IMPACT OF PRE-STROKE FRAILTY ON OUTCOME THREE YEARS AFTER ACUTE STROKE: THE NOR-COAST STUDY

Munthe-Kaas, R[1,2]; Lydersen, S[3]; Quinn, TJ[4]; Aam, S[5,6]; Pendlebury, ST[7,8]; Ihle-Hansen, H[9,10]

1) Department of Medicine, Kongsberg Hospital, Vestre Viken Hospital Trust, Norway
2) Department of Medicine, Bærum Hospital, Vestre Viken Hospital Trust, Norway

3) Regional Centre for Child and Youth Mental Health, Faculty of Medicine and Health Science, NTNU-Norwegian University of Science and Technology, Trondheim, Norway, Department of Mental Health,
4) University of Glasgow, , Institute of Cardiovascular and Medical Sciences, Glasgow, United Kingdom
5) Department of Geriatric Medicine, Clinic of Medicine, St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway
6) Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Science, NTNU-Norwegian University of Science and Technology, Trondheim, Norway
7) Wolfson Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University Of Oxford,
8) NIHR Oxford Biomedical Research Centre, and the Departments of Acute Internal Medicine and Gerontology, John Radcliffe Hospital, Oxford, UK8) Institute of Clinical Medicine, University of Oslo, Oslo, Norway
9) Oslo University Hospital, Oslo, Norway, Department of Acute Medicine, Institute of internal medicine
10) University of Oslo, Norway. Center for medical ethics.

Abstract

Background

We aimed to explore the predictive value of pre-stroke frailty index (FI) on functional dependency and mortality three years after stroke.

Methods:

Based on the Rockwood 36-item FI score, we calculated the pre-stroke FI from medical conditions recorded at baseline in the multicenter prospective Nor-COAST study 2015-2017. Participants with a FI score and a modified Rankin scale (mRS) 0-6 three years post-stroke were included in this study.

We used logistic regression analysis with unfavourable mRS (over 2 vs 0-2) at 3 years, or dead within 3 years, as dependent variable, and frailty and pre-stroke mRS, one at a time, and simultaneously, as predictors. The analyses were carried out unadjusted, and adjusted for the following variables one at a time: Age, sex, years of education, NIHSS at admission, infections treated with antibiotics and stroke progression. We report OR per 0.10 increase in FI.

Results:

At baseline, the 609 included patients had mean age 72.8 (SD 11.8), 261 (43%) were females, and had a FI mean score of 0.16 (SD 0.12), range 0 to 0.69. During three years, 138 (23%) had died. Both the FI, and pre-stroke mRS, were strong predictors for unfavorable mRS (OR 4.1 and 2.7) and dead within 3 years (OR 2.2 and 1.7). The OR for pre-stroke mRS decreased relatively more than the OR for FI when entered as predictors simultaneously. FI was a strong predictor (OR=4.1, 95% CI 3.2 to 5.2) for unfavorable outcome post-stroke. Only adjusting for age (OR=2.8, CI 2.2 to 3.6) affected the results. FI was also a strong predictor for death within three years (OR=2.2, CI 1.8 to 2.7), adjusted for age and sex. Adjusting for any of the other listed variables gave approximately the same results.

Conclusions:

As a strong predictor of poor outcome, FI can be included in prognostication after stroke.

Clinical Trial Registration: ClinicalTrials.gov Identifier: NCT02650531

Background:

Stroke is an acute condition prevalent in older populations and those with multiple long term conditions. Mortality and disability are common after stroke, despite advances in emergency treatment. With more older adults surviving previously fatal strokes, it is important to consider longer term functional outcomes (1).

There is substantial heterogeneity in outcome after stroke, even in milder strokes. The mechanism causing this heterogeneity, and predictors of outcome are uncertain. While increasing age is generally associated with poor outcome, the individual relationships of age and outcome are highly variable (2). Also common ~~, but feared,~~ complications in the acute phase of a stroke, ~~like~~ such as urinary tract infections, pneumonia or stroke progression~~s~~ may significantly impact stroke recovery, especially in older adults (3).

Over recent years the frailty concept has gained international attention, and is central to research, practice and policy in Geriatric Medicine (4). We define frailty as a state of vulnerability with an increased risk of adverse health outcomes (5). Despite differing operational definitions, there is an agreement in three aspects; 1) frailty is a multidimensional concept, including both physical and psychosocial factors , 2) frailty is not the same as normal ageing, and 3) it is a dynamic state, with possibility to intervene to prevent or reverse frailty (6). Frailty measures can support decision making in treatment of older patients, and objective assessment with a frailty scale is preferred over clinical judgement for predicting adverse treatment outcome (7).

