IMPACT OF PRE-STROKE FRAILTY ON OUTCOME THREE YEARS AFTER ACUTE STROKE:

THE NOR-COAST STUDY

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Short Title: IMPACT OF PRE-STROKE FRAILTY ON OUTCOME AFTER ACUTE STROKE

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Abstract

Introduction:

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, stroke severity at admission, infections treated with antibiotics and stroke progression. We report Odds Ratio (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). Only adjusting for age affected the result. The OR for pre-stroke mRS decreased relatively more than the OR for FI when entered as predictors simultaneously.

Conclusions:

FI is a stronger predictor than premorbid mRS for prognostication after stroke.

Introduction:

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 complications in the acute phase of a stroke, such as urinary tract infections, pneumonia or stroke progression 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]. There are many different scales for measuring frailty, which reflects the uncertainty regarding the optimal way to assess this syndrome. The Frailty Index (FI), developed by Rockwood and colleagues, describes frailty by measuring accumulated deficits across multiple systems such as comorbidity, physical function, nutritional status, and cognitive function [8, 9], and, based on the number of deficits, calculates a FI. When at least 30 variables are included, research has shown a remarkable robustness of this index for prediction of mortality [5]. A higher index indicates higher grade of frailty and predicts adverse

outcomes [10]. The FI is time-consuming to perform for clinicians, and Rockwood et al therefore developed another pragmatic (global) frailty tool, the Clinical Frailty Scale (CFS), scored using a nine-point scale based primarily on function [11], which is increasingly used in clinical work.
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 is frail pre-stroke, but there is 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.

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, Scandinavian speaking 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). 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 decided by the treating physician during acute stay YES/NO), and infections treated with antibiotics [12], during the acute stay [13].

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 [14], by an unstructured interview.

Based on the Rockwood 36-item FI score [10, 15], we generated pre-stroke FI from medical conditions recorded at baseline, as described in earlier work [16]. We followed best practice in the creation of the index list [16, 17]. 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 [18]. 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 [19].

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 separately adjusted for one of the following variables at a time: age, sex, education, NIHSS, stroke progression and infections. Additionally, we adjusted separately for one the above listed variables one at a time.

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 [16].

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). Among the 609 participants, 604 were Caucasian, one was African, one was Asian, and three had missing ethnicity. 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 1a, Table 2, Figure 2). Those not included were older, more women, and had a slightly higher FI at baseline than those included (Table 1 and Figure 1).

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 (OR 1.31 and 1.16) than the OR for FI (OR 3.46 and 2.01) (Table 3).

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:0.85 vs 0.76) and death within 3 years (AUC:0.83 vs 0.75).

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, 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, 20, 21], with prevalence of frailty reported as up to 40% at mean age of 82 years [20]. As there are 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 [22].

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 [23]. 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 [20]. 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 [24]. 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 [25]. As frailty measures in busy acute settings require short administration time screens, tools, like the Clinical Frailty Scale (CFS), may be most appropriate [11, 20, 26].

In stroke medicine, the mRS is the most used assessment for pre-stroke functional status [27], 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 [28, 29]. 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 [20].

This study has limitations. FI pre-stroke was assessed post-hoc, as previously described [16]. 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 [29]. 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 [16, 30]. The Nor-COAST study was only conducted in Norway so the generalizability to other populations may be limited.

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 preferred over pre-stroke mRS in prognostication after stroke.

Statements

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Statement of Ethics:

Ethics approval and consent to participate

The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REK) North, (REC number 2015/171). All methods were performed in accordance with the relevant guidelines and regulations.

Participants gave informed written consent; if unable to give consent, informed written consent was given by a family proxy.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

RMK were responsible for writing the present report with additional critical input from the co-authors. RMK, HIH and SL performed the statistical analysis. TQ, SA and STP contributed with critical input and knowledge, and all authors interpreted the data and read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to Norwegian legal regulations. Requests to obtain anonymized study data can be addressed to the corresponding author.

