

Title Page

Title: Pre-existing comorbidity burden is independently associated with patient-rated perceived stroke impact within the first-year post-stroke.

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Abstract

Background

Pre-existing comorbidities can compromise recovery post-stroke. However, the association between comorbidity burden and patient-rated perceived impact has not been systematically investigated. To date, only observer-rated outcome measures of function, disability and dependence have been used, despite the complexity of the impact of stroke on an individual.

Aim

Our aim was to explore the association between comorbidity burden and patient-rated perceived impact and overall recovery, within the first-year post-stroke, after adjusting for stroke severity, age and sex.

Methods

The sample comprised 177 stroke survivors from 18 hospitals throughout Australia and New Zealand. Comorbidity burden was calculated using the Charlson Comorbidity Index (CCI). Perceived impact and recovery were measured by the Stroke Impact Scale (SIS) index and SIS overall recovery scale. Quantile regression models were applied to investigate the association between comorbidity burden and perceived impact and recovery.

Results

Significant negative associations between the CCI and the SIS index were found at 3-months. At the .25 quantile, a one-point increase on the CCI was associated with 6.80-points decrease on the SIS index (95%CI: -11.26, -2.34; $p=.003$). At the median and .75 quantile, a one-point increase on the CCI was associated, respectively, with 3.58-points decrease (95%CI: -5.62, -1.54; $p=.001$) and 1.76-points decrease (95%CI: -2.80, -0.73; $p=.001$), on the SIS index. At 12-months, at the .25 and .75 quantiles, a one-point increase on the CCI was associated, respectively, with 6.47-points decrease (95%CI: -11.05, -1.89; $p=.006$) and 1.26-points decrease (95%CI: -2.11, -0.42; $p=.004$) on the SIS index. For the SIS overall recovery measure, significant negative associations were found only at the median at 3-months, and at the .75 quantile at 12-months.

Conclusion

Comorbidity burden is independently associated with patient-rated perceived impact within the first-year post-stroke. The addition of patient-rated impact measures in personalised rehabilitation may enhance the use of conventional observer-rated outcome measures.

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Introduction

The presence of comorbidities, particularly when numerous or severe, can compromise recovery outcomes post-stroke. Comorbidities have been shown to be associated with higher mortality rates,¹⁻⁵ longer lengths of stay in hospital,⁶ increased re-hospitalisation rates,⁷ reduced function,^{7,8} and greater disability and dependence.^{1,3,5} A high prevalence of comorbidities exists among stroke survivors;² stroke without comorbidities occurs in less than six per cent of the stroke population.⁴ The association between comorbidity burden and stroke outcomes has been studied using independently observed measures of function, disability and dependence.⁹ This association, for example, has been demonstrated using the Functional Independence Measure¹⁰ at discharge⁸ and six-months post-stroke,⁷ and the modified Rankin Scale (mRS)¹¹ at discharge,³ six-months⁵ and one-year¹ post-stroke. However, the association between comorbidity burden and stroke impact and recovery – as perceived by the stroke survivor – has not yet been systematically explored.

The notion of patient-rated perceived recovery refers to an individual's own experience and assessment of the impact of the stroke on their level of function and general health. Patient-rated perceived recovery and impact are important to consider, in addition to conventional observer-rated measures of recovery, because in patient-perceived evaluations, the patient can account for, and synthesise, a range and complexity of factors they believe are important to their recovery. These factors include the individual's particular circumstances and psychosocial factors, such as: sense of stroke impact on prior health status; sense of loss relating to the effect of stroke on premorbid roles and responsibilities; hope and expectation for good recovery; worry and fear of poor recovery; prior experience and resilience to adverse events; ability to accept and adjust to impairment; availability of family and community supports; self-esteem and confidence in social situations; and motivation to engage in rehabilitation. Understanding the perceived stroke impact on an individual, in addition to undertaking independently observed measures, aligns with a patient-centred approach and should enable the refinement of treatment plans to better meet individual needs.¹² The degree of perceived recovery and impact may differ from observer-rated scores generated by conventional measures of function, disability and dependence.¹³