As stroke is common in older adults, the interaction between frailty and stroke should be of interest. However, frailty assessment is not yet part of routine stroke care (6). Recent reviews suggest that one in four acute stroke patients ~~were~~ is frail pre-stroke, but there i~~wa~~s substantial uncertainty in this estimate, with short term follow-up and high risk of bias (1). Thus, there is a need for further large, robust, and long-term studies of frailty prevalence and outcomes in an acute stroke population.

Aims:

We aimed to explore the predictive value of pre-stroke frailty, measured using frailty index (FI), on functional dependency and mortality three years after stroke, and compare it with the predictive value of pre-stroke modified Rankin Scale (mRS). As frailty increases vulnerability for both acute stressors and adverse outcome, we assessed for and included stroke related complications of stroke progression and infections treated with antibiotics in the acute phase.

Methods:

The Nor-COAST study, a multicenter observational study, recruited consecutive participants in the acute phase of stroke from five Norwegian stroke units 2015-2017, and followed them for three years. The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REK) North, (REC number 2015/171) (7). If participants were unable to give informed written consent, a family proxy was approached.

We assessed the demographic characteristics: age, sex and years of education, vascular risk factors, National Institutes of Health Stroke Scale (NIHSS) score, acute stroke progression (defined as neurological progression during acute phase YES/NO), and infections treated with antibiotics, at baseline (8).

Trained study nurses assessed the level of global function pre-stroke by mRS, a seven-level scale running from zero up to six, representing the entire range of functional outcomes from no symptoms to death (9), by an unstructured interview.

Based on the Rockwood 36-item FI score (10), we generated pre-stroke FI from medical conditions recorded at baseline (11). We followed best practice in the creation of the index list (12). The FI is not a dichotomized scale, however Rockwood and colleagues have described that 0.25 can be an empirical cut-off between fit and frail (13). For a *descriptive presentation*, the participants were

categorized as ‘fit’ if FI was below 0.12, ‘mild’ if FI was between 0.12 and 0.24, ‘moderate frail’ if FI was between 0.24 and 0.36, and ‘severe frail' if FI was higher than 0.36 (14).

Participants with both a FI score and a mRS at three years were included in the study.

Statistical analyses

We used logistic regression running analyses with either dichotomized unfavorable mRS over 2 versus 0-2, or death before three years as the dependent variable. We assessed pre-stroke frailty and/or pre-stroke mRS as the main covariate. This was done unadjusted, and adjusted for the following variables one at a time: age, sex, education, NIHSS, stroke progression and infections.

We reported odds ratios (OR) per 0.10 increase in the pre-stroke frailty score FI.

Further, we assessed the predictive values of pre-stroke mRS and FI by the area under the receiver operating characteristic (ROC) curve (AUC). Added value of FI compared to pre-stroke mRS in terms of increased AUC were estimated by using the “somersd” command in the add-on package snp15_7 in Stata 16. This method takes into account that part of pre-stroke mRS was included in the FI, and these are associated, as described in earlier work (11).

Missing values were handled using available case analysis, that is, in each analysis, we included all patients with data on the variables in that analysis. Where relevant, 95% confidence intervals (CI) were reported, and we regarded a two-sided p-value<0.05 to represent statistical significance.

Results:

Of 815 patients in Nor-COAST, 609 had both FI at baseline and mRS after three years and were included (Fig 1). Mean age was 72.8 years (SD 11.8), 261 (43%) were females, mean FI score was 0.16 (SD 0.12), range 0 to 0.69 (Table 1). During three years, 138 (23%) had died. Mean pre-stroke mRS was 0.95 (SD 1.15), mean stroke severity was NIHSS 4.6 (SD 6.2), 48 (8%) had progression in stroke in acute phase and 99 (16%) had an infection treated with antibiotics during acute stay (Table 1).

In the study population, 277 (45%) were fit at baseline (FI grade <0.12), 200 (33%) had a mild frailty (FI 0.12-0.24), 72 (12%) had moderate frailty (FI 0.24 to 0.36) and 60 (10%) were categorized as severely frail (FI >0.36). Patients with higher grade of frailty pre-stroke had a lower functional status post-stroke or had died at three years (Table 2, Figure 2), observed for all levels of frailty.

Both FI, and pre-stroke mRS, were strong predictors for unfavorable mRS (OR 4.09 and 2.70) and death within 3 years (OR 2.22 and 1.67)(Table 3). When FI and pre-stroke mRS were entered as predictors simultaneously, the OR for pre-stroke mRS decreased relatively more than the OR for FI.

FI was a strong predictor (OR=4.1, 95%CI:3.2 to 5.2) for unfavorable outcome post-stroke(Table 4). Only adjusting for age (OR=2.8, 95%CI:2.2 to 3) affected the result (Table 4). FI was a strong predictor for death before 3 years (OR=2.2, 95%CI:1.8 to 2.7), adjusted for age and sex. Adjusting for stroke progression or infections did not affect the result significantly. Any of the other prespecified variables gave similar results (Table 4).

