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 Clinical Rehabilitation

**The prevalence of frailty amongst acute stroke patients, and
evaluation of method of assessment**

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Abstract

Objective: We aimed to determine prevalence of pre-stroke frailty in acute stroke and describe validity of a Frailty Index based assessment.

Design: Cross-sectional.

Setting: Single, UK, urban teaching hospital.

Subjects: Consecutive acute stroke unit admissions, recruited in 4 waves (May 2016-August 2018). We performed assessments within first week and attempted to include all admissions.

Main Measures: Our primary measure was a Frailty Index, based on cumulative disorders. A proportion of participants were also assessed with the 'Frail non-disabled' questionnaire. We evaluated concurrent-validity of Frailty Index against variables associated with frailty in non-stroke populations. We described predictive validity of Frailty Index for stroke severity and delirium. We described convergent validity, quantifying agreement between frailty assessments and a measure of pre-stroke disability (modified Rankin Scale) using Kappa statistics and correlations.

Results: We included 546 patients. A Frailty Index defined frailty syndrome was observed in 427/545 (78%), of whom, 151/545 (28%) had frank frailty and 276/545 (51%) were pre-frail. Phenotypic frailty was observed in 72/258 (28%). We demonstrated concurrent-validity via significant associations with all variables (all $p < 0.01$). We demonstrated predictive-validity for stroke severity and delirium ($p < 0.01$). Agreement between the frailty measures was poor (Kappa=-0.06), convergent-validity was moderate (Frail non-disabled 'Cramer's V'= 0.25; modified Rankin Scale 'Cramer's V'=0.47).

Conclusions: Frailty is present in around 1 in 4 patients with acute stroke; if pre-frailty is included, then a frailty syndrome is seen in 3 out of 4 patients. The Frailty Index is a valid

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3 measure of frailty in stroke; however, there is little agreement between this scale and other
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5 measurements of frailty.
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For Peer Review

The prevalence of frailty amongst acute stroke patients, and evaluation of method of assessment

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Running title: Frailty in stroke.

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Tables and Figures:

Table 1. Population demographics

Table 2. Correlations between pre-stroke variables and Frailty index

Table 3. Regression analysis of the association of the Frailty index with stroke severity (NIHSS) and odds of post-stroke delirium onset

Table 4. Agreement between frailty/disability measures

Figure 1. Frailty and disability overlap based on method of assessment

Key words:

Stroke, frailty, prevalence, assessment

Introduction

Stroke and frailty are prevalent conditions in the elderly and are associated with mortality, long-term hospitalisation, and disability.¹⁻⁶ Frailty assessment is increasingly being incorporated into routine practice in the acute care setting.⁷ However, the prevalence of frailty and methods for frailty assessment are largely unstudied in the acute stroke population.

Frailty is widely recognised as a clinical condition; however, there is currently no universally accepted operational definition. The two predominant positions on the frailty concept are the Rockwood ‘accumulated deficits’ and the Fried ‘frailty phenotype.’^{8,9} The Rockwood model defines frailty as a state of heightened risk of adverse health that is a by-product of the accumulation of age-related health conditions. The Fried model frames frailty as a biological syndrome characterised by common factors including weight loss, exhaustion, slow mobility, limited physical activity and weakness. In addition to frank frailty, there is also a potential state of ‘pre-frailty’, defined as a state of heightened risk for becoming frail but not currently considered frail.

There are variable methods of frailty assessment, depending upon the definition applied. A Frailty Index can be calculated as a measure of cumulative deficits.¹⁰ Alternatively, the frailty phenotype can be detected via self-report questionnaire.¹¹ These two approaches are validated in older adults and increasingly used in clinical practice and research. However, neither assessment has been adequately validated in stroke. In stroke, pre-stroke function is often measured using the modified Rankin Scale. This has been used as a proxy of frailty but was never designed for this purpose and is not well suited to describing the pre-stroke state.¹²

Given the frailty state’s association with adverse outcomes,¹³ it is important to establish frailty prevalence and validate the predominant means of assessment within the stroke population.

