

Frailty to predict unplanned hospitalization, stroke, bleeding and death in atrial fibrillation

Rebecca Gugganig^{1,2*}, Stefanie Aeschbacher^{1,2*}, Darryl P. Leong³, Pascal Meyre^{1,2}, Steffen
Blum^{1,2}, Michael Coslovsky⁴, Jürg H. Beer⁵, Giorgio Moschovitis⁶, Dominic Müller¹,
Daniela Anker⁷, Nicolas Rodondi^{7,8}, Samuel Stempfel^{1,2}, Christian Müller^{1,2}, Christine
Meyer-Zürn^{1,2}, Michael Kühne^{1,2}, David Conen^{1,2,3}, Stefan Osswald^{1,2}, for the Swiss-AF
investigators

* Contributed equally, shared first authors

¹ Cardiovascular Research Institute Basel, University Hospital Basel, University of
Basel, Switzerland

² Division of Cardiology, Department of Medicine, University Hospital Basel,
University of Basel, Switzerland

³ Population Health Research Institute, McMaster University, Hamilton, Canada

⁴ Clinical Trial Unit Basel, Department of Clinical Research, University Hospital Basel,
Switzerland

⁵ Department of Medicine, Cantonal Hospital of Baden and Molecular Cardiology,
University Hospital of Zürich, Switzerland

⁶ Department of Cardiology, Ospedale Regionale di Lugano, Switzerland

⁷ Institute of Primary Health Care (BIHAM), University of Bern, Switzerland

⁸ Department of General Medicine, Inselspital, Bern University Hospital, University of
Bern, Switzerland

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Address for correspondence:

Stefan Osswald MD
University Hospital Basel
Petersgraben 4
4031 Basel
Email: stefan.osswald@usb.ch
Phone: +41 61 265 5226

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Abstract

Aims: Atrial fibrillation (AF) and frailty are common, and the prevalence is expected to rise further. We aimed to investigate the prevalence of frailty and the ability of a frailty index (FI) to predict unplanned hospitalizations, stroke, bleeding and death in patients with AF.

Methods and results: Patients with known AF were enrolled in a prospective cohort study in Switzerland. Information on medical history, lifestyle-factors and clinical measurements were obtained. The primary outcome was unplanned hospitalization; secondary outcomes were all-cause mortality, bleeding and stroke. The FI was measured using a cumulative deficit approach, constructed according to previously published criteria and divided into three groups (non-frail, pre-frail, frail). The association between frailty and outcomes was assessed using multivariable adjusted Cox regression models. Of the 2369 included patients, prevalence of pre-frailty and frailty was 60.7% and 10.6%, respectively. Pre-frailty and frailty were associated with a higher risk of unplanned hospitalizations (adjusted hazard ratio [aHR] 1.82; 95% confidence interval [CI], 1.49-2.22, $p<0.001$; and aHR 3.59; 95%CI 2.78-4.63, $p<0.001$), all-cause mortality (aHR 5.07; 95%CI 2.43-10.59, $p<0.001$; and aHR 16.72; 95%CI 7.75-36.05, $p<0.001$), and bleeding (aHR 1.53; 95%CI 1.11-2.13, $p=0.01$; and aHR 2.46; 95%CI 1.61-3.77, $p<0.001$). Frailty, but not pre-frailty was associated with a higher risk of stroke (aHR 3.29; 95%CI 1.29-8.39, $p=0.01$).

Conclusion: Over two thirds of patients with AF are pre-frail or frail. These patients have a high risk for unplanned hospitalizations and other adverse events. These findings emphasize the need to carefully evaluate these patients. However, whether screening for pre-frailty and frailty and targeted prevention strategies improve outcomes needs to be shown in future studies.

Keywords: Atrial fibrillation, elderly, frailty, hospitalization, mortality

Clinical trial registration information: Clinicaltrials.gov identifier number: NCT02105844

Introduction

Frailty is a common condition in geriatric patients, characterized by a reduced biological reserve and high vulnerability to adverse outcomes including death.¹ Depending on the assessment tool and the population studied, the prevalence of frailty in patients with cardiovascular disease (CVD) was estimated from 10% to 60%.²

Atrial fibrillation (AF) is associated with substantial comorbidity, such as heart failure, or stroke, which by itself could contribute to frailty and disability in this patient group.³⁻⁵ AF patients are treated with anticoagulants and other potent cardiovascular drugs. This may impose additional risks, such as bleeding and/or fainting,^{6,7} especially to frail AF patients.

