The Impact of Cognitive Impairment on Poststroke Outcomes: A 5-Year Follow-Up.

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The impact of cognitive impairment on post-stroke outcomes: A five-year follow-up

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Meetings at which this work was presented

Rohde D, Gaynor E, Large M, Mellon L, Brewer L, Hall P, Bennett K, Williams D, Callaly E, Dolan E, Hickey A. Outcomes of cognitive impairment post-stroke: A five-year follow-up of the ASPIRE-S cohort. 2018 Northern Ireland Stroke Conference, Belfast, Northern Ireland, 12 June 2018. **Winner, highest scoring abstract presentation.**

Rohde D, Gaynor E, Large M, Mellon L, Brewer L, Hall P, Bennett K, Williams D, Callaly E, Dolan E, Hickey A. Outcomes of cognitive impairment post-stroke: A five-year follow-up of the ASPIRE-S cohort. 15th Annual Psychology, Health & Medicine Conference, Ulster University, Northern Ireland, 1 June 2018.

Key words

Cerebrovascular disorders, stroke, cognitive impairment, independence, activities of daily living, depression, quality of life

Abstract

Aim: To explore the impact of cognitive impairment post-stroke on outcomes at five years.

Methods: Five-year follow-up of the Action on Secondary Prevention Interventions and Rehabilitation in Stroke (ASPIRE-S) prospective cohort. 226 ischemic stroke survivors completed Montreal Cognitive Assessments (MoCA) at six months post-stroke. Outcomes at five years included independence in activities of daily living, receipt of informal care, quality of life, and depressive symptoms. Data were analyzed using logistic and linear regression models. Adjusted ORs (95% CI) and Beta coefficients (95% CI) are reported.

Results: 101 stroke survivors were followed up at five years. Cognitive impairment at six months was independently associated with, worse quality of life [B (95% CI): -0.595 (-0.943, -0.248)], lower levels of independence [B (95% CI): -3.605 (-5.705, -1.505)], increased likelihood of receiving informal care [OR (95% CI): 6.41 (1.50, 27.32)], and increased likelihood of depressive symptoms [OR (95% CI): 4.60 (1.22, 17.40)].

Conclusion: Cognitive impairment post-stroke is associated with a range of worse outcomes. More effective interventions are needed to improve outcomes for this vulnerable group of patients.

Introduction

Cognitive impairment is common among stroke survivors, and is associated with increased risk of mortality, higher levels of disability and dependency, depressive symptoms and worse quality of life.[1-5] Even in patients with excellent functional recovery, over half experience cognitive impairment, while a third report depressive symptoms.[6] The chronic phase of the condition accounts for a considerable proportion of the total costs of stroke care, with increasingly greater numbers of stroke survivors living for longer following stroke.[7] A greater focus on multiple levels of recovery, including more holistic outcome assessments, is needed to inform the organization and allocation of healthcare resources and interventions to optimize long-term recovery post-stroke.[6, 8, 9] Knowledge of the factors that contribute to worsening longer-term outcomes can be used to inform stroke survivors and caregivers, to aid social care and health service planning, and to guide the development of research and interventions to improve poor outcomes.[8, 10, 11] Cognitive impairment has been identified as a key priority for further research by stroke survivors, family members and healthcare professionals; however longer-term studies of outcomes are relatively scarce, with many focusing on disability or a limited range of outcomes only.[4, 5, 10, 12, 13] To our knowledge, this is the first study to specifically explore the impact of cognitive impairment on a range of longer-term outcomes post-stroke.

Aim

The aim of this exploratory study was to investigate the potential impact of cognitive impairment at six months post-stroke on levels of independence in instrumental activities of daily living, receipt of informal care, quality of life, and depressive symptoms at five years post-stroke.

Materials and Methods

Study design

This was a five-year follow-up of the Action on Secondary Prevention Interventions and Rehabilitation in Stroke (ASPIRE-S) prospective observational cohort of ischemic stroke survivors.[1, 14] The design and methods of this follow-up study have been described previously.[15]

Study sample

The ASPIRE-S study recruited 256 acute ischemic stroke patients in hospital and followed them up in the community at six months post-stroke. All stroke survivors from the original study were eligible to participate. Of 226 patients with cognitive assessments at six months post-stroke, 48 (21.2%) died during the follow-up period. We previously reported on predictors of mortality at five years post-stroke in this cohort;[2] therefore, deceased patients were excluded from the present analysis. A further 78 stroke survivors (34.5%) were lost to follow-up. Stroke survivors lost to follow-up tended to be older, were more likely to be female, and more likely to have a moderate to severe disability and cognitive impairment at six months post-stroke than those who participated in the five-year follow-up study (Table 1). 101 stroke survivors were followed up at five years post-stroke (Figure 1). The mean follow-up time was 5.1 years (SD 0.4) from date of stroke.

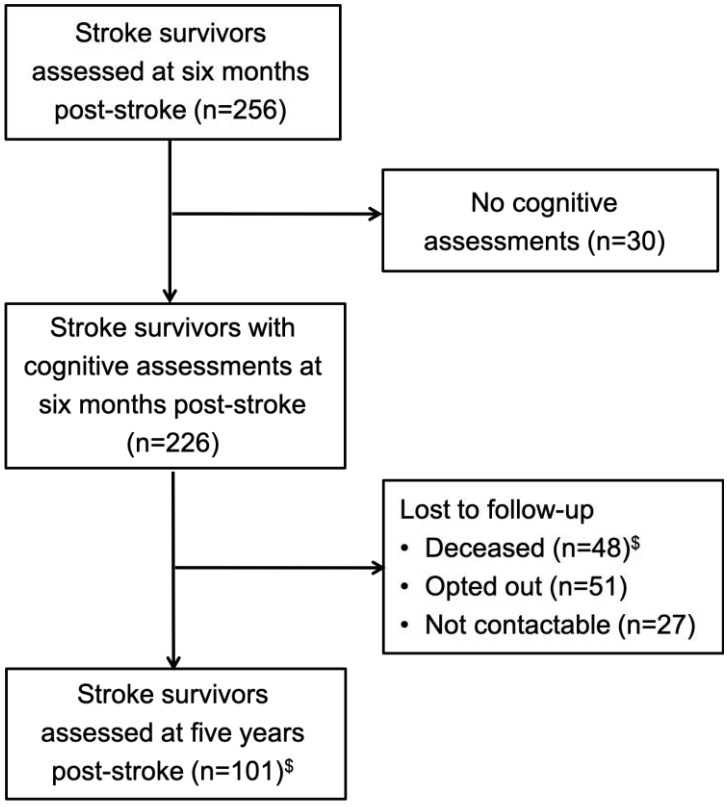

Figure 1. Flowchart of ASPIRE-S stroke survivors followed up at five years post-stroke

$One stroke survivor was followed up at five years, but subsequently died before the end of the study period

Table 1. Demographic and clinical profile of ASPIRE-S stroke survivors at six months post-stroke by follow-up status at five years

		Followed up	Lost to follow-up
		N (%)	
Demographics	Age (Mean, SD)	64.3 (12.4)	68.7 (12.7)*
	Male	73 (67.6)	40 (46.5)**
	Married (vs. not married)	72 (66.7)	51 (59.3)
TOAST classification	Large artery artherosclerosis	19 (17.6)	12 (14.0)
	Cardioembolism	36 (33.3)	34 (39.5)
	Small vessel occlusion	15 (13.9)	11 (12.8)
	Other	38 (35.2)	29 (33.7)
Bamford classification	Total anterior circulation stroke	7 (6.5)	4 (4.7)
	Partial anterior circulation stroke	39 (36.1)	35 (40.7)
	Posterior circulation syndrome	32 (29.6)	27 (31.4)
	Lacunar syndrome	28 (25.9)	18 (20.9)
	Unclassifiable	2 (1.9)	2 (2.3)
Stroke severity (SSS score <43)	Moderate or severe	18 (16.7)	20 (23.3)
Vascular risk factors at six months	Hypertension	76 (71.0)	62 (72.9)
	Elevated total cholesterol	23 (22.1)	17 (21.8)
	Impaired fasting glucose	11 (10.8)	14 (18.0)
	Overweight/obese	60 (56.1)	52 (61.9)
	Smoker	28 (25.9)	28 (32.6)
	History of alcohol abuse	18 (16.7)	10 (11.6)
	Previous stroke/TIA	24 (22.2)	19 (22.1)
	History of heart disease	30 (27.8)	24 (27.9)
	History of carotid stenosis	18 (16.7)	13 (15.1)
	History of atrial fibrillation	32 (29.6)	29 (33.7)
Cognitive impairment	MoCA <24	27 (26.7)	35 (44.9)*
Depression	Depressive symptoms	14 (14.1)	15 (19.7)
Disability (mRS ≥3)	Moderate to severe	18 (16.7)	25 (29.1)*