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3 We aimed to describe the prevalence of pre-stroke frailty in a ‘real world’ acute stroke setting
4 and validate a commonly used method for determining frailty status. Our primary focus was
5 frailty assessment using the Rockwood Frailty Index approach. We then assessed concurrent,
6 predictive and convergent validity of the Frailty Index. To allow comparison, we also
7 assessed frailty as measured by a phenotypic (Fried) approach and using the modified Rankin
8 Scale as a pre-stroke disability assessment.
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20 **Method**

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23 We conducted a cross-sectional analysis, based on prospectively collected anonymised
24 patient level data. Full NHS research ethics approval was granted for this project
25 (ws/16/0001). The design, conduct and reporting of this study was informed by the STROBE
26 (Strengthening the Reporting of Observational Studies in Epidemiology)¹⁴ and STROND
27 (Standards of Reporting of Neurological Disorders) guidance.¹⁵ The data that support the
28 findings of this study are available from the corresponding author upon reasonable request.
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38 We recruited patients consecutively admitted to the acute stroke unit at a single urban
39 teaching hospital. The unit is part of a nationally funded healthcare service and admits all
40 suspected and confirmed stroke and transient ischaemic attack (TIA) patients and operates no
41 exclusions around age, disability or comorbidity.
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48 Patient recruitment occurred in 4 waves, chosen to ensure no confounding from temporal
49 variation in stroke case-mix: wave 1 was from May 2016 to Feb 2017; wave 2 from April to
50 June 2017; wave 3 from October to December 2017; and wave 4 July 2018 to August 2018.
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54 All patients with stroke were included. Our approvals allowed for inclusion of patients who
55 were unable to consent to assessment.
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3 Clinical and demographic data were collected for each patient at point of assessment by
4 trained researchers. Assessments occurred on day of admission up to 5 days after admission.
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6 Data collected were a mix of prospective assessment and retrospective chart review. Pre-
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8 stroke functioning was established using modified Rankin Scale;¹⁶ where a cut-off of ≥ 2 was
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10 used to define disability. In addition, stroke severity was determined by National Institutes of
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12 Health Stroke Scale (NIHSS);¹⁷ pre-stroke cognitive impairment and post-stroke delirium
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14 were assessed by stroke physicians guided by the informant section of the General
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16 Practitioner cognitive assessment¹¹ (cut-off ≥ 3 used to identify pre-stroke cognitive
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18 impairment) and the '4 A's test' (www.the4AT.com) (cut-off ≥ 4 used to identify possible
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20 delirium). Age, medication count, and pre-stroke care-home residence were established via
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22 medical notes.
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29 We used two methods for assessment of pre-stroke frailty; one conformed to the Rockwood
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31 accumulated deficits concept, the other to the Fried 'frailty phenotype' model. Based on the
32
33 former, a 33-item Frailty Index was created according to recommended guidelines.¹⁹ (see
34
35 supplementary materials figure S1) Patient medical records were used to identify medical
36
37 conditions present before the stroke. Frailty Index scores were then generated for all patients
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39 by two researchers (MT and GC). We created a list of 33 frailty indicator conditions,
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41 symptoms or problems. The Frailty Index was created by dividing the number of pre-
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43 specified conditions on our list that were present before the stroke by the total number of
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45 conditions defined in the index list (i.e. 33). Thus, possible scores ranged from 0.0-1.0, with
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47 scores closer to 1.0 suggesting greater frailty. Patients were categorised as 'robust', 'pre-
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49 frail' and 'frail' using recommended cut-points of < 0.08 ; $0.08-0.24$ and > 0.24 , respectively.²⁰
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54 An assessment of Fried phenotype frailty was added to the prospective dataset after first wave
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56 data collection was complete. We used the self-report 'Frail non-Disabled' questionnaire.²¹
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58 This frailty assessment method was introduced to complement (and did not replace) the
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3 Frailty Index assessment method. Patients were categorised as frail if they and/or a proxy
4 reported any one of the following: unintentional loss of more than 4kg of weight over the
5 previous year; self-reported exhaustion for more than two days in the week before admission;
6 less than 4 hours of physical activity over a 2-week period before admission. Patients who
7 could not fully complete the self-report Frail non-Disabled questionnaire for any reason (e.g.
8 unconscious, too confused, severely aphasic) were deemed non-testable.
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20 *Analyses*