The CHA₂DS₂-VASc score has been designed and validated to specifically estimate the risk of stroke for patients with AF.⁸ In some studies it has also proven to be predictive for mortality and bleeding in AF patients, as well as for death and major cardiovascular events in patient presenting to the emergency department with syncope.⁹⁻¹¹ Despite the fact that AF is the most common arrhythmia with a prevalence of 13-15% in patients over 75 years¹² and in older people strongly associated with frailty,¹³ only limited data on frailty and its association with adverse outcome events in AF patients are available.

A recent review reported a prevalence of frailty in AF patients in sixteen studies, with a range from 6% in a registry of outpatients up to 100% in a nursing home population.¹⁴ This review reported an association between frailty and mortality, but also highlighted the lack of data on frailty and its association with other adverse outcomes in AF patients in a community setting.

Therefore this study aimed to investigate the prevalence of frailty and the ability of a frailty index (FI) to predict adverse clinical outcomes in a large observational community cohort of contemporarily treated AF patients.

Methods

Study design

The Swiss Atrial Fibrillation Cohort Study (Swiss-AF) is an ongoing prospective, observational, multicenter cohort study across 14 centers in Switzerland. Detailed information on the study design has been published previously.¹⁵ The study complies with the Declaration of Helsinki, the study protocol has been approved by the local ethics committees, and informed written consent was obtained from each participant.

Study population

Overall, 2415 patients with documented AF were enrolled between 2014 and 2017. The pre-specified inclusion criteria of the cohort study were a history of previously documented AF (documented by ECG or rhythm monitoring device within the last 60 months) and age ≥ 65 years. In order to assess the socioeconomic aspects of AF in individuals who are part of the active workforce we enrolled additionally 10% of participants aged between 45 and 65 years. Patients with exclusively short, reversible form of AF (e.g. AF following cardiac surgery) were excluded. Of the 2415 patients 46 (1.9%) were excluded from this analysis; 30 (1.2%) due to study termination other than death before first follow-up visit, 7 (0.3%) due to not yet completed first follow-up and 9 (0.4%) due to missing/invalid date of the primary endpoint, resulting in a total number of 2369 (98.1%) patients remaining.

Assessment of study variables

Information about patient characteristics, risk-factors, comorbidities, physical activity, nutrition, current medications and medication adherence were collected by standardized case report forms and validated questionnaires. Cognitive assessment was evaluated by centrally trained study personnel using the Montreal Cognitive Assessment.¹⁶ Depressive symptoms were measured with the Geriatric Depression Scale.¹⁷ Health related quality of life was measured with the European Quality of life-5 Dimensions questionnaire (EQ-5D).¹⁸ The Barthel-Index was used to assess disability.¹⁹

Body height and weight were directly measured using standardized devices and BMI was calculated. Blood pressure was measured three times in a supine position after at least 5 minutes of rest using a validated device. A resting 16-lead electrocardiogram (ECG) of 5 minutes duration was acquired in every study center. Atrial fibrillation type was classified according to the guidelines of the European Society of Cardiology into paroxysmal, persistent or permanent AF.⁶ The degree of peripheral edema and/or rales was assessed by local investigators.

Non-fasting venous blood samples were collected from each patient at baseline. The samples were stored at -80°C in a centralized biobank at the University Hospital Basel. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD- EPI) equation.²⁰

Follow up assessments and clinical outcome events

Yearly follow-up examinations were performed to update and re-assess all information and measures, and to collect information about adverse outcome events. Follow-up information was collected by local study personnel at each study center. If a clinical outcome event was reported by the patient or detected in available medical records, detailed information from the corresponding hospital and/or treating physicians was collected. All-cause death, stroke and bleeding were independently adjudicated by two physicians using a standardized form. In case of disagreement, a third physician reviewed the respective outcome event.

The primary outcome for this analysis was any unplanned hospitalization. Secondary outcomes included first cardiovascular hospitalization, first non-cardiovascular hospitalization, all-cause mortality, any bleeding, defined as major and clinically relevant non- major bleeding, and all stroke, defined as ischemic or hemorrhagic stroke. Detailed definitions of outcomes are provided in Supplementary table 1.