When predictive values were measured, FI was a stronger predictor than pre-stroke mRS (Table 5), both for unfavorable mRS (AUC:0.847 vs 0.756) and death within 3 years (AUC:0.831 vs 0.754).

Discussion:

When assessing for the impact of pre-stroke frailty on function and mortality three years post-stroke, we found that frailty pre-stroke was a strong predictor for both functional status and mortality, even when we adjusted for important risk factors of stroke severity and age. While stroke complications like infections and stroke progression were common in the frail group, they did not explain the variability in outcomes. Patients with higher grade of frailty pre-stroke were overrepresented with lower functional status or death at three years. The relationship is clear and linearly associated. Both pre-stroke mRS and FI, are strong predictors of unfavorable outcomes. However, when comparing these two predictors, FI is the stronger predictor.

There is an increasing awareness of frailty as a predictor for poor outcome in the general hospital setting (4, 15, 16), with prevalence of frailty reported as up to 40% at mean age of 82 years (15). As there are~~is~~ rising numbers of patients living with frailty admitted to hospital, and given the dynamic nature of frailty, there is a need to better understand the consequences of frailty on prognosis. Our study population of stroke survivors showed all levels of frailty, with around one in four categorized as frail, which is in keeping with previous estimates (17).

The association between frailty and outcome after stroke is less studied than prevalence. A recently published paper demonstrated poor outcome after thrombectomy in stroke patients with pre-stroke frailty (18). According to our results, even without an emergency procedure such as thrombectomy, the outcome in patients with pre-stroke frailty is significant poorer than for fit older adults. The finding that poor outcome in frail stroke patients is independent of stroke severity is in keeping with general hospital cohorts where frailty is predictive irrespective of illness severity (15).~~–~~ However, our study excluded patients with expected survival of less than three month, probably those with highest grade of frailty.

Frailty measures are increasingly included to support decision-making in medicine. For transcatheter valve therapies, frailty assessment is included in the pre-procedural selection process, as studies have shown significantly higher mortality rates in frail patients (19). In oncology, frailty assessment has gained an important role, for guiding choice of treatment. The feasibility and tolerability of systemic cancer treatments in older patients can be improved by a preliminary geriatric assessment including frailty grade (20). As frailty measures in busy acute settings require short administration time screens, tools, like the Clinical Frailty Scale (CFS), may be most appropriate (15, 21).

In stroke medicine, the mRS is the most used assessment for pre-stroke functional status (22), however the tool was never intended for this purpose and has several limitations. When compared with other pre-stroke measures, the clinical properties of the pre-stroke mRS have, at best, modest validity (23, 24). The heterogeneity seen in older adults, is not considered thoroughly enough when assessed by mRS, which may be better reflected by measuring frailty (6). In this study, we demonstrated that both pre-stroke mRS and FI predict longer term outcome but when comparing the tools, FI was superior (Table 5), probably as it offers a more holistic assessment.

As demonstrated in this study, pre-stroke frailty is strongly associated with poorer outcome, and many other risk factors for poor outcome are of less importance. In stroke medicine, we should implement frailty measures as a routine tool for both prognostication and decision-making regarding treatment options in the acute phase. There is no established guideline for frailty assessment, timing, or choice of frailty assessments in stroke. Generating a FI can be time consuming, often derived in retrospect using several data sources, and thus probably not suitable for real time clinical decision making. While we recommend routine frailty screening in acute stroke, FI may be better suited to database and registry analysis while the CFS, which has a good evidence base in other acute settings, may be more feasible for real time assessment (15).

This study has limitations. FI pre-stroke was assessed post-hoc, as previously described (11). The CFS baseline was not collected in this study, and we lacked data to derive this. Another limitation is

assessment of pre-stroke mRS, this was not standardized and risks inter-rater reliability (24). As our study population had similar baseline characteristics, but better pre-stroke health and milder stroke, than the non-included stroke patients, the results may be more valid for patients who experience milder strokes (11, 25).

Strengths in this study were the high number of included acute patients, correction for important confounders and the longitudinal design with few lost to follow-ups.

Our results have implications for policy and practice. Stroke centers should implement routine frailty assessment, as frailty grade is such a strong predictor of outcome. Preventing frailty in older age should be an important public health goal, reducing vulnerability to age-related diseases and thereby improving outcomes and quality of life.

Conclusions:

FI is a strong predictor for poor outcome post-stroke and this tool, or other measures of frailty, should be included in prognostication after stroke.

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Figure legends

Figure 1: Flowchart

Figure 2: **Distribution functional status at three years based on frailty grade pre-stroke**