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23 For analysis of prevalence of pre-stroke frailty, we performed a sample size calculation,
24 based on expected prevalence of 15% and error of 0.05; we required a minimum of 196
25 participants, to give us an estimate of prevalence with 95% confidence.
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31 We described prevalence of 'frailty', 'pre-frailty' and 'robust' status based upon observed
32 percentages within the population; confidence intervals were generated for each prevalence
33 estimate via z-tests. As Frail non-Disabled questionnaire data were only available for a
34 proportion of patients, we conducted a post-hoc logistic regression analysis with Frail non-
35 Disabled (testable/untestable) as the dependent variable and stroke severity (NIHSS score) as
36 the independent variable to examine cause of missing frailty phenotype data.
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45 To evaluate the Frailty Index as a measure of frailty in stroke we conducted a series of
46 validity assessments. We assessed concurrent validity by exploring associations between
47 Frailty Index and a series of factors plausibly related to frailty: age, sex,²² number of
48 medications, pre-stroke cognitive impairment and care home residence. We used Spearman's
49 correlation for continuous variables and Chi-square for dichotomous variables.
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57 We assessed predictive validity of the Frailty Index as a measure of pre-stroke frailty based
58 on associations with a common complication of stroke that frail patients are typically
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3 vulnerable to—post-stroke delirium. We used a logistic regression analysis with incident
4 delirium as the dependent variable and score on Frailty Index as the independent variable. As
5 frail patients are generally vulnerable to acute stressors, we also examined if pre-stroke frailty
6 was associated with stroke severity (NIHSS) using linear regression analysis with score on
7 NIHSS as the dependent variable and Frailty Index as the independent variable. We then used
8 multiple regression analyses, controlling for age, sex, and number of medications to further
9 explore the associations between scores on the Frailty Index and delirium and stroke-severity.
10 All variables were forced into the regression model.
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22 We assessed convergent validity describing Chi-square correlation between Frailty Index
23 (dichotomised: frail/non-frail), phenotypic frailty (dichotomised: frail/robust) and pre-stroke
24 modified Rankin Scale (dichotomised: disabled/non-disabled). We also explored agreement
25 between the measures using Kappa statistics; and overlap in frailty assessment results were
26 compared for the differing frailty measures via 2x2 tables and Venn diagram.
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34 We used SPSS statistics for Windows, version 24.0, Armonk, NY: IBM Corp, for all
35 analyses.
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43 **Results**

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45 Five-hundred-forty-six patients were included. Population descriptive statistics can be seen
46 in Table 1.
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50 ***Frailty prevalence***

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52 Frailty Index data were available for 545/546 (99.8%) patients of whom 151/545 (28%; 95%
53 Confidence Intervals [CI]:24%-31%) were frail according to Frailty Index. A further 276/545
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3 (51%) were pre-frail and 118/545 (22%; 95%CI:46%-55%) were robust. Median Frailty
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5 Index score was 0.18 (Inter Quartile Range [IQR]=0.09-0.26).
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8 Phenotypic frailty data were available for 258/347 patients; 89/347 (26%) patients' full data
9
10 were missing due to inability to complete the Frail non-Disabled questionnaire. Of patients
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12 with data available, 72/258 (28%; 95%CI= 23%-34%) were frail. Our post-hoc logistic
13
14 regression analysis indicated that more severe strokes were associated with non-completion
15
16 of the Frail non-Disabled questionnaire (Odds Ratio [OR]=1.21, 95%CI=1.13-1.29; p<0.01).
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19 (See supplementary materials table S2)
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22 ***Concurrent validity***

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26 Frailty Index scores were significantly associated with all our pre-specified pre-stroke
27
28 variables. Specifically, older patients, women, patients on higher numbers of medication,
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30 patients with pre-stroke cognitive impairment, and patients in a care home had significantly
31
32 higher Frailty Index scores. Strength of correlations are described in Table 2.
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35 ***Predictive validity***

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38 Frailty Index was significantly associated with both the NIHSS (Unstandardised Beta=0.085,
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40 95%CI=0.046-0.125; p<0.01) and incident delirium (OR=1.06, 95%CI=1.04-1.08; p<0.01)
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42 on univariate analysis. Specifically, as Frailty Index scores increased so too did NIHSS
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44 scores and odds of delirium. However, after controlling for age, sex and medication count,
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46 only the association between Frailty Index and delirium remained borderline significant
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48 (OR=1.03, 95%CI=1.00-1.05; p=0.05). (Table 3)
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52 ***Convergent validity***