Frailty index score

Data of all variables included in the Frailty Index (FI) are provided in Table 1. Based on the available dataset the “deficit accumulation” approach was used. The FI was developed using 40 unweighted variables, including symptoms, signs, diseases and disabilities.²¹ The variables were selected according to a standard procedure to create a frailty index score as described before.²² All variables were coded according to published or self-evident cut-offs and mapped to a 0-1 interval (indicating the occurrence and severity of a deficit). For each patient the FI score was calculated as the proportion of deficits present in relation to the number of deficits available. FI is a continuous variable scaled from 0-1 and was, similar to prior reports divided into the predefined levels non-frail ($FI \leq 0.1$), pre-frail ($FI > 0.1$ and < 0.25) and frail ($FI \geq 0.25$).²³

Statistical analysis

We used data up to October 1st, 2018 and included patients with at least one year of follow up. Baseline characteristics were stratified by frailty levels. Categorical variables are presented as counts (percentages) and compared using Chi-square tests. The distribution of continuous variables was analyzed using skewness, kurtosis and visual inspection of the histogram. Normally distributed continuous variables are presented as mean \pm standard deviation (SD) and compared using ANOVA. Skewed variables are presented as median (interquartile range) and compared using the Kruskal-Wallis Rank Sum-test.

Person-years of follow-up were calculated from the date of study entry to the first occurrence of an outcome event, death, date of the last visit or lost-to-follow-up, whatever occurred first. To estimate the cumulative incidence of outcomes across frailty levels we used the cumulative incidence function. To assess the association between frailty and a clinical outcome event we constructed multivariable (cause-specific) Cox regression models to calculate hazard ratios (HR) (95% confidence intervals [95% CI]). Multivariable models were adjusted for age, sex, type of oral anticoagulation (i.e. vitamin K antagonist (VKA), direct oral anticoagulants (DOAC), or no OAC), any antiplatelet therapy (i.e. Aspirin (ASS) or other

antiplatelets), type of AF, education and smoking. For relative risk calculations the group of non-frail patients was used as reference. We estimated the population-attributable risk (PAR) proportion of frailty and pre-frailty for each outcome event, using the formula $pd \times (HR-1/HR)$, where pd is the proportion of frailty and pre-frailty among all patients with the outcome event and HR is the adjusted HR.²⁴ A receiver operating characteristic curve was constructed to assess the area under the curve for the age- and sex adjusted FI and the CHA₂DS₂-VASc score for the prediction of stroke within one year, and for the other outcomes. The Spearman's correlation coefficient was conducted for the correlation between FI and CHA₂DS₂-VASc score.

Pre-specified subgroup analyses were performed for age (≥ 75 y), sex, AF type and type of OAC. As a sensitivity analysis we recalculated the main models using Subdistribution Hazard regression as described by Fine and Gray, in order to take into account the competing risk of death.²⁵ A p-value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using RStudio (R version 3.4.1).

Results

Baseline characteristics

Baseline characteristics stratified by frailty level are presented in Table 2. Overall, mean (\pm SD) age was 73 (\pm 8) years, 647 (27.3%) were female and 2141 (90.4%) were treated with OAC. Among participants, 28.7% were non-frail, 60.7% were pre-frail and 10.6% were frail. Frail patients were more likely to be older, current or past smokers and to have permanent AF. The mean CHA₂DS₂-VASc score was 2.1, 3.8 and 5.4 among non-frail, pre-frail and frail patients, respectively ($p < 0.001$). Compared to non-frail and pre-frail patients, frail patients were more often treated with VKA (27.2%, 43.1% and 52%), but the overall frequency of OAC use did not differ across frailty levels.

Outcomes

During a median follow-up of 2.0 years, 762 of 2369 (32.2%) patients had one or more unplanned hospitalization for any cause. Of these first unplanned hospitalizations of any cause, 281 (36.9%) were cardiovascular and 481 (63.1%) were non-cardiovascular.