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Figure legends

Figure 1: **Flowchart**

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

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

Tables:

Table 1: Baseline characteristics	
Demographics	(N=609)
Mean/SD age, years	72.8/11.8
Female sex*	261 (42.9)
Mean/SD education, years	12.2/3.8
Mean/SD pre-stroke mRS	0.95/1.15
TOAST classification	(N=539)
Large-vessel disease	51 (9.5)
Cardioembolic disease	133 (24.7)
Small-vessel disease	105 (19.5)
Other etiology	17 (3.2)
Undetermined etiology	233 (43.2)
Assessments	(N=609)
Mean/SD NIHSS (0–42) at admittance **	4.6/6.2
mRS 0-2 at three years	385(63.2)
mRS over 2 at three years	224(36.8)
mRS 0 at three years	*118 (19.4)*
mRS 1 at three years	*152 (25.0)*
mRS 2 at three years	*115 (18.9)*
mRS 3 at three years	*54 (8.9)*
mRS 4 at three years	*25 (4.1)*
mRS 5 at three years	*7 (1.1)*
mRS 6 (dead) at three years	*138 (22.7)*
Mean/SD Frailty Index baseline	0.16/0.12
Frailty grade	(N =609)
Fit (FI < 0.12,)	277 (45.4)
Mild frailty (FI 0.12 to 0.24)	200 (32.8)
Moderate frailty (FI 0.24 to 0.36)	72 (11.8)
Severe frailty (FI > 0.36)	60 (9.9)
Complications during the acute phase	
Acute stroke progression†	48 (8.0)
Infection treated with antibiotics‡	99 (16.4)

SD = Standard deviation, mRS = modified Rankin Scale, TOAST = Trial of Org 10172 in Acute Stroke Treatment, NIHSS = National Institutes of Health Stroke Scale,

* *numbers are n (%), unless otherwise specified*

** *N=593*

† *N=597*

‡ *N=605*

Table 1a: Baseline characteristics for each frailty group					
	Total sample	Frailty grade			
Demographics	(N=609)	Fit [1] (n=277)	Mild frailty [2] (n=200)	Moderate frailty [3] (n=72)	Severe frailty [4] (n=60)
Mean/SD age, years	72.8/11.8	66.6/11.7	75.2/9.2	81.3/6.9	83.1/7.5
Female sex*	261 (42.9)	114 (41.2)	76 (38.0)	42 (58.3)	29 (48.3)
Mean/SD education, years	12.2/3.8	13.4/3.7	11.9/3.8	10.3/2.8	10.5/3.2
Mean/SD pre-stroke mRS	0.95/1.15	0.32/0.57	0.86/0.83	2.0/1.1	2.3/1.1
TOAST classification	(N=539)				
Large-vessel disease	51 (9.5)	19 (7.7)	17 (9.6)	10 (15.6)	5 (9.6)
Cardioembolic disease	133 (24.7)	52 (21.1)	45 (25.4)	18 (28.1)	18 (34.6)
Small-vessel disease	105 (19.5)	54 (22.0)	40 (22.6)	7 (10.9)	4 (7.7)
Other etiology	17 (3.2)	10 (4.1)	5 (2.8)	2 (3.1)	0 (0.0)
Undetermined etiology	233 (43.2)	111 (45.1)	70 (39.5)	27 (42.2)	25 (48.1)
Assessments	(N=609)				
Mean/SD NIHSS (0–42) at admittance **	4.6/6.2	3.8/5.6	4.8/6.2	5.3/6.7	6.7/7.5
mRS 0-2 at three years	385(63.2)	245 (88.4)	116 (58.0)	18 (25.0)	6 (10.0)
mRS over 2 at three years	224(36.8)	32 (11.6)	84 (42.0)	54 (75.0)	54 (90.0)
Mean/SD Frailty Index baseline	0.16/0.12	0.07/0.03	0.17/0.03	0.29/0.03	0.44/0.07
Complications in the acute phase					
Acute stroke progression†	48 (8.0)	15 (5.5)	15 (7.6)	8 (11.3)	10 (17.2)
Infection treated with antibiotics‡	99 (16.4)	29 (10.5)	32 (16.1)	15 (21.1)	23 (39.0)