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55 For the 258 patients with Frail non-Disabled questionnaire data available, the Frailty Index
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57 demonstrated a moderate positive correlation with the Frail non-Disabled questionnaire
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3 (X²=15.76; Cramer's V=0.25). Similarly, for the 524 patients with pre-stroke modified
4 Rankin scale data available, the Frailty Index demonstrated a moderate correlation with the
5 pre-stroke modified Rankin scale (X²=116.55; Cramer's V=0.47).
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10 There was only slight agreement between Frailty Index and phenotypic frailty (kappa=-0.06)
11 with just 16/81 (20%) frail patients categorized as frail on both frailty measures. (Table 4)
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13 For Frailty Index and pre-stroke modified Rankin Scale, agreement was moderate
14 (kappa=0.45) with 110/216 (51%) patients classified as disabled according to pre-stroke
15 modified Rankin Scale also classified as frail according to the Frailty Index. There was only
16 slight agreement between phenotypical frailty and modified Rankin Scale (kappa=-0.02) with
17 28/68 (41%) patients classified as phenotypically frail being classified as disabled according
18 to the modified Rankin Scale. (Figure 1)
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33 **Discussion**

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35 We sought to investigate the prevalence of frailty in stroke. We found that almost 80% of
36 patients admitted to an acute stroke unit were either frail or prefrail according to Frailty Index
37 criteria. Both the Frailty Index and frailty phenotype approach gave respective prevalence
38 rates of 28%. These rates contrast with the 14% rate reported within a non-stroke hospital
39 population and the 11% prevalence reported in community settings.^{23,24} Our results suggest
40 that frailty presents a particularly significant burden in stroke, beyond what is typically
41 observed in undifferentiated older adult populations. The pre-frail categorisation is
42 contentious, but that more than half of our sample were considered pre-frail before the stroke
43 is particularly relevant. These patients may be at risk of becoming frail following stroke,
44 with the stroke event pushing many across a threshold from 'pre-frail' to 'frail' status.
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3 There are different ways to measure frailty. We chose to primarily evaluate the Frailty Index
4 approach as this has been well validated in other acute settings and is being adopted in acute
5 care settings; we also anticipated that it would be available for the majority of stroke
6 admissions. Our intention was not to create a novel tool, rather we operationalised our
7 Frailty Index using the same process that was used to develop the electronic Frailty Index that
8 is being introduced in NHS England.²⁵
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17 Our concurrent validity analyses were reassuring, confirming Frailty Index associations with
18 variables previously demonstrated to be associated with frailty (age, sex, medication count,
19 pre-stroke cognitive impairment and care-home residence).^{20,24,26,27} The core concept in
20 frailty is vulnerability to an acute stressor, with adverse outcomes when the person is exposed
21 to acute illness or other insult. In this regard, our assessment of the association of frailty and
22 incident delirium offers the most compelling validation, as delirium is considered an
23 exemplar manifestation of the frailty state.
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34 Our comparative analyses suggest that method chosen for assessing frailty in stroke is
35 important. There were only modest correlations between the Frailty Index, the phenotype
36 measure and pre-stroke modified Rankin Scale. Similar correlations were found by
37 Rockwood's group in an earlier paper.²⁰ Although prevalence rates suggested by our two
38 frailty measures were similar, there was little agreement regarding which patients were
39 classified as frail: only 20% of frail patients were categorised as such by both frailty
40 measures and kappa based measures of agreement were little better than chance. These
41 findings may be partly explained by non-completion bias for the phenotype measure,
42 although previous studies have also highlighted issues with frailty identification based upon
43 definition and assessment methods used. As few as 9.4% of frail patients were categorised as
44 such by both a frailty phenotype and Frailty Index measure in one study;²⁸ while others
45 reported that 30% of patients categorised as frail by an Frailty Index were categorised as
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3 'robust' according to a Fried phenotype measure.²⁶ This lack of agreement likely reflects the
4 differences in the respective concepts of frailty that are applied by our two measures. Our
5 analyses are not designed to suggest a favoured approach to frailty assessment. An important
6 assessment in this regard would be to compare post-stroke outcomes according to frailty
7 defined using differing models and this could be the basis for future research around stroke
8 and frailty.

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10 We have conducted a highly inclusive study with sequential recruitment involving patient
11 groups (e.g. aphasic, acutely unwell, physically disabled, cognitively impaired) that are
12 typically excluded from stroke studies. We have also incorporated frailty measures assessing
13 the two predominant frailty concepts.

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15 However, there are some important limitations to our study. First of all, while inclusive, our
16 population was restricted to a single urban teaching hospital that admits a largely
17 socioeconomically deprived and Caucasian population. As such, our frailty prevalence rates
18 may not be generalisable to settings with a very different case-mix.²⁹ Our measure of the
19 frailty phenotype may be more indicative of frailty symptoms rather than full phenotypical
20 frailty per se. Moreover, this measure was introduced during study recruitment and could
21 have been biased by missing data. Finally, our comparisons between 'phenotypic' and
22 'cumulative deficits' frailty models should recognise that the two measures were never
23 designed to be equivalent. The Frail non-Disabled scale is intended to be used as a screening
24 tool and its properties will differ from a Frailty Index, which is said to be diagnostic.