Overall, 322 (13.6%) patients had a first cardiovascular hospitalization and 523 (22.1%) a first non-cardiovascular hospitalization, 50 (2.1%) a stroke, 273 (11.5%) a major bleeding or clinically relevant non- major bleeding and 159 (6.7%) died. The cumulative incidence of any unplanned hospitalization, all-cause mortality, stroke and bleeding stratified by frailty level are shown in Figure 1.

Association of frailty level and unplanned hospitalizations

The associations between frailty levels and unplanned hospitalization are presented in Table 3. The overall incidence of any hospitalization was 19.8 per 100 patient-years, and it was 10.6, 21.5 and 45.0 per 100 patient-years in non-frail, pre-frail and frail patients, respectively. Compared to non-frail patients, the multivariable adjusted HR for hospitalization in pre-frail and frail patients were 1.82 (95% CI 1.49-2.22) and 3.59 (95% CI 2.78-4.63), respectively. We estimated that 42% of all unplanned hospitalizations could be attributable to pre-frailty or

frailty.

Similar results were found for the association of pre-frailty and frailty with first cardiovascular hospitalization (adjusted HR 2.51, 95%CI 1.77-3.55; and adjusted HR 4.96, 95%CI 3.28-7.49) and first non-cardiovascular hospitalization (adjusted HR 1.48, 95%CI 1.17-1.87; and adjusted HR 2.67, 95%CI 1.97-3.62).

Association of frailty level and secondary outcomes

The overall incidence of all-cause mortality was 3.3 per 100 person-years, compared with 0.6, 3.2 and 11.6 per 100 person-years in non-frail, pre-frail and frail patients, respectively. Pre-frailty and frailty were significantly associated with all-cause mortality (adjusted HR 5.07, 95%CI 2.43-10.59; and adjusted HR 16.72, 95%CI 7.75-36.05). Of all deaths we estimated that 81% could be attributable to pre-frailty or frailty (Table 4).

The incidence for stroke was 1.0 per 100 person-years overall, and 0.7, 1.0 and 2.3 for non-frail, pre-frail and frail patients. For bleeding, the overall incidence was 7.0 per 100 person-years, and 3.7, 6.4 and 10.5 for non-frail, pre-frail and frail patients. Multivariable Cox regression for pre-frailty and frailty showed consistent results for bleeding (adjusted HR 1.53, 95%CI 1.11-2.13; and adjusted HR 2.46, 95%CI 1.61-3.77), but not for stroke (adjusted HR 1.43, 95%CI 0.67-3.06; and adjusted HR 3.29 95%CI 1.29-8.39). We estimated that 32% of all bleedings and 32% of all strokes could be attributable to pre-frailty or frailty (Table 4).

Sensitivity and subgroup analyses

Competing risk models for the main analyses revealed similar findings (Supplementary table 2). Subgroup analyses for the association of frailty levels with any unplanned hospitalizations and the secondary outcomes showed consistent results, and none of the interaction terms were statistically significant (Supplementary table 3). Due to the small number of outcome events, subgroup analyses for stroke were not performed.

Receiver Operating Characteristic (ROC) curve of the age and sex adjusted FI and CHA₂DS₂-VASc score

For the prediction of stroke after one year the age and sex adjusted FI performed comparably to the CHA₂DS₂-VASc score with an AUC of 0.657 (0.557–0.745) and 0.636 (0.516–0.742), respectively (Figure 2). For the other outcomes, for which the CHA₂DS₂-VASc score was not designed, the FI performed slightly better than the CHA₂DS₂-VASc score (Supplementary figure 1). The correlation coefficient between the FI and the CHA₂DS₂-VASc score was 0.6625, $p < 0.001$.

Discussion

Several findings emerged from this large community-based cohort study of AF patients. First, while the prevalence of frailty was low, almost two thirds of patients were pre-frail. Second, the majority of adverse outcomes was attributable to pre-frailty. These findings emphasize to carefully evaluate frail, and in particular pre-frail, patients. Third, the applied FI has proven to be a powerful tool to predict outcomes, with both pre-frailty and frailty being strongly associated with unplanned hospitalizations. Similar results were found for stroke, bleeding and death. Compared to the CHA₂DS₂-VASc score, the FI had a similar predictive power. Fifth, the prevalence of OAC did not differ among frailty groups, but frail patients were more likely to receive VKA. Further studies are needed to determine whether screening for frailty and targeted prevention strategies potentially reduce adverse outcomes and consecutive health related costs.