SD = Standard deviation, mRS = modified Rankin Scale, TOAST = Trial of Org 10172 in Acute Stroke Treatment, NIHSS = National Institutes of Health Stroke Scale,

** numbers are n (%), unless otherwise specified*

***N=593*

†N=597

‡N=605

1 (FI < 0.12,), 2 (FI 0.12 to 0.24), 3 (FI 0.24 to 0.36), 4 (FI > 0.36)

Table 2: Distribution of Frailty grade		
Distribution of frailty grade pre-stroke	mRS at three years >2	Dead before three years
Fit (0 to 0.12), n=277	32 (12%)	17 (6%)
Mild frailty (0.12 to 0.24), n=200	84 (42%)	43 (22%)
Moderate frailty (0.24 to 0.36), n=72	54 (75%)	32 (44%)
Severe frailty (>0.36), n=60	54 (90%)	46 (77%)

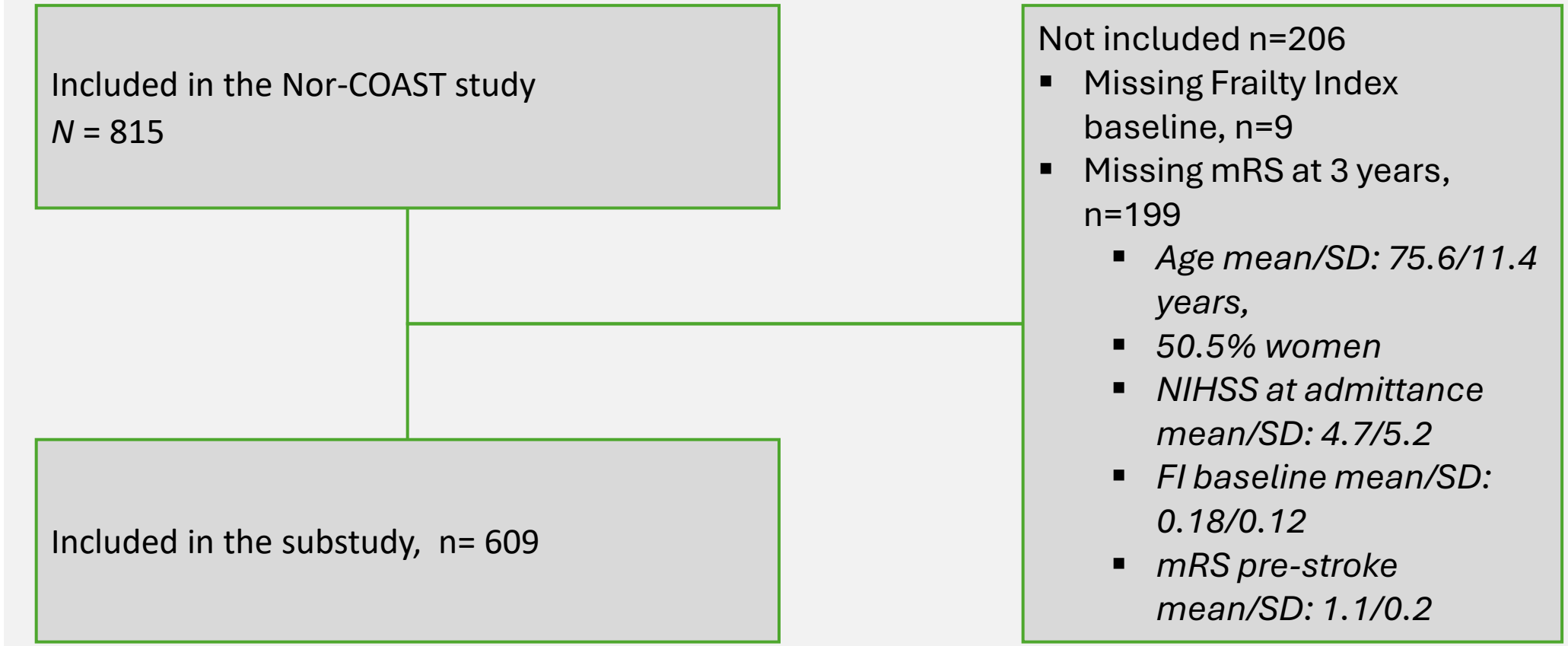
Table 3: Logistic regression analysis with mRS at 3 years (over 2 vs 0-2) or dead within 3 years as dependent variable, frailty and mRS as predictors n=609 unless otherwise specified. Estimate, CI, p-value		
	OR for mRS at 3 years (over 2 vs 0-2)	**OR for dead within 3 years**
One predictor at a time		
Frailty	4.09 (3.20 to 5.23)), <0.001	2.22 (1.80 to 2.74), <0.001
mRS pre-stroke n=608	2.70 (2.24 to 3.24), <0.001	1.67 (1.05 to 2.67), <0.001
Both predictors simultaneously n=608		
Frailty	3.46 (2.57 to 4.64), <0.001	2.01 (1.51 to 2.67), <0.001
mRS pre-stroke	1.31 (1.02 to 1.70), 0.038	1.16 (0.88 to 1.52), 0.29