*p<.05, **p<.01. MoCA: Montreal Cognitive Assessment. TIA: Transient Ischemic Attack. SSS: Scandinavian Stroke Scale. mRS: modified Rankin Scale.

Five-year assessments

Five-year follow-up data were collected using face-to-face assessments and self-report questionnaires. Self-report questionnaires were sent by post prior to the face-to-face assessments and checked for completion by a member of the research team. If stroke survivors were unable to complete the questionnaires on their own, family members,

caregivers, or a member of the research team provided assistance. This method was also used during the original six-month assessment of this cohort.[1, 14]

Cognitive function

Cognitive function was assessed at both six months and five years post-stroke using the Montreal Cognitive Assessment (MoCA), a rapid, 30-point screening tool that assesses several cognitive domains.[16] While the MoCA has demonstrated higher sensitivity for cognitive impairment in stroke cohorts than the Mini Mental State Examination (MMSE),[17] concerns have been raised over the lack of specificity of the original cut-off.[17-20] Therefore, we used a cut-off of <24 to identify stroke survivors with evidence of cognitive impairment.[18, 20] This cut-off has been used previously to identify cognitive impairment in a general population sample of older adults in Ireland.[21]

Outcomes

Independence in instrumental activities of daily living (IADLs) was assessed with the Nottingham Extended Activities of Daily Living scale (NEADL). This 22-item measure assesses independence in activities that may be important to stroke survivors who have been discharged home, including mobility, kitchen, domestic and leisure activities. Scores range from 0 to 22, with higher scores indicating greater independence.[22] Receipt of informal care was categorized according to whether stroke survivors reported receiving any assistance with their care from family, friends or neighbors. Quality of life was assessed using the Stroke Specific Quality of Life Scale (SSQOL).[23] This measure consists of 49 items in 12 domains, including social and family roles, mood, personality, language, thinking and vision, energy, mobility, and upper extremity use, and self-care and work/productivity. Scores on each item range from 1 (representing the response options total help/couldn't do at all/strongly agree) to 5 (representing the response options no help needed/no trouble at all/strongly disagree). Item scores within each domain are averaged to create a mean domain score; the mean domain scores are then averaged to produce an overall SSQOL score ranging from 1 to 5, with higher scores indicating greater quality of life.[23, 24] Depressive symptoms at five years post-stroke were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), with the recommended cut-off of ≥16 to identify individuals at risk of clinical depression.[25]

Covariates

Covariates included demographic factors (age and sex) and vascular risk factors assessed at six months post-stroke.[1, 14] Clinical measures collected at six months included blood pressure, lipid profiles, fasting glucose levels, weight, history of stroke/TIA, history of heart disease, history of carotid stenosis and presence of atrial fibrillation. We classified vascular risk factors according to European secondary prevention targets.[27] TOAST and Bamford classifications of the index stroke were collected as part of the original ASPIRE-S study. Stroke severity was assessed with the Scandinavian Stroke Scale,[28] with scores of 0-25 considered severe, 26-42 moderate, and 43-58 categorized as mild strokes.[29] The presence of depressive symptoms at six months post-stroke was assessed using the Hospital Anxiety and Depression Scale depression subscale (HADS-D), with the recommended cut-off of scores ≥8 used to identify participants with depressive symptoms.[32] Communication difficulties, which may affect performance on cognitive assessments, were assessed using the Frenchay Aphasia Screening Test (short form) (FAST), with scores <14 considered to be indicative of aphasia.[33]

Ethical approval

This study adhered to the principles of the Declaration of Helsinki. Ethical approval was granted by the Research Ethics Committees at Beaumont Hospital (ref. 16/26), Mater Misericordiae University Hospital (1/378/1855), Connolly Hospital Blanchardstown (28/11/2016), and the Royal College of Surgeons in Ireland (REC 1355). All participants gave informed, written consent.

Statistical analysis

Univariate associations with each outcome were explored using chi-square tests, t-tests and one-way ANOVAs as appropriate. Multivariable logistic and linear regression models were used to investigate associations between cognitive status at six months and outcomes at five years. Stroke categories and subtypes were excluded from multivariable analyses due to the small numbers in some subgroups. Stroke severity was included in multivariable models as a continuous variable (total Scandinavian Stroke Scale score). Multivariable models initially controlled for age, sex, stroke severity and depressive symptoms at six months, as well as any factors significantly associated with the outcome in univariate analysis. Due to sample size limitations and the risk of

overfitting, variables that were not statistically significant after adjustment in multivariable analysis were dropped from the final models (age and stroke severity were retained in all models). As all stroke survivors with evidence of aphasia at six months also scored below the MoCA cut-off (indicating the presence of cognitive impairment), we conducted sensitivity analyses excluding participants with aphasia. Adjusted Odds Ratios (ORs) (95% CI) and Beta coefficients (B) (95% CI) are reported. As this was an exploratory analysis with a small sample size potentially lacking in statistical power, we did not adjust for multiple comparisons. Data were analyzed using Stata 13 (Statacorp, College Station, TX).

Results

At six months post-stroke, 92 of 226 stroke survivors (40.7%) had evidence of cognitive impairment according to MoCA scores <24. Of the 101 stroke survivors included in this five-year follow-up study, 27 (26.7%) had evidence of cognitive impairment at six months post-stroke, while 46 (45.5%) had evidence of cognitive impairment at five years. 97 stroke survivors completed the MoCA at both time points. Of those with evidence of cognitive impairment at six months post-stroke, 88.0% (n=22) remained cognitively impaired at five years. An additional 20 stroke survivors (27.8%) without evidence of cognitive impairment at six months post-stroke were classified as cognitively impaired at five years. Three stroke survivors with evidence of cognitive impairment at six months were no longer classified as impaired at five years.

Cognitive impairment at six months post-stroke was associated with significantly greater likelihood of being in receipt of informal care at five years, with 63.0% of those with cognitive impairment at six months receiving informal care at five years, compared to 17.8% of those without cognitive impairment. Cognitive impairment at six months post-stroke was associated with significantly lower levels of ADL independence (mean NEADL scores of 12.6 vs. 18.8) and worse quality of life (mean SSQOL scores 3.40 vs. 4.06). Cognitive impairment at six months was also associated with a significantly increased likelihood of depressive symptoms at five years, with 42.3% of stroke survivors with cognitive impairment at six months reporting depressive symptoms at five years, compared to 20.9% of those without cognitive impairment at six months post-stroke (Table 2).

Table 2. Clinical characteristics and five-year outcomes by cognitive status at six months

Clinical characteristics (n=101)	**No cognitive impairment**	**Cognitive impairment**
Age (Mean, SD)	66.1 (12.0)	75 (11.1)**
Male (n, %)	51 (68.9)	17 (63.0)
Moderate or severe stroke (SSS <43) (n, %)	8 (10.8)	6 (22.2)
Aphasia (FAST <14, n=100) (n, %)	0	2 (7.4)*
Five year outcomes		
Quality of life (SSQOL) (n=91) (Mean, SD)	4.06 (0.71)	3.40 (0.76)***
IADL Independence (NEADL) (n=93) (Mean, SD)	18.8 (4.5)	12.6 (7.3)***
In receipt of any informal care (n=100) (n, %)	13 (17.8)	17 (63.0)***
Depressive symptoms (n=100) (n, %)	14 (20.9)	11 (42.3)*
Cognitive impairment (MoCA<24) (n=97) (n, %)	20 (27.8)	22 (88.0)***

***p<.001, **p<.01, * p<0.05.

n=total number of stroke survivors included in each univariate analysis

SSS: Scandinavian Stroke Scale

FAST: Frenchay Aphasia Screening Test

SSQOL: Stroke Specific Quality of Life Scale

NEADL: Nottingham Extended Activities of Daily Living Scale.

Multivariate analyses indicated that cognitive impairment at six months post-stroke was independently associated with worse quality of life, lower levels of independence in activities of daily living, greater likelihood of receiving informal care, and increased likelihood of experiencing depressive symptoms at five years post-stroke, controlling for a number of potential confounders (Table 3). Excluding stroke survivors with aphasia at six months post-stroke did not substantially alter the size, direction, or interpretation of these effects (Table 3).

Table 3. Adjusted associations between cognitive impairment at 6 months and outcomes at 5 years post-stroke

Model	Outcome	Cognitive impairment at 6 months post-stroke					
		Including stroke survivors with aphasia			Excluding stroke survivors with aphasia		
		B (95% CI)	β	Model	B (95% CI)	β	Model
1	Quality of life	-0.595 (-0.943, -0.248)	-.324**	n=88 F(5,82)=9.14, R^2=0.319	-0.651 (-1.016, -0.286)	-.342**	n=85 F(5,79)=9.27, R^2=0.330
2	IADL independence	-3.605 (-5.705, -1.505)	-.263**	N=88 F(4,83)=26.74, R^2=0.542	-3.509 (-5.729, -1.289)	-.249**	n=85 F(4,80)=25.39, R^2=0.537
		OR (95% CI)		Model	OR (95% CI)		Model
3	Informal care	6.41 (1.50, 27.32)*		n=93 X^2(4)=52.38, R^2=0.460	5.92 (1.32, 26.45)*		n=90 X^2(4)=49.96, R^2=0.454
4	Depressive symptoms	4.60 (1.22, 17.40)*		n=88 X^2(5)=17.57, R^2=0.178	6.64 (1.57, 28.02)*		n=85 X^2(5)=20.24, R^2=0.213

*p<.05, **p<.01, ***p<.001.

n=total number of stroke survivors included in each analysis. Model 1 adjusted for age, stroke severity, depressive symptoms and history of heart disease at six months. Model 2 adjusted for age, stroke severity, and recurrent events at five years. Model 3 adjusted for age, stroke severity and recurrent events at five years. Model 4 adjusted for age, stroke severity, history of heart disease, and depressive symptoms at six months. R^2: adjusted (linear), McFadden's (logistic).

Discussion

Cognitive impairment at six months post-stroke was independently associated with worse outcomes at five years, including, worse quality of life, reduced independence in instrumental activities of daily living, and increased likelihood of experiencing depressive symptoms. Previous research has reported links between cognitive impairment and dependency, depressive symptoms, and poorer quality of life in the shorter term post-stroke,[3] while recovery of cognitive function has been reported to reduce levels of disability.[34] We previously reported that cognitive impairment in the ASPIRE-S cohort was associated with significantly increased mortality risk within five years.[2] Further, stroke survivors with cognitive impairment at six months post-stroke were significantly more likely to be lost to follow-up. It would therefore seem likely that the associations between cognitive impairment and poorer outcomes reported here are underestimated. Given that presence of cognitive impairment significantly predicts progression to dementia,[11, 35, 36] it seems reasonable to speculate that a proportion of ASPIRE-S stroke survivors with cognitive impairment at six months post-stroke who were lost to follow-up at five years may now have dementia.

The majority of stroke survivors with evidence of cognitive impairment at six months post-stroke in our cohort remained cognitively impaired at five years, highlighting the persistent nature of cognitive deficits post-stroke. Further, around a quarter of survivors without evidence of cognitive impairment at six months post-stroke were classified as cognitively impaired at five years. Knowledge of outcomes associated with cognitive impairment post-stroke can be used to inform patients and caregivers, to plan health and social care services, inform interventions, and ascertain the overall burden of stroke.[11]

Our findings suggest that a significant number of stroke survivors continue to have on-going rehabilitation needs, with a need for improved access to psychological and occupational therapy services and interventions in the longer term. Cognitive decline of stroke survivors has been linked with increased levels of anxious and depressive symptoms among family caregivers, who may also require additional supports.[38] However, rehabilitation tends to focus only on the weeks and months immediately following stroke, and largely fails to include any cognitive components, thereby failing to meet the evolving needs of stroke survivors and caregivers in the longer term.[39]

Our study also highlights the importance of regular screening for cognitive impairment in stroke survivors. Screening could help to identify a particularly vulnerable group of patients at risk of poorer outcomes, who may require additional health and social care services and supports,[2] including help with management and administration of secondary prevention medications[37] (authors' manuscript under review, 2019). There is a need to monitor cognitive impairment in stroke survivors both in the short and longer term, and to develop cost-effective ways of managing the long-term needs of this growing and vulnerable group of patients.[40] Unfortunately, interventions for the rehabilitation of cognitive function in stroke survivors have shown limited efficacy,[42] and there is a need for further research to identify effective interventions for post-stroke cognitive impairment.

Limitations and strengths

Our study has a number of limitations. A third of our sample was lost to follow-up; a rate of attrition equivalent to another recently reported study conducted over a similar timeframe.[44] Loss to follow-up is a common issue in longer-term studies of stroke survivors, with the South London Stroke Register similarly reporting rates of attrition of about 20% per year between 1 and 5 years post-stroke.[10] Considering that stroke survivors lost to follow-up in our study were more likely to be older and to have cognitive impairment and moderate to severe disability at six months post-stroke, it seems likely that the poor outcomes reported in this study are underestimated. As this is a follow-up study, the sample size was based on the availability of participants, rather than a statistical power calculation. It is possible that the analyses for some associations of interest were underpowered. Due to the exploratory nature of this study and the small sample size and potential lack of statistical power, analyses were not adjusted for multiple comparisons. While a number of known confounders were assessed and adjusted for in multivariate models, due to the observational nature of this study, there may be other unknown or unmeasured confounding factors. It was not possible to examine the impact of stroke location, as these data were not collected as part of the original ASPIRE-S study. Left hemisphere lesions have been found to significantly predict post-stroke cognitive impairment[5, 45] and dementia,[11] and should be considered in future studies on outcomes of cognitive impairment post-stroke.

While the MoCA has been reported to have high sensitivity and specificity in predicting cognitive impairment post-stroke,[46] the assessment may miss important deficits in apraxia, neglect and number processing.[47] MoCA scores can be confounded by language impairments such as aphasia, as the majority of items require substantial verbal abilities.[47] Indeed, all stroke survivors with evidence of aphasia at six months post-stroke in our study also had evidence of cognitive impairment according to the MoCA. While we conducted sensitivity analyses excluding stroke survivors with aphasia, future research could consider the use of tools such as the Oxford Cognitive Screen,[47, 48] which assesses domain specific cognitive impairments and includes measures of aphasia, apraxia and neglect. Information on domain-level cognitive deficits could also aid identification of and referral to appropriate rehabilitation services.[47]

Strengths of this study include the length of follow-up and comprehensive assessment of outcomes. Longer-term follow-up studies of stroke survivors are relatively scarce, with many previous studies involving historical cohorts that may not reflect modern acute stroke care and secondary prevention efforts.[49] Our study provides an updated account of post-stroke outcomes in the longer-term, and is, to our knowledge, the first to explore a range of longer-term outcomes of post-stroke cognitive impairment.

Conclusion

Post-stroke cognitive impairment affects a significant number of stroke survivors and is associated with a range of poorer outcomes. There is a need for regular screening and more effective interventions and continued access to rehabilitation services to improve outcomes for this vulnerable group of patients.

Acknowledgements

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Data availability

The data that support the findings of this study are available on request from the corresponding author, DR.

Author contributions

DR, AH, KB and DW conceived the study. DR, AH, KB, DW, ED, EC, EG, LM and LB were involved in protocol development, and gaining ethical approval. DR, EG, ML, KB, LM, LB and PH were involved in patient recruitment and data collection/extraction. DR conducted the data analysis and wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Conflicting interests

DW is an Advisory Board Member for Boehringer Ingelheim, Daiichi Sankyo, Bristol Myers Squibb, and Bayer and has received personal fees for this outside the submitted work. DW is Speaker Honorarium for Boehringer Ingelheim and has received personal fees for this outside the submitted work. All other authors have no conflicts of interest to declare.

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