The prevalence of frailty among patients with AF was 10.6% and close to the lower bound of the previously reported range of 6% to 100% in a recent review.²⁶ This may be explained by the stable condition of our patients compared to those in other studies, which included sicker and predominantly in-hospital patients, or patients from nursing homes. Another explanation could be the possible non-participation of frail patients. In addition, there are two different approaches to measure frailty (“phenotypic” vs. “deficit accumulation” frailty).^{21, 27} Furthermore the variable components of a given FI vary between studies.

Most patients in our study were pre-frail, accounting for the highest attributable risk for all adverse outcomes. Taking a public and economic health perspective, special attention should be given to this large pre-frail patient group. Multidisciplinary programs have been shown to be an effective strategy to increase the days alive and out of hospital in AF patients.²⁸ In addition, multicomponent exercise interventions have been shown to reverse frailty.²⁹ Screening for frailty on a population basis is not yet recommended.³⁰ But screening for frailty in AF patients together with a disease specific management, comprehensive geriatric assessment and care³¹ and multicomponent exercise interventions, would be a

proactive approach to a population with a high percentage of pre-frailty and frailty. However, whether screening for frailty and targeted prevention strategies for pre-frail and frail AF patients improve outcomes needs to be shown in future studies.

We observed that >40% of any unplanned hospitalizations were attributable to pre-frailty and frailty (Take home figure). Nguyen and colleagues showed in a small cohort of in-hospital AF patients no association between frailty and re-hospitalization.³² Further comparisons are difficult due to the lack of data addressing the association of frailty and unplanned hospitalizations in AF patients. It might appear unexpected that the rate for unplanned hospitalizations was higher for non-cardiovascular than cardiovascular reasons. Partly, this is explained by the older age and higher comorbidity burden in the frail group. Other explanations might be compromised immune response, accounting for more infections and cancer in frail patients^{33, 34} and the higher comorbidity-rate in AF patients leading to a higher risk of non-cardiovascular disease in general. Unfortunately, we were not able to further clarify the exact reasons for hospitalizations. To identify modifiable risk factors and possibly preventable reasons for hospitalizations in pre-frail and frail AF patients further studies are needed.

We also found a strong association between frailty and stroke, bleeding and all-cause mortality, which is consistent with previous findings.^{32, 35} The low incidence of stroke in our cohort may be explained by the high prevalence of oral anticoagulation. Nevertheless, after multivariable adjustment (including type of OAC) frailty remained an independent predictor of stroke. Compared to the CHA₂DS₂-VASc score, the FI had a similar predictive power in this study of AF patients for the prediction of unplanned hospitalization, stroke, bleeding and death, with a strong correlation. When interpreting these results one should note that a simple clinical risk score such as the CHA₂DS₂-VASc score not validated for frailty performs comparably to our 40-item frailty score.

While the CHA₂DS₂-VASc score was highest in frail patients, the prevalence of OAC did not differ among frailty groups, with a high overall prevalence of 90.4%. This high

prevalence is in line with other studies assessing the prescription of OAC in AF patients in Europe at the time of our study.³⁶ Although DOACs with their better risk/benefit ratio seem preferable in frail patients,³⁷ in our study frail patients were more likely to receive VKA. This finding may partly be explained by a physician preference for close INR monitoring, especially in elderly or frail AF patients.³⁸ A study from the U.S. found, that DOACs were less likely prescribed to elderly patients with an increased risk for stroke and bleeding, and to those with more comorbidities.³⁹ However, the higher rate of renal dysfunction in frail patients cannot explain this observation alone. Another explanation may be the time period of patient enrollment to our study (2014-2017), since the first DOAC in Switzerland for prevention of stroke in AF was approved 2012. A study in Swiss AF patients found an increase of DOAC use between 2010 and 2015, but most patients stayed on their initial therapy with VKA.⁴⁰ As expected the bleeding risk seemed to be higher on OAC in all frailty groups. But there were no significant differences in bleeding risk with regard to the type of OAC, may be due to the small number of events in the subgroups. To clarify the question about OAC in frail AF patients, more clinical trials in this particular population are needed.

