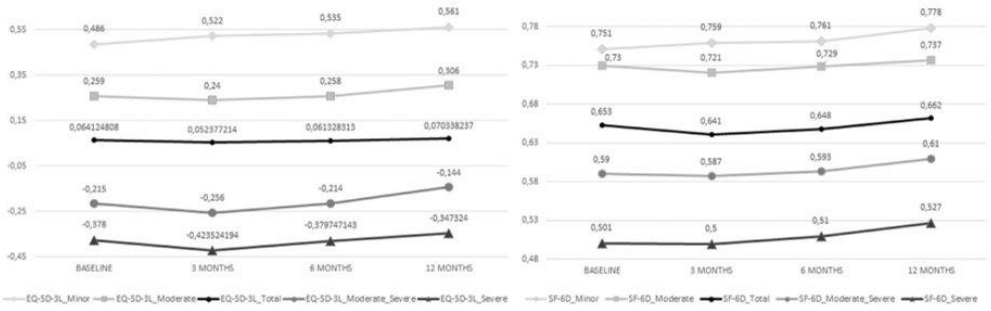


Fig. 2. *EQ-5D-3L and SF-6D in the first year after stroke stratified by stroke-related severity (NHISS).*

Changes in HRQoL over one year were significantly lower in the study population than in the general reference population, with mean differences of 0.204 (SF-6D) and 0.701 (EQ-5D-3L). This is consistent with previous studies that have shown a 19-23% reduction in HRQoL after one,[6,34,35] five or seven years[15,36] post-stroke compared to population norms.

The evolution of HRQoL over time differs in the literature.[6,7] Some studies show an early increase in HRQoL immediately after the acute event. Similar to other studies (6, 15, 37), we observed a sharp initial fall of SF-6D and EQ-5D-3L at 3 months, followed by a rise after 6 months, surpassing baseline values of HRQoL only after 12 months. In our results, this was observed for all except the mild stroke group. Our sample have high average severity, disability, and daily life dependence, potentially explaining a larger loss in HRQoL compared to other studies.[7,12,13,15]

A strength of this study was the inclusion of severe stroke patients. In order to do this, preservation of language was defined as a selection criterion and a higher initial sample was required at recruitment recruitment to accommodate a loss of greater than 23% of patients.

The main objective of the study was to understand the importance of different HRQoL predictors in post stroke survivors. We sought predictors that allowed a closer reading of the impact of the complex interaction between the patient, their social and clinical context, and the health systems on HRQoL, a relevant outcome for clinical and organizational decision-making.

We found that baseline stroke severity, disability, functional status, and access and frequency of rehabilitation

Table 4. *Multivariate association of predictors of quality of life at 3 and 12 months of follow-up.*

		SF6D_INDEX				EQ5D_INDEX			
		3 months follow-up		12 months follow-up		3 months follow-up		12 months follow-up	
		β	95%CI	β	95%CI	β	95%CI	β	95%CI
Pre-Stroke	Age (years)	0.001	0.000; 0.002	**0.018**	**0.010; 0.026**	0.001	−0.001; 0.003	**0.024**	**0.017; 0.039**
	Sex								
	Male	0.001	−0.004; 0.024	0.001	−0.015; 0.017	0.001	−0.032; 0.035	0.004	−0.045; 0.052
	Female	ref		ref		ref		ref	
	Scholarity±								
	Elementary School	ref		ref		ref		ref	
	Middle School	−0.003	−0.023; 0.016	−0.001	−0.023; 0.021	0.022	−0.019; 0.064	−0.001	−0.063; 0.061
	High School	0.003	−0.015; 0.021	0.014	−0.007; 0.034	**0.048**	**0.002; 0.094**	**0.068**	**0.007; 0.114**
	Current Residence								
	Home	ref		ref		ref		ref	
	Institutionalized	0.005	−0.009; 0.019	0.004	−0.011; 0.039	0	−0.016; 0.049	0.001	−0.048; 0.082
	Occupation								
	Retired	ref		ref		ref		ref	
	Employed	**0.023**	**0.004; 0.042**	0.024	−0.007; 0.049	−0.007	−0.011; 0.164	0.025	−0.059; 0.110
	Patient Monthly Income (€)								
	≤1000	ref		ref		ref		ref	
	>1000	0	−0.008; 0.004	0.001	−0.004; 0.017	0.001	−0.015; 0.012	0.003	−0.023; 0.021
Clinical	Baseline mRS Scale								
	Slight disability	ref		ref		ref		ref	
	Moderate disability	0.009	−0.021; 0.040	**0.017**	**0.005; 0.040**	**−0.099**	**−0.170;−0.028**	**−0.113**	**−0.212; 0.014**
	Moderately severe disability	**−0.013**	**−0.050;−0.023**	**−0.025**	**−0.065;−0.014**	**−0.379**	**−0.463;−0.294**	**−0.242**	**−0.362;−0.122**
	Severe disability	**−0.308**	**−0.350;−0.264**	**−0.311**	**−0.342;−0.248**	**−0.558**	**−0.659;−0.458**	**−0.382**	**−0.524;−0.239**
	Baseline NHISS Scale	**−0.250**	**−0.293;−0.083**	**−0.195**	**−0.255;−0.067**	**−0.230**	**−0.284;−0.193**	**−0.275**	**−0.342;−0.105**
	Baseline Mini Mental State Examination	**0.066**	**0.040; 0.151**	**0.087**	**0.047; 0.168**	**0.035**	**0.014; 0.083**	**0.069**	**0.029; 0.090**
	Baseline Barthel Score	**0.21**	**0.171; 0.254**	**0.268**	**0.190; 0.273**	**0.206**	**0.156; 0.247**	**0.255**	**0.233; 0.287**
Health Care	Baseline Fast Path Emergency Care (Door to neurological examination time)	0	−0.005; 0.004	0	−0.002; 0.017	−0.001	−0.033; 0.014	0.001	−0.003; 0.021
	Length of hospital stay (days)								
	≥ 15 week	ref		ref		ref		ref	
	< 15 week	**0.016**	**0.003; 0.064**	0	−0.001; 0.002	**0.033**	**0.009; 0.051**	**0.011**	**0.000; 0.024**
	In Rehabilitation care	**0.151**	**0.103; 0.211**	**0.083**	**0.046; 0.112**	**0.127**	**0.078; 0.169**	**0.064**	**0.028; 0.096**
	Consecutive rehabilitation care	**0.103**	**0.036; 0.147**	**0.036**	**0.008; 0.081**	**0.096**	**0.024; 0.128**	**0.026**	**0.008; 0.074**
	Satisfaction with rehabilitation care	**0.019**	**0.008; 0.064**	**0.026**	**0.012; 0.087**	**0.034**	**0.003; 0.091**	**0.057**	**0.010; 0.104**

na, not applicable

±scholarity defined as 'elementary school' (equal or less than 6y), 'middle school' (7-9y) and 'high school' (≥10y)

Bold values denote statistical significance at the $p < 0.05$ level

had the greatest impact on HRQoL in the first-year post-stroke, particularly for patients with severe stroke, while socio-demographic characteristics such as age, education, and occupation had greater predictive value for mild to moderate strokes. Our results confirm the association between NIHSS severity score and HRQoL among stroke survivors observed both in cross-sectional,[13,38] and longitudinal studies.[9,14,15] On the other hand, disability assessed by mRS, recommended as a primary outcome by the European Stroke Organization Outcome[9] has demonstrated its relevance as an inverse predictor of HRQoL measure. Both outcomes were consistently independent predictors of HRQoL at 3 and 12 months, regardless of the level of severity, with comparable effect sizes, supporting the positive impact of preserved brain tissue that can modulate post-stroke recovery.[17]

Among clinical predictors, BI is not consensual in the literature as HRQoL predictor because of the ceiling effect observed in mild and moderate stroke individuals.[8,12] In our sample with more severe participants, BI was found to have a noteworthy influence on stroke-specific HRQoL in agreement with different studies,[9,13,37,38,39] supporting the role of rehabilitation in improving functional outcomes throughout the different post-stroke recovery phases and severity levels.[38]

Moreover, we found that high MMSE score was an important predictor for HRQoL over the 12 months following the first stroke event. Similar results were found in previous studies that used a different HRQoL instrument.[8,39] Good cognition can predict better memory, communication, social function and adherence to rehabilitation.[39]

Reduced hospital length of stay ($\leq$ 15 week) is a criterion of clinical quality and benchmarking in health management. In this study it proved to be a predictor of better HRQoL in the short and long term, although with low predictive value. However, future research will be important to assess the long mean length of stay found in this study, which was due to constraints in the continuing care network of the Portuguese health system that prevents a timely referral process. The access to a fast track in emergency care has not been shown to be a predictor in our final model. One speculation could be that this occurred because there was a change in the referral criteria for this procedure during the period of data collection.

Although evidence shows that many rehabilitative interventions are cost-effective,[40] there is scarce evidence in the literature identifying rehabilitation as a determinant of post-stroke HRQoL.[41] In our sample, access and frequency to rehabilitation care have been shown to be relevant predictors over the first 12 months by contributing to scores of both SF-6D and EQ-5D-3L indexes.

Only two previous studies were found that highlight the access to rehabilitation care.[13,42] One of these was a multicenter study showing that monthly contact with the physical therapist is positively associated with higher HRQoL scores.[42] Several general principles underpin the process of stroke rehabilitation, but substantial evidence supports high intensity therapy.[43,44] The consecutive rehabilitation care variable shows that this aspect of rehabilitation care can be a predictor of HRQoL, both in the short and long term.

Involvement in health care planning is one of the main determinants of satisfaction of stroke patients,[45] and, as found in this study, the assessment of satisfaction with rehabilitation care can be relevant as a predictor of HRQoL. In contrast, the literature points out that the highest rate of dissatisfaction with stroke services was with the amount of therapy received.[46] This may explain the decrease in satisfaction between the 3- and 12-month follow-up period, which would have occurred as patients experienced a decrease in the frequency and intensity of rehabilitation care.

The pre-stroke sociodemographic independent predictors for stroke specific HRQoL levels were lower age, higher education, and employment status. This finding confirms that sociodemographic factors impact the socially relevant aspects of the subjective HRQoL, which is consistent with previous large prospective cohort studies.[15,36]

This study has some potential limitations. The generalizability of our results is limited by the fact that the study is based on a single-center cohort of 391 stroke survivors. With a prospective follow-up study design, some individuals were lost to follow up. Despite home visits, reminder calls and text messaging, the loss to follow- up rate was 22%. Another possible limitation is that HRQoL was measured using the generic EQ-5D-3L and SF-6D rather than a stroke-specific measure. This decision was made because we wanted to compare HRQoL levels of stroke survivors with those of their age-and gender-matched counterparts in the general population. For future studies a stroke specific measure, such as the HRQoL in stroke patients' questionnaire (HRQoLISP-40 or SIS), could contribute to a more sensitive analysis of the disease nuances, and changes. Thirdly, although depression in post-stroke patients may influence their HRQoL, depression was not assessed separately in this study by a specific measure. It was assessed by dimensions within EQ-5D-3L and SF-6D and was, therefore, included in the indexes of the measures.

This is the first study conducted in Portugal that measures HRQoL after stroke across a 1-year period and that compares patients' HRQoL with the general Portuguese population. Therefore, this study enables comparisons between health systems and policies at an international level. Additional strengths of this study relate to the unique data representing a large sample of stroke patients identified since the acute event and followed through chronic phase, with a wide range of age, stroke subtypes, degrees of severity and rehabilitation data collected over the year. The patient-level data (medical records and

standardized face-to-face) allowed us to collect much richer information to include in our models. Excluding patients with recurrent stroke from the study aimed to increase the robustness of the results and minimizing selection bias, as it would be impossible to control for the statistical confounders imposed by the repetition of the event and the interaction between the various predictors over time. In addition, as we excluded data from patients that had died and with communication impairments which may create selection bias, we excluded proxy responses as proxies tend to overrate the severity of a patient's condition,[47] and the pre-stroke HRQoL was also not assessed retrospectively to prevent recall bias.

Finally, the longitudinal HRQoL evaluation with two widely used instruments enables comparison with other studies and gives us more confidence in the results. The fact that no important differences were found between the predictors and their weighted values on the HRQoL scores of both instruments, increases robustness of the results particularly the evolution of stroke HRQoL over time and the role of clinical and health care predictors, namely quantity, quality, and satisfaction with rehabilitation care. Confidence in these data, can be perceived as a first step in understanding what changes can be made to improve stroke management. This is especially relevant when the projections from the Burden of Stroke in Europe indicate that in 2047 the total number of stroke survivors in the European Union will increase by 27%, with an increasing socioeconomic impact over time.[5]

Conclusion

We found that HRQoL of stroke survivors of varying degrees of severity is progressively influenced mostly by clinical factors, rehabilitation care and sociodemographic characteristics. These findings can be translated into current stroke practice, allowing a more complete perspective on healthcare planning, and into the development of future health policies with a special focus on rehabilitation and its fundamental role in recovery of HRQoL in post-stroke patients.

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Informed consent

Written informed consent was obtained from all subjects before the study.

Ethical approval

Ethical approval for this study was obtained from Ethics Committee of the Local Health Unit of Matosinhos (No. 57/14/RS).

Trial registration

Not Applicable because the observational study design.

Contributorship

Pedro Barbosa, Helena Szrek and Lara Ferreira researched literature and conceived the study. Pedro Barbosa, Helena Szrek, Lara Ferreira and Augusta Silva were involved in protocol development, gaining ethical approval, patient recruitment and data analysis. Pedro Barbosa wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript

Declaration of Competing Interest

The Author(s) declare(s) that there is no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2021.106300.

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Healthcare, Clinical Factors and Rehabilitation Predicting Quality of Life in First-time Stroke Patients: A 12-month Longitudinal Study

Pedro Maciel Barbosa [a b], Lara Noronha Ferreira [c d e], Vitor Tedim Cruz [b f], Augusta Silva [g], Helena Szrek [h]

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Appendix S1 - Cross-sectional comparison of SF and EQ index scores with adjusted population norms.

	n	Expected mean	Observed mean (SD)	Difference	p-value
SF6D					
Baseline	391	0.854	0.65 (0.120)	0.206	<0.001
3 months follow-up	377	0.854	0.64 (0.112)	0.228	<0.001
6 months follow-up	367	0.854	0.64 (0.107)	0.224	<0.001
12 months follow-up	349	0.854	0.65 (0.099)	0.215	<0.001
EQ5D					
Baseline	391	0.758	0.04 (0.409)	0.760	<0.001
3 months follow-up	377	0.758	0.04 (0.388)	0.723	<0.001
6 months follow-up	367	0.758	0.04 (0.395)	0.720	<0.001
12 months follow-up	349	0.758	0.10 (0.392)	0.701	<0.001

Appendix S2 - Pre-stroke factors associated with the SFD6 scale and EQ5D3L scale from baseline to 12 months follow-up

	SF6D_INDEX (mean, SD)								EQ5D3L_INDEX (mean, SD)							
	n	**Baseline**	**n**	**3 months**	**n**	**6 months**	**n**	**12 months**	**n**	**Baseline**	**n**	**3 months**	**n**	**6 months**	**n**	**12 months**
Age (years)[a]	391	r= –0.176	377	r= –0.188	367	r= –0.203	349	r= –0.188	351	r= –0.236	377	r= –0.214	367	r= –0.223	349	r= –0.213
p-value		0.001		0.001		<0.001		0.001		<0.001		<0.001		<0.001		<0.001
Age (years)																
≤60	60	0.66 (0.126)	57	0.65 (0.118)	56	0.67 (0.117)	53	0.67 (0.105)	59	0.16 (0.459)	57	0.14 (0.433)	56	0.16 (0.443)	53	0.21 (0.447)
61-80	177	0.66 (0.118)	171	0.65 (0.109)	166	0.65 (0.102)	158	0.66 (0.094)	177	0.10 (0.412)	171	0.08 (0.386)	166	0.08 (0.393)	158	0.15 (0.374)
81-100	155	0.63 (0.116)	149	0.61 (0.108)	145	0.62 (0.105)	138	0.63 (0.098)	155	–0.07 (0.358)	149	–0.06 (0.351)	145	–0.06 (0.353)	138	–0.01 (0.363)
p-value[b]		0.005		0.008		0.004		0.012		<0.001		0.001		<0.001		<0.001
Sex, n (%)																
Male	185	0.67 (0.119)	178	0.66 (0.108)	174	0.66 (0.105)	165	0.66 (0.092)	185	0.11 (0.426)	178	0.09 (0.403)	174	0.10 (0.407)	165	0.15 (0.400)
Female	206	0.63 (0.119)	199	0.62 (0.113)	193	0.63 (0.108)	184	0.64 (0.104)	206	–0.02 (0.386)	199	–0.02 (0.370)	193	–0.01 (0.381)	184	0.05 (0.383)
p-value[c]		0.002		0.004		0.011		0.067		0.003		0.022		0.019		0.022
Marital status																
Married/Civil Union	206	0.65 (0.122)	199	0.64 (0.112)	193	0.65 (0.106)	184	0.65 (0.094)	206	0.06 (0.412)	199	0.05 (0.392)	193	0.06 (0.400)	184	0.12 (0.365)
Single/Widowed/Divorced	185	0.64 (0.119)	178	0.63 (0.112)	174	0.64 (0.109)	165	0.64 (0.104)	185	0.02 (0.412)	178	0.02 (0.386)	174	0.020 (0.392)	165	0.08 (0.393)
p-value[c]		0.332		0.572		0.551		0.557		0.296		0.488		0.390		0.415
Scholarity*																
Elementary School	192	0.63 (0.122)	185	0.62 (0.113)	180	0.63 (0.107)	171	0.64 (0.100)	192	–0.02 (0.395)	185	–0.02 (0.372)	180	–0.02 (0.377)	171	0.04 (0.340)
Middle School	125	0.65 (0.120)	120	0.64 (0.112)	117	0.65 (0.106)	111	0.66 (0.100)	125	0.06 (0.413)	120	0.05 (0.404)	117	0.04 (0.408)	111	0.100 (0.394)
High School	75	0.69 (0.109)	72	0.68 (0.100)	70	0.68 (0.097)	67	0.67 (0.086)	75	0.27 (0.381)	72	0.23 (0.368)	70	0.24 (0.369)	67	0.281 (0.340)
p-value[b]		0.004		0.005		0.002		0.018		<0.001		<0.001		<0.001		<0.001
Current Residence																
Home	323	0.65 (0.121)	311	0.65 (0.110)	303	0.65 (0.106)	288	0.65 (0.096)	323	0.07 (0.421)	311	0.06 (0.298)	303	0.06 (0.206)	288	0.12 (0.301)
Institutionalized	68	0.63 (0.120)	66	0.62 (0.114)	64	0.62 (0.107)	61	0.62 (0.105)	68	–0.01 (0.379)	66	–0.02 (0.310)	64	–0.01 (0.325)	61	0.01 (0.311)
p-value[b]		0.118		0.039		0.040		0.044		0.100		0.048		0.047		0.048
Occupation																
Employed	109	0.67 (0.118)	105	0.66 (0.111)	102	0.66 (0.107)	63	0.67 (0.096)	109	0.13 (0.425)	105	0.11 (0.397)	102	0.11 (0.408)	63	0.15 (0.393)
Retired	271	0.64 (0.637)	261	0.63 (0.111)	254	0.63 (0.105)	275	0.64 (0.099)	271	–0.00 (0.392)	262	–0.00 (0.379)	254	0.00 (0.386)	275	0.06 (0.385)
p-value[c]		0.035		0.032		0.022		0.030		0.036		0.024		0.030		0.074
Patient Monthly income																
≤1000 €	252	0.64 (0.120)	244	0.63 (0.112)	238	0.63 (0.107)	227	0.64 (0.098)	252	0.00 (0.411)	244	0.01 (0.392)	238	0.02 (0.400)	227	0.06 (0.397)
>1000 €	139	0.66 (0.120)	133	0.66 (0.110)	129	0.65 (0.106)	122	0.66 (0.099)	139	0.09 (0.402)	133	0.07 (0.381)	129	0.07 (0.388)	122	0.151 (0.381)
p-value[c]		0.042		0.049		0.182		0.213		0.043		0.044		0.048		0.041

Appendix S3 - Clinical factors associated with the SFD6 scale and EQ5D3L scale from baseline to 12 months follow-up

	SF6D_INDEX (mean, SD)								EQ5D3L_INDEX (mean, SD)							
	n	**Baseline**	n	**3 months**	n	**6 months**	n	**12 months**	n	**Baseline**	n	**3 months**	n	**6 months**	n	**12 months**
OXFORD classification																
PACI	144	0.66 (0.120)	138	0.64 (0.111)	134	0.65 (0.109)	128	0.65 (0.097)	143	0.07 (0.404)	138	0.06 (0.379)	134	0.07 (0.380)	128	0.12 (0.383)
LACI	90	0.63 (0.123)	89	0.62 (0.113)	86	0.62 (0.107)	82	0.64 (0.102)	92	0.01 (0.416)	89	0.00 (0.398)	86	0.00 (0.400)	82	0.06 (0.410)
POCI	73	0.64 (0.124)	69	0.63 (0.119)	68	0.64 (0.111)	64	0.64 (0.106)	72	–0.00 (0.391)	69	–0.01 (0.378)	68	–0.02 (0.381)	64	0.04 (0.372)
TACI	32	0.66 (0.101)	31	0.64 (0.100)	30	0.65 (0.100)	29	0.65 (0.082)	32	0.09 (0.451)	31	0.08 (0.435)	30	0.08 (0.453)	29	0.18 (0.442)
Haemorrhagic	51	0.66 (0.120)	50	0.66 (0.106)	49	0.66 (0.101)	46	0.67 (0.097)	52	0.06 (0.415)	50	0.06 (0.391)	49	0.07 (0.409)	46	0.15 (0.374)
p-value[b]		0.343		0.265		0.408		0.682		0.641		0.629		0.519		0.394
Baseline NHISS Scale [a]	391	r= –0.726	377	r= –0.710	367	r= –0.690	349	r= –0.606	391	r= –0.812	377	r= –0.805	367	r= –0.805	349	r= –0.764
p-value		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001
Baseline NHISS Scale																
Minor	63	0.76 (0.044)	61	0.74 (0.042)	59	0.75 (0.005)	56	0.73 (0.050)	63	0.59 (0.130)	61	0.52 (0.171)	59	0.54 (0.170)	56	0.54 (0.176)
Moderate	151	0.73 (0.080)	146	0.71 (0.073)	142	0.71 (0.072)	135	0.70 (0.065)	151	0.35 (0.324)	146	0.34 (0.277)	142	0.33 (0.303)	135	0.36 (0.279)
Moderate to severe	108	0.59 (0.102)	103	0.59 (0.100)	100	0.59 (0.096)	96	0.61 (0.098)	107	–0.22 (0.237)	103	–0.22 (0.243)	100	–0.22 (0.241)	96	–0.13 (0.304)
Severe	70	0.50 (0.048)	67	0.50 (0.047)	66	0.51 (0.055)	62	0.53 (0.063)	70	–0.35 (0.058)	67	–0.35 (0.073)	66	–0.37 (0.072)	62	–0.34 (0.141)
p-value[b]		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001
Baseline mRS Scale [a]	391	r= –0.732	377	r= –0.721	367	r= –0.708	349	r= –0.689	391	r= –0.838	377	r= –0.819	367	r= –0.812	349	r= –0.796
p-value		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001
Baseline mRS Scale																
No significant disability	7	-	7	-	7	-	7	-	7	-	7	-	7	-	7	-
Slight disability	66	0.77 (0.033)	64	0.75 (0.039)	62	0.75 (0.035)	59	0.73 (0.039)	66	0.66 (0.200)	64	0.66 (0.200)	62	0.64 (0.242)	59	0.65 (0.242)
Moderate disability	156	0.75 (0.057)	149	0.72 (0.053)	145	0.72 (0.053)	138	0.72 (0.044)	156	0.44 (0.146)	149	0.44 (0.146)	145	0.37 (0.144)	138	0.38 (0.152)
Moderately severe disability	98	0.68 (0.091)	94	0.67 (0.077)	92	0.67 (0.078)	87	0.67 (0.078)	98	0.00 (0.304)	94	0.00 (0.304)	92	0.02 (0.310)	87	0.08 (0.315)
Severe disability	65	0.54 (0.076)	63	0.54 (0.078)	61	0.54 (0.079)	58	0.57 (0.090)	65	–0.35 (0.058)	63	–0.33 (0.076)	61	–0.33 (0.108)	58	–0.24 (0.242)
p-value[b]		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001
Baseline Mini Mental State Examination	391	r=0.680		r=0.578		r=0.577		r=0.512	391	r=0.752		r=0.673		r=0.664		r=0.638
p-value		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001
Baseline Barthel scale																
Slight dependency	30	0.73 (0.039)	29	0.75 (0.035)	28	0.75 (0.039)	27	0.77 (0.033)	30	0.33 (0.303)	29	0.35 (0.324)	28	0.37 (0.144)	27	0.38 (0.152)
Moderate Dependency	179	0.67 (0.077)	173	0.68 (0.093)	168	0.69 (0.106)	160	0.69 (0.088)	179	0.11 (0.367)	173	0.12 (0.354)	168	0.16 (0.375)	160	0.26 (0.349)
Severe Dependency	143	0.59 (0.102)	137	0.62 (0.111)	134	0.63 (0.123)	127	0.63 (0.106)	143	0.02 (0.391)	137	0.03 (0.400)	134	0.03 (0.411)	127	0.10 (0.404)
Total Dependency	39	0.50 (0.048)	38	0.51 (0.055)	37	0.53 (0.063)	35	0.54 (0.079)	39	–0.24 (0.242)	38	–0.33 (0.108)	37	–0.33 (0.076)	35	–0.35 (0.058)
p-value[b]		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001

sd, standard deviation

*scholarity defined as 'elementary school' (equal or less than 6y), 'middle school' (7-9y) and 'high school' (≥10y)

[a]Pearson correlation

[b]One-way ANOVA

[c]Student's t-test

Bold values denote statistical significance at the p < 0.05 level

Appendix S4 - Health Care factors associated with the SFD6 scale and EQ5D3L scale from baseline to 12 months follow-up

	SF6D_INDEX (mean, SD)								EQ5D3L_INDEX (mean, SD)							
	n	Baseline	n	3 months	n	6 months	n	12 months	n	Baseline	n	3 months	n	6 months	n	12 months
Fast Path Emergency Care (Door-to-Needle)																
Yes	217	0.66 (0.115)	209	0.65 (0.107)	204	0.66 (0.096)	194	0.66 (0.084)	217	0.10 (0.408)	209	0.09 (0.387)	204	0.11 (0.242)	194	0.12 (0.315)
No	174	0.64 (0.123)	168	0.62 (0.114)	163	0.65 (0.096)	155	0.65 (0.099)	174	–0.01 (0.405)	168	–0.01 (0.384)	163	0.01 (0.170)	155	0.02 (0.279)
p-value		0.026		0.041		0.126		0.221		0.034		0.038		0.081		0.185
Length of hospital stay (days), mean[a]	391	r= –0.121	377	r= –0.126	367	r= –0.137	349	r= –0.149	391	r= –0.162	377	r= –0.188	367	r= –0.198	349	r= –0.200
p-value		0.153		0.105		0.227		0.199		0.081		0.187		0.373		0.145
Length of hospital stay																
≤ 15 week	108	0.63 (0.110)	104	0.68 (0.113)	101	0.67 (0.104)	96	0.69 (0.088)	108	0.13 (0.408)	104	0.15 (0.382)	101	0.20 (0.208)	96	0.25 (0.216)
≥ 15 week	283	0.50 (0.047)	273	0.54 (0.078)	266	0.54 (0.078)	253	0.57 (0.091)	283	–0.03 (0.317)	273	–0.01 (0.405)	266	0.04 (0.298)	253	0.05 (0.328)
p-value		0.024		0.020		0.023		0.009		0.002		<0.001		<0.001		<0.001
In Rehabilitation care*																
Yes	–	–	367	0.63 (0.125)	325	0.67 (0.113)	253	0.69 (0.088)	–	–	378	0.09 (0.387)	325	0.13 (0.408)	253	0.14 (0.393)
No	–	–	10	0.50 (0.047)	42	0.51 (0.055)	96	0.53 (0.063)	–	–	10	–0.01 (0.405)	42	–0.01 (0.384)	96	–0.00 (0.391)
p-value		–		<0.001		<0.001		<0.001		–		<0.001		<0.001		<0.001
Consecutive rehabilitation care*	–	–	377	r=0.408	367	r=0.267	349	r=0.182	–	–	377	r=0.389	367	r=0.312	349	r=0.264
p-value		–		0.023		0.009		<0.001		–		0.034		0.002		<0.001
Satisfaction with rehabilitation care*	–	–	377	r=0.186	367	r=0.108	349	r=0.116	–	–	377	r=0.246	367	r=0.213	349	r=0.164
p-value		–		0.005		0.012		0.041		–		0.002		0.021		0.032

Appendix S5 - Multivariate association of predictors of SF6D quality of life at 3 and 12 months of follow-up of stroke by NIHSS severity scale categories

		SF6D_INDEX MILD STROKE				SF6D_INDEX MODERATE STROKE				SF6D_INDEX MODERATE_SEVERE STROKE				SF6D_INDEX SEVERE STROKE			
		3 months		12 months		3 months		12 months		3 months		12 months		3 months		12 months	
		β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI
Pre-Stroke	Age (years)	**0.012**	**0.002; 0.021**	**0.023**	**0.015; 0.031**	**0.008**	**0.001; 0.022**	**0.022**	**0.013; 0.042**	0.004	0.000; 0.017	**0.020**	**0.012; 0.034**	0.001	0.000; 0.001	**0.017**	**0.008; 0.024**
	Sex																
	Male	0.004	– 0.001; 0.024	0.002	- 0.011; 0.026	0.003	– 0.002; 0.013	0.001	– 0.006; 0.013	0.003	- 0.004; 0.008	0.000	– 0.008; 0.010	0.001	– 0.004; 0.018	0.001	– 0.018; 0.011
	Female	ref		ref		ref		ref		ref		ref		ref		ref	
	Scholarity±																
	Elementary School	ref		ref		ref		ref		ref		ref		ref		ref	
	Middle School	0.001	–0.011; 0.012	0.003	–0.010; 0.026	0.000	–0.021; 0.002	0.001	–0.017; 0.014	–0.001	-0.018; 0.003	0.001	–0.017; 0.014	–0.004	–0.028; 0.010	–0.001	–0.027; 0.024
	High School	0.011	–0.005; 0.027	**0.019**	**0.009; 0.038**	0.007	-0.0011; 0.018	**0.011**	**0.001; 0.029**	0.006	-0.007; 0.014	0.013	–0.002; 0.032	0.006	–0.007; 0.014	0.013	–0.002; 0.032
	Current Residence																
	Home	ref		ref		ref		ref		ref		ref		ref		ref	
	Institutionalized	0.000	–0.0016; 0.011	0.001	–0.021; 0.014	0.000	–0.0023; 0.008	0.001	–0.032; 0.011	0.002	–0.0011; 0.01	0.003	–0.026; 0.015	0.006	–0.008; 0.024	0.005	–0.016; 0.041
	Occupation																
	Retired	ref		ref		ref		ref		ref		ref		ref		ref	
	Employed	**0.026**	**0.010; 0.048**	**0.028**	**0.005; 0.069**	**0.024**	**0.006; 0.047**	**0.025**	**0.0011; 0.052**	**0.027**	**0.009; 0.040**	0.029	–0.001; 0.062	**0.021**	**0.002; 0.051**	0.022	–0.011; 0.033
	Patient Monthly Income (€)																
	≤1000	ref		ref		ref		ref		ref		ref		ref		ref	
	>1000	0.001	– 0.003; 0.012	0.003	- 0.001; 0.022	0.003	– 0.001; 0.020	0.002	– 0.004; 0.013	0.001	- 0.006; 0.019	0.002	– 0.010; 0.020	0.000	– 0.011; 0.002	0.001	– 0.003; 0.015
Clinical	Baseline mRS Scale	**0.022**	**0.000; 0.043**	**0.008**	**0.001; 0.036**	**0.015**	**0.004; 0.56**	**–0.008**	**–0.019; 0.096**	**–0.011**	**-0.050;–0.023**	**–0.047**	**–0.085;–0.014**	**–0.316**	**-0.361; –0.284**	**–0.324**	**–0.370; –0.253**
	Baseline NHISS Scale	**–0.018**	**–0.065;–0.009**	**0.010**	**0.001; 0.051**	**–0.032**	**–0.053;–0.003**	**–0.041**	**–0.076;–0.011**	**–0.084**	**-0.103;–0.021**	**–0.114**	**–0.176;–0.041**	**–0.260**	**–0.303;–0.112**	**–0.207**	**–0.264; –0.072**
	Baseline Mini Mental State Examination	**0.051**	**0.003; 0.081**	**0.073**	**0.046; 0.112**	**0.061**	**0.013; 0.098**	**0.068**	**0.021; 0.108**	**0.060**	**0.018; 0.108**	**0.078**	**0.029; 0.124**	**0.077**	**0.051 0.162**	**0.091**	**0.058; 0.172**
	Baseline Barthel Score	**0.002**	**0.001; 0.002**	**0.001**	**0.000; 0.001**	**0.027**	**0.008; 0.047**	**0.061**	**0.014; 0.088**	**0.102**	**0.066; 0.150**	**0.154**	**0.112; 0.208**	**0.217**	**0.194; 0.262**	**0.275**	**0.199; 0.304**
Health Care	Baseline Fast Path Emergency Care (Door to neurological examination time)	0.005	–0.009; 0.019	0.000	-0.001; 0.000	0.003	–0.001; 0.023	0.000	–0.003; 0.005	0.001	-0.002; 0.008	0.000	–0.004; 0.012	0.000	– 0.007; 0.006	0.000	– 0.006; 0.025
	Length of hospital stay (days)																
	≥ 15 week	ref		ref		ref		ref		ref		ref		ref		ref	
	≤ 15 week	**0.083**	**0.046; 0.112**	**0.026**	**0.014; 0.078**	**0.053**	**0.031; 0.84**	**0.018**	**0.006; 0.046**	**0.021**	**0.009; 0.054**	0.008	–0.004; 0.026	**0.014**	**0.002; 0.051**	0.000	–0.005; 0.012
	Rehabilitation care	**0.131**	**0.093; 0.183**	**0.111**	**0.055; 0.167**	**0.138**	**0.084; 0.201**	**0.119**	**0.104; 0.171**	**0.139**	**0.077; 0.218**	**0.103**	**0.073 0.181**	**0.166**	**0.112; 0.231**	**0.097**	**0.055; 0.134**
	Consecutive rehabilitation care	**0.048**	**0.002; 0.094**	**0.062**	**0.017; 0.114**	**0.056**	**0.024; 0.103**	**0.048**	**0.026; 0.092**	**0.064**	**0.037; 0.118**	**0.047**	**0.013; 0.071**	**0.124**	**0.057; 0.154**	**0.028**	**0.006; 0.091**
	Satisfaction with rehabilitation care	**0.023**	**0.004; 0.042**	**0.024**	**0.007; 0.049**	**0.027**	**0.010; 0.051**	**0.028**	**0.006; 0.047**	**0.022**	**0.008; 0.048**	**0.027**	**0.010; 0.053**	**0.015**	**0.004; 0.053**	**0.025**	**0.012; 0.082**

na, not applicable

±scholarity defined as 'elementary school' (equal or less than 6y), 'middle school' (7-9y) and 'high school' (≥10y)

Appendix S6 - Multivariate association of predictors of EQ5D3L quality of life at 3 and 12 months of follow-up of stroke by NIHSS severity scale categories

		EQ5D3L_INDEX MILD STOKE				EQ5D3L_INDEX MODERATE STROKE				EQ5D3L_INDEX MODERATE_SEVERE STROKE				EQ5D3L_INDEX SEVERE			
		3 months		12 months		3 months		12 months		3 months		12 months		3 months		12 months	
		β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI	β	95%CI
Pre-Stroke	Age (years)	**0.008**	**0.004; 0.023**	**0.032**	**0.016; 0.053**	**0.006**	**0.001; 0.013**	**0.028**	**0.014; 0.047**	0.004	– 0.001; 0.012	**0.026**	**0.016; 0.043**	0.000	- 0.002; 0.004	**0.020**	**0.014; 0.034**
	Sex																
	Male	0.002	- 0.024; 0.016	0.005	- 0.035; 0.047	0.001	- 0.017; 0.015	0.002	- 0.014; 0.033	0.002	– 0.026; 0.010	0.003	– 0.017; 0.037	0.002	- 0.036; 0.021	0.005	– 0.007; 0.061
	Female	ref		ref		ref		ref		ref		ref		ref		ref	
	Scholarity±																
	Elementary School	ref		ref		ref		ref		ref		ref		ref		ref	
	Middle School	0.022	–0.019; 0.064	–0.001	–0.063; 0.061	0.016	–0.021; 0.031	–0.001	–0.045; 0.020	0.016	–0.021; 0.031	–0.001	–0.045; 0.020	0.024	–0.026; 0.071	–0.001	–0.048; 0.062
	High School	**0.038**	**0.002; 0.084**	**0.048**	**0.012; 0.104**	**0.034**	**0.002; 0.061**	**0.037**	**0.007; 0.085**	**0.036**	**0.008; 0.071**	**0.041**	**0.007; 0.091**	**0.036**	**0.008; 0.071**	**0.041**	**0.007; 0.091**
	Current Residence																
	Home	ref		ref		ref		ref		ref		ref		ref		ref	
	Institutionalized	0.000	–0.023; 0.017	0.001	–0.054; 0.032	0.000	–0.036; 0.009	0.001	–0.051; 0.017	0.001	–0.013; 0.009	0.000	–0.033; 0.012	0.000	–0.023; 0.052	0.001	–0.053; 0.082
	Occupation																
	Retired	ref		ref		ref		ref		ref		ref		ref		ref	
	Employed	–0.001	–0.007; 0.083	**0.025**	**0.009; 0.131**	–0.003	–0.015; 0.034	**0.022**	**0.004; 0.091**	–0.002	–0.010; 0.084	0.024	–0.004; 0.105	–0.009	–0.014; 0.172	0.027	–0.066; 0.145
	Patient Monthly Income (€)																
	≤1000	ref		ref		ref		ref		ref		ref		ref		ref	
	>1000	0.001	- 0.013; 0.022	0.004	–0.008; 0.030	0.002	- 0.007; 0.034	0.004	–0.011; 0.021	0.003	– 0.005; 0.030	0.003	–0.011; 0.034	0.001	- 0.020; 0.008	0.003	–0.027; 0.014
Clinical	Baseline mRS Scale	**0.026**	**0.007; 0.042**	**0.011**	**0.002; 0.045**	**–0.104**	**-0.186;–0.014**	**–0.119**	**-0.227; –0.036**	**–0.234**	**–0.366;–0.084**	**–0.279**	**-0.327; –0.106**	**–0.584**	**–0.691;–0.472**	**–0.393**	**–0.541; –0.254**
	Baseline NHISS Scale	**–0.059**	**-0.178;–0.002**	**0.043**	**0.015; 0.071**	**–0.066**	**-0.092;–0.024**	**–0.034**	**-0.067;–0.010**	**–0.166**	**–0.192;–0.074**	**–0.234**	**–0.267;–0.127**	**–0.244**	**–0.292;–0.201**	**–0.293**	**–0.352; –0.130**
	Baseline Mini Mental State Examination	**0.027**	**0.008; 0.069**	**0.064**	**0.028; 0.096**	**0.057**	**0.017; 0.076**	**0.072**	**0.037; 0.098**	**0.042**	**0.011; 0.086**	**0.070**	**0.028; 0.101**	**0.041**	**0.024; 0.096**	**0.078**	**0.035; 0.104**
	Baseline Barthel Score	**0.006**	**0.005; 0.007**	**0.006**	**0.004; 0.007**	**0.037**	**0.016; 0.051**	**0.042**	**0.014; 0.067**	**0.127**	**0.082; 0.191**	**0.189**	**0.134; 0.227**	**0.222**	**0.167; 0.273**	**0.266**	**0.237; 0.291**
Health Care	Baseline Fast Path Emergency Care (Door to neurological examination time)	0.006	–0.017; 0.049	0.000	–0.001; 0.000	0.004	–0.008; 0.054	0.000	–0.006; 0.011	0.000	–0.014; 0.023	0.000	–0.024; 0.016	–0.001	–0.041; 0.026	0.001	– 0.016; 0.034
	Length of hospital stay (days)																
	≥ 15 week	ref		ref		ref		ref		ref		ref		ref		ref	
	≤ 15 week	**0.064**	**0.028; 0.096**	**0.028**	**0.018; 0.056**	**0.050**	**0.019; 0.073**	**0.014**	**0.018; 0.056**	**0.041**	**0.017; 0.067**	**0.011**	**0.008; 0.036**	**0.025**	**0.004; 0.074**	**0.008**	**0.000; 0.019**
	Rehabilitation care	**0.087**	**0.054; 0.123**	**0.053**	**0.018; 0.106**	**0.94**	**0.066; 0.130**	**0.067**	**0.024; 0.137**	**0.119**	**0.047; 0.154**	**0.071**	**0.027; 0.112**	**0.133**	**0.080; 0.172**	**0.076**	**0.034; 0.106**
	Consecutive rehabilitation care	**0.034**	**0.015; 0.88**	**0.046**	**0.020; 0.094**	**0.062**	**0.041; 0.107**	**0.039**	**0.016; 0.081**	**0.077**	**0.031; 107**	**0.033**	**0.011; 0.047**	**0.114**	**0.027; 0.139**	**0.021**	**0.005; 0.064**
	Satisfaction with rehabilitation care	**0.027**	**0.011; 0.104**	**0.035**	**0.019; 0.130**	**0.030**	**0.015; 0.087**	**0.038**	**0.014; 0.098**	**0.033**	**0.020; 0.092**	**0.046**	**0.019; 0.088**	**0.043**	**0.002; 0.106**	**0.062**	**0.008; 0.111**

na, not applicable

±scholarity defined as 'elementary school' (equal or less than 6y), 'middle school' (7-9y) and 'high school' (≥10y)

Bold values denote statistical significance at the $p < 0.05$ level

4.2 PAPER 2

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ARTICLE

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From healthcare system to individuals through stroke rehabilitation pathways. Outcomes, information, and satisfaction along 12 months prospective cohort in Portugal

Pedro Maciel Barbosa [a,b,c], João Firmino-Machado [d,e,f,g], Lara Noronha Ferreira [h,i,j], Vitor Tedim Cruz [b,d], and Helena Szrek [k]

[a]Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal; [b]Hospital Pedro Hispano, Unidade Local de Saúde, EPE, Portugal; [c]Centro de Investigação em Reabilitação, Escola Superior de Saúde, Politécnico do Porto, Portugal; [d]EPIUnit – Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal; [e]Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina da Universidade do Porto, Porto, Portugal; [f]Centro Académico Clínico Egas Moniz, Aveiro, Portugal; [g]Centro Hospitalar Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal; [h]Universidade do Algarve – ESGHT, Portugal; [i]Centre for Health Studies and Research of the University of Coimbra/Centre for Innovative Biomedicine and Biotechnology, Portugal; [j]Research Centre for Tourism, Portugal; [k]Centre for Economics and Finance, University of Porto, Porto, Portugal

ABSTRACT

Background: The nature and quality of stroke survivor rehabilitation varies throughout Europe, including in Portugal, having not been widely monitored or benchmarked.

Objectives: This study analyses the stroke care pathway from three perspectives: healthcare system, process, and patient.

Methods: The study uses data from a one-year single-center prospective cohort of first stroke patients, assessed at baseline, 3, 6, and 12 months. Care pathways and settings were described in terms of organizational model, funding, patient involvement, frequency and intensity and multi-disciplinary team. Patient-level information and satisfaction were evaluated using a 10-point numeric rating scale. Kruskal – Wallis and post-hoc tests were used to compare EQ-5D-3 L, National Institute of Health Stroke Scale (NIHSS), Modified Rankin Scale (mRS), Barthel Index, Mini-Mental State Examination scores between pathways and settings.

Results: A total of 391 acute stroke patients, with a mean disability of 3.7 (mRS) and severity of 11.7 (NIHSS) participated. Six pathways and eight settings were described. A lack of compliance between guidelines and care was identified. There were significant differences in the four outcomes between the six pathways (p-values 0.007 to 0.020) suggesting inefficiency and inequalities, with an inadequate level of information and patient satisfaction. After post-hoc analysis, pathways 1 and 2 showed highest outcomes (p-values 0.001 to 0.002). Within settings, short-term units showed high scores, followed by rehabilitation center, outpatient hospital, and community clinic (p-values 0.001 to 0.040).

Conclusion: A multilevel characterization of the post-stroke rehabilitation pathway showed a more complete perspective on stroke management which may contribute to future rehabilitation and stroke policies

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Stroke; pathway; rehabilitation; outcomes; satisfaction

Introduction

Despite considerable advances across the care pathway (prevention, treatment, and rehabilitation), stroke is a leading cause of adult disability in Europe,[1,2] with major health, economic and societal implications.[3] Although rehabilitation can be a cost-effective service,[4] it has not been prioritized in many countries, is under-resourced,[5] and has been largely neglected by the research field.[6]

There are no universally agreed guidelines and outcomes for rehabilitation in post-stroke patients across European countries,[7–9] where different health service structures and payment systems often determine inconsistent pathways of care.[10] Stroke survivors across Europe face long waiting lists to start rehabilitation. Often, rehabilitation takes place over a short period, without being sufficiently intensive, and often fails to address depression and cognitive impairment.[6,11,12] Many patients express dissatisfaction and refer to a high burden of unmet needs,[13] with very few receiving follow-up reviews and long-term support.[12]

CONTACT Pedro Maciel Barbosa p.macielbarbosa@gmail.com Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal

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Recent reports have shown that rehabilitation policies aimed at increasing quality of care across Europe are not widely monitored or benchmarked.[6,11] A few countries have well established audit programs,[11] although most completely lack or have fragmented healthcare data collection for quality improvement.[12] Stroke treatment services in Portugal rank among the less developed in Europe,[14] with scarce and outdated information about the rehabilitation setting.[11] This study analyses the Portuguese stroke post-acute care system and contributes to the understanding between different stroke health and rehabilitation care systems in Europe.

New settings of care should be designed to meet the targets set for 2030 by the *Action Plan for Stroke*.[10] It is also imperative to overcome the gap between the rhetoric around unsustainable healthcare systems and the investment in the transformative change that is required for the widespread uptake of integrated care models and an effective navigation through complex health systems.[10,15] To achieve this, data about stroke rehabilitation settings and pathways of care, need to be forthcoming.[16]

The general approach we adopted in this study was a three-level analysis of the stroke care pathway, at the system, process, and patient level. The primary aims were to (i) describe alternative coexisting stroke pathways in Portugal, (ii) describe each rehabilitation pathway regarding the care settings, characteristics. Secondary aims were to (iii) determine the level of information available and patient satisfaction throughout the duration of the stroke care pathway.

Methods

Study design

This study used data from a one-year single-center prospective cohort study of 391 acute first stroke patients and their primary caregivers. Patients were interviewed up to four times, once in the first seven days after stroke, and three follow-up home visits at 3, 6 and 12 months after discharge. Data was collected from September 2018 to November 2020, with the last enrollment in November 2019.

After admission to a large public hospital in the North of Portugal all stroke cases were flagged through an automatic digital search query ($n = 523$) and then screened for eligibility using clinical records. Participants and primary caregivers were informed and invited to participate in the study by a healthcare professional from the hospital, independent of the research team, who explained the study to the potential participants and obtained informed consent. The study was reviewed and approved by the Ethics Committee of the Local Health Unit of Matosinhos (No. 57/14/RS).

The study sample was restricted to patients able to respond to patient-reported outcome measures independently. Patient-level data was obtained from in-person interviews combined with data from clinical records, while system and process-level data were extracted from patient interviews combined with data from institutional records. The interviewer followed a data collection guideline to standardize the procedure.

To improve continued participation, subjects were contacted by phone one week before each interview and reminded one day before the visit. If a participant did not answer phone calls on three different days or deceased, they were considered lost to follow-up. The sample diagram can be consulted in the supplementary material (Appendix S1). There was no missing data in the study variables.

Further details of the study design and of the sample are reported elsewhere.[17] This manuscript conforms to the STROBE Guidelines.

Pathways, settings of care, patients characteristics and outcomes

Portugal has a healthcare system based on a National Health System (NHS), with eight rehabilitation care settings described as follows: Short-term Unit (Short-term), Medium-term Unit (Medium-term), Long-Term Unit (Long-term), Rehabilitation Centre (Rehab-center), Home-based Rehabilitation (Home-based), Day Hospital (Day-hospital), Community Clinic (Community-clinic), Private Clinic (Private-clinic).

The pathway variable was defined using the sequences of different settings of rehabilitation care over the first-year post-stroke. In each follow-up assessment, patients were asked about the setting where the rehabilitation plan had taken place

since the last assessment, building up a multistep care sequence during rehabilitation.

The research data was organized into system, process, and patient levels.

At the healthcare system level, the rehabilitation care pathway was described and for each rehabilitation setting, six variables were collected: 1) the sector of care, 2) the model of care, 3) the nature of provider, 4) funding source and 5) patient co-payment, 6) time frame from admission to discharge.

At the process level, each rehabilitation setting was described using six variables: 1) admission assessment, 2) discharge plan, 3) patient involvement in the definition of rehabilitation goals, 4) multidisciplinary team available, 5) frequency and 6) duration of clinical sessions.[11]

At the patient level, the data collected was organized into five groups: 1) pre-stroke sociodemographic characteristics, 2) healthcare characteristics, 3) outcomes, 4) information level and 5) satisfaction level. Pre-stroke disability level was not available in the clinical records and was not assessed retrospectively to prevent recall bias. Cardiovascular risk factors followed the standardized values for the population.

Outcomes were assessed using the following instruments: stroke severity – National Institute of Health Stroke Scale (NHISS Scale),[18] functional status – Barthel Index (BI),[19] neurological disability – Modified Rankin Scale (mRS),[20] neurocognitive function – Mini Mental State Examination (MMSE),[21] and HRQoL – EQ-5D-3 L.[22]

The information and satisfaction levels were measured by a 10-point numeric rating scale (NRS).[23–25] Zero represents the lowest perceived level and 10 represents the highest.

At hospital discharge, each patient assessed their level of information over eight dimensions: 1) primary diagnosis, 2) functional prognostic/expected outcomes, 3) daily care training, 4) medication plan, 5) professional of contact, 6) costs of subsequent rehabilitation care, 7) next rehabilitation services and facilities and 8) geographical location of next rehabilitation setting.

At each rehabilitation setting, every patient assessed their level of satisfaction over six dimensions: 1) referral process, 2) available information, 3) rehabilitation outcomes, 4) intensity of rehabilitation care, 5) family involvement, and 6) patient involvement.

Statistical analysis

Categorical variables were described using frequencies and percentages and continuous variables were described with means and standard deviations or medians and interquartile ranges for variables without normal distributions. The satisfaction level for each setting resulted from the average of the scores of the six dimensions.

Outcomes were assessed by setting of care and by pathway. For the setting assessment, the moment of entry was defined as the moment of evaluation. For the pathway assessment, moment of entry was defined as the 12-month follow-up.

The Kruskal – Wallis test was used to compare continuous variables (i.e. mRS, EQ-5D-3 L, BI and MMSE) between groups (i.e. the different settings and pathways). Whenever a statistically significant result was determined, a post-hoc test (Bonferroni) was used to explore the existence of statistically significant differences among the different groups being compared.

The significance level was fixed at 0.05. Whenever multiple comparisons were applied, a Bonferroni correction of the alpha level was used to correct for the family-wise error; in these circumstances, a significance value of 0.002 was assumed. All the analyses were conducted using SPSS v.28.

Results

Sample description

The final cohort consisted of 391 patients, and 349 (89%) were followed up to 12 months (Appendix S1). Participants had a mean age of 74.4 years (SD = 12.9), and 52.7% were women. Approximately 85% of stroke patients were older than 60 years of age.

Stroke disability upon first assessment was ≥3 in 81.5%, and functional status showed a mean/sd of 60.1/29.5 (Barthel Index). The sample functional state was 60.2 and the neurocognitive function mean was 24.2. Regarding healthcare variables, the mean acute hospital inpatient stay was 43 days (SD = 16 days), and the proportion of consecutive weeks

Table 1. Sample description.

Pre-Stroke Characteristics (n=391)		Baseline Clinical and Health Care Characteristics (n=391)	
Age (years), mean (sd)	74.4 (12.9)	Subtype of stroke OXFORD, n (%)	
20-40	4 (0.9)	PACS	144 (36.4)
41-60	56 (14.2)	LACS	90 (23.6)
61-80	177 (45.3)	POCS	73 (18.5)
81-100	155 (39.6)	TACS	32 (8.3)
Sex, n (%)		Hemorrhagic	51 (13.2)
Male	185 (47.3)	mRS Scale, mode	3
Female	206 (52.7)	mRS Scale, n (%)	
Marital status, n (%)		No symptoms at all (0)	0 (0)
Married/Civil Union	206 (52.7)	No significant disability (1)	7 (1.7)
Divorced	138 (35.4)	Slight disability (2)	66 (16.8)
Widowed	28 (7.1)	Moderate disability (3)	156 (39.9)
Single	19 (4.8)	Moderately severe disability (4)	98 (25.1)
Education, n (%)		Severe disability (5)	65 (16.5)
Elementary School	192 (49.0)	Mini Mental State Examination, mean (sd)	24.2 (3.1)
Middle School	125 (31.9)	Barthel Index, mean (sd)	60.2 (29.5)
High School	75 (19.1)	Slight dependency (91–99)	30 (7.7)
Current Residence, n (%)		Moderate Dependency (61–90)	179 (45.8)
Home	323 (82.6)	Severe Dependency (21–60)	143 (36.5)
Institutionalized	68 (17.4)	Total Dependency (0–20)	39 (9.9)
Occupation, n (%)		EQ-5D-3 L, mean (sd)	0,15 (0,41)
Retired	271 (69.2)	Length of acute hospital stay (days), mean (sd)	41 (16.7)
Employed	109 (27.9)	≤15 days, n (%)	108 (27.6)
Unemployed	11 (2.8)	≥15 days, n (%)	283 (72.4)
Patient monthly income (€), n (%)		Consecutive rehabilitation (weeks), mean (sd)	
≤1000	252 (64.5)	At 3 months follow-up	10.2 (0.8)
>1000	139 (35.5)	At 12 months follow-up	19.9 (6.4)

sd – standard deviation; % - frequency; mRS – Modified Rankin Scale; EQ-5D-3 L – EuroQol 5D.
PACS – Partial Anterior Classification Stroke; TACS – Total Anterior Circulation Stroke; POCS – Posterior Circulation Stroke; LACS – Lacunar Stroke.

of rehabilitation care decreased from 85.3% (10.2/12) at 3 months to 41.5% (19.9/48) at 12 months (Table 1).

Stroke care pathways

Eleven pathways are graphically displayed in Figure 1, however, due to sample size limitations, the analysis was performed between the six most prevalent pathways (Appendix S2).

After hospital discharge, most patients were referred to Medium-term (41.3%), followed by Short-term, Rehab-center, and Day-hospital with percentages between 17.4 and 19.9%. Finally, 13.4% of patients were referred to Long-term.

At the 3-month follow-up, the use of the Medium-term setting became even more dominant ensuring care for 62.1% of patients. Between the 6- and 12-month follow-up, there was a change in the use of available settings. Community clinics led caring for between 63.8 and 76.8% of patients. At six months, 21.4% of patients received Home-based care, and some began using Private-clinic and continued to do so for at least 12 months (8.6%-14.5%) (Figure 1).

Settings of rehabilitation care

The characteristics of the different settings are outlined in Table 2 and described further in Appendix S3.

Healthcare systems-level data showed that six rehabilitation settings are managed within the health sector, and two integrate health and social sectors. In six settings, the NHS is the funder and provider, while in one setting the NHS finances but care is provided by a private partner. In the Private-clinic, the financier and provider are both private. Among the seven options financed by the NHS, in five, the patient is not charged, and in two, payment varies according to the patient's income. In the private sector, payment is fully out-of-pocket.

Process-level data demonstrated that the time-frame of each setting varied between a maximum of 30 days and unlimited time. In all settings, the patient received a clinical assessment upon admission. Only three settings involved the patient in the definition of rehabilitation plan goals, and in three they did not receive a discharge plan.

Access to multidisciplinary care was heterogeneous between settings. All settings provided medical and physiotherapy care, 75% of the settings provided speech therapy, 50% included

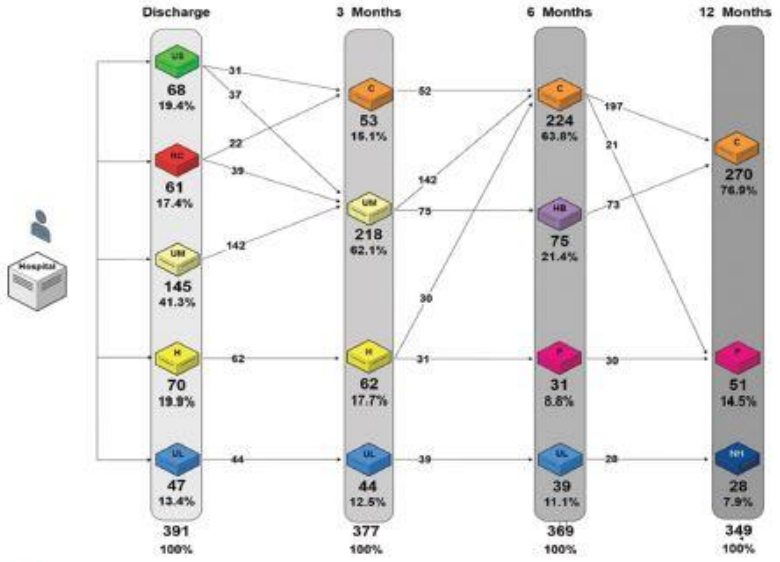


Figure 1. Eleven rehabilitation pathways in the first year after stroke in Portuguese NHS. Note: US - Short-term Unit; UM - Medium-term Unit; UL - Long-Term Unit; RC - Rehabilitation Center; HB - Home-based; H - Hospital; C - Community Clinic; P - Private Rehabilitation.

rehabilitation nursing, 38% involved occupational therapy, and only 25% offered psychology/cognitive rehabilitation. The frequency of physiotherapy sessions ranged from 3 to 12 sessions per week and the duration of rehabilitation sessions ranged from 30 to 60 minutes each.

Outcomes

At the patient-level data, the four outcomes – mRS, EQ-5D-3 L, BI and MMSE were evaluated by pathway and by setting.

At 12-month follow-up, pathways 1 and 2 showed the highest scores at the four outcomes followed by pathway 5 (Figure 2 and Appendix S4). The Kruskal-Wallis test showed significant differences in the four outcomes between the six pathways (p-values between 0.007 and 0.020). After post-hoc analyses, all comparisons showed significant differences (p-values between 0.001 and 0.002), except for pathway 1 and 2 at all outcomes, for pathway 3 and 4 at EQ-5D-3 L, BI and MMSE, for pathway 1 and 5 at MMSE, and pathway 2 e 5 at EQ-5D-3 L, mRS and MMSE.

At entry level, Short-term units showed higher values, followed by Rehab-center, Day-hospital, Private-clinic, and Community-clinic with moderate values, and Home-base, Medium-term and Long-term with lower values (Figure 3). Significant differences were found in all four outcomes between the eight settings after conducting post-hoc analyses (p-value between 0.0001 and 0.002) (Figure 2 and Appendix S5).

Patient information and satisfaction

At hospital discharge, patients self-reported being fully informed (9/10) about the geographic location of the next rehabilitation setting, moderately informed (5-7/10) about the medication plan, primary diagnosis, and costs, poorly informed (2-3/10) about functional prognosis, expected outcomes, expected services and contact professional (Figure 4). The results by item can be found in Appendix S6.

Between setting, patients reported high satisfaction at the Rehab-Center (9/10), Short-term (8/10), and Day-hospital (7/10) with an emphasis on intensity of care, outcomes obtained and patient involvement dimensions. They reported moderate satisfaction with rehabilitation care in Private-clinic (6/10) and Medium-term (5/10), and they reported low

Table 2. Settings of care description.

	US	UM	UL	RC	HB	H	C	P
CLINICAL SETTING	Short-term Rehabilitation Unit	Medium-term Rehabilitation Unit	Long-term Rehabilitation Unit	Rehabilitation Center	Home-based Rehabilitation	Day Hospital	Community Rehabilitation Clinic	Private Rehabilitation
CARE SERVICES	Health	Health/Social	Health/Social	Health	Health	Health	Health	Health
MODEL OF CARE	Inpatient	Inpatient	Inpatient	Inpatient	Home-based	Outpatient	Outpatient	Home-based/ Outpatient
PROVIDER	Public (NHS)	Public (NHS)	Public (NHS)	Public (NHS)	Public (NHS)	Public (NHS)	Private	Private
STATE FUNDING	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
PATIENT FUNDING	Free	Progressive according to Income	Progressive according to Income	Free	Free	Free	Free	Total
ADMISSION TO DISCHARGE TIME (days)	30	30 - 90	≥90	50-60	60-120	30-150	Unlimited	Unlimited
ADMISSION ASSESSMENT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
DISCHARGE PLAN	Yes	Yes	Yes	Yes	Yes	No	No	No
AGREE REHAB GOALS	Yes	Yes	No	Yes	No	No	No	No
MULTIDISCIPLINARY TEAM	P/PT/ST	P/PT/ST	P/PT	P/PT/RN/PSI/ST/OT	P/PT/RN	P/PT/ST/RN	P/PT/ST/OT	P/PT/ST/OT/PSI
FREQUENCY OF PHYSIO SESSIONS (week)	8–12 s	5	3	10 - 12S	3 - 4s	5	3 - 5s	3 - 5s
PHYSIO SESSION DURATION (min)	60	45	30	60	30	45	45	60

US – Short-term Unit; UM – Medium-term Unit; UL – Long-Term Unit; RC – Rehabilitation Center; HB – Home-based; H – Hospital; C – Community Clinic; P – Private Rehabilitation.
NHS – National Health System.
P – Physician; PT – Physiotherapist; ST – Speech Therapist; OT – Occupational Therapist; RN – Rehabilitation Nurse; PSI – Psychologist.

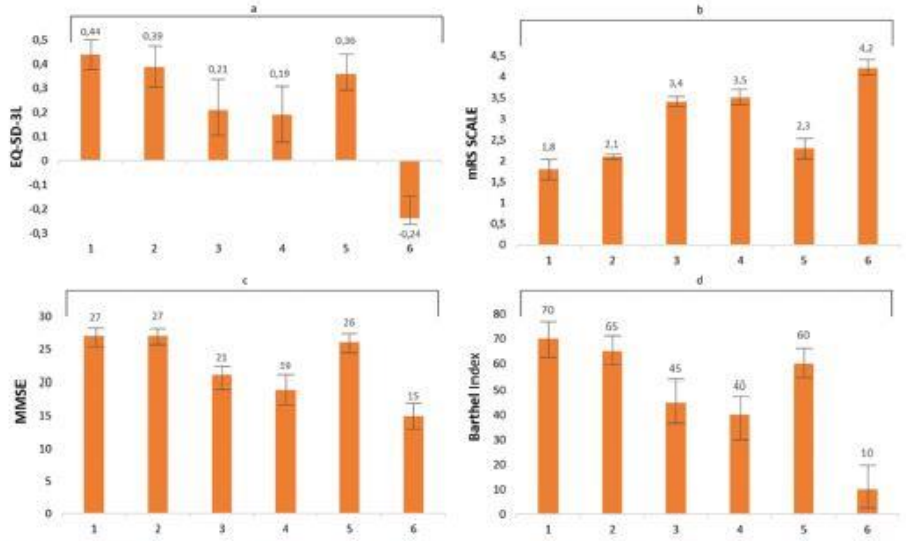


Figure 2. Final outcomes by pathway. Overall p-value: a=0,002; b=0,007; c=0,02; d=0,004. All post-hoc comparisons showed significant differences (p-value between 0.0003 and 0.002), except for pathway 1 vs 2 at all outcomes, for pathway 3 vs 4 at EQ-5D-3L, BI and MMSE, for pathway 1 vs 5 at MMSE, and pathway 2 vs 5 at EQ-5D-3L, mRS and MMSE.

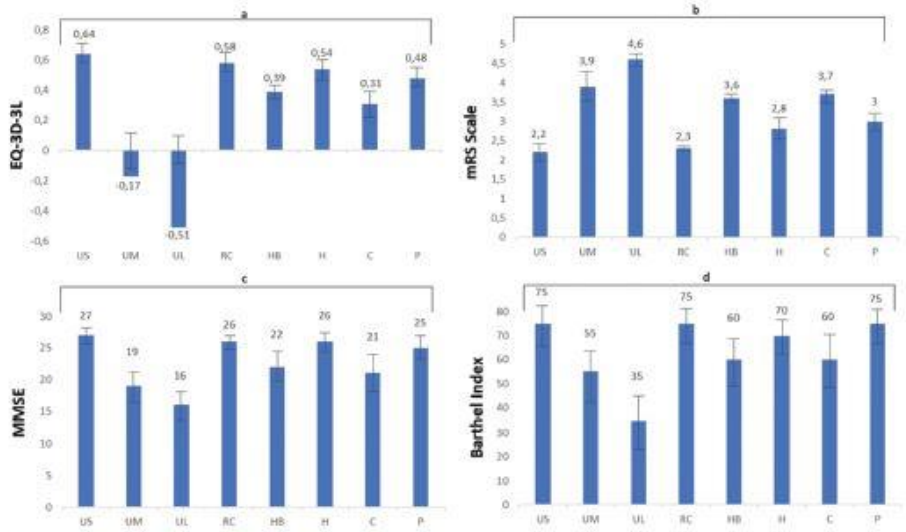


Figure 3. Baseline outcomes by setting of care. Note: US - Short-term Unit; UM - Medium-term Unit; UL - Long-Term Unit; RC - Rehabilitation Centre; HB - Home-based; H - Hospital; C - Community Clinic; P - Private Rehabilitation.

satisfaction levels with the Home-base, Community- clinic (3/10) and Long-term (2/10) settings

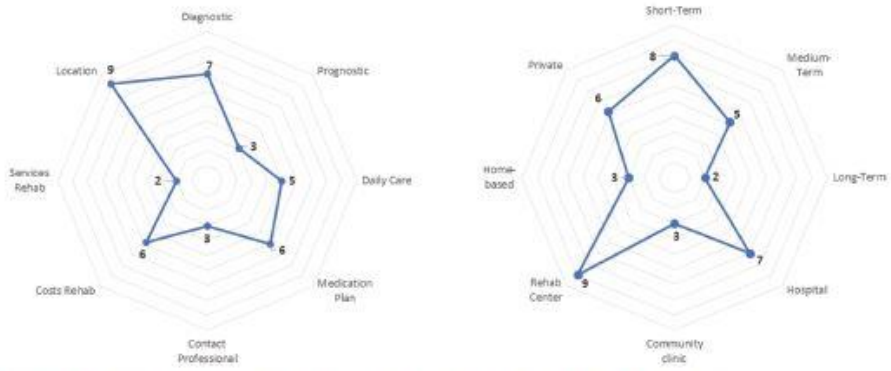


Figure 4. Information level [0-10] at hospital discharge and satisfaction level [0-10] by clinical setting.

(Figure 4). The results by item can be found in Appendix S7.

Discussion

The results highlighted six main rehabilitation pathways in a combination of eight different health care settings in Portugal.

The existence of multiple care options and alternatives can be seen as positive from a person-centered care perspective, where healthcare solutions are adapted to patient needs.[26,27] However, fragmentation of settings and pathways is not always synonymous with more developed health systems. Our results showed pathways with similar outcomes after 12 months of care, suggesting inefficiency. Simultaneously, important outcome differences were found between other pathways of the same healthcare system, which raises questions about the equity of care.

The process of fragmentation of care through differentiation can have implications for all stakeholders.[28] The element of payment loses efficiency and coordination, and the provider becomes solely responsible for its intervention linked to its own culture and organization.[29] The patient can be disoriented throughout the healthcare system, may have low levels of information regarding the available therapeutic options, as well as the specificity of each level of intervention.[30,31] This explains losses in access and quality, a scenario that leads to lower gains and increased costs.[31]

Given the complex health care delivery network, this study, based on system and process data sought to understand whether the existing solutions of care followed best practice guidelines [32–35]. This is consistent with European reports that describe flaws in the type and quality of stroke care,[11,12] which are common challenges for European health systems.

Portuguese guidelines on patient referral determine that mild stroke patients should be referred to a Day-hospital or Rehab-center [36]. In the study sample, one third of patients were referred to Short-term units not considered at national guideline. Furthermore, severe stroke patients under 55 years have indication for specialized hospital admission,[36] while the results showed that the norm was never respected. Referral appears to be more accurate in the mild and severe stroke cases. While the intermediate categories of age and severity, as they include higher samples, with a greater range of clinical manifestations and individual characteristics, tend to present less compliance with the norms.

On other hand, as early hospital discharge is recommended,[32–35] our study sample's mean hospital stay was 43 days (SD = 16 days), which warns that the transfer to the subacute phase is not fast and continuous. Furthermore, merely the Short-term and Rehab-center settings guarantee the suggested interdisciplinary and intense care, however restricted to 30–60 days, which means that only 30% of the study sample was able to obtain such care. This demonstrates the need to invest in more intensive settings.

Finally, the guidelines point to the relevance of transition planning between settings,[32] but only 60% offer transition planning and only 35% involve the patient in goal setting.

This lack of agreement between the good practice defined by guidelines and the care provided occurs in different European countries[37–39] and may suggest two phenomena. The first possibility is that there is a lack of knowledge and systemic integration of the guidelines into the decision-making process by professionals and health systems.[40] The second is that the guidelines are not adapted to the complexity of the process[41]. These findings show that professional and policy strategies are required to overcome barriers to evidence-based stroke rehabilitation.[41,42]

At patient-level, the results demonstrate that the pathway after stroke is not followed by an adequate level of information aligned with the literature.[16,43] This leads to unstable and disorganized navigation accompanied by a reduced perception of control, a combination of factors that justify distrust in the healthcare system.[13] Concurrently, our data shows that patient satisfaction is consistent with best practice intention,[28] with higher values in settings with more intensive and multidisciplinary care and greater involvement of the patient/caregiver. The gaps in the level of information and patient satisfaction are similar to the European trend in this field.[11,12,44]

The projections from the Burden of Stroke in Europe indicate that in 2047 the total number of stroke survivors in the European Union will increase by 27%.[11] Thus, it is paramount that the Helsingborg Declaration that defended that "all stroke patients in Europe have access to the continuum of rehabilitation care from the acute stage" be revisited.[10]

As emergency stroke care was optimized in the past, new simpler rehabilitation pathways must be created that are less fragmented, more homogeneous and closer to the guidelines.

The possibility of cooperating in providing information on the rehabilitation stroke pathways from healthcare system to patient perspective with a wide range of age, stroke subtypes, degrees of severity and rehabilitation data collected over the year, is one of the main strengths of this paper. In fact, to the best of our knowledge, this is the first article that systematically accesses and describes the real pathways of stroke in Portugal.

This study also has some potential limitations. The generalizability of our results is limited by the fact that the study is based on a single-center cohort of 391 stroke survivors from the Portuguese health system. In addition, the exclusion of the data from patients with communication impairments or deceased may have created a selection bias. For that, a higher initial sample was required at recruitment to accommodate a loss of greater than 23% of patients, as can be consulted in Appendix S1. Proxy responses were excluded, as proxies tend to overrate the severity of a patient's condition.[45] With a prospective follow-up study design, it was inevitable that some individuals were lost to follow-up, a potential form of selection bias. In addition, it was not possible to assess some pathways due to the impact of stratification by the various rehabilitation options, and therefore, studies with a larger sample size and of a multicentric design are needed. Future studies should consider some patient characteristics like associated comorbidities, ICU stay, and ventilatory requirement.

Conclusion

This study provides a useful contribution to the literature by characterizing the post-stroke rehabilitation pathway, allowing us to understand the existence of a heterogeneous healthcare system, with losses in effectiveness and efficiency. These findings can contribute toward the innovation and transformation of rehabilitation care for stroke survivors, leading to improvement of care and stronger bonds of trust between patients and the health system.

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Disclosure statement

The authors report that they have no competing interests to declare.

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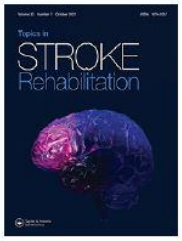
ORCID

Pedro Maciel Barbosa http://orcid.org/0000-0003-4189-674X
João Firmino-Machado http://orcid.org/0000-0001-9410-633X
Lara Noronha Ferreira http://orcid.org/0000-0003-2378-7750
Vitor Tedim Cruz http://orcid.org/0000-0002-5333-4771
Helena Szrek http://orcid.org/0000-0002-5154-4679

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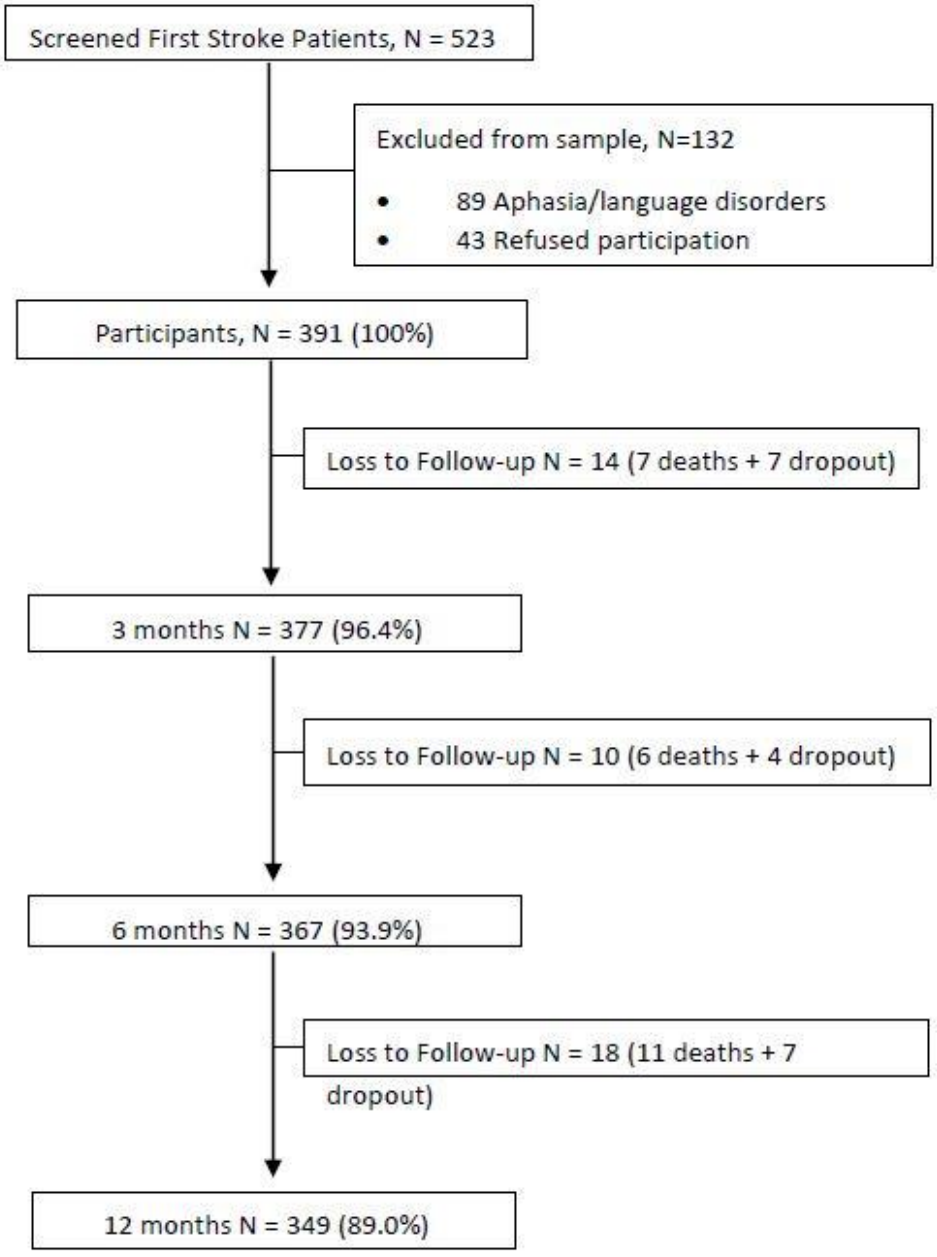
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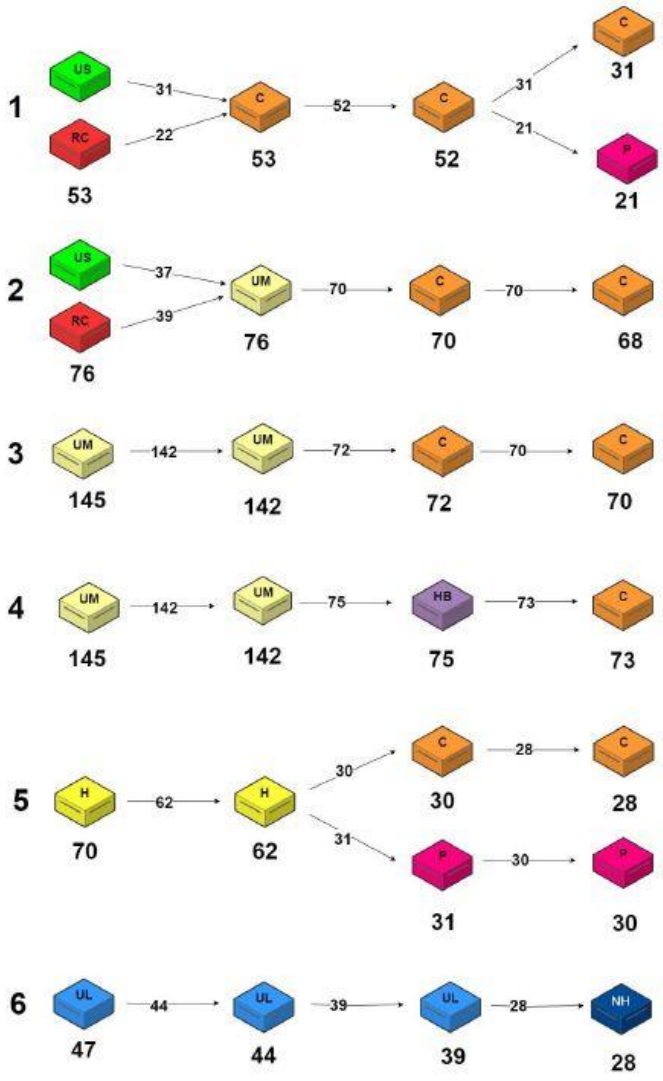
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Appendix S1 – Flow diagram of sample screening and participants



Appendix S2 - The 6 most prevalent rehabilitation care pathways during the first year after stroke in Portuguese NHS.

SU - Short-Term Unit; MU - Medium-term Unit; LU - Long-Term Unit; RC - Rehabilitation Center; HB - Home-based; DH - Day Hospital; CC - Community Clinic; PC - Private Clinic.

Appendix S3 - Sample Description by settings of care

	US	UM	UL	RC	HB	H	C	P
	n=68	n=215	n=47	n=61	n=75	n=70	n=225	n=28
Age (years), mean (sd)								
20-40	-	-	-	4	-	-	-	-
41-60	19	31	-	26	-	11	24	16
61-80	49	128	8	31	34	39	148	12
81-100	-	56	39	-	41	20	53	-
Sex, n (%)								
Male	32	101	22	28	35	33	106	13
Female	36	114	25	33	40	37	119	15
Marital status, n (%)								
Married/Civil Union	34	106	16	30	34	25	121	10
Divorced	23	64	2	22	30	30	84	14
Widowed	-	45	29	-	11	13	12	-
Single	11	-	-	9	-	2	8	4
Education, n (%)								
Elementary School	14	120	38	10	34	31	126	-
Middle School	25	87	9	30	41	26	94	12
High School	29	8	-	21	-	13	5	16
Current Residence, n (%)								
Home	68	181	21	61	75	70	216	28
Institutionalized	-	34	26	-	-	-	9	-
Occupation, n (%)								
Retired	-	119	47	-	49	39	102	-
Employed	60	87	-	52	26	27	113	27
Unemployed	8	9	-	9	-	4	10	1
Patient monthly income (€), n (%)								
≤1000	37	137	42	28	51	57	166	-
>1000	31	78	5	33	24	13	59	28
Subtype of stroke OXFORD, n (%)								
PACS	25	77	18	23	38	27	78	16
LACS	17	53	10	15	19	18	56	8
POCS	13	30	-	10	4	8	37	4
TACS	3	21	-	4	-	3	17	-
Haemorrhagic	10	34	19	9	14	14	37	-

US - Short-term Unit; UM - Medium-term Unit; UL - Long-Term Unit; RC - Rehabilitation Center; HB - Home-based; H - Hospital; C - Community Clinic; P - Private Rehabilitation.

Appendix S4 - Outcomes Description by Pathway

	1	2	3	4	5	6	
	n=52	n=76	n=67	n=75	n=70	n=47	
EQ-3D-3L							Overall p-value
Mean (sd)	0,49 (0,06)	0,42 (0,16)	0,25 (0,21)	0,22 (0,23)	0,42 (0,08)	–0,18 (0,17)	
Median (Interquartile deviation)	0,44 (0,12)	0,39 (0,18)	0,21 (0,23)	0,19 (0,23)	0,36 (0,14)	–0,24 (0,11)	0,002 (a)
Percentile 25	0,24	0,21	0,09	0,08	0,19	–0,34	
Percentile 75	0,68	0,65	0,34	0,31	0,57	–0,12	
mRS Scale							
Mean (sd)	2,1 (0,3)	2,3 (0,2)	3,6 (0,4)	3,7 (0,9)	2,7 (0,6)	4,5 (0,1)	
Median (Interquartile deviation)	1,8 (0,4)	2,1 (0,1)	3,4 (0,2)	3,5 (0,3)	2,3 (0,4)	4,6 (0,3)	0,007 (b)
Percentile 25	1	1	2	2	1	4	
Percentile 75	2	3	4	4	3	5	
No symptoms at all (0)	-	-	-	-	-	-	
No significant disability (1)	2	6	-	-	8	-	
Slight disability (2)	19	29	-	-	25	-	
Moderate disability (3)	31	41	15	21	37	-	
Moderately severe disability (4)	-	-	32	38	-	30	
Severe disability (5)	-	-	20	16	-	17	
Mini Mental State Examination							
Mean (sd)	28,4 (0,8)	28,5 (0,5)	23,5 (1,1)	24,1 (1,6)	27,1 (0,8)	17,7 (3,3)	
Median (Interquartile deviation)	27 (3,0)	27 (2,5)	21 (3,5)	19 (4,5)	26 (3,0)	15 (4,1)	0,02 (c)
Percentile 25	23	24	18	16	22	12	
Percentile 75	29	29	25	25	28	20	
Barthel Index,							
Mean (sd)	77,1 (13,1)	71,2 (9,6)	56,3 (12,8)	53,4 (12,8)	68,2 (8,4)	21,3 (4,6)	
Median (Interquartile deviation)	75 (17,5)	70 (12,5)	55 (17,5)	50 (17,5)	65 (12,5)	20 (7,5)	0,004 (d)
Percentile 25	55	55	35	30	50	5	
Percentile 75	90	80	70	65	75	20	
Slight dependency (91-99)	16	18	-	-	19	-	
Moderate Dependency (61-90)	36	58	15	17	51	-	
Severe Dependency (21-60)	-	-	40	44	-	5	
Total Dependency (0-20)	-	-	12	14	-	42	

Final Outcomes by Pathway. Overall p-value: a=0,002; b=0,007; c=0,02; d=0,004.

All post-hoc comparisons showed significant differences (p-value between 0.0003 and 0.002), except for pathway 1 vs 2 at all outcomes, for pathway 3 vs 4 at EQ-5D-3L, BI and MMSE, for pathway 1 vs 5 at MMSE, and pathway 2 vs 5 at EQ-5D-3L, mRS and MMSE.

Appendix S5 - Outcomes Description by care setting

	TOTAL	US	UM	UL	RC	HB	H	C	P	
	n=391	n=68	n=215	n=47	n=61	n=75	n=70	n=225	n=28	
EQ-3D-3L										Overall p-value
Mean (sd)	0,15 (0,14)	0,69 (0,07)	–0,13 (0,18)	–0,47 (0,10)	0,61 (0,06)	0,41 (0,08)	0,56 (0,07)	0,37 (0,13)	0,54 (0,05)	
Median (Interquartile deviation)	–0,07 (0,39)	0,64 (0,11)	–0,17 (0,21)	–0,51 (0,16)	0,58 (0,11)	0,39 (0,08)	0,54 (0,12)	0,31 (0,15)	0,48 (0,11)	0,001 (a)
Percentile 25	–0,34	0,53	–0,28	–0,64	0,49	0,31	0,41	0,22	0,39	
Percentile 75	0,43	0,75	0,12	–0,33	0,71	0,47	0,64	0,51	0,61	
mRS Scale										
Mean (sd)	3,5 (0,7)	2,1 (0,3)	3,8 (0,8)	4,4 (0,1)	2,4 (0,2)	3,5 (0,4)	2,5 (0,4)	3,4 (0,9)	2,8 (0,6)	
Median (Interquartile deviation)	3 (0,5)	2,2 (0,4)	3,9 (0,7)	4,6 (0,3)	2,3 (0,1)	3,6 (0,2)	2,8 (0,5)	3,7 (0,3)	3,0 (0,4)	0,003 (b)
Percentile 25	3	1	2	4	1	2	1	2	2	
Percentile 75	4	2	4	5	3	4	3	4	4	
No symptoms at all (0)	0	-	-	-	-	-	-	-	-	
No significant disability (1)	7	4	-	-	1	-	3	-	-	
Slight disability (2)	66	21	-	-	24	-	18	-	3	
Moderate disability (3)	156	43	64	-	36	18	49	84	13	
Moderately severe disability (4)	98	-	104	30	-	34	-	106	6	
Severe disability (5)	65	-	47	17	-	23	-	35	6	
Mini Mental State Examination										
Mean (sd)	24.2 (3.1)	28,9 (1,5)	21,5 (2,6)	18,7 (3,1)	28,6 (0,3)	24,8 (1,6)	27,8 (0,9)	24,3 (2,8)	26,7 (1,1)	
Median (Interquartile deviation)	23 (6,1)	27 (2,5)	19 (4,5)	16 (4,0)	26 (2,0)	22 (4,5)	26 (3,0)	21 (5,5)	25 (3,5)	0,04 (c)
Percentile 25	14,6	24	15	12	25	17	23	16	21	
Percentile 75	28,7	29	24	20	29	26	29	27	28	
Barthel Index,										
Mean (sd)	60.2 (29.5)	68,4 (8,1)	42,1 (10,3)	14,3 (2,6)	61,2 (9,6)	51,3 (12,8)	57,6 (11,1)	52,1 (12,8)	78,4 (6,94)	
Median (Interquartile deviation)	58 (30,1)	65 (12,5)	40 (17,5)	15 (4,5)	60 (12,5)	50 (17,5)	55 (15,0)	50 (17,5)	75 (15,0)	0,009 (d)
Percentile 25	15	50	25	10	45	35	40	30	55	
Percentile 75	75	75	60	20	70	70	70	65	85	
Slight dependency (91-99)	30	21	-	-	18	-	12	-	-	51
Moderate Dependency (61-90)	179	47	62	-	43	14	54	79	16	315
Severe Dependency (21-60)	143	-	111	5	-	37	4	112	10	279
Total Dependency (0-20)	144	-	42	42	-	24	-	34	2	144

SU - Short-Term Unit; MU - Medium-term Unit; LU - Long-Term Unit; RC - Rehabilitation Center; HB - Home-based; DH - Day Hospital; CC - Community Clinic; PC - Private Clinic.

Overall p-value: a=0.001; b=0.003; c=0.040; d=0.009. All post-hoc comparisons showed significant differences, except for RC vs SU at EQ-5D-3L, for RC vs SU vs DH at mRS, for RC vs DH and MU vs CC at MMSE, and for RC vs SU vs DH for BI.

Appendix S6 - Information level at hospital discharge

	n=391 mean (sd)
Diagnostic	7,12 (0,03)
Prognostic	3,05 (0,12)
Daily Care	5,01 (0,41)
Medication Plan	5,96 (0,08)
Contact Professional	3,04 (0,74)
Costs Rehab	5,81 (0,06)
Services Rehab	2,04 (0,15)
Location	9,13 (0,01)

sd, standard deviation

Appendix S7 - Satisfaction Level by care setting

n=391, mean (sd)

	US	UM	UL	RC	HB	H	C	P
Available Information	8,0 (0,3)	6,1 (0,2)	2,2 (0,4)	9,4 (0,6)	4,4 (0,1)	7,2 (0,6)	3,2 (0,3)	6,1 (0,1)
Referral Process	7,3 (0,8)	6,1 (0,7)	2,6 (0,3)	7,7 (0,4)	5,0 (0,8)	8,4 (0,3)	3,1 (0,7)	5,1 (0,2)
Rehabilitation Outcomes	8,1 (0,1)	5,3 (0,3)	2,1 (0,8)	8,4 (0,1)	2,2 (0,3)	7,0 (0,8)	4,3 (0,1)	7,4 (0,6)
Intensity of rehabilitation	8,2 (0,4)	4,2 (0,9)	1,4 (0,2)	10,0 (0,1)	3,2 (0,6)	6,7 (0,4)	4,4 (0,4)	6,3 (0,1)
Family involvement	7,4 (0,8)	5,4 (0,1)	2,3 (1,1)	8,5 (0,6)	2,7 (0,4)	5,8 (0,3)	3,3 (0,2)	5,2 (0,8)
Patient involvement	9,0 (0,3)	4,1 (0,2)	2,1 (0,6)	9,4 (0,3)	2,3 (0,8)	5,5 (0,1)	4,1 (0,8)	6,4 (0,1)
INDEX	8,1	5,2	2,1	9,0	3,3	6,8	3,4	6,3

US - Short-term Unit; UM - Medium-term Unit; UL - Long-Term Unit; RC - Rehabilitation Center; HB - Home-based; H - Hospital; C - Community Clinic; P - Private Rehabilitation.

4.3 PAPER 3

Stroke rehabilitation pathways during the first year: a cost-effectiveness analysis from a cohort of 460 individuals. [Annals of Physical and Rehabilitation Medicine, accepted for publication, article reference REHAB_101824]

Stroke rehabilitation pathways during the first year: a cost-effectiveness analysis from a cohort of 460 individuals.

Pedro Maciel Barbosa, MD

Corresponding author contact details – p.macielbarbosa@gmail.com

Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas 135, 4050-600 Porto, Portugal.

Hospital Pedro Hispano, Unidade Local de Saúde, EPE, Rua de Alfredo Cunha 365, 4450-021 Matosinhos, Portugal.

ORCID ID: 0000-0003-4189-674X

Helena Szrek, PhD - hszrek@gmail.com

Centre for Economics and Finance, University of Porto, R. Dr. Roberto Frias, 4200-464 Porto, Portugal.

ORCID ID: 0000-0002-5154-4679

Lara Noronha Ferreira, PhD - lnferrei@ualg.pt

ESGHT, Universidade do Algarve, Estr. da Penha 139, 8005-246 Faro, Portugal

Centre for Health Studies and Research of the University of Coimbra, Avenida Dias da Silva 165 3004-512 Coimbra, Portugal

Research Centre for Tourism, Sustainability and Well-Being (CinTurs), Portugal

ORCID ID: 0000-0003-2378-7750

Vitor Tedim Cruz, PhD - vtedimcruz@gmail.com

EPIUnit, Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas 135, 4050-600 Porto, Portugal.

Hospital Pedro Hispano, Unidade Local de Saúde, EPE, Rua de Alfredo Cunha 365, 4450-021 Matosinhos, Portugal.

ORCID ID: 0000-0002-5333-4771

João Firmino-Machado, PhD - firmino.firminomachado@gmail.com

EPIUnit, Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas 135, 4050-600 Porto, Portugal.

Centro Académico Clínico Egas Moniz, 810-193 Aveiro, Portugal

Centro Hospitalar Vila Nova de Gaia/Espinho, R. Conceição Fernandes S/N, 4434-502 Vila Nova de Gaia, Portugal.

ORCID: 0000-0001-9410-633X

Abstract

Background: Stroke burden challenges global health and social and economic policies. Although stroke recovery encompasses a wide range of care, including in-hospital, outpatient, and community-based rehabilitation, there are no published cost-effectiveness studies of integrated post-stroke pathways.

Objective: To determine the most cost-effective rehabilitation pathway during the first 12 months after a first-ever stroke.

Methods: A cohort of people in the acute phase of a first stroke was followed after hospital discharge; 51% women, mean (SD) age 74.4 (12.9) years, mean National Institute of Health Stroke Scale score 11.7 (8.5) points, and mode modified Rankin Scale score 3 points. We developed a decision tree model of 9 sequences of rehabilitation care organised in 3 stages (3, 6 and 12 months) through a combination of public, semi-public and private entities, considering both the individual and healthcare service perspectives. Health outcomes were expressed as quality-adjusted life years (QALY) over a 1-year time horizon. Costs included healthcare, social care, and productivity losses. Sensitivity analyses were conducted on model input values.

Results: From the individual perspective, pathway 3 (Short-term Inpatient Unit » Community Clinic) was the most cost-effective, followed by pathway 1 (Rehabilitation Centre » Community Clinic). From the healthcare service perspective, pathway 3 was the most cost-effective followed by pathway 7 (Outpatient Hospital » Private Clinic). All other pathways were considered strongly dominated and excluded from the analysis. The total 1-year mean cost ranged between €12104 and €23024 from the individual's perspective and between €10992 and €31319 from the healthcare service perspective.

Conclusion: Assuming a willingness-to-pay threshold of one times the national gross domestic product (€20633/QALY), pathway 3 (Short-term Inpatient Unit » Community Clinic) was the most cost-effective strategy from both the individual and healthcare service perspectives. Rehabilitation pathway data contribute to the development of a future integrated care system adapted to different stroke profiles.

Keywords: pathway, stroke, rehabilitation, outcomes, cost-analysis, health policy.

Highlights

- First cost-effectiveness analysis of different stroke rehabilitation pathways.
- An inpatient unit followed by a community clinic was the most cost-effective pathway.
- A day hospital followed by a community clinic was also a cost-effective pathway.
- Cost-effectiveness analysis is consistent with stroke evidence-based practice.
- The incremental cost-effectiveness ratios are coherent between both perspectives

List of abbreviations:

C | Outpatient Community Clinic

H | Outpatient Day Hospital

HB | Home-based Rehabilitation

ICER | Incremental Cost-Effectiveness Ratio

MMSE | Mini Mental State Examnation

mRS | modified Rankin Scale

N | Nursing Home

NHS | National Health System

NIHSS | National Institute of Health Stroke Scale

P | Outpatient Private Clinic

QALY | Quality-Adjusted Life Year

RC | Rehabilitation Inpatient Centre

UL | Long-Term Inpatient Unit

UM | Medium-term Inpatient Unit

US | Short-term Inpatient Unit

WHO | World Health Organization

WTP | willingness-to-pay

Introduction

Stroke rehabilitation should be intensive, timely, and multidisciplinary, with coordinated transfers between settings, and effective interfacing with social and community care [1]. However, post-stroke care is considered disorganized and fragmented even in the best health systems [2], and many survivors express dissatisfaction [3]. There are no universally agreed best practices across European countries, where different health service structures and payment systems often lead to inconsistent care pathways, types, and quality of therapies [4,5].

Stroke defies worldwide health, social and economic policies, as a global leading cause of mortality and disability [6]. By 2047 there will be an additional 40,000 incident stroke cases (+3%) and 2.58 million prevalent stroke cases (+ 27%) [7], and the corresponding economic burden will increase [8]. Approximately 3 to 4% of total health expenditures in Western countries are allocated to stroke [9]. In 2017, 32 European countries spent €60 billion on stroke care, of which 45% was for health care, 8% for social care, and 47% for direct and indirect productivity losses. Of the €27 billion spent on stroke healthcare, only 18% was spent on rehabilitation [10].

Despite recovery from a stroke is an arduous journey that takes months or years [11] and covers a whole spectrum of care, including in-hospital, outpatient, and community-based rehabilitation [12], there are no published cost-effectiveness studies of integrated post-stroke pathways [13]. Our previous work showed 9 different rehabilitation pathways, that suggested heterogeneity, inefficiency, and inequalities, followed by a heterogeneous satisfaction level [14].

In the last years, there has been a call to design new care settings that ensure greater consistency and effectiveness to meet the targets set for 2030 by the *Action Plan for Stroke* [4]. The extent of the challenge, combined with limited healthcare budgets emphasizes the need for an evidence-based and cost-effective analysis that contributes to post-stroke decision-making [15], bridging the gap between clinical guidelines, organizational models, and the provision of care.

This study evaluated the cost-effectiveness of post-stroke rehabilitation pathways using high-quality individual participant-level data. It aimed to (i) determine the cost structure of each pathway and ii) determine the most cost-effective rehabilitation post-stroke care pathway from the perspective of the individuals with stroke and that of the healthcare service.

Methods

Stroke Rehabilitation Pathways in Portugal

Portugal has a healthcare system based on a National Health System (NHS), with 8 rehabilitation care settings described as follows: Short-term Inpatient Unit (US), Medium-term Inpatient Unit (UM), Long-Term Inpatient Unit (UL), Rehabilitation Inpatient Centre (RC), Home-based Rehabilitation (HB), Outpatient Day Hospital (H), Outpatient Community Clinic (C), Outpatient Private Clinic (P), Nursing Home (N) [16]. A detailed description of outcomes and process level data for each set is provided in Appendix A1 using the following 6 variables: 1) admission assessment, 2) discharge plan, 3) stroke survivor involvement in the definition of rehabilitation goals, 4) multidisciplinary team available, 5) frequency and 6) duration of clinical sessions.

Considering the care circuits observed over the 4 follow-up stages (first 7 days, 3, 6 and 12 months after stroke), the 9 most common pathways were selected for this study, using the sequences of the 8 different rehabilitation settings mentioned above through a combination of public, semi-public and private organisations over the first year post-stroke. In each follow-up assessment, participants were asked about the setting where the rehabilitation had taken place since the last assessment, building up a multistep pathway of 4 rehabilitation settings. Graphic presentation and outcome descriptions by pathway are available in Appendix A2, and further details are reported elsewhere [16].

Model Overview

We estimated the cost-effectiveness of the pathways from the individual and the healthcare service perspective during the first 12 months after stroke in Portugal. This was a secondary analysis that considered all the participants from a prospective cohort derived from our previous work [14, 16]. It included a total of 460 individuals in the acute phase of a first stroke, 418 (90%) of whom were followed up to 12 months (Figure 1). In total, 51% of participants were women, the mean (SD) age was 74.4 (12.9) years, the mean severity score was 11.7 (8.5) (NIHSS - National Institute of Health Stroke Scale), the mode disability score was 3 (mRS – Modified Rankin Scale) and mean neurocognitive function score was 24.2 (3.1) (MMSE - Mini-Mental State Examination). After admission to a large public hospital in Portugal, individuals were screened for the following eligibility criteria: a) diagnosis of stroke confirmed by clinicians and supported by neuroimaging, b) first episode of stroke, and c) not globally aphasic. The study sample was restricted to individuals who could complete the participant-reported outcome measure - Health-related Quality of Life (EQ-5D-3L) independently. The remaining outcomes (NHISS, mRS, MMSE), health benefits and costs were retrieved from person-level data of our cohort study and when unavailable national data sources were considered, as described in detail in Appendix A3. All participants signed informed consent and the study was approved by the ethics and data protection committee (No. 57/14/RS). Further details of the sample are reported elsewhere [14, 16].

A decision tree model was used to analyse cost-effectiveness, considering individual participant-level data retrieved from our previous cohort study. Since post-stroke recovery-related processes are time-dependent, the Stroke Roundtable Consortium designate 6 months as the start of the chronic phase, when spontaneous recovery is usually at its limit [17]. Therefore,

this study considered a 1-year time horizon, so that the cost-effectiveness ratio included the benefits of the main functional gains and utilities. This model considered the following outcomes: i) cost per quality-adjusted life year (QALY), ii) cost per pathway, and iii) cost per stroke survivor. We defined 9 competing pathways for our cost-effectiveness model (figure1) : 1: RC-C-C-C; 2: US-C-C-C; 3: RC-UM-C-C; 4: US-UM-C-C; 5: UM-UM-C-C; 6: UM-UM-HB-C; 7: H-H-C-C; 8: H-H-P-P; and 9: UL-UL-UL-NH. The tree model was implemented and analysed in TreeAgePro 2023. This manuscript conforms to the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS2022).

Health benefits

The health benefits considered in the decision model are summarized in Table 1 and their calculation is detailed in Appendices A4 and A5. The initial hospital sample was distributed as follows for each pathway: 8% for Pathway 1, 8% for Pathway 2, 10% for Pathway 3, 11% for Pathway 4, 18% for Pathway 5, 19% for Pathway 6, 7% for pathway 7, 8% for pathway 8 and 11% for pathway 9.

The 3-month, 6-month, and 1-year relative survival estimates and utility values assigned to each health state of the decision model were obtained from previously published national studies [18,19]. A first-ever-in-a-lifetime stroke in Portugal was considered to have a 1-year relative survival rate of 0.73; 6-month relative survival of 0.77; and, a 3-month relative survival of 0.81 [18,19]. These parameters varied by 10% in the sensitivity analysis, to consider the variation in stroke epidemiology over time.

Utility values for the different health states ranged from a minimum of -0.324 to a maximum of 0.616, representing a health state value as worse than death and a value as good health, respectively [20]. All pathways presented positive 1-year mean utility values, except for pathway 9. Although in the Portuguese EQ-5D, tariff utility values for each health state range from -0.497 to 0.766 [20], negative values were considered as 0 in the decision model (Appendix A4).

Stroke survivors were considered to have a 1-year mean utility value of 0.388 for Pathway 1, 0.438 for Pathway 2, 0.242 for Pathway 3, 0.285 for Pathway 4, 0.041 for Pathway 5, 0.021 for Pathway 6, 0.166 for Pathway 7, 0.177 for pathway 8, and -0.231 for pathway 9.

The minimum and maximum benefit values observed for each individual in a certain pathway were used as range values in the sensitivity analysis (Table 1 and Appendix A5). The 1-year-benefits were retrieved from utility data determined in the same year. Therefore, the decision model did not incorporate discounts over time, as recommended by the World Health Organization (WHO) [21].

Costs

Costs were calculated assuming the following 2 independent payer perspectives: i) the healthcare service perspective, which includes only the costs and effects for the NHS part; ii) the individual perspective, which includes the cost and the effects for the individual with stroke. The underlying concepts of NHS and stroke costs followed by Drummond et al [22] and guidelines on good research practices [23].

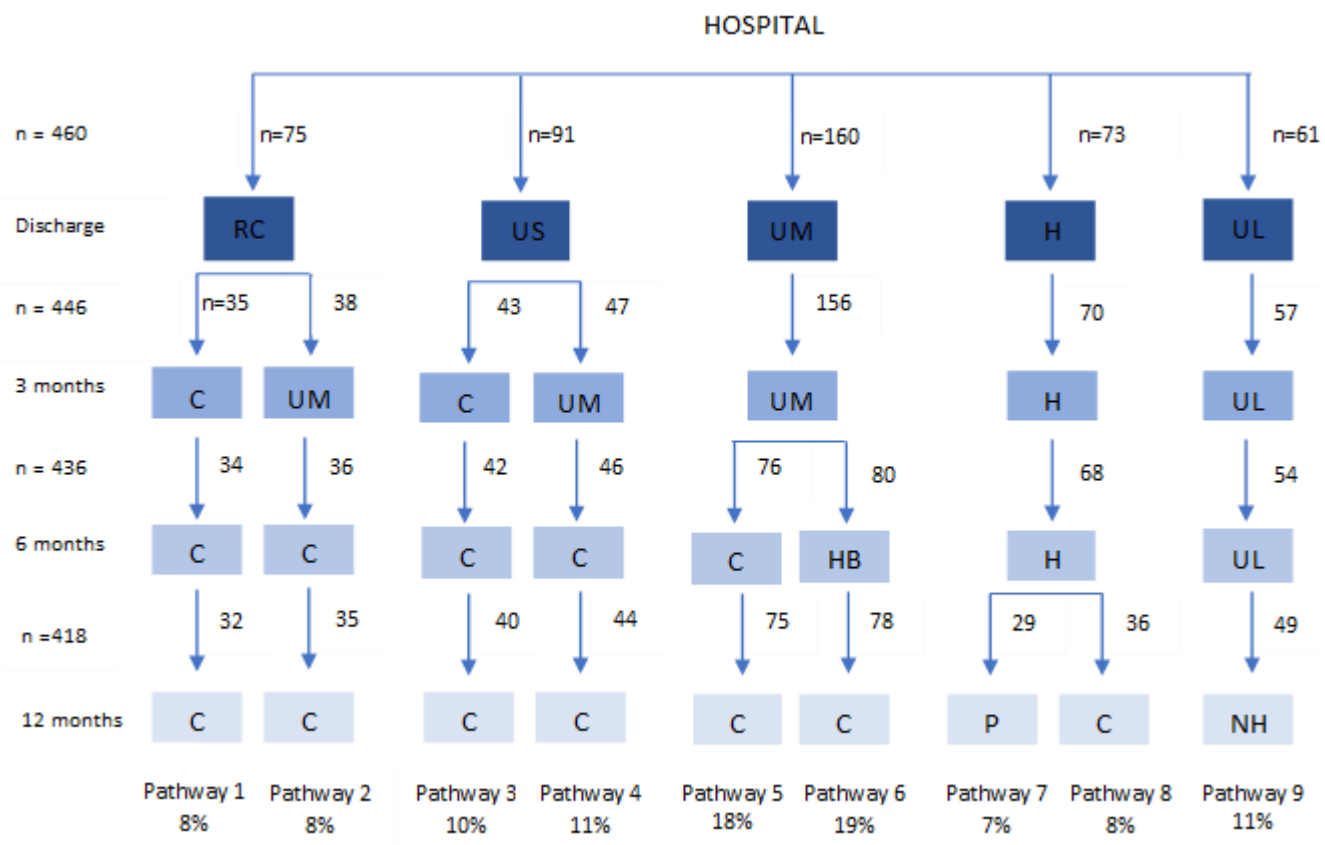


Figure 1 - Decision tree model overview

The figure depicts the 9 competing pathways of the cost-effectiveness model, during the first 12 months after a first-ever stroke. The transition probability between steps was defined as 1. The difference between the initial and final sample of each pathway is caused by follow-up losses by dropout or death: pathway 1 - 5 losses; pathway 2 - 3 losses; pathway 3 - 4 losses; pathway 4 - 3 losses; pathway 5 - 3 losses; pathway 6 - 4 losses; pathway 7 - 4 losses; pathway 8 - 4 losses; pathway 9 - 12 losses. A brief description of each pathway is presented as follows: 1 – Rehabilitation care at a Rehabilitation Centre from discharge to 3 months and at a Community Clinic from 3 to 12 months. 2 – Rehabilitation care at a Rehabilitation Centre from discharge to 3 months, at a Medium-term Unit from 3 to 6 months and at Community Clinic from 6 to 12 months. 3 – Rehabilitation care at a Short-term Unit from discharge to 3 months, and at Community Clinic from 3 to 12 months. 4 – Rehabilitation care at a Short-term Unit from discharge to 3 months, at a Medium-term Unit from 3 to 6 months and at Community Clinic from 6 to 12 months. 5 – Rehabilitation care at a Medium-term Unit from discharge to 3 months and at Community Clinic from 3 to 12 months. 6 – Rehabilitation care at a Medium-term Unit from discharge to 3 months, at Home-based from 3 to 6 months, and at Community Clinic from 6 to 12 months. 7 – Rehabilitation care at a Day Hospital from discharge to 6 months and at a Community Clinic from 6 to 12 months. 8 – Rehabilitation care at a Day Hospital from discharge to 6 months and at a Private Clinic from 6 to 12 months. 9 – Rehabilitation care at a Long-Term Unit from discharge to 6 months and at Nursing Home from 6 to 12 months.

C - Community Clinic; H - Hospital; HB - Home-based; P - Private Rehabilitation; RC - Rehabilitation Centre; UL - Long-Term Unit; UM - Medium-term Unit; US - Short-term Unit.

Both individual and healthcare service perspective costs include 2 main domains – health and social costs (Appendix A6). Although the cost items for NHS and individual costs are the same, the point of view is different. The stroke rehabilitation pathways have important effects on costs across the healthcare service or the individual. There are items whose cost is fully supported by the healthcare service, others with costs shared between the healthcare service and the individual, and others that are paid totally by the individual. Each cost fraction was assigned to each perspective item by item. A detailed description of the cost calculation details by both perspectives is provided in Appendix A3.

Health costs comprise health intervention costs and individual transport costs. Social costs include social service costs (e.g. formal caregiver, day centre, nursing home), technical aid costs (e.g. walker, crutches, tripod, adjustable bed, recliner chair, wheelchair, shower chair, house adaptation for reduced mobility), and individual and informal caregiver productivity losses.

Health and Social costs were calculated using official legal publications from the Ministry of Health/Social Security, which define the value of the health and social service, as well as the criteria for attributing the cost to the healthcare service payer perspective or the individual payer perspective [24-32]. The only cost items whose value did not result from official publications and legal rules were the cost of technical aids and the cost of the Private setting, for which a market study was carried out based on the cost of 4 different providers.

Each pathway involved individuals with different health and social needs, so that, the minimum and maximum costs observed for each individual in a given pathway were used as range values in the sensitivity analysis (Table 1 and Appendix A6). The year considered for all cost calculations was 2021. All the costs were determined in the reference year and obtained from Portuguese data sources, so there was no correction for inflation or purchasing power, as proposed by the WHO [21].

Cost-effectiveness analysis

The incremental cost-effectiveness ratio (ICER) was calculated as the additional costs divided by the additional health benefits of one strategy compared to the next less-costly strategy. The ICERs were compared to the 2021 Portuguese gross domestic product per capita (ie, €20873), which is considered the external willingness-to-pay (WTP) threshold to identify the most cost-effective pathway. The "base case" was considered the non-dominated pathway with the lowest cost, ie, the reference strategy against which the other pathways in the model were compared. Reporting of the cost-effectiveness analysis followed the Consolidated Health Economic Evaluation Reporting Standards [23].

Table 1 Summary of decision tree model parameters

Description of cost parameters By Societal Perspective	Base case (€) [α]	Range (€) [a]	Further Details
Pathway 1	12104	7672; 27833	Includes Health (health care + transport) and Social (social care + technical aids + productivity losses) Costs. See Supplementary Appendices 3 and 6 for calculation details.
Pathway 2	16537	10352; 29323	
Pathway 3	12532	8437; 23093	
Pathway 4	15409	7679; 27064	
Pathway 5	19950	12104; 35960	
Pathway 6	19902	10844; 33665	
Pathway 7	16336	7792; 30677	
Pathway 8	23024	13598; 36897	
Pathway 9	21856	12877; 39048	
Description of cost parameters By Provider Perspective	**Base case (€) [α]**	**Range (€) [a]**	**Further Details**
Pathway 1	26428	24131; 36617	Includes Health (health care + transport) and Social (social care + technical aids + productivity losses) Costs. See Supplementary Appendices 3 and 6 for calculation details.
Pathway 2	31319	28814; 38378	
Pathway 3	15124	11659; 21750	
Pathway 4	18424	16301; 21750	
Pathway 5	25567	18896; 27091	
Pathway 6	24761	18740; 36670	
Pathway 7	10992	8102; 36765	
Pathway 8	11623	6637; 23177	
Pathway 9	14857	15189; 40044	
Description of health state	**Base case (QALY/year) [β]**	**Range (QALY/year) [b]**	**Further Details**
Pathway 1	0,388	0,306; 0,417	Includes one-year Quality-adjusted survival for each competing rehabilitation pathway. See Supplementary Appendices 4 and 5 for benefits details.
Pathway 2	0,272	0,199; 0,297	
Pathway 3	0,438	0,354; 0,475	
Pathway 4	0,305	0,220; 0,317	
Pathway 5	0,041	0,004:0,091	
Pathway 6	0,021	0; 0,049	
Pathway 7	0,177	0,110; 0,211	
Pathway 8	0,166	0,131; 0,221	
Pathway 9	0	0	

QALY, quality-adjusted life years; α, considers Portuguesa data sources (appendices 3 and 6); β, considers previously published national cohort studies (appendices 4 and 5).

a: The parameter to be varied in the sensitivity analysis is the minimum and maximum cost values observed for each pathway. All the costs were determined in the reference year and obtained from Portuguese data sources, so there was no correction for inflation or purchasing power.

b: The parameter to be varied in the sensitivity analysis is the minimum and maximum benefit values observed for each individual in each pathway. Benefits were retrieved from utility data determined in the same year; therefore, the decision model did not incorporate discounts over time.

Results

The 1-year costs and benefits as cost-effectiveness results are presented in Table 2 and Appendices A5 and A6.

One-year costs and benefits

From the individual perspective, the total 1-year mean cost was lowest for pathway 1 and highest for pathway 9, ranging from €12104 to €21856, respectively. Health costs accounted for 24% of the total costs in pathway 8, and <9% in pathways 1, 3, 5, 6, 7 and 9. Pathways 1, 3 and 7 are free, whereas pathway 8 has costs >€4700 per survivor. Transportation costs range from €670 to 820 for pathways 1, 2, 3, 4, 7 and 8, and €0 for all the other pathways. Social costs ranged from 76% of Pathway 8 to 95% of Pathway 7 of the total cost. Stroke-related social care expenditure was about €1000 in pathways 5, 6 and 9, and varied between €500 to €800 in the other pathways. Loss of productivity costs ranged from €10,000 per individual in pathways 1 and 3, and up to €18000 in pathway 9.

From the healthcare service perspective, the total 1-year mean cost ranged from a minimum of €10992 for pathway 7 to a maximum of €31319 for pathway 2. From this perspective, the relative weight of health costs exceeded 75% of the total cost in pathways 1 and 2, and 55% in pathways 3, 4, 5, 6 and 9. Health care costs ranged from €1500 in pathways 7 and 8, to €20000 in pathways 1 and 2. Transport costs varied between €150 on Pathway 9 and €1800 on Pathway 5. Social costs ranged from 25% of the total cost in pathways 1 and 2 to 85% in pathway 8. Stroke-related social care expenditure was about €1300 in Pathways 1 and 3, and €3800 in Pathway 5. Loss of productivity costs ranged from €4000 in pathway 3, up to €7000 in pathway 9.

The quantification of QALYs showed that pathway 9 was the least effective, with -0,342 QALYs per individual over 1 year, whereas pathways 3 and 4 were the most effective, with 0,306 and 0,354 QALYs per individual, respectively.

Cost-effectiveness results

From the individual perspective, pathways 2 and 4 to 9 were strongly dominated by pathway 1, ie, they were costlier and less effective. Pathway 3 had an ICER of €8560 per QALY. From the healthcare service perspective, pathways 1, 2, 4, 5, 6, 8, and 9 were strongly dominated by pathway 7. Pathway 3 had an ICER of €19279 per QALY. All strongly dominated pathways were excluded from the analysis.

One-way sensitivity analysis

Sensitivity analysis results are detailed in Table 3. From the individual perspective, pathways 2, 4, 6, and 7 were not strongly dominated when the sensitivity analysis considered their minimal specific costs. Nevertheless, the most cost-effective pathways were always 1 and 3 for all the tested parameters. For the extreme cost value in Pathway 1, along with the minimum cost value in Pathway 3, the most cost-effective strategy was Pathway 3. For all the other tested parameters, pathway 1 was the most cost-effective strategy.

From the healthcare service perspective, pathway 8 was not strongly dominated when the sensitivity analysis considered its minimal costs or maximum benefits. The most cost-effective pathways were always 7 and 3 for all the tested parameters. For minimum benefits and maximum cost of pathway 3, pathways 1 and 4 were considered undominated, respectively.

Table 2 Costs, benefits, and incremental cost-effectiveness ratios, by pathway, from the individual and healthcare service perspective

	1-year costs and benefits		
	Incremental Costs (€)	Incremental Benefits (QALY)	ICER (cost/QALY) [a]
Societal Perspective			
Pathway 1	-	-	-
Pathway 3	428	0,05	8560
Pathway 4	2877	-0,13	SD
Pathway 7	3804	-0,26	SD
Pathway 2	4005	-0,17	SD
Pathway 6	7370	-0,42	SD
Pathway 5	7418	-0,40	SD
Pathway 9	9324	-0,44	SD
Pathway 8	10492	-0,27	SD
Provider Perspective			
Pathway 7	-	-	-
Pathway 8	1531	-0,01	SD
Pathway 9	4765	-0,18	SD
Pathway 3	5032	0,26	19279,69
Pathway 4	3300	-0,13	SD
Pathway 6	9637	-0,41	SD
Pathway 5	10443	-0,40	SD
Pathway 1	11304	-0,05	SD
Pathway 2	16195	-0,17	SD

ICERs were calculated using TreeAge software, which considers a larger number of decimal places than presented in the table. Therefore, the ICERs differ from calculations using the cost and QALY values are presented in the table.

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; SD, strongly dominated.

a: The difference in cost divided by the difference in benefits of one pathway, compared with the next more effective pathway.

Table 3 Sensitivity analysis

The parameter to be varied in the sensitivity analysis		Parameter range [a]	Pathway [b]	ICER (societal perspective) [c]	The parameter to be varied in the sensitivity analysis		Parameter range [a]	Pathway [b]	ICER (provider perspective) [c]
Benefits Pathway 1	Minimum	0,306	1	-	Benefits Pathway 7	Minimum	0,11	7	-
			3	3242,42				3	15341,46
	Maximum	0,417	1	-				8	27339,29
			3	20380,95		Maximum	0,211	7	-
Benefits Pathway 3	Minimum	0,354	1	-				3	22167,40
			3	SD	Benefits Pathway 3	Minimum	0,354	7	-
	Maximum	0,475	1	-				3	28429,38
			3	4919,54				1	332470,59
Costs Pathway 1	Minimum	€7672	1	-		Maximum	0,475	7	-
			3	97200				3	16885,91
	Maximum	€27833	3	-	Costs Pathway 7	Minimum	€8102	7	-
			1	SD				3	26904,21
Costs Pathway 3	Minimum	€8437	3	-		Maximum	€21292	7	-
			1	SD				3	12871,32
	Maximum	€23093	1	-	Costs Pathway 3	Minimum	€11659	7	-
			3	219780				3	6003,83
Costs Pathway 2	Minimum	€10352	2	-		Maximum	€21750	7	-
			1	15103,45				3	44666,67
			3	13132,53				4	65093,75
Costs Pathway 4	Minimum	€7679	4	-	Benefits Pathway 8	Maximum	0,221	7	-
			1	53313,25				3	19279,69
			3	36488,72				8	34795,45
Costs Pathway 6	Minimum	€12104	5	-	Cost Pathway 8	Minimum	€6637	8	-
			1	3433,24				3	31202,21
			3	8560,00				7	31409,91
Costs Pathway 7	Minimum	€7792	7	-					
			1	20436,02					

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; SD, strongly dominated. a: The table depicts the minimum and maximum values of the parameters assumed in the sensitivity analysis and the corresponding ICERs. b: only undominated pathways were depicted in the table. c: The difference in cost divided by the difference in benefits of one pathway, compared with the next more effective pathway. All the ICER values were computed using a cost-effectiveness model that assumes as an outcome the number of quality-adjusted life years.

Discussion

Pathway 3 provides rehabilitation care to people with a first-ever stroke at a short-term inpatient unit (ie, from discharge to 3 months) followed by an outpatient community clinic from 3 to 12 months. This pathway was the most cost-effective strategy, both from the individual and healthcare service perspectives. Although at a national level, there is no universally accepted threshold for the WTP for a QALY, we interpreted the results according to the cut-offs commonly applied in cost-effectiveness analyses, which are set at one times the national gross domestic product per capita (ie, €20873 per QALY in Portugal in 2021).

However, policymakers may have short-term budget constraints that prevent them from adopting the most cost-effective pathway. Furthermore, the level of severity and clinical complexity of stroke is very varied, so a comprehensive rehabilitation provision model must include differentiated care pathways [1, 7]. Pathway 1 from the stroke survivor's perspective, and pathway 7 from the healthcare service's perspective, were both the least costly pathways and were still cost-effective in the final decision model, and therefore could be implemented.

From the individual perspective, pathways 3 and 1 were the most cost-effective, probably because both are free in terms of health care costs, have standardised transport costs, have the lowest social costs, and have the greatest health benefits. The sensitivity analysis showed that pathways 2, 4, 6 and 7 would be cost-effective if a minimum cost is assumed among the tested parameters. These results were obtained for very extreme values, which we consider unlikely to occur. However, they refer to a relevant aspect from the point of view of health policy and care pathway definition: the importance of costs in the final decision [10]. Indeed, in the case of an impactful health condition such as stroke, it is important to reflect on whether the choice and access to the optimal rehabilitation pathway should rely on cost considerations. Alternatively, decision-makers may fix a different threshold according to the severity of the stroke and the corresponding rehabilitation potential. These results are in line with other studies that highlight a lack of guidance to aid rehabilitation decision-making that is influenced by participant-level and organizational factors that occur across services and countries [33].

From a healthcare system perspective, the cost-effective pathways 3 and 7 are distinguished by their low healthcare costs compared to the pathways considered dominant. This difference is partly explained by the fact that pathways 3 and 7 involve reduced exposure to inpatient settings, which are more expensive for the health service (NHS). However, evidence has shown the advantages of these settings for the rehabilitation of certain pathologies, including acute ischemic stroke [34, 35]. Considering the health system's financial sustainability [36], it should be noted that all the pathways are currently operationally available but only 30% were considered cost-effective in our study. So, future healthcare planning should seek to define a more efficient rehabilitation system with a smaller number of pathways and more clearly defined, individualised pathways according to different stroke severity profiles. Analyses of health system efficiency determinants in the literature report that specific institutional arrangements should be avoided, namely gatekeeping and the fragmented presence of multiple healthcare services [37]. The existence of multiple care options may reduce health benefits and increase costs [38].

Our data show that stroke rehabilitation pathway cost-effectiveness analysis is consistent with evidence-based practice [39], with better incremental cost-effectiveness ratios assigned to pathways in which care settings offer more intensive and multidisciplinary rehabilitation [40]. We found that only the cost-

effective pathways 1, 3 and 7, which started in Rehabilitation Inpatient Centres, Short-term Inpatient Units and Outpatient Day Hospital settings respectively, guarantee the recommended interdisciplinary and intense care. However, this care is restricted to 30 to 60 days, which means that only 30% of the study sample was able to obtain such care. Beyond that, only 35% of pathways include the individual in goal setting and only 60% of pathways plan coordinated transitions. This underscores the necessity of funding more comprehensive and integrated care approaches.

This discrepancy between the care given and recommended good practice has been found in various European health systems and nations [41]. Two hypotheses may be suggested to explain this. The first is that professionals and health systems are not aware of the guidelines or have not integrated them systemically into their decision-making process [42]. The second is that the guidelines do not account for the process's complexity. These results demonstrate the need for policy approaches to overcome barriers to evidence-based stroke rehabilitation [43].

The current study provides the first detailed 1-year cost-effectiveness analysis of different multistep pathways of stroke rehabilitation. Models of integrated rehabilitation care and individual itineraries have been little reported in the literature. An econometric study evaluated an integrated care pathway for people after a stroke, however, no alternatives were compared and the focus was only on outpatient community rehabilitation, with no evaluation after 6 months [44]. In contrast, there is plenty of literature analysing the cost-effectiveness of individual models of care, such as early supported discharge services [45], home rehabilitation [46], stroke units [34], and stroke services [35]; however, individuals' needs, expectations, and concerns are not translated into research. The main wish of people after a stroke is to have timely access to health services and, when necessary, to be easily guided from one service to another, without obstacles, delays, or loss of information [47]. Therefore, research should develop study models that provide the data needed for decision-making and development of care provision.

The major strength of this study is that it essentially considered rehabilitation pathways using participant-level data drawn from a robust original cohort study [14, 16]. The present study also adds to most previous cost-effectiveness analyses on this topic by including people with moderate and severe stroke, estimating costs and benefits from both the individual and health service perspectives, and involving a 1-year analysis [13]. It should be noted that the cost parameters were all obtained in Portugal in the reference year, which excludes the need for correction for purchasing power and inflation and increases the data robustness.

Study Limitations

Although we recognise that the single-centre methodological design restricts external validity, we do not consider this to be a limitation, as the results are applicable in countries with similar organisational models. Moreover, it is acknowledged by the Action Plan for Stroke that new settings of care should be designed to meet the targets set for 2030 [5]. So, the present analysis of different integrated pathways of stroke rehabilitation is required for the widespread uptake of integrated care models and effective navigation through complex health systems [3,4]. The Portuguese stroke rehabilitation system, despite being fragmented, includes different models of care (inpatient, outpatient, and home-based) whose organisational characteristics are common to different countries and health systems. Data relating to the access of different severity and socio-demographic stroke profiles to different levels of care and their distribution within each level of care invite comparison and contribute to the international discussion about policies that enhance transitions across different environments [2]. However, some limitations of

our study need to be addressed. Impairment of cognitive function may have reduced the accuracy of the information reported by the individuals with stroke, however, this phenomenon is not differential between the majority of sub-samples/pathways. Besides, only the EQ-5D-3L outcome was self-reported, so cognitive status is expected to have a minor contribution to information bias, with little impact on the internal validity of the results. Considering the stroke pathways, parameters were obtained from the cohort study that described 11 pathways; but, because of sample size limitations, the analysis was performed on the 9 most prevalent. This can be considered a selection bias that limits the full analysis of the healthcare system. Additionally, despite including a wide range of ages, stroke subtypes and severity grades, a stratified econometric analysis was not carried out, as we did not expect a substantial difference based on previous results of this cohort. On the other hand, as the Portuguese NHS is completely public, the results cannot be extrapolated to itineraries initially started from a private hospital. Furthermore, when compared with the 5L version, the EQ-5D-3L overestimates health problems, which consequently underestimates utilities and discriminatory power [48]. Future studies should consider the more complete version of the EQ-5D to increase the sensitivity and accuracy of benefit analysis. In addition, different pathways have shown different weightings of health and social costs, however, exploring the model from both the stroke survivor and healthcare service perspectives showed that this difference does not affect the conclusion about the most cost-effective intervention. Finally, the present study considers a timeframe of 1 year instead of a longer period. It would be important to consider longer follow-ups in future studies that evaluate the impact of long-term costs and benefits, such as the return to professional activity.

Conclusion

Our study provides evidence for policymakers to designate pathway 3 as the new standard-of-care pathway for stroke rehabilitation, under a WTP threshold of one times the national gross domestic product (€20873 per QALY). Given the complexity of the clinical heterogeneity of stroke, other pathways may be considered, such as pathway 1 from the individual perspective, and pathway 7 from the healthcare service perspective, which were still cost-effective in the final decision model. This allows the planning and organization of a comprehensive, integrated, and efficient system adapted to the different stroke profiles.

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Supplementary Appendix A1 - Settings of Care Description

	US	UM	UL	RC	HB	H	C	P
CLINICAL SETTING	Short-term Rehabilitation Unit	Medium-term Rehabilitation Unit	Long-term Rehabilitation Unit	Rehabilitation Center	Home-based Rehabilitation	Day Hospital	Community Rehabilitation Clinic	Private Rehabilitation
CARE SERVICES	Health	Health/Social	Health/Social	Health	Health	Health	Health	Health
MODEL OF CARE	Inpatient	Inpatient	Inpatient	Inpatient	Home-based	Outpatient	Outpatient	Home-based/ Outpatient
PROVIDER	Public (NHS)	Public (NHS)	Public (NHS)	Public (NHS)	Public (NHS)	Public (NHS)	Private	Private
STATE FUNDING	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
INDIVIDUAL FUNDING	Free	Progressive according to income	Progressive according to income	Free	Free	Free	Free	Total
ADMISSION TO DISCHARGE TIME (days)	30	30 - 90	≥ 90	50-60	60-120	30-150	Unlimited	Unlimited
ADMISSION ASSESSMENT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
DISCHARGE PLAN	Yes	Yes	Yes	Yes	Yes	No	No	No
AGREE REHAB GOALS	Yes	Yes	No	Yes	No	No	No	No
MULTIDISCIPLINARY TEAM	P/PT/ST	P/PT/ST	P/PT	P/PT/RN/PSI/ST/OT	P/PT/RN	P/PT/ST/RN	P/PT/ST/OT	P/PT/ST/OT/PSI
FREQUENCY OF PHYSIO SESSIONS (week)	8 to 12	5	3	10 to 12	3 to 4	5	3 to 5	3 to 5
PHYSIO SESSION DURATION (min)	60	45	30	60	30	45	45	60

Settings: C - Community Clinic; H - Hospital; HB - Home-based; P - Private Rehabilitation; RC - Rehabilitation Center; UL - Long-Term Unit; UM - Medium-term Unit; US - Short-term Unit. NHS - National Health System. Multidisciplinary team: OT - Occupational Therapist; P - Physician; PSI – Psychologist; PT - Physiotherapist; RN - Rehabilitation Nurse; ST - Speech Therapist.

Supplementary Appendix A1 – Sample Profile Description by Care Settings

AGE (YEARS), MEAN	US	UM	UL	RC	HB	H	C	P
20-40	-	-	-	4	-	-	-	-
41-60	19	31	-	26	-	11	24	16
61-80	49	128	8	31	34	39	148	12
81-100	-	56	39	-	41	20	53	-
SEX, N								
Male	32	101	22	28	35	33	106	13
Female	36	114	25	33	40	37	119	15
CURRENT RESIDENCE, N								
Home	68	181	21	61	75	70	216	28
Institutionalized	-	34	26	-	-	-	9	-
OCCUPATION, N								
Retired	-	119	47	-	49	39	102	-
Employed	60	87	-	52	26	27	113	27
Unemployed	8	9	-	9	-	4	10	1
MONTHLY INCOME, N								
≤1000€	37	137	42	28	51	57	166	-
>1000€	31	78	5	33	24	13	59	28
SUBTYPE OF STROKE OXFORD, N								
PACS	25	77	18	23	38	27	78	16
LACS	17	53	10	15	19	18	56	8
POCS	13	30	-	10	4	8	37	4
TAGS	3	21	-	4	-	3	17	-
Haemorrhagic	10	34	19	9	14	14	37	-

C - Community Clinic; H - Hospital; HB - Home-based; P - Private Rehabilitation; RC - Rehabilitation Center; UL - Long-Term Unit; UM - Medium-term Unit; US - Short-term Unit.

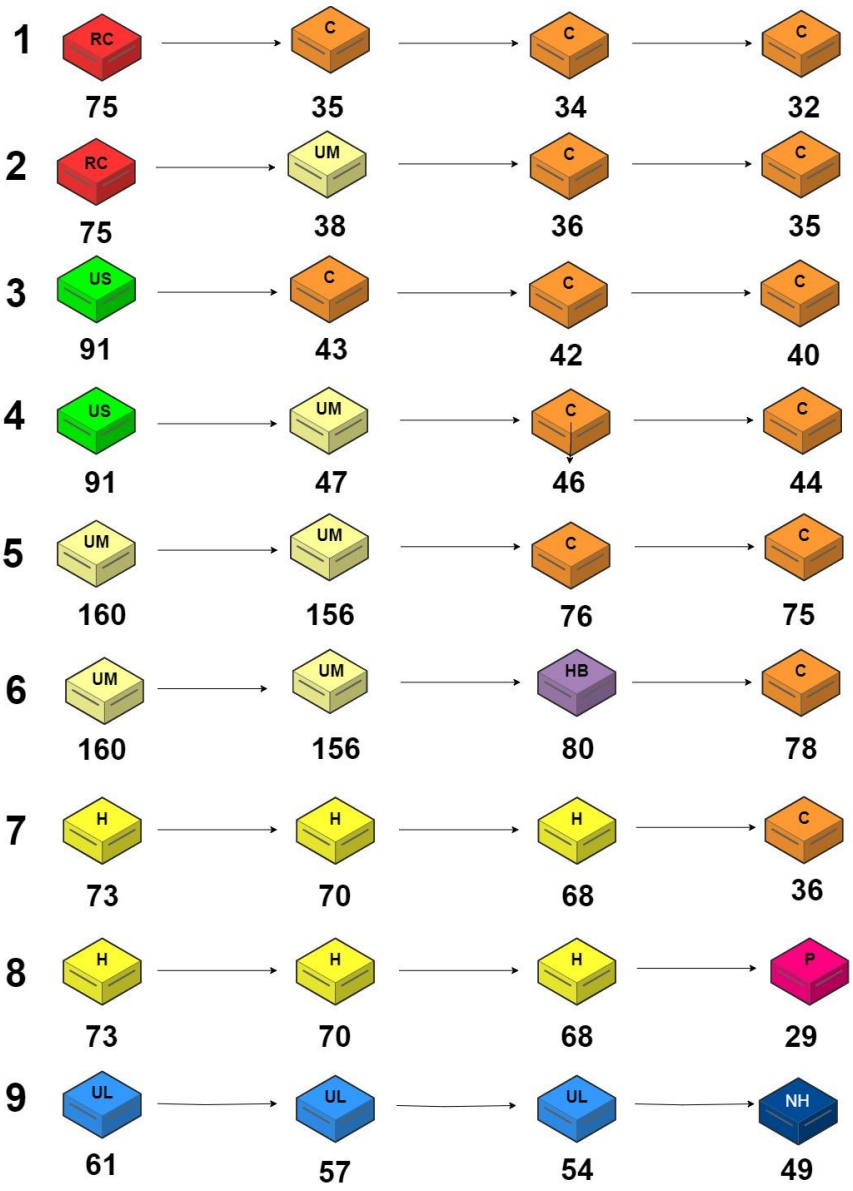
Supplementary Appendix A1 - Outcomes Description by care setting

	TOTAL	US	UM	UL	RC	HB	H	C	P	
	n=391	n=68	n=215	n=47	n=61	n=75	n=70	n=225	n=28	
EQ-3D-3L										Overall p-value
Mean (sd)	0,15 (0,14)	0,69 (0,07)	–0,13 (0,18)	–0,47 (0,10)	0,61 (0,06)	0,41 (0,08)	0,56 (0,07)	0,37 (0,13)	0,54 (0,05)	
Median (Interquartile deviation)	–0,07 (0,39)	0,64 (0,11)	–0,17 (0,21)	–0,51 (0,16)	0,58 (0,11)	0,39 (0,08)	0,54 (0,12)	0,31 (0,15)	0,48 (0,11)	0,001 (a)
Percentile 25	–0,34	0,53	–0,28	–0,64	0,49	0,31	0,41	0,22	0,39	
Percentile 75	0,43	0,75	0,12	–0,33	0,71	0,47	0,64	0,51	0,61	
mRS Scale										
Mean (sd)	3,5 (0,7)	2,1 (0,3)	3,8 (0,8)	4,4 (0,1)	2,4 (0,2)	3,5 (0,4)	2,5 (0,4)	3,4 (0,9)	2,8 (0,6)	
Median (Interquartile deviation)	3 (0,5)	2,2 (0,4)	3,9 (0,7)	4,6 (0,3)	2,3 (0,1)	3,6 (0,2)	2,8 (0,5)	3,7 (0,3)	3,0 (0,4)	
Percentile 25	3	1	2	4	1	2	1	2	2	
Percentile 75	4	2	4	5	3	4	3	4	4	
No symptoms at all (0)	0	-	-	-	-	-	-	-	-	
No significant disability (1)	7	4	-	-	1	-	3	-	-	0,003 (b)
Slight disability (2)	66	21	-	-	24	-	18	-	3	
Moderate disability (3)	156	43	64	-	36	18	49	84	13	
Moderately severe disability (4)	98	-	104	30	-	34	-	106	6	
Severe disability (5)	65	-	47	17	-	23	-	35	6	
Mini Mental State Examination										
Mean (sd)	24.2 (3.1)	28,9 (1,5)	21,5 (2,6)	18,7 (3,1)	28,6 (0,3)	24,8 (1,6)	27,8 (0,9)	24,3 (2,8)	26,7 (1,1)	
Median (Interquartile deviation)	23 (6,1)	27 (2,5)	19 (4,5)	16 (4,0)	26 (2,0)	22 (4,5)	26 (3,0)	21 (5,5)	25 (3,5)	
Percentile 25	14,6	24	15	12	25	17	23	16	21	
Percentile 75	28,7	29	24	20	29	26	29	27	28	0,04 (c)
Barthel Index,										
Mean (sd)	60.2 (29.5)	68,4 (8,1)	42,1 (10,3)	14,3 (2,6)	61,2 (9,6)	51,3 (12,8)	57,6 (11,1)	52,1 (12,8)	78,4 (6,94)	
Median (Interquartile deviation)	58 (30,1)	65 (12,5)	40 (17,5)	15 (4,5)	60 (12,5)	50 (17,5)	55 (15,0)	50 (17,5)	75 (15,0)	
Percentile 25	15	50	25	10	45	35	40	30	55	
Percentile 75	75	75	60	20	70	70	70	65	85	
Slight dependency (91-99)	30	21	-	-	18	-	12	-	-	0,009 (d)
Moderate Dependency (61-90)	179	47	62	-	43	14	54	79	16	
Severe Dependency (21-60)	143	-	111	5	-	37	4	112	10	
Total Dependency (0-20)	144	-	42	42	-	24	-	34	2	

C - Community Clinic; H - Hospital; HB - Home-based; P - Private Rehabilitation; RC - Rehabilitation Center; UL - Long-Term Unit; UM - Medium-term Unit; US - Short-term Unit.

Overall p-value: a=0.001; b=0.003; c=0.040; d=0.009. All post-hoc comparisons showed significant differences, except for RC vs SU at EQ-5D-3L, for RC vs SU vs DH at mRS, for RC vs DH and MU vs CC at MMSE, and for RC vs SU vs DH for BI.

Supplementary Appendix A2 – Graphic presentation of the nine Rehabilitation Pathways.



C - Community Clinic; H - Hospital; HB - Home-based; P - Private Rehabilitation; RC - Rehabilitation Center; UL - Long-Term Unit; UM - Medium-term Unit; US - Short-term Unit.

Supplementary Appendix A2 - Outcomes Description by Rehabilitation Pathway

	1		2		3		4		5	
EQ-3D-3L	**Baseline**	**12 months**	**Baseline**	**12 months**	**Baseline**	**12 months**	**Baseline**	**12 months**	**Baseline**	**12 months**
Mean (sd)	0.41 (0.08)	0.49 (0.06)	0.35 (0.13)	0.41 (0.08)	0.18 (0.07)	0.25 (0.12)	0.37 (0.09)	0.42 (0.16)	0.18 (0.07)	0.25 (0.12)
Median (Interquartile deviation)	0.39 (0.08)	0.44 (0.12)	0.29 (0.15)	0.39 (0.08)	0.14 (0.11)	0.21 (0.14)	0.31 (0.11)	0.39 (0.18)	0.14 (0.11)	0.21 (0.14)
Percentile 25	0.31	0.34	0.24	0.31	0.04	0.10	0.22	0.31	0.04	0.10
Percentile 75	0.47	0.58	0.39	0.47	0.22	0.34	0.51	0.55	0.22	0.34
mRS Scale										
Mean (sd)	3.4 (0.4)	2.5 (0.4)	3.5 (0.9)	2.8 (0.6)	3.7 (0.9)	3.6 (0.4)	3.4 (0.9)	2.6 (0.2)	3.7 (0.9)	3.6 (0.4)
Median (Interquartile deviation)	3.6 (0.2)	2.8 (0.5)	3.7 (0.3)	3.0 (0.4)	3.5 (0.3)	3.4 (0.2)	3.7 (0.3)	2.9 (0.1)	3.5 (0.3)	3.4 (0.2)
Percentile 25	2	1	2	2	2	2	2	1	2	2
Percentile 75	4	3	4	4	4	4	4	3	4	4
Mini-Mental State Examination										
Mean (sd)	24.8 (1.6)	28.4 (0.8)	18.7 (3.1)	26.7 (1.1)	19.7 (0.8)	23.5 (1.1)	24.3 (2.8)	28.5 (0.5)	19.7 (0.8)	23.5 (1.1)
Median (Interquartile deviation)	22 (4.5)	27 (3.0)	16 (4.0)	25 (3.5)	14.6 (1.4)	21 (3.5)	21 (5.5)	27 (2.5)	14.6 (1.4)	21 (3.5)
Percentile 25	17	23	12	21	12	18	16	24	12	18
Percentile 75	26	29	20	28	21	25	27	29	21	25
Barthel Index										
Mean (sd)	51.3 (12.8)	77.1 (13.1)	42.1 (10.3)	68.4 (8.1)	40.5 (7.1)	55.3 (13.1)	52.1 (12.8)	71.2 (9.6)	40.5 (7.1)	55.3 (13.1)
Median (Interquartile deviation)	50 (15.1)	75 (12.3)	40 (11.5)	65 (12.5)	35 (11.5)	50 (15.0)	50 (17.5)	70 (12.5)	35 (11.5)	50 (15.0)
Percentile 25	35	55	25	50	20	35	30	55	20	35
Percentile 75	70	90	60	75	55	65	65	80	55	65

Supplementary Appendix A2 - Outcomes Description by Pathway

	6		7		8		9		12 months Overall p-value
EQ-3D-3L	**Baseline**	**12 months**	**Baseline**	**12 months**	**Baseline**	**12 months**	**Baseline**	**12 months**	
Mean (sd)	0.15 (0.10)	0.22 (0.13)	0.34 (0.09)	0.42 (0.08)	0.31 (0.13)	0.39 (0.07)	–0.23 (0.18)	–0.18 (0.17)	0,002 (a)
Median (Interquartile deviation)	0.07 (0.09)	0.19 (0.10)	0.29 (0.11)	0.36 (0.12)	0.28 (0.09)	0.34 (0.11)	–0.37 (0.11)	–0.24 (0.11)	
Percentile 25	0.04	0.08	0.20	0.29	0.22	0.23	–0.48	–0.34	
Percentile 75	0.26	0.31	0.48	0.57	0.36	0.45	–0.16	–0.12	
mRS Scale									
Mean (sd)	3.5 (0.7)	2.8 (0.6)	3.5 (0.7)	2.7 (0.6)	3.4 (0.4)	2.6 (0.4)	4.6 (0.1)	4.5 (0.1)	0,007 (b)
Median (Interquartile deviation)	3.1 (0.5)	3.0 (0.4)	3 (0.5)	2.3 (0.4)	3.1 (0.2)	2.4 (0.5)	4.6 (0.3)	4.6 (0.3)	
Percentile 25	3	2	3	1	2	1	4	4	
Percentile 75	4	4	4	3	4	3	5	5	
Mini-Mental State Examination									
Mean (sd)	20.5 (2.6)	24.1 (1.6)	24.2 (3.1)	27.1 (0.8)	22.1 (3.6)	26.1 (1.7)	17.7 (3.3)	18.7 (3.1)	0,02 (c)
Median (Interquartile deviation)	17 (4.5)	19 (4.5)	23 (6.1)	26 (3.0)	18 (5.7)	25 (2.2)	15 (4.1)	16 (4.0)	
Percentile 25	14	16	16.6	22	14	23	12	12	
Percentile 75	23	25	28.7	29	25	29	20	20	
Barthel Index									
Mean (sd)	40.1 (10.3)	53.4 (12.8)	60.2 (9.5)	68.2 (8.4)	61.2 (9.6)	66.4 (6.1)	14.3 (2.6)	21.3 (4.6)	0,004 (d)
Median (Interquartile deviation)	38 (17.5)	50 (17.5)	58 (10.1)	65 (12.5)	60 (12.5)	65 (9.8)	15 (4.5)	20 (7.5)	
Percentile 25	20	30	35	50	45	50	5	5	
Percentile 7	50	65	65	75	65	75	20	20	

Final Outcomes by Pathway. Overall p-value: a=0,002; b=0,007; c=0,02; d=0,004. All post-hoc comparisons showed significant differences (p-value between 0.0003 and 0.002), except for pathway 1 vs 2 at all outcomes, for pathway 3 vs 4 at EQ-5D-3L, BI and MMSE, for pathway 1 vs 5 at MMSE, and pathway 2 vs 5 at EQ-5D-3L, MMSE.

Supplementary Appendix A3 – Detailed description of the item-by-item cost calculation details from the individual and healthcare service perspectives.

COST ITEMS:

1. HEALTH INTERVENTION COST

The intervention costs of the different settings were entirely attributed to the healthcare service, except for the Medium-term Inpatient Unit (UM), Long-Term Inpatient Unit (UL) settings which involve shared costs for the healthcare service and the individual, and Private (P) setting which is paid in full by the individual.

2. INDIVIDUAL TRANSPORT COSTS

Transport is paid for by the healthcare service only to those considered unable to drive by themselves/their families.

3. TECHNICAL AID COST

The technical aid cost was attributed to the healthcare service perspective only in the case of individuals with a disability greater than 60% and a weak financial condition as defined by law.

4. SOCIAL CARE COST

The social services were paid by the healthcare service between 45-90% of household family income, according to the number and type of services (hygiene, laundry, food, cleaning, day centre, nursing home).

5. PRODUCTIVITY LOSSES

The loss of productivity, from the individual perspective resulted from the multiplication between daily income and the number of days lost. From the health service perspective, the cost of loss productivity increases as the period of absence grows, according to the current legal definition.

Supplementary Appendix A3 – Detailed description of the item-by-item cost calculation details from the individual and healthcare service perspectives

INDIVIDUAL PERSPECTIVE			
	Cost (€) per Day	Data source	Auxilliary information for calculation
HEALTH INTERVENTION COST			
Short-term Rehabilitation Unit	0	National law$^{\alpha}$	
Medium-term Rehabilitation Unit	Maximum 39.46	National law$^{\beta}$	HCI ranges according to the SSI to a maximum of 39€46 ǂ
Long-term Rehabilitation Unit	Maximum 21.82	National law$^{\beta}$	85% of HCI to a maximum of 21€82 ¥
Home-based Rehabilitation	0	National law$^{\alpha}$	
Rehabilitation Center	0	National law$^{\mu}$	
Day Hospital	0	National law$^{\mu}$	
Community Rehabilitation Clinic	0	National law$^{\mu}$	
Private Rehabilitation	32.4	Market study	The average value of 4 national providers
STROKE SURVIVOR TRANSPORT COSTS			
Stroke survivor Transport	Fuel and tolls*Km	Reference travel budget$^{\partial}$	
TECHNICAL AID COST			
Walker	42.45	Market study	The average value of 4 national providers
Wheel Walker	66.49	Market study	The average value of 4 national providers
Crutches	16.16	Market study	The average value of 4 national providers
Tripod	32.26	Market study	The average value of 4 national providers
Adjustable bed	1059.25	Market study	The average value of 4 national providers
Stroke survivor Recliner chair	445.25	Market study	The average value of 4 national providers
Wheelchair	117.25	Market study	The average value of 4 national providers
Shower chair	117.50	Market study	The average value of 4 national providers
Bathroom Adaptation	1118.70	Market study	The average value of 4 national providers
SOCIAL CARE COST			
Formal Caregiver	From 45 to 65% of HCI	National law$^{\prod}$	45-65% of HCI according to the number of services (hygiene, food, cleaning, laundry)
Day Center	60% of HCI	National law$^{\prod}$	A maximum of 60% of the HCI
Nursing Home	From 75 to 90% of HCI	National law$^{\prod}$	75-90% of HCE according to the degree of dependency
PRODUCTIVITY LOSSES			
Stroke survivor Loss of Income	Income value*days	Participant-level data	Income value per day * number of days lost
Informal Caregiver Loss of Income	Income value*days		Income value per day * number of days lost

HCI – household per capita income value; National law: Decreto-Lei n.70/2010. **SSI** – social support index; National law: Portaria n.294/2021. **ǂ** - HCI ranges according to the SSI; if HCI≤50% SSI pay 30 of %HCI; if 50%<HCI≤75% SSI pay of 35%HCI; if 75%<HCI≤100% SSI - 42,5% of HCI; if 100%<HCI≤150% SSI pay 50% of HCI; if HCI>150% do SSI pay 60% of HCI. **α** – National law: Decreto-Lei n.101/2006. **β** – National Law: Despacho normativo n.34, 2007, artigo 8º; Portaria 1087-A/2007; Portaria n. 272/2022. **µ** - National Law: Decreto-Lei n.37/2022. **∂** - reference travel budget website (https://www.viamichelin.pt/); Assessed on 19/02/2023. **∏** - National Law: Decreto-Lei n. 33/2014; Portaria n. 196-A/2015.

HEALTHCARE (NHS) PERSPECTIVE			
	Cost (€) per Day	Data source	Auxilliary information for calculation
HEALTH INTERVENTION COST			
Short-term Rehabilitation Unit	110.8	National law[α]	€94,85 (health costs) + €15,95 (material costs)
Medium-term Rehabilitation Unit	95.84	National law[α]	€57,84 (health costs) + €17,45 (material costs) + €20,55 (social costs)
Long-term Rehabilitation Unit	75.48	National lawα	€26,64 (health costs) + €17,37 (material costs) + €31,47 (social costs)
Home-based Rehabilitation	17.79	Gray Literature[β]	Academic publication
Rehabilitation Center	294.00	National law[μ]	
Day Hospital	7.27	System-level data[γ]	Institution analytical financial data
Community Rehabilitation Clinic	13.38	National law[Ω]	
Private Rehabilitation	0	-	NHS does not support this setting
TRANSPORT COSTS			
Stroke survivor Transport	0,56/km + 0,1 (0.56/km)	National law[∂]	≤15 km a maximum amount of €9 ≥ 15km cost according to the distance
TECHNICAL AID COST			
Technical Aids	Free if disability ≥60%	National law[∏]	Social Security support[¥]
Bathroom Adaptation	Disability/HCI status	National law[∏]	Local programs to support housing adaptation[§]
SOCIAL CARE COST			
Formal Caregiver	From 132.7 to 294.9[¶]	National law[Δ]	Social security supports around 80% of the estimated costs, whereby the remaining costs come from family contributions.
Day Center	125	National law[Δ]	
Nursing Home	From 530 to 877 [Ø]	National law[Δ]	
PRODUCTIVITY LOSSES			
Stroke survivor Loss of Income	From 55 to 75% of DI[*]	National law[Σ]	Ranges of DI according to the duration of the absence
Informal Caregiver Loss of Income	0	National law[Σ]	The right to be absent is unpaid

DI – daily income, corresponds to income from 14 months divided by 12 months and 30 days. **α** – National law: Portaria 1087-A/2007; Portaria n.272/2022. **β** - Gray Literature: PhD final thesis (https://repositorio.ucp.pt/handle/10400.14/20705); Assessed on 19/02/2023. **μ** – National law: Circular Normativa ACSS_03/2021. **γ** - the cost per day resulted from analytical financial data of the institution provided to this investigation after approval of the local ethics committee. **Ω** – National law: Circular Normativa ACSS_32/2011. **∂** – National law: Despacho n.7980-A/2022. **ǂ** - For transport less or equal to 15 km, a maximum amount of €9 will be paid for each stroke survivor and/or companion; for transport over 15km, €0,56 is charged per km, and each companion costs 10% of the value of the respective accompanied stroke survivor. **∏** - National Law: Decreto-Lei n.93/2009; Despacho n.7197/2016; Decreto-Lei n.37/2018; Decreto-Lei n.74/2022; Portaria n.301/2019. **¥** - 100% of cost supported if medically confirmed disability higher than 60%. **§** - In the case of a permanent disability caused by illness and lower household per capita income value, there is a local subsidy for housing readaptation. In this sample, there is a maximum of 60* social support index - 28.825,80€. **¶** - the cost depends on the number of services contracted (food, hygiene, clothing, cleaning...); €294,90 (4 services); €265,41 (3 services); €250,66 (2 services); €132,7 (weekend). **Ø** - from 530 to 877€ according to the degree of disability. **Δ** - National Law: Despacho Normativo n.75/92; Commitment Protocol of Cooperation for the Social and Solidarity Sector. **∑** - National Law: Decreto-Lei n.28/2004. ***** - DI ranges according to the duration of absence: 0,55*DI ≤ 30 days, 0,6*DI ≥31 to ≤ 90 days; 0,7*DI ≥91 to ≤365 days; 0,75*DI ≥365 days.

Supplementary Appendix A4 – Detailed description of the utilities for each competing rehabilitation pathway

Utilities EQ-5D-3L			
Baseline			
	MEAN	MIN	MAX
Pathway 1	0.394	0.283	0.434
Pathway 2	0.229	0.175	0.282
Pathway 3	0.486	0.383	0.569
Pathway 4	0.279	0.167	0.312
Pathway 5	-0.065	-0.105	0.112
Pathway 6	-0.086	-0.128	0.001
Pathway 7	0.164	0.082	0.214
Pathway 8	0.179	0.094	0.245
Pathway 9	-0.278	-0.526	-0.320
3 months follow-up			
	MEAN	MIN	MAX
Pathway 1	0.461	0.319	0.496
Pathway 2	0.270	0.135	0.315
Pathway 3	0.532	0.413	0.571
Pathway 4	0.334	0.245	0.393
Pathway 5	-0.002	-0.005	0.137
Pathway 6	-0.016	-0.015	0.054
Pathway 7	0.192	0.119	0.243
Pathway 8	0.210	0.141	0.216
Pathway 9	-0.324	-0.481	-0.298
6 months follow-up			
	MEAN	MIN	MAX
Pathway 1	0.497	0.395	0.551
Pathway 2	0.314	0.238	0.328
Pathway 3	0.555	0.427	0.603
Pathway 4	0.371	0.311	0.402
Pathway 5	0.037	0.026	0.105
Pathway 6	0.011	0.008	0.075
Pathway 7	0.214	0.134	0.285
Pathway 8	0.226	0.167	0.311
Pathway 9	-0.280	-0.434	-0.225
12 months follow-up			
	MEAN	MIN	MAX
Pathway 1	0.549	0.492	0.556
Pathway 2	0.366	0.280	0.393
Pathway 3	0.589	0.532	0.616
Pathway 4	0.406	0.317	0.442
Pathway 5	0.154	0.049	0.103
Pathway 6	0.117	0.028	0.082
Pathway 7	0.240	0.195	0.286
Pathway 8	0.251	0.223	0.311
Pathway 9	-0.267	-0.295	-0.202

Supplementary Appendix A5 – Detailed description of the Health Benefits/Quality-adjusted survival for each competing rehabilitation pathway

Health Benefits – Quality-adjusted survival			
From Baseline to 3 months follow-up (QALY)			
	MEAN	MIN	MAX
Pathway 1	0.097	0.068	0.105
Pathway 2	0.056	0.035	0.068
Pathway 3	0.115	0.090	0.129
Pathway 4	0.069	0.047	0.080
Pathway 5	-0.008	-0.012	0.028
Pathway 6	-0.012	-0.016	0.006
Pathway 7	0.040	0.023	0.052
Pathway 8	0.044	0.027	0.052
Pathway 9	-0.068	-0.114	-0.070
From 3 to 6 months follow-up (QALY)			
	MEAN	MIN	MAX
Pathway 1	0.095	0.071	0.104
Pathway 2	0.058	0.037	0.064
Pathway 3	0.108	0.083	0.116
Pathway 4	0.070	0.055	0.079
Pathway 5	0.003	0.002	0.024
Pathway 6	0.000	-0.001	0.013
Pathway 7	0.040	0.025	0.052
Pathway 8	0.043	0.030	0.052
Pathway 9	-0.060	-0.091	-0.052
From 6 to 12 months follow-up (QALY)			
	MEAN	MIN	MAX
Pathway 1	0.197	0.167	0.208
Pathway 2	0.128	0.097	0.135
Pathway 3	0.215	0.180	0.229
Pathway 4	0.146	0.118	0.159
Pathway 5	0.025	0.014	0.039
Pathway 6	0.014	0.007	0.030
Pathway 7	0.085	0.062	0.107
Pathway 8	0.090	0.074	0.117
Pathway 9	-0.103	-0.137	-0.080
1-year Quality-adjusted survival (QALY)			
	MEAN	MIN	MAX
Pathway 1	0.388	0.306	0.417
Pathway 2	0.272	0.199	0.297
Pathway 3	0.438	0.354	0.475
Pathway 4	0.285	0.220	0.317
Pathway 5	0.041	0.004	0.091
Pathway 6	0.021	-0.010	0.049
Pathway 7	0.166	0.110	0.211
Pathway 8	0.177	0.131	0.221
Pathway 9	-0.231	-0.342	-0.202

Supplementary Appendix A6 – Detailed description of the cost structure for each competing pathway of stroke rehabilitation care.

INDIVIDUAL PERSPECTIVE

TOTAL REHABILITATION COST PER INDIVIDUAL (€)

	MIN	MEAN	MAX
Pathway 1	7672	12104	27833
Pathway 2	10352	16538	29323
Pathway 3	8437	12533	23093
Pathway 4	7679	16022	27064
Pathway 5	12104	19950	35960
Pathway 6	10944	19902	33665
Pathway 7	7792	15406	30677
Pathway 8	13598	20905	36897
Pathway 9	12877	21856	39048

HEALTH COST PER INDIVIDUAL (€)

	Total Health Cost (€)			Health Intervention (€)			Survivor Transport (€)			Relative weight Health Cost
	MIN	MEAN	MAX	STANDARD VALUE			MIN	MEAN	MAX	% of TOTAL
Pathway 1	446	763	1524	0			446	763	1524	6
Pathway 2	2263	2420	3063	1721			542	698	1342	14
Pathway 3	510	820	1736	0			510	820	1736	7
Pathway 4	2160	2416	2893	1746			414	670	1147	15
Pathway 5		1851		1851				0		9
Pathway 6		1751		1751				0		9
Pathway 7	435	712	1306	0			435	712	1306	5
Pathway 8*	4594	5538	7160	4116	4782	5880	478	756	1280	24
Pathway 9		1448		1448				0		7

SOCIAL COST PER INDIVIDUAL (€)

	Total Social Cost (€)			Social Care (€)			Technical Aids (€)			Productivity Losses (€)			Relative weight Social Cost
	MIN	MEAN	MAX	MIN	MEAN	MAX	MIN	MEAN	MAX	MIN	MEAN	MAX	% of TOTAL
Pathway 1	7226	11341	26309	281	574	1638	45	305	461	6900	10462	24210	94
Pathway 2	8089	14118	26260	324	870	1640	60	430	1120	7705	12756	23500	86
Pathway 3	7927	11713	21357	268	655	1847	38	324	964	7621	10734	18546	93
Pathway 4	5519	13606	24171	370	746	2434	80	515	1860	5069	12218	19877	85
Pathway 5	10253	18099	34109	468	1167	2800	140	865	2847	9645	16067	28462	91
Pathway 6	9093	18151	31914	564	1133	2960	94	872	2410	8435	16145	26544	91
Pathway 7	7357	14694	29371	420	873	1860	67	491	1630	6870	13518	25881	95
Pathway 8	9004	15367	29737	470	784	1970	71	437	1647	8463	14147	26120	76
Pathway 9	11429	20408	37600	604	940	3070	84	853	2070	10741	18615	32460	93

HEALTHCARE (NHS) PERSPECTIVE

TOTAL REHABILITATION COST PER PATHWAY (€)

	MIN	MEAN	MAX
Pathway 1	24131	26428	36617
Pathway 2	28814	31319	38378
Pathway 3	11659	13124	21750
Pathway 4	16301	18872	27091
Pathway 5	18896	24706	36670
Pathway 6	18740	24274	36765
Pathway 7	8102	10992	21292
Pathway 8	6637	11623	23177
Pathway 9	15189	20979	40044

HEALTH COST PER PATHWAY (€)

	Total Health Cost (€)			Health Intervention (€)	Individual Transport (€)			Relative weight Health Cost
	MIN	MEAN	MAX	STANDARD VALUE	MIN	MEAN	MAX	% OF TOTAL
Pathway 1	20165	20211	21288	19701	464	511	1587	76
Pathway 2	23544	23975	24301	23277	267	698	1024	74
Pathway 3	7738	7842	8572	7301	437	541	1271	59
Pathway 4	11357	11640	11991	11006	351	634	985	60
Pathway 5	12201	13143	13615	11275	926	1868	2340	54
Pathway 6	12441	13382	13978	11763	678	1619	2215	55
Pathway 7	2598	3024	3512	2263	335	761	1249	27
Pathway 8	1545	2144	2390	1217	328	927	1173	16
Pathway 9	8049	8106	8369	7959	90	147	410	55

SOCIAL COST PER PATHWAY (€)

	Total Social Cost (€)			Social Care (€)			Technical Aids (€)			Productivity Losses (€)			Relative weight Social Cost
	MIN	MEAN	MAX	MIN	MEAN	MAX	MIN	MEAN	MAX	MIN	MEAN	MAX	% OF TOTAL
Pathway 1	3966	6217	15329	940	1381	1945		0		3026	4836	13384	24
Pathway 2	5270	7344	14077	1430	2346	2674		0		3840	5834	11403	26
Pathway 3	3921	5282	13178	1100	1317	2500		0		2821	3965	10678	41
Pathway 4	4944	7232	15100	1270	2288	2430		0		3674	5264	12670	40
Pathway 5	6695	11563	23055	2755	3860	4240	130	1332	2415	3810	6372	16400	46
Pathway 6	6299	10892	22787	2170	3256	4650	110	1157	1905	4019	6478	16232	45
Pathway 7	5504	7968	17780	1760	1980	3200	80	496	1130	3664	5492	13450	73
Pathway 8	5092	9479	20787	1640	2475	3410	72	466	967	3380	6538	16410	84
Pathway 9	7140	12873	31675	2480	3759	4890	160	1837	2740	4500	7278	24045	45

5

Discussion

The present thesis is based on an original prospective cohort study that sought to investigate the current system of rehabilitation care for first-time stroke patients. The collected data and analysis contribute to the projection and development of future national strategies for stroke treatment and the implementation of the European Stroke Action Plan 2030 [20].

This work covers the rehabilitation of stroke survivors after clinical stabilisation and the hospital's acute stage, offering a reflection from public health to a patient-level perspective, through three articles. The first paper studied the evolution and the predictors of HRQoL one year post-stroke, which clarified the contribution of biological, socioeconomic, and healthcare factors. It highlighted rehabilitation care as a specific predictor of one-year HRQoL [108].

Afterwards, we integrated a paradigm shift in the conceptualisation and analysis of post-stroke care. We ran a multilevel assessment including health system, clinical process, and individual data, regarding the rehabilitation pathways of each stroke survivor. This allowed a joint reflection between the macro points of view of organisation and care planning, crossed with the insights from people's perception of access, quality, and value of care. Findings from this study demonstrated nine alternative and diverse coexisting stroke pathways and eight settings of care in Portugal. After mapping the care circuits, they were characterised, evaluated, and compared [109].

Finally, an economic analysis of the main rehabilitation pathways was carried out, both from the societal and the provider's perspective, offering a policy perspective on the decision-making process in stroke care [110].

5.1 WHAT IS THE CONTRIBUTION OF THIS THESIS?

This work is the first to provide a prospective analysis of the determinants of HRQoL and a comparison of stroke patients' HRQoL with the general Portuguese population norms. It fulfils an innovative description and evaluation of stroke pathways of care and, it discusses the first detailed cost-effectiveness analysis of alternative multistep pathways of stroke rehabilitation across 1 year.

The present study also adds the inclusion of data representing a large sample of stroke patients identified since the acute event, with a wide range of age, stroke subtypes, degrees of severity and rehabilitation data compared to other previous stroke rehabilitation studies [111-114].

Additionally, this study used valuable patient-level data resulting from a combination of medical records and standardized face-to-face interviews. This allowed us to minimize missing data issues, as well as collect much richer information to include in our evaluation models [115, 116].

Throughout the three papers, a comprehensive analysis of the global model of care for stroke patients was obtained through system, process, and patient-level data, for the first time in Portugal. The different care pathways and integrated settings were described in terms of organization, services, resources, funding, and patient profiles. These data revealed a lack of evidence-based practice, significant differences in the outcomes between pathways, and an inadequate level of information and patient satisfaction through the circuit of care.

This investigation culminated in an original estimate of the costs and benefits of alternative pathways of care, considering the first year after stroke, as the period with the greatest rehabilitation potential [31]. All the cost parameters were obtained in Portugal in the reference year, which increases the robustness of the data [117]. These different aspects favour the dissertation. Finally, the data, models and analysis developed in this thesis will continue to support future research in the area, as well as guide stroke policy in Portugal and Europe.

These different aspects, besides supporting future research in this area, favour the international comparability between health systems and policies and guarantee the novelty of this dissertation.

From a more detailed analysis, it is important to underline some specific results.

Firstly, although some studies show an early increase in HRQoL right after the acute event [118-120], in our sample we verified a sharp initial fall of both SF-6D and EQ-5D-3L scores at 3 months, followed by a rise after 6 months, surpassing baseline values of HRQoL only after 12 months. This may result from a higher level of severity, disability, and daily life dependence in comparison to other study samples [111-114]. Regarding HRQoL predictors, through regression models estimated globally and by severity groups, we found that access and frequency of rehabilitation had a relevant impact on HRQoL first-year post-stroke in both analyses. Literature shows that many rehabilitative interventions are cost-effective [121], however, there is relatively scarce literature confirming rehabilitation as a determinant of post-stroke HRQoL [122]. Furthermore, the influence of lower age, higher education, employment status, baseline stroke severity, disability, and functional status on HRQoL after stroke confirmed on our data [123-126], should be considered in a broad and effective post-hospital referral model, that helps build the appropriate rehabilitation care circuit immediately after baseline.

Once the pathways were identified, we compared them with the best practice reference [127-130]. Consistent with European reports that describe flaws in the type and quality of stroke care [45-47], a lack of agreement was found between guidelines and care in our studies. Overall, only 30% of the study sample was able to obtain multidisciplinary and intensive care, only 60% of the settings offered transition care planning between them, and only 35% involved the patient in goal setting. Also, the mean hospital stay was 43 days which warns that the transfer to the subacute phase was not fast and continuous enough. In terms of the referral model, a large part of the patients did not comply with the recommended national standard of the *Direção-Geral da Saúde* [131]. Particularly, in the moderate severity categories, which include the largest

percentage of stroke survivors and higher individual and clinical heterogeneity [109]. Considering these results, a strategy is needed to facilitate the translation of knowledge from guidelines into the decision-making process by professionals and health systems [132, 133].

Post-stroke care is considered disorganized and fragmented even in the best health systems [41, 134]. Although stroke rehabilitation occurs in different levels of care from inpatient, outpatient, home, and community-based services, there is a lack of studies comparing the pathways of care [135, 136]. From the perspective of effectiveness, our results suggested inefficiency and inequities within the nine rehabilitation pathways available in Portugal. National guidelines should be adapted to include clear navigation through the complexity of the care network, defining specific pathways by clinical profiles [33], and taking into consideration the needs of survivors and their careers.

Patient satisfaction is consistent with best practice intention [27], with higher values attributed to pathways with more intensive and multidisciplinary care and greater involvement of the patient/caregiver [48, 49]. Of note, a concerningly low level of patient information was identified, mainly about functional prognosis, expected outcomes, expected services, and contact professionals. This limits an informed decision process and explains a low perception of control. Ultimately, this phenomenon leads to constraints and barriers to a person-centred practice and justifies distrust in the healthcare system [27, 46, 47].

Finally, from the economic evaluation of the different pathways, our study provides evidence for policymakers to define pathway 3 (short-term inpatient unit from discharge to 3 months and an outpatient community clinic from 3 to 12 months) as the new standard-of-care pathway for stroke rehabilitation, under a willingness-to-pay threshold of one time the national gross domestic product (€20873 per QALY). Pathway 3 was the most cost-effective, both from the perspective of the patient and the NHS. This result is coherent with what is determined in the guidance of good practices, as it ensures the principles of evidence-based rehabilitation [33, 127-130].

Stroke survivors have different levels of severity and clinical complexity, so a complete rehabilitation model must guarantee differentiated care pathways [137-139]. Two other pathways were considered cost-effective in the primary analysis, namely, pathway 1 from the societal perspective, and pathway 7 from the provider perspective. Additionally, the sensitivity analysis showed that other pathways if considered at minimum cost would be cost-effective. This is more common in pathways with free access to healthcare from the patient's perspective, or with reduced exposure to inpatient settings considered more expensive from the provider's perspective. Given this, it is important to reflect on whether the choice and access to the optimal rehabilitation pathway should rely on cost considerations, assuming a global analysis of the pathways that should remain on a sustainable rehabilitation network [21].

5.2 BRIDGING THE GAP

Our findings generate a call to action. There is an opportunity to improve the quality of stroke care and strengthen the bonds of trust between patients and the health system.

The results from this thesis can be translated into current stroke practice and help decision-making about innovative health policies focused on stroke survivors. Four transformative processes require the collective effort of the different stakeholders to ensure the value of care in patient health outcomes: i) the sentinel stroke national rehabilitation audit programme, ii) the integrated electronic clinical stroke information system, iii) an update in the stroke referral guideline, iv) a new strategic rehabilitation plan after stroke.

Firstly, this research has demonstrated the lack of and difficulty in accessing structured data on stroke survivors. No integrated information source or audit tools were found to identify, collect, and organise up-to-date and real-time information on the provision of rehabilitation care in stroke. We identified eight different models of care. In none of these models is it possible to publicly access data about the typology, frequency, intensity, initial and final assessment, transition, and referral processes. On the other hand, there is no real monitoring of the utilisation of these models. Survivors enter a system of care with multiple options, and it is not possible to know how many patients are and how long they stay in each pathway, how much cost each pathway, and the users' perception of the quality of care.

This lack of information at the process and organisational level means that the first transformative process required is to develop a sentinel audit and assessment programme [47] for reporting rehabilitation care, that monitors the transfer of the best available evidence into clinical practice and guides informed care management.

Secondly, rehabilitation crosses different models and levels of care but does not ensure the integration of clinical information. Clinical records are often saved in different data systems without interoperability mechanisms between them. The data used in this thesis was obtained from four different clinical records, otherwise, it would not have been possible to obtain the clinical information circuit.

Given this shortcoming, the second transformative process required is the implementation of a unique electronic clinical information process [45, 46], which stimulates the development of integrated and individual rehabilitation plans that collect data from different professionals and levels of care.

Thirdly, although the 2011 national guideline on the prescription of physical medicine and rehabilitation defines criteria for clinical stratification and care referral, a lack of compliance was found between the definition and clinical practice. This probably derives from the fact that the national guideline is outdated. It does not consider the eight existing care settings or the concept of pathways. It defines exclusively one-step referral after the acute phase. It does not define medium/long-term care. It does not include the socioeconomic background of the patient, its family support, its prognostic profile, and the costs of different pathways from a societal perspective. It does not set a care manager and procedures for articulating and integrating care without losses of follow-up [140-142].

So, the third transformative process should involve updating the referral national guideline [142] both from the point of view of the comprehensive care network and reviewing the criteria to be considered in the decision tree regarding the orientation of patients through different care pathways.

Finally, when analysing outcomes by pathway, we found different opportunities for patients starting with similar severity profiles, and at the same time, we found inefficiency when different itineraries ended with comparable outcomes. In addition, we have documented that most of the pathways were not considered cost-effective, and the cost analysis demonstrated barriers to accessing rehabilitation care according to the pathway chosen. For example, a patient with moderate severity can start rehabilitation in a Short-term Unit, in a Rehabilitation Centre or as an outpatient in a Day Hospital and has no costs in the first phase of rehabilitation (pathways 1,2,3,4,7 and 8). On the other hand, if the same moderate patient is referred to the Medium-term Unit, which is the type that absorbs more patients (35%), the survivor may have to pay out-of-pocket up to €700 per month according to their income (pathways 5 and 6). Moreover, the non-cost settings offer care with greater frequency and intensity than the settings with a direct healthcare cost to the patient, constituting a double penalty for the patient using these pathways.

From a social point of view, within a constitutional framework of an NHS that tends to be free and protects the clinically fragile patient, these results raise important ethical questions about the national treatment strategy for stroke patients. In the same way that it is unacceptable for a cancer patient to be required to pay out of pocket for care, it may be pertinent to reconsider the patient's cost for rehabilitation during the first months, when stroke is one of the most important causes of long-term morbidity and disability [32]. A transformative reflection is urgently needed.

These challenges require a fourth transformative process which is the development of a national stroke management strategy plan. This plan should define cost-effective pathways of care from the emergency to the final phase of rehabilitation, adapted to clinical and prognostic profiles, respecting equity, and effectiveness, and including survivors' perspectives about quality and informed-based decisions [45-47, 96].

On the other hand, from the point of view of efficiency and financial system sustainability, it should be noticed that our data showed that the non-cost settings offer better results and more evidence-based practice. So, these strategies, besides offering a more equitable solution, increase the opportunity of reducing later social costs and productivity losses [121, 122]. So, the future stroke rehabilitation plan should consider the hypothesis of offering universal free access to rehabilitation in the first stage after the acute phase, to ensure an equitable response. In the second rehabilitation stage, the fragmentation of pathways available should be reduced, and a comprehensive, integrated, and costly care circuit adapted to the prognostic and socio-economic profile of each patient needs to be defined.

Recent government investments in improving emergency and acute stroke care are not being matched by updates in the stroke rehabilitation stage in Portugal [47, 50]. The literature considers Portugal to be one of the European countries with the greatest potential for reducing the incidence and prevalence of strokes in the next years [14], which should motivate a challenge to build up a stroke treatment policy based on the best available evidence and respecting the necessary balance between the financial sustainability and the best possible health outcomes.

6
Conclusion

This thesis offers a comprehensive perspective on the rehabilitation of post-stroke patients in Portugal.

Our results highlight the negative impact of stroke on HRQoL through both SF-6D and EQ-5D-3L indexes. Longitudinal analysis revealed that HRQoL is significantly lower in stroke survivors than in the general population, regardless of the type of stroke. In our sample we verified a sharp initial fall of both SF-6D and EQ-5D-3L at 3 months, followed by a rise after 6 months, surpassing baseline values only after 12 months. We found that the HRQoL of stroke survivors is influenced mostly by clinical factors and sociodemographic characteristics, with a special focus on rehabilitation and its fundamental role in the recovery of quality of life in post-stroke patients.

We identified nine main rehabilitation pathways in a combination of eight different healthcare settings in Portugal. A lack of compliance between guidelines and care was identified. Significant differences in outcomes between the nine pathways suggest inefficiency and inequalities, followed by inadequate information and patient satisfaction.

Under a WTP threshold of one time the national gross domestic product (€20873 per QALY), our analysis provides evidence for policymakers to establish pathway 3 (short-term unit for the first months followed by care in an outpatient community clinic) as the new standard-of-care pathway for stroke rehabilitation. Other pathways, which were still cost-effective in the final decision model, may be considered given the complexity of the stroke survivor's clinical heterogeneity, such as pathway 1 (rehabilitation inpatient centre in the first months followed by outpatient community clinic) from the societal perspective and pathway 7 (outpatient day hospital service in the first months followed by outpatient community clinic) from the provider perspective. These findings are critical in enabling the setup of an extensive, integrated, and effective system that is tailored to the various stroke patient profiles.

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