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RESEARCH PAPER

Clinical frailty independently predicts early mortality after ischaemic stroke

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Abstract

Background:: Clinical frailty is an important syndrome for clinical care and research, independently predicting mortality and rates of institutionalisation in a range of medical conditions. However, there has been little research into the role of frailty in stroke.
Objective:: This study investigates the effect of frailty on 28-day mortality following ischaemic stroke and outcomes following stroke thrombolysis.
Methods:: Frailty was measured using the Clinical Frailty Scale (CFS) for all ischaemic stroke admissions aged ≥75 years. Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS). 28-day mortality and clinical outcomes were collected retrospectively. Analysis included both dichotomised measures of frailty (non-frail: CFS 1–4, frail: 5–8) and CFS as a continuous ordinal scale.
Results:: In 433 individuals with ischaemic stroke, 28-day mortality was higher in frail versus non-frail individuals (39 (16.7%) versus 10 (5%), $P < 0.01$). On multivariable analysis, a one-point increase in CFS was independently associated with 28-day mortality (OR 1.03 (1.01–1.05)). In 63 thrombolysed individuals, median NIHSS reduced significantly in non-frail individuals (12.5 (interquartile range (IQR) 9.25) to 5 (IQR 10.5), $P < 0.01$) but not in frail individuals (15 (IQR 11.5) to 16 (IQR 16.5), $P = 0.23$). On multivariable analysis, a one-point increase in CFS was independently associated with a one-point reduction in post-thrombolysis NIHSS improvement (coefficient 1.07, $P = 0.03$).
Conclusion:: Clinical frailty is independently associated with 28-day mortality after ischaemic stroke and appears independently associated with attenuated improvement in NIHSS following stroke thrombolysis. Further research is needed to elucidate the underlying mechanisms and how frailty may be utilised in clinical decision-making.

Keywords: frailty, mortality, stroke, thrombolysis, older people

Key points

- Clinical frailty is independently associated with 28-day mortality after ischaemic stroke.
- Improvement in stroke severity following thrombolysis is attenuated with frailty, independent of cardiovascular risk factors.
- Frailty in stroke is common and has implications for clinical prognostication and service delivery.

Introduction

Clinical frailty is an important clinical syndrome entailing a state of vulnerability characterised by the cumulative multi-system decline of physiological reserves to maintain homeostasis following stressor events [1, 2]. It is more nuanced than simply the number of co-morbidities, with a frailty phenotype described that is independent of co-morbidities and disability [3]. Frailty results in increased vulnerability to illness, poorer functional outcomes, higher rates of institutionalisation and increased mortality in a range of acute medical and surgical conditions [3–5], yet its role in stroke outcomes remains poorly understood.

Understanding how premorbid frailty affects prognosis in the acute setting after stroke is a pressing clinical issue given increasingly older populations. The prevalence of frailty rises with age, with an estimated prevalence of 6.5% for those aged 60–69 years, rising to 65% in those aged over 90 years in the UK [6]. Frailty within stroke is common with a frank frailty syndrome observed in a quarter of acute stroke admissions, and a pre-frail syndrome identified in a further half of admissions, at one centre [7]. Consequently, changing demographics will likely result in increased service pressures on stroke services due to the additional complexity in the management of stroke patients with frailty.

Screening for frailty has been advised in all individuals aged 70 years and over [2]. One validated measure is the Canadian Study of Health and Aging Clinical Frailty Scale (CFS), an ordinal scale based upon clinical judgement that correlates with rates of institutionalisation and death in the medium-term for a general population [8].

This study aimed to establish the relationship between clinical frailty and 28-day mortality after acute ischaemic stroke. As an exploratory outcome, the effect of frailty on stroke severity was also considered in the subgroup receiving thrombolysis.

Patients and methods

In this cohort study, premorbid CFS was collected prospectively within 72 h of admission for individuals aged 75 years and over presenting with ischaemic stroke at our centre between July 2013 and November 2016. Premorbid frailty assessment of individuals aged over 75 years is routine clinical care at our centre, and is assessed by the admitting physician as part of a mandated geriatric assessment that scores frailty based upon judgement of their premorbid function during the month prior to admission. [4] This clinical assessment considers cognition, mobility, function and co-morbidities through direct history from the individual or collateral history. The National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) were scored by the acute stroke specialist nurses at initial assessment, separately from and blinded to the frailty assessment of the treating physician. Pre-specified outcomes and variables—28-day mortality, age, sex, cardiovascular risk factors and post-thrombolysis NIHSS—were collected retrospectively from electronic records and blinded to CFS.

Frailty was considered as both an ordinal scale and a dichotomous variable (CFS 1–4 classed 'non-frail' and CFS 5–8 classed 'frail') as pre-specified analyses. This division was made as CFS 5 is the first to use the term 'frail'. 'Terminally ill' (CFS 9) individuals were excluded as this category includes individuals who may not be evidently frail but are known to be approaching the end of life.

The project was approved by the local Institutional Review Board (Safety and Quality Support Department, Cambridge University Hospitals NHS Foundation Trust, approval PRN7567).

Statistical analyses

Data was tested for normality using Shapiro–Wilk testing. Groups were compared using Mann–Whitney U test (non-parametric data), t-test (parametric data) or the Z test for two population proportions. Multivariable analyses included all variables from the univariable analysis with refinement via stepwise regression using backwards elimination determined by the Akaike information criterion method. Assumptions for linear regression modelling were tested and fulfilled.

Results

Participants

In total, 433 individuals were included: 199 (46.0%) 'non-frail' and 234 (54.0%) 'frail'. The frail group was older with a higher proportion of women, with all other variables matched between groups (Table 1).

Outcomes for all ischaemic strokes

On univariable analysis, 28-day mortality was higher in the frail cohort (39, 16.7%) than in the non-frail cohort (10, 5.0%) ($P < 0.01$). Increasing frailty (as a continuous measure of CFS) remained independently associated with 28-day mortality after adjustment for cardiovascular risk factors and stroke severity (OR 1.03 (1.01–1.05) for each one-point increase in CFS) (Table 2).

Outcome after thrombolysis

The thrombolysed subgroup (63 individuals: 36 non-frail and 27 frail) showed no significant difference in baseline median NIHSS between non-frail and frail cohorts (12.5 (interquartile range [IQR] 7–16.25) versus 15 (IQR 8–19.5), $P = 0.17$), but 24-h median NIHSS differed significantly between non-frail and frail cohorts following thrombolysis (5 (IQR 1.75–12.25) versus 16 (IQR 4.5–21), $P < 0.01$), indicating a significant improvement in NIHSS in the non-frail $P < 0.01$) but not in the frail cohort $P = 0.23$). After adjustment for cardiovascular risk factors, door-to-needle time and baseline stroke severity, each one-

Table 1. Clinical characteristics for all ischaemic strokes.

	Non-frail (CFS 1–4)	Frail (CFS 5–8)	Significance
Number	199	234	
Median baseline NIHSS (IQR)	3 (1–7)	4.5 (1–12)	$P = 0.14$
Median age (IQR)	83 (77–86)	87 (83–92)	$P < 0.01$
Male sex	103 (51.8%)	87 (37.2%)	$P < 0.01$
Hypertension	129 (64.8%)	152 (65.0%)	$P = 0.98$
Diabetes mellitus	40 (20.1%)	48 (20.5%)	$P = 0.92$
Ischaemic heart disease	44 (22.1%)	50 (21.4%)	$P = 0.54$
Atrial fibrillation	92 (46.2%)	119 (50.9%)	$P = 0.34$
Thrombolysed	36 (18.1%)	27 (11.5%)	$P = 0.05$
28-day mortality	10 (5.0%)	39 (16.7%)	$P < 0.01$

Table 2. Logistic regression for 28-day mortality for all ischaemic strokes.

	Odds ratio (95% CI)	Significance
CFS	1.03 (1.01–1.05)	$P < 0.01$
Baseline NIHSS	1.01 (1.001–1.02)	$P = 0.03$
Thrombolysis	0.82 (0.70–0.95)	$P = 0.01$
Age	1.00 (0.99–1.01)	$P = 0.26$
Male sex	0.72 (0.28–1.87)	$P = 0.50$
Hypertension	0.94 (0.88–1.01)	$P = 0.11$
Diabetes mellitus	1.04 (0.95–1.13)	$P = 0.43$
Atrial fibrillation	1.07 (0.97–1.17)	$P = 0.18$

Table 3. Linear regression model for interval NIHSS change (Intercept −10.03) in the thrombolysed subgroup. The intercept represents a 10.03 point improvement in NIHSS following thrombolysis, with positive coefficients representing attenuated NIHSS improvement and negative coefficients larger NIHSS improvement.

Interval NIHSS change		
	Coefficient	Significance
CFS	1.07	$P = 0.03$
Diabetes mellitus	4.65	$P = 0.04$
Age	0.03	$P = 0.82$
Male sex	0.23	$P = 0.88$
Hypertension	0.26	$P = 0.87$
Atrial fibrillation	−0.24	$P = 0.88$
Baseline NIHSS	−0.06	$P = 0.63$

point increase in the CFS attenuated the NIHSS improvement by 1.07 points (i.e. NIHSS improvement of 8.96 for CFS 1, 7.89 for CFS 2, 6.82 for CFS 3, etc.) (Table 3).

There was no statistically significant association between CFS and premorbid mRS ($r_s = 0.21$, $P = 0.09$).

Discussion

Clinical frailty is independently associated with 28-day mortality after acute ischaemic stroke. Furthermore, frailty appears independently associated with reduced improvement in NIHSS following stroke thrombolysis.

The mechanism by which frailty influences stroke outcome, particularly death, is poorly understood. Frailty is associated with a range of factors affecting cerebrovascular health, including hypertension, ischaemic heart disease, diabetes, atrial fibrillation and reduced anticoagulant prescribing for atrial fibrillation [3, 9–11]. However, our results indicate clinical frailty was independent of conventional vascular risk factors, suggesting that a global reduction in physiological reserve may account for the poorer outcomes following ischaemic insult. To what extent frailty may include a loss of 'cerebrovascular reserve' to survive an insult is unclear.

The observed effect of frailty was modest but cumulative. Only a few studies have considered the link between frailty and stroke and typically considered longer-term functional outcomes. Reduced ability to perform activities of daily living (as a surrogate of frailty) was associated with poorer functional outcome and higher risk of institutionalisation following stroke at 6 months [12]. Pre-stroke frailty has also been implicated as an independent moderator of post-stroke cognition [13]. The 6 -min walk test independently predicts death following stroke [14]. Similarly, reduced premorbid grip strength and walking speed were associated with both cognitive decline and death after stroke, although stroke severity was not considered [15]. However, assessments such as the 6 -min walk test and grip strength are impractical in the setting of acute stroke and cannot be obtained retrospectively. In contrast, CFS assessment of premorbid frailty was feasible in the acute setting in our 'real world' cohort.

In our study, there was no explicit use of the CFS to guide thrombolysis decisions given the unknown association with outcomes. However, a holistic assessment of the individual will have been made at the time of thrombolysis assessment and will include consideration of some features inherent to clinical frailty, such as premorbid function and co-morbidities. However, the approximate even division between frail and non-frail individuals receiving thrombolysis suggests frailty did not stop thrombolysis. Our results indicate that an active consideration of frailty may help inform prognostication.

The finding of no statistically significant association between CFS and mRS is notable and may be due to several considerations. Although previous work found reasonable agreement between these scales in a small cohort, there remained some discrepancy between frailty and disability/dependence. [16] In our cohort of typically older frailer individuals, this discrepancy may have been more pronounced. Alternatively, our limited sample size

may have failed to detect the relationship. Replication in a larger sample would be advantageous in elucidating this relationship and may have implications for how pre-stroke function is assessed for eligibility in research studies.

A strength of this study is the use of "real world" clinical data to give a more representative impression of the clinical trajectory of older individuals presenting with stroke typically seen in clinical practice, in contrast to research populations where older frailer individuals are typically excluded. However, it is not without limitations. Although there was no significant difference in stroke severity at admission, repeat NIHSS at 24 h was only collected for the thrombolysed subgroup. Consequently, it is impossible to conclude whether frailty was associated with changes in stroke severity in those not thrombolysed in the acute setting. We did not classify cause of death, although in this setting we feel that the early mortality outcome after stroke represents an important consideration in the clinical management of the frailer stroke patient, regardless of the actual cause of death. Finally, the limited study size (particularly in the thrombolysed subgroup) means that these findings would benefit from replication in a larger prospective study or meta-analysis.

Conclusion

The predicted rise in the prevalence of frailty within the total population poses a challenge for stroke services, especially in an era of increasingly interventional approaches. Elucidating how frailty influences early mortality and neurological recovery may benefit prognostication, clinical decision-making and service provision. Furthermore, clinical frailty represents an important but overlooked variable in stroke research that is distinct from chronological age. We advocate the importance of including measures of frailty to further quantify, support and inform future research and clinical practice.

Declaration of Conflicts of Interest: None.

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