Our study has the advantage of being a large community-based cohort of well-characterized patients with a very low rate of missing values, which enabled us to build a strong FI. Also, the clinical outcomes were collected accurately and validated by independent experts. However, some potential limitations need to be considered. First, being an observational study, we cannot confirm causality, and residual confounding may persist despite comprehensive multivariable adjustment. Second, we used only a single measurement of frailty at study entry, which is associated with some risk of misclassification. Nevertheless, our results and those of others have shown, that a FI based on random composites of deficits is a robust model and capable to appropriately predict outcomes.⁴¹ Third, study patients were mostly >65 years old, which limits the generalizability of these findings.

Conclusions

In this large cohort of elderly AF patients, the FI was a powerful tool to predict unplanned hospitalizations and other adverse outcomes. The risk of unplanned hospitalization was highest among frail patients, but pre-frail patients accounted for the largest proportion of total number of hospitalizations, a finding that emphasizes the clinical need to carefully evaluate these patients. To determine whether screening and specific interventions for pre-frail and frail AF patients can potentially reduce adverse outcomes and its socio-economic consequences further studies are needed.

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Conflict of interest

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Figure legends

Figure 1. Cumulative incidence of clinical outcomes stratified by levels of frailty

Cumulative incidence of unplanned hospitalizations (a), all-cause mortality (b), bleeding (c) and stroke (d) stratified by frailty level.

Figure 2. Receiver Operating Characteristic (ROC) curve of the adjusted FI and

CHA₂DS₂-VASc score for stroke

Take home figure. Prevalence and impact of frailty in patients with AF

Table 1. Variables of the Frailty Index Score stratified by level of frailty

	Stratified by frailty level			
	Overall	non-frail	pre-frail	frail
n	2369 (100)	681 (28.7)	1436 (60.7)	252 (10.6)
Physical activity (Yes/No)	1095 (46.3)	495 (72.9)	562 (39.2)	38 (15.1)
History of myocardial infarction	385 (16.3)	22 (3.2)	267 (18.6)	96 (38.1)
History of PTCA/ Stent	561 (23.7)	45 (6.6)	397 (27.6)	119 (47.2)
History of Stroke / TIA	473 (20.0)	67 (9.8)	312 (21.8)	94 (37.3)
History of systemic embolism	125 (5.3)	11 (1.6)	84 (5.9)	30 (11.9)
History of congestive heart failure	613 (25.9)	38 (5.6)	413 (28.8)	162 (64.3)
History of hypertension	1642 (69.3)	288 (42.3)	1123 (78.2)	231 (91.7)
History of diabetes mellitus	403 (17.0)	10 (1.5)	268 (18.7)	125 (49.6)
History of peripheral vascular disease	190 (8.0)	7 (1.0)	112 (7.8)	71 (28.2)
History of chronic kidney disease	498 (21.0)	16 (2.4)	336 (23.4)	146 (57.9)
History of thyroid disease	343 (14.5)	50 (7.3)	224 (15.6)	69 (27.4)
History of malignancy	378 (16.0)	55 (8.1)	247 (17.2)	76 (30.2)
History of major bleeding	149 (6.3)	12 (1.8)	92 (6.4)	45 (17.9)
History of minor bleeding	253 (10.7)	23 (3.4)	168 (11.7)	62 (24.6)
History of gastric ulcera	106 (4.5)	9 (1.3)	57 (4.0)	40 (15.9)
Recurrent falls	198 (8.4)	9 (1.3)	115 (8.0)	74 (29.4)
Other medical problems	639 (27.0)	107 (15.7)	422 (29.4)	110 (43.7)
Edema	494 (20.9)	34 (5.0)	341 (23.8)	119 (47.2)
Rales	75 (3.2)	3 (0.4)	43 (3.0)	29 (11.5)
Body mass index	28.0 ± 4.8	26.5 ± 3.8	28.0 ± 4.9	29.0 ± 5.5
Systolic blood pressure	134 ± 18.7	131 ± 15.4	135 ± 19.4	134 ± 22.0
Doing usual activity (EQ- 5D)				
unable	20 (0.8)	0 (0.0)	8 (0.6)	12 (4.8)
some problems	324 (13.7)	13 (1.9)	192 (13.4)	119 (47.2)
no problems	2024 (85.4)	667 (97.9)	1236 (86.1)	121 (48.0)
Having pain or other physical issues (EQ- 5D)				
a lot of pain	60 (2.5)	1 (0.1)	35 (2.4)	24 (9.5)
some pain	1023 (43.2)	176 (25.8)	679 (47.3)	168 (66.7)
no pain	1283 (54.2)	503 (73.9)	721 (50.2)	59 (23.4)
Feeling worried, sad or unhappy (EQ- 5D)				
very	15 (0.6)	2 (0.3)	8 (0.6)	5 (2.0)
a bit	453 (19.1)	80 (11.7)	285 (19.8)	88 (34.9)
not	1900 (80.2)	598 (87.8)	1143 (79.6)	159 (63.1)
Self-rated health	72 ± 17.5	82 ± 11.6	71 ± 16.9	56 ± 18.8
Orientation (Part of MoCA)				
0	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	3 (0.1)	0 (0.0)	0 (0.0)	3 (1.2)
3	4 (0.2)	1 (0.1)	3 (0.2)	0 (0.0)
4	17 (0.7)	2 (0.3)	10 (0.7)	5 (2.0)
5	144 (6.1)	25 (3.7)	90 (6.3)	29 (11.5)
6	2198 (92.8)	652 (95.7)	1331 (92.8)	215 (85.3)
Mathematical performance (Part of MoCA)				
0	19 (0.8)	1 (0.1)	12 (0.8)	6 (2.4)
1	44 (1.9)	7 (1.0)	29 (2.0)	8 (3.2)
2	175 (7.4)	32 (4.7)	109 (7.6)	34 (13.5)
3	2127 (89.8)	639 (93.8)	1285 (89.5)	203 (80.6)
Delayed recall (Part of MoCA)				