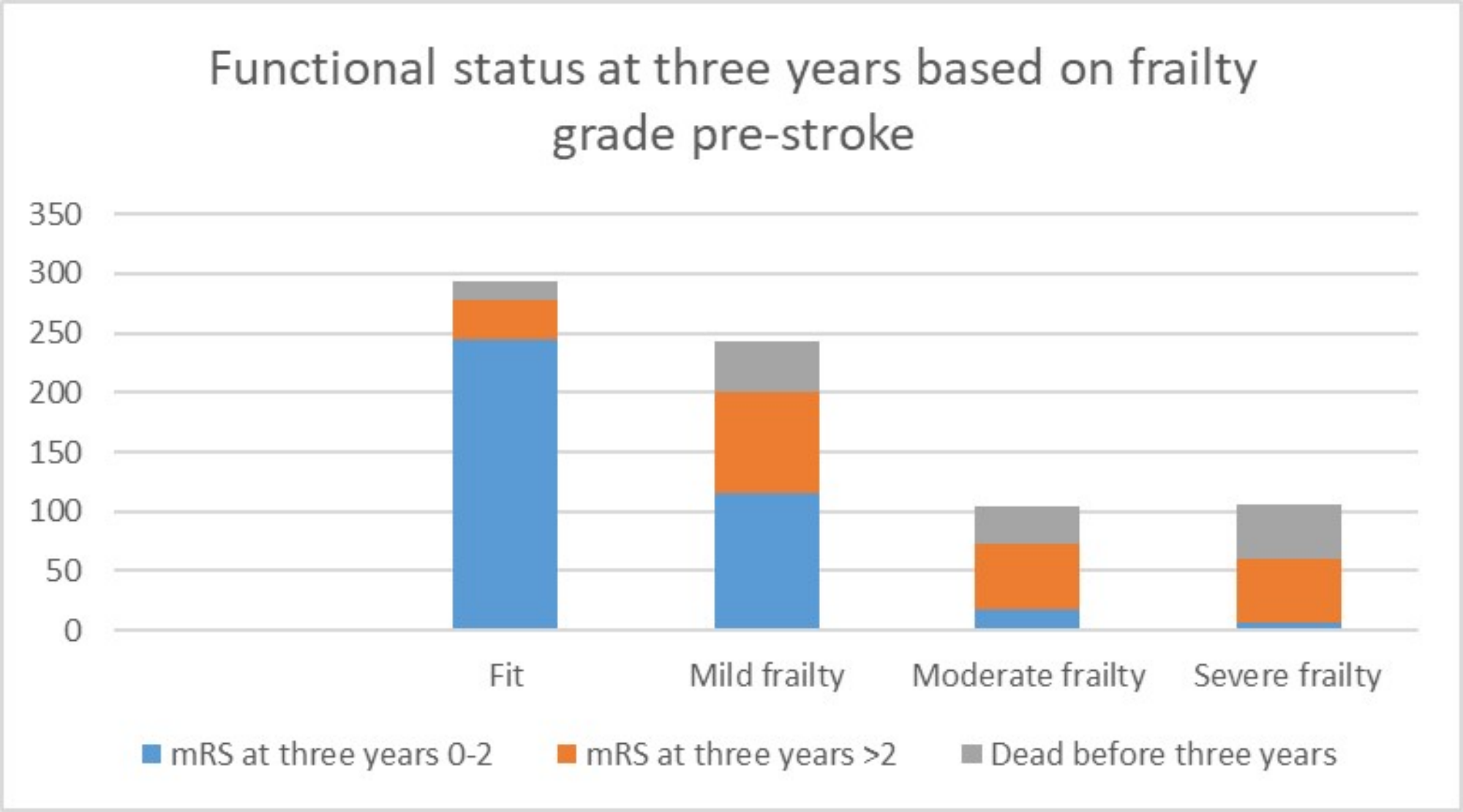
Table 4: Logistic regression with mRS at 3 years (over 2 vs 0-2) or Dead within three years as dependent variable*		
N=609†	mRS over 2(over 2 vs 0-2)	Dead within three years
	OR (95% CI)	
Frailty unadjusted	4.1 (3.2 to 5.2)	
Frailty adjusted for age and sex		2.2 (1.8 to 2.7)
Frailty adjusted separately for		Frailty adjusted for age and sex, and also separately for
Age	2.8 (2.2 to 3.6)	
Sex	4.1 (3.2 to 5.2)	
Education	3.7 (2.9 to 4.8)	2.2 (1.8 to 2.8)
NIHSS sum score at admittance‡	4.4 (3.3 to 5.7)	2.3 (1.9 to 2.9)
Acute stroke progression§	4.0 (3.1 to 5.1)	2.2 (1.8 to 2.7)
Infection treated by antibiotics||	3.9 (3.1 to 5.1)	2.1 (1.7 to 2.7)

mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale,

**All p-values were <0.001*
† unless otherwise specified
‡N=593
§N=597
\|\|N= 605

Table 5: ROC analyses. AUC (CI), all p-values are <0.001. n=608		
	mRS at 3 years (over 2 vs 0-2)	**dead within 3 years**
Frailty	0.85 (0.82 to 0.88)	0.83 (0.79 to 0.87)
mRS pre-stroke	0.76 (0.72 to 0.75)	0.75 (0.71 to 0.80)
difference	0.09 (0.06 to 0.13)	0.08 (0.04 to 0.12)


Included in the Nor-COAST study
N = 815
Included in the substudy, n= 609
Not included n=206
Missing Frailty Index baseline, n=9
Missing mRS at 3 years, n=199
Age mean/SD: 75.6/11.4 years,
50.5% women
NIHSS at admittance mean/SD: 4.7/5.2
FI baseline mean/SD: 0.18/0.12
mRS pre-stroke mean/SD: 1.1/0.2


Functional status at three years based on frailty grade pre-stroke
350
300
250
200
150
100
50
0
Fit
Mild frailty
Moderate frailty
Severe frailty
mRS at three years 0-2
mRS at three years >2
Dead before three years