The aim of this study was to explore the association between comorbidity burden and patient-rated perceived stroke impact and recovery, within the first-year post-stroke, after adjusting for factors known to influence recovery outcomes – age at stroke onset¹⁴, sex of the stroke survivor¹⁵ and stroke severity.¹⁶

Methods

Study Design

This study was a prospective, observational, longitudinal cohort design comprising 219 ischaemic stroke survivors. Participants were recruited via the Stroke Imaging Prevention and Treatment (START) collaborative research program which comprised two arms: the Prediction and Prevention to Achieve Optimal Recovery Endpoints after stroke (START PrePARE) cohort – for participants recruited within three days post-stroke;¹⁷ and the Extending the Time for Thrombolysis in Emergency Neurological Deficits (START EXTEND) cohort – for those recruited between 4.5 and 9 hours post-stroke.¹⁸

Participants and Centres

Eligibility for the START program required participants to be diagnosed with ischaemic stroke, be at least 18 years of age, be proficient in the English language and have no premorbid significant disability, as determined by a score of less than three on the mRS. Additional inclusion criteria associated with eligibility for the thrombolysis with tissue Plasminogen-Activator (tPA) were required for participants recruited via the START EXTEND study.¹⁸ Between June 2010 and April 2013, at hospitals throughout Australia and New Zealand – all of which had specialised stroke units – all eligible, consecutive patients presenting with ischaemic stroke were invited to take part in the study. Informed consent for participation, prior to the commencement of data collection, was obtained from the patient, or their family member or legally responsible person. Following recruitment, all participants were contacted again, at each assessment time-

point, and invited to continue participating in the study. The study was approved by the ethics committees responsible for each recruiting hospital site and the tertiary institution involved.

Measures

Standardised assessments were undertaken by health professionals trained in the conduct of the measures, between 3- and 7-days (± 1 day), at 3- and 12-months (± 7 days) post-stroke, at hospital recruitment sites or in participants' homes. Demographic data, including the participant's age at stroke onset and sex, was collected on admission. Stroke severity was measured by the National Institutes of Health Stroke Scale (NIHSS) between 3- and 7-days (± 1 day) following stroke onset. The NIHSS assesses neurological status post-stroke and correlates highly with stroke severity.¹⁹ Scores on the NIHSS range from 0 to 42; low scores indicate mild severity and higher scores denote greater neurological deficit.

Comorbidity burden was estimated by the Charlson Comorbidity Index (CCI) and calculated retrospectively from questionnaires, and patient or proxy reports collected on admission. The index has been validated to predict functional outcome within the stroke population.²⁰ The CCI was scored by assigning a value of 1, 2, 3 or 6 to each medical condition, based on its one-year mortality risk, that antedated the onset of the stroke.²¹ In this study, all participants received a score of at least '1' for the presence of 'cerebrovascular disease'. The score for each existing condition was summated to yield a total score for each participant, reflecting their cumulative burden of comorbidities – with higher scores indicating greater comorbidity burden²² (Table S1, supplement).

Patient-rated perceived impact of stroke and overall recovery were determined using the Stroke Impact Scale (SIS) version 3.0²³ at 3- and 12-months post-stroke. The SIS comprises 59 items across eight domains: strength, memory, emotion, communication, activities of daily living, mobility, hand function and social participation. Perceived impact of stroke was measured by the SIS index; this was generated by aggregating each domain score and standardising the total on a 100-point scale, with higher scores indicating less perceived stroke impact. The SIS index has been validated among a cohort of stroke patients.²⁴ Patient-rated perceived overall recovery was measured by the final item on the SIS, independent of the eight domains. This item, referred to as 'SIS overall recovery' hereafter, asks the respondent to provide a single score on a visual analogue scale from 0 to 100, representing their perceived global recovery, with higher scores signifying a better perceived overall recovery.²⁵

Data Analysis

Statistical analyses were conducted using Stata 14.0.²⁶ A large portion of cases with high scores recorded in both outcome measures was observed; the Breusch-Pagan test²⁷ confirmed the presence of heteroscedasticity in the data ($p=.005$). Therefore, quantile regression models were applied, in lieu of parametric regression models, to investigate the association between the CCI scores and the SIS index and overall recovery scores. Quantile regression provides a comprehensive statistical representation of the association across the distribution of the outcome variable;²⁸ for each SIS measure, regression models were fitted at the .25, median and .75 quantiles, for both time-points. The covariates, age, sex and baseline stroke severity, were adjusted for in each regression model. The Variance Inflation Factor (VIF) and Condition Index (CI) were used to detect multicollinearity; a mean VIF of 1.10 and CI of 15.23 were observed, indicating a low degree of interaction between the covariates. Lastly, a Bonferroni correction ($\alpha=.025$) was undertaken because two regression analyses were applied to the dataset.

Results

Participant Flow

From the initial START cohort of 219, participants were excluded from this analysis if no CCI nor NIHSS scores had been documented (9 exclusions). At 3-months, participants were excluded, respectively, from each of the two arms of the analysis if: (a) no SIS index had been recorded (33 exclusions); or (b) no SIS overall recovery scale had been recorded (37 exclusions). These criteria yielded, for this time-point, 177 inclusions in the SIS index analysis and 173 inclusions in the SIS overall recovery scale analysis. At 12-months, remaining participants were excluded, respectively, from each of the two arms of the analysis if: (a) no SIS index had been recorded (21 exclusions); or (b) no SIS overall recovery scale had been recorded (17 exclusions). This yielded 156 inclusions in each of the 12-month analyses. Reasons for attrition from baseline included: inability to contact the participant, participant withdrawal and participant death.

Demographic and Clinical Characteristics

At 3-months, the study sample comprised 177 stroke survivors; 119 (67%) were male and the sample mean age at stroke onset was 68 (SD=13) years. There was a median CCI score of 3 (IQR=2) and a median NIHSS score of 3 (IQR=7), indicating primarily mild neurological severity (Table S2 & Figure S3, supplement). A total of 36 (31%) participants had received thrombolysis with tPA, either as part of the START EXTEND¹⁸ study, or as part of clinical care in the START PrePARE¹⁷ cohort study (Table 1). Mann-Whitney tests indicated a statistically significant difference between participants included (n=177) and those excluded (n=42) in regard to their age at stroke (p=.029), comorbidity burden (p=.002) and stroke severity (p=.001). Chi-square tests demonstrated a significant group difference relative to the sex of the individual (p=.037); however, in relation to administration of tPA, there was no significant difference (p=.138). Descriptive statistics, including measures of central tendencies, were calculated for the outcome measures at both time points (Table 2).

Table 1. Demographic and Clinical Characteristics of Included and Excluded Participant Groups for SIS Index Analysis at 3-months

	included participants (n = 177)				excluded participants (n = 42)				p-value
	n	mean (SD)	range	med. (IQR)	n	mean (SD)	range	median (IQR)	
Age at stroke, years	177	68 (13)	28, 91	69 (17)	42	73 (13)	42, 95	76 (20)	0.029
male	119				21				0.037
female	58				21				
Comorbidity burden, CCI (0-35)	177	2.73 (1.41)	1, 8	3 (2)	42	3.43 (1.23)	1, 6	3 (2)	0.002
Stroke severity at day 3 to 7, NIHSS (0-42)	177	5.28 (6.32)	0, 32	3 (7)	35	10.34 (8.17)	0, 32	11 (14)	0.001
Thrombolysis with tissue Plasminogen-Activator (tPA)	36				13				0.138

Table 2. Descriptive Statistics for SIS Index and SIS Overall Recovery Scale

	n	mean (SD)	range	median (IQR)
SIS index (0-100)				
3-months	177	80.70 (20.99)	12.61, 100	88.36 (20.32)
12-months	156	83.71 (20.35)	0, 100	92.04 (24.83)
SIS overall recovery scale (0-100)				
3-months	173	74.09 (23.64)	0, 100	80 (40)
12-months	156	78.65 (22.06)	0, 100	85 (25)

Association between CCI and SIS Index and SIS Overall Recovery Scale

Quantile regression models yielded significant negative associations between the CCI and the SIS index at each quartile at 3-months post-stroke after adjusting for covariates. A one-point increase on the CCI was associated with 6.80-points decrease on the SIS index at the .25 quantile (95%CI: -11.26, -2.34; $p=.003$), with 3.58-points decrease at the median (95%CI: -5.62, -1.54; $p=.001$) and with 1.76-points decrease at the .75 quantile (95%CI: -2.80, -0.73; $p=.001$). At 12-months, the association followed a similar trend; however, this was only significant, based on the adjusted alpha, at the lower and upper quartiles. A one-point increase on the CCI was associated with 6.47-points decrease on the SIS index at the .25 quantile (95%CI: -11.05, -1.89; $p=.006$) and with 1.26-points decrease at the .75 quantile (95%CI: -2.11, -0.42; $p=.004$). Quantile regression also yielded negative associations between the CCI and the SIS overall recovery scale; however, the association was only statistically significant at the median at 3-months, and the upper quartile at 12-months. A one-point increase on the CCI was associated with 4.02-points decrease on the SIS overall recovery scale at the median (95%CI: -7.53, -0.51; $p=.025$) at 3-months and 2.50-points decrease on the SIS overall recovery scale at the .75 quantile (95%CI: -4.59, -0.41; $p=.019$) at 12-months (Table 3).

Table 3. Association between CCI and SIS Index and Overall Recovery Scale (Quantile Regression)

	CCI coefficient (95%CI)	p-value	<i>n</i>
SIS index			
3-months post-stroke			
.25 quantile	-6.80 (-11.26, -2.34)	.003	177
median	-3.58 (-5.62, -1.54)	.001	
.75 quantile	-1.76 (-2.80, -0.73)	.001	
12-months post-stroke			
.25 quantile	-6.47 (-11.05, -1.89)	.006	156
median	-2.57 (-5.18, 0.04)	.053	
.75 quantile	-1.26 (-2.11, -0.42)	.004	
SIS overall recovery scale			
3-months post-stroke			
.25 quantile	-3.01 (-8.50, 2.49)	.281	173
median	-4.02 (-7.53, -0.51)	.025	
.75 quantile	-2.57 (-5.00, -0.14)	.038	
12-months post-stroke			
.25 quantile	-2.56 (-7.99, 2.88)	.354	156
median	-2.27 (-4.60, 0.07)	.057	
.75 quantile	-2.50 (-4.59, -0.41)	.019	

The model was adjusted for age at stroke onset, sex of the stroke survivor and baseline stroke severity. Coefficients in bold indicate statistically significant results based on the adjusted alpha ($\alpha=.025$).

Discussion

Our findings advance the current literature by demonstrating for the first time, to our knowledge, the independent association between comorbidity burden and patient-rated perceived stroke impact, as measured by the SIS index. The results demonstrate that greater comorbidity burden is associated with greater stroke impact, as perceived by persons with stroke, after adjustment for other factors impacting recovery – stroke severity, age and sex. The association between comorbidity burden and patient-rated perceived stroke impact was significant across all quartiles of the distribution of perceived impact at 3-months, and for the .25 and .75 quantiles at 12-months. The strength of the association was greatest in magnitude at the lower quantiles, indicating a strong association between comorbidity burden and perceived stroke impact for participants with lower scores on the SIS index (i.e. those who experienced a greater impact of their stroke) at both time-points. The association between comorbidity burden and perceived overall recovery was also inverse; however, the relationship was only statistically significant at the median at 3-months, and at the .75 quantile

at 12-months, post-stroke. This association may be weaker because the SIS overall recovery scale requires the respondent to make a global judgement via a single score, and may therefore be open to heuristic biases, including factors pertaining to primacy and recency.

Recovery post-stroke is complex and multi-dimensional; it may be that it cannot be adequately assessed solely by independently observed measures. In this study, our approach represents a shift in focus from utilising only observer-rated measures to using patient-rated perceived measures, to explore the impact of stroke in relation to an indicator of an individual's prior experience of health – pre-existing comorbidity burden. Existing literature has demonstrated strong associations between variants of the SIS and observer-rated outcome measures, such as the mRS and the Barthel Index; however, the purpose and design of these outcome measures differ from the SIS index. The SIS index is likely to provide a more nuanced representation of outcome because it includes items that assess for the possible presence of non-physical effects of stroke, such as memory, emotion and social participation. It may be that measures of patient-rated perceived impact are more able to account for an individual's particular circumstances and psychosocial factors. For this reason, we argue that patient-rated perceived stroke impact should be considered in the assessment of recovery, alongside conventional observer-rated measures, in order to attain a more 'complete' picture of recovery. Further, the notion of perceived impact and recovery is important in the context of the widely adopted healthcare practice of patient-centred care. Perceived impact should be central in informing clinical decision-making, individualised treatment plans and the optimal allocation of healthcare resources.

There are potential limitations to the validity and generalisability of the study. First, the participants included in this study sample significantly differed from those excluded in terms of their age, sex, stroke severity and comorbidity burden. The reason for non-inclusion was the inability to obtain data at each time-point, despite all participants being contacted for follow-up according to a uniform protocol. The findings are valid relative to the characteristics of the group observed; however, they may not be valid for those excluded that had, on average, greater comorbidity burden, more severe strokes and who were older. Second, the mean age at stroke of participants included in this sample ($\mu=68$, $SD=13$) was lower than population samples ($\mu=73$, $SD=14$), as was the proportion of females (33%) compared with the Australian Stroke Clinical Registry (46%)²⁹. Third, participants were recruited from hospitals with specialised stroke units, which may have contributed to better recovery outcomes compared with patients receiving care in hospitals without such units. Fourth, 36 included participants had undergone thrombolysis with tPA, within the first few hours of presentation, based on decisions made by their treating clinicians. While these decisions were very likely to have been influenced by patients' acute NIHSS scores on arrival at hospital, this very early phase of stroke management precedes the day 3 to 7 NIHSS score on which our current study is based. However, this does raise the question of whether the association between comorbidity burden and perceived impact and recovery, may be attenuated by acute treatments. Alternatively, it may be that patients with greater comorbidity burden are less likely to receive thrombolysis, or acute stroke rehabilitation, which may therefore produce a pseudo-association between comorbidity burden and recovery outcomes. We recommend that further research be undertaken to address these questions. Last, most participants in this sample (72%) experienced a stroke of mild neurological severity (Figure S3, supplement). Despite assessment modification to actively encourage their inclusion, relatively few patients with severe neurological deficits or aphasia participated in this study, limiting the findings' generalisability. The prevalence of mild stroke, however, has increased due to greater public awareness, reduction of risk factors and advances in acute stroke care. In recent times it has been suggested that half of all stroke survivors experience a mild stroke;³⁰ accordingly, it may be that survivors of mild stroke should be of particular interest and importance when considering recovery outcomes. Patients with mild stroke are often expected to achieve full, or close to full, recovery, and subsequently may be discharged with minimal outpatient rehabilitation and follow-up support. However, complete recovery does not occur for a substantial proportion of mild stroke survivors.³¹ Our findings highlight that even for those categorised as having mild stroke, there was an independent association between pre-existing comorbidities and perceived stroke impact. Further, perceived impact of stroke has

been shown to become more prominent over time; even in the case for persons with mild to moderate stroke severity.³²

Conclusion

Increasing comorbidity burden is associated with greater patient-rated perceived stroke impact within the first-year post-stroke – independent of age at stroke onset, sex and stroke severity. Further, our study highlights the use of patient-rated measures of perceived stroke impact; we recommend their use, alongside conventional observer-rated measures, in future stroke practice and research.

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Declarations

The authors declare no conflict of interest.