0	304 (12.8)	39 (5.7)	204 (14.2)	61 (24.2)
1	184 (7.8)	30 (4.4)	130 (9.1)	24 (9.5)
2	372 (15.7)	82 (12.0)	237 (16.5)	53 (21.0)
3	501 (21.2)	137 (20.1)	317 (22.1)	47 (18.7)
4	541 (22.8)	188 (27.6)	316 (22.0)	37 (14.7)
5	463 (19.6)	202 (29.7)	231 (16.1)	30 (11.9)
Verbal fluency (Part of MoCA)	10 ± 4.0	12 ± 4.0	9 ± 3.8	8 ± 3.2
Depression (GDS)	1 (1.9)	1 (1.4)	2 (1.9)	3 (2.6)
Feeding (Barthel- Index)				
unable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
needs help	8 (0.3)	0 (0.0)	3 (0.2)	5 (2.0)
Independent	2359 (99.7)	679 (100)	1433 (99.8)	247 (98.0)
Personal grooming (Barthel- Index)				
needs help	12 (0.5)	1 (0.1)	1 (0.1)	10 (4.0)
independent	2357 (99.5)	680 (100.0)	1435 (99.9)	242 (96.0)
Bathing (Barthel- Index)				
needs help	48 (2.0)	0	8 (0.6)	40 (15.9)
independent	2321 (98.0)	681 (100.0)	1428 (99.4)	212 (84.1)
Dressing (Barthel- Index)				
dependent	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
needs help	33 (1.4)	0 (0.0)	6 (0.4)	27 (10.7)
independent	2335 (98.6)	681 (100.0)	1430 (99.6)	224 (88.9)
Toilet use (Barthel- Index)				
dependent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
needs help	12 (0.5)	0 (0.0)	5 (0.3)	7 (2.8)
independent	2357 (99.5)	681 (100.0)	1431 (99.7)	245 (97.2)
Urinary continence (Barthel- Index)				
incontinent	29 (1.2)	0 (0.0)	15 (1.0)	14 (5.6)
occasional accident	183 (7.7)	21 (3.1)	121 (8.4)	41 (16.3)
continent	2157 (91.1)	660 (96.9)	1300 (90.5)	197 (78.2)
Bowel continence (Barthel- Index)				
incontinent	7 (0.3)	0 (0.0)	3 (0.2)	4 (1.6)
occasional accident	51 (2.2)	1 (0.1)	36 (2.5)	14 (5.6)
continent	2311 (97.6)	680 (99.9)	1397 (97.3)	234 (92.9)
Transfer (Barthel- Index)				
unable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
major help	3 (0.1)	0 (0.0)	2 (0.1)	1 (0.4)
minor help	31 (1.3)	0 (0.0)	11 (0.8)	20 (7.9)
independent	2334 (98.6)	680 (100.0)	1423 (99.1)	231 (91.7)
Mobility (Barthel- Index)				
immobile	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
wheelchair independent	7 (0.3)	0 (0.0)	1 (0.1)	6 (2.4)
walks with help of one person	68 (2.9)	0 (0.0)	23 (1.6)	45 (17.9)
independent (but may use any aid)	2293 (96.8)	681 (100.0)	1411 (98.3)	201 (79.8)
Stairs (Barthel- Index)				
unable	17 (0.7)	1 (0.1)	3 (0.2)	13 (5.2)
needs help	61 (2.6)	0 (0.0)	26 (1.8)	35 (13.9)
independent	2291 (96.7)	680 (99.9)	1407 (98.0)	204 (81.0)