25
26 The timely, accurate and acceptable identification of frailty in practice is a current clinical
27 priority.^{30,31,32} Advances have been made in frailty assessment in community, care-home and
28 older adult secondary care settings, but it is equally important to determine the most suitable
29 methods of assessing frailty in stroke. Our results are not definitive and further

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3 epidemiological and validation work around frailty assessment and stroke is required. While
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5 it would be premature to make recommendations around practice or policy based on our data,
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7 we can offer cautious suggestions. The high prevalence of frailty and pre-frailty reminds us
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9 that vulnerable, older adults are core business in stroke-care. There is a danger that this may
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11 be forgotten in the move towards increasingly aggressive interventional strategies for acute
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13 stroke. The relationship of frailty with the complication of incident delirium may suggest
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15 that a brief frailty assessment could become part of the initial 'work-up' in stroke. This
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17 would mirror changes in practice in other healthcare settings where front-door frailty
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19 screening is being introduced.
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24 Our results have implications for research. Pre-stroke modified Rankin Scale is often used as
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26 exclusion criterion or case-mix adjustor in stroke trials. The modified Rankin Scale was
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28 never designed for this purpose and previous studies have suggested it may not be the best
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30 measure as it may both under and over-estimate function.³³ Using a simple measure of frailty
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32 as a baseline measure in trials could improve efficiency and our data suggest that assessing a
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34 Frailty Index is relatively simple in an inpatient stroke population.
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39 Future studies of frailty in stroke should offer longitudinal follow-up to determine the longer-
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41 term prognostic validity of frailty measures. Frailty has previously been associated with
42
43 long-term prognosis in older adult populations.³⁴ It is highly likely that this will also be the
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45 case in the stroke population; hence, this is an important area for future research. Finally, our
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47 work suggests that different tests of frailty may be assessing differing constructs. We now
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49 need more comparative studies of the different frailty measures (and concepts) when used in
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51 the stroke population.
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59 **Conclusions**

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3 The prevalence of frailty in acute stroke is substantial; the condition appears to exist, before
4 the stroke occurs, in around one in every four patients, or around three out of every four
5 patients if pre-frailty is included. Identification of frailty may be influenced by assessment
6 method employed. Our results suggest that the Frailty Index approach is valid for use in
7 stroke and can be employed for assessment of almost all stroke patients; albeit, it has limited
8 agreement with other measures of frailty. More research is needed to describe the optimal
9 method of assessing frailty and the prognostic and treatment implications when a frailty
10 diagnosis is made in stroke.
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25 **Clinical Messages**

- 26 • **Frailty exists in around one-quarter of all stroke patients.**
 - 27 • **A Frailty Index based assessment is valid in acute stroke settings and can be**
28 **completed for almost all stroke patients.**
 - 29 • **Identification of which stroke patients are frail will differ substantially based**
30 **upon the assessment method employed.**
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Conflicts of interest

None.

Author Contributions

MT and TQ conceived the study. MT, TQ, and GC drafted the paper. MT, GC, TQ, RS, BD, RK, and EE contributed to patient assessment and recruitment. DS contributed to data interpretation and supervision. All authors contributed to writing.

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TABLES

Table 1. Population demographics

	(Total included=546)
Age (Years) (Mean; S.D.)	69 (14)
Sex (Male) (Number; %)	290/540 (54%)
National Institutes for Health Stroke Scale (Median; IQR)	3 (1-5)
Pre-stroke modified Rankin Scale ≥ 2 (Number; %)	216/524 (41%)
Pre-stroke cognitive impairment (Number; %)	49/277 (18%)
Pre-stroke medication count (Median; IQR)	7 (4-10)
Pre-stroke care-home resident (Number; %)	21/546 (3.8%)
Post-stroke delirium* (Number; %)	138/523 (26%)

*Diagnosed based on stroke physician impression guided by the '4 A's test' using cut-point of ≥ 4 . S.D.= Standard deviation; IQR=Interquartile range.

Table 2. Correlations between pre-stroke variables and Frailty index

Variable	Frailty Index (Mean score)	Correlation (χ^2/Rho; p-value)
Sex (Female)	0.19	9.19;<0.01*
Sex (Male)	0.16	
Pre-stroke care-home resident (Yes)	0.31	30.92;<0.01*
Pre-stroke care-home resident (No)	0.17	
Pre-stroke cognitive impairment (Yes)	0.25	15.92;<0.01*
Pre-stroke cognitive impairment (No)	0.18	
Age (Years)	NA	0.54; <0.01 [#]
Medication count (Number)	NA	0.58; <0.01 [#]

*Analysed via Chi-square test (frailty dichotomised at >0.24); [#]Analysed via Spearman's Rho test (Frailty as continuous scale).

Table 3. Regression analysis of the association of the Frailty Index with stroke severity (NIHSS) and odds of post-stroke delirium onset.

Regression variable	NIHSS (Beta)*	(p)	Delirium (OR; 95%CI)%	(p)
Frailty Index (Score)	0.09	0.21	1.03 (1.00-1.05)	0.05
Age (Years)	0.21	<0.01	1.06 (1.04-1.08)	<0.01
Sex (Female)	-0.01	0.92	0.86 (0.54-1.37)	0.53
Medication count (Number)	0.01	0.93	1.01 (0.94-1.71)	0.85

*Linear regression; %Logistic regression. All variables were forced into the model.

NIHSS = National Institutes of Health Stroke Scale. Frailty entered as continuous variable.

Table 4: Agreement between frailty/disability measures

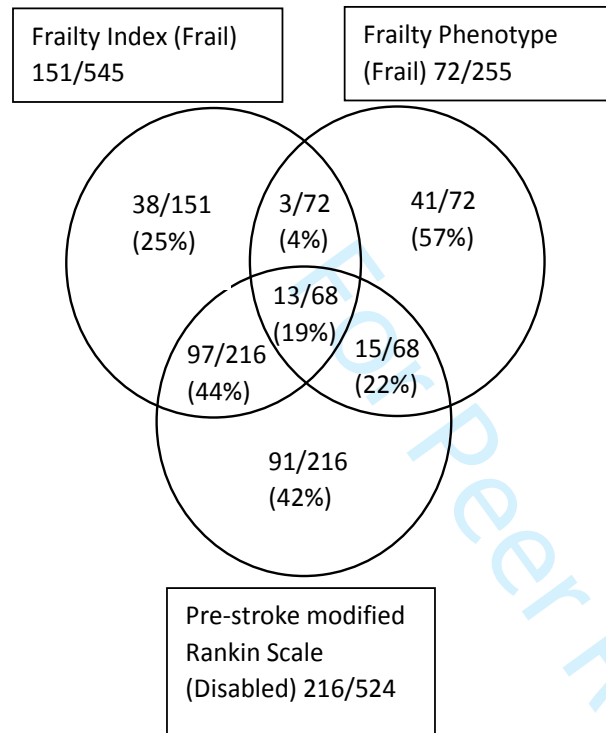
	Frailty index	Frail non-Disabled	Modified Rankin Scale
Frailty index		86	280
Frail non-Disabled	16		78
Modified Rankin Scale	111	28	

White cells correspond to frailty positive comparisons; grey scales to frailty negative comparisons. Frail non-Disabled: Frail Non-Disabled questionnaire.

For Peer Review

Figures

Figure 1. Frailty and disability overlap based on method of assessment



Frailty Prevalence supplementary materials

Supplementary material 1: Frailty Index

Frailty Index		
Depression	Haemoglobin (low)	Liver disease
Anxiety	Care-home resident	Peptic ulcer
Polypharmacy	Carers	Arthritis
Hypertension	Hearing aid	Impaired external ADL
Atrial Fibrillation	Sensory impairment (e.g.	Impaired ADL
Previous cerebrovascular	blind/deaf)	Mobility aid
disease	Continence bladder	Assistance walking
Diabetes	Continence bowel	Calcium
Vascular disease	Falls	Albumin (low)
Hyperlipidaemia	Fracture	High glucose
Heart failure	Chronic Obstructive	Renal failure
Previous Myocardial infarction	Pulmonary Disease	
	Cancer	

Supplementary material 2: Logistic regression output of the 'Frail Non-disabled' questionnaire and stroke severity (NIHSS)

		Variables in the Equation					95% C.I. for EXP(B)		
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Step 1 ^a	NIHSS	.189	.034	30.801	1	.000	1.208	1.130	1.292
	Constant	-2.534	.266	90.936	1	.000	.079		

a. Variable(s) entered on step 1: NIHSS.

* NIHSS= National Institutes of Health Stroke Scale