Data are presented as mean ± standard deviation, or median (interquartile range), or number (percentage)

Levels of frailty: frail (frailty index ≥ 0.25), pre- frail (frailty index <0.25 and >0.1), non- frail (frailty index ≤ 0.1)

Missing values: Physical activity n = 3, History of Stroke/TIA n = 2, History of congestive heart failure n = 2, History of chronic kidney disease n = 2, History of minor bleeding n = 2, Edema n = 3, Rales n = 3, Systolic blood pressure n = 16, Diastolic blood pressure n = 16, Verbal fluency n = 3, Depression n = 4

Table 2. Baseline characteristics (not part of the Frailty Index Score) stratified by frailty level

	Stratified by frailty level				p- value
	Overall	non-frail	pre-frail	frail	
n (%)	2369 (100)	681 (28.7)	1436 (60.7)	252 (10.6)	
Age, years	73 ± 8	69 ± 8	75 ± 8	77 ± 7	<0.001
Female Sex	647 (27.3)	163 (23.9)	412 (28.7)	72 (28.6)	0.06
Smoking					<0.001
Current	172 (7.3)	41 (6.0)	104 (7.2)	27 (10.7)	
Past	1157 (48.8)	301 (44.2)	717 (49.9)	139 (55.2)	
Never	1040 (43.9)	339 (49.8)	615 (42.8)	86 (34.1)	
CHA ₂ DS ₂ -VASc Score	3.5 ± 1.7	2.1 ± 1.3	3.8 ± 1.4	5.4 ± 1.3	<0.001
Atrial fibrillation- Type					<0.001
Paroxysmal	1062 (44.8)	357 (52.4)	608 (42.3)	97 (38.5)	
Persistent	694 (29.3)	217 (31.9)	421 (29.3)	56 (22.2)	
Permanent	613 (25.9)	107 (15.7)	407 (28.3)	99 (39.3)	
Type of oral anticoagulation					<0.001
VKA	936 (39.5)	186 (27.2)	619 (43.1)	131 (52.0)	
DOAC	1205 (50.9)	416 (61.1)	698 (48.6)	91 (36.1)	

No OAC	228 (9.6)	79 (11.6)	119 (8.3)	30 (11.9)	
Aspirin	399 (16.8)	52 (7.6)	278 (19.4)	69 (27.4)	<0.001
Other antiplatelet therapy	147 (6.2)	16 (2.4)	109 (7.6)	22 (8.7)	<0.001
Dual antiplatelet therapy	76 (3.2)	8 (1.2)	54 (3.8)	14 (5.6)	0.001
eGFR <30ml/min/1.73m ² (CKD- EPI)	144 (6.2)	3 (0.4)	98 (7.0)	43 (17.6)	<0.001

Data are presented as mean \pm standard deviation , or numbers (percentage); estimated glomerular filtration rate (eGFR)

Levels of frailty: frail (frailty index ≥ 0.25), pre- frail (frailty index <0.25 and >0.1), non- frail (frailty index ≤ 0.1)

Missing values: Smoking n = 3, CHA₂DS₂-VASc Score n = 3, other antiplatelet therapy n = 5, eGFR n = 53

Table 3. Cox Regression for the Association between frailty and unplanned hospitalizations

Level of frailty	Events/no.at risk	Person-years	Incidence rate per 100 person-years	Population attributable risk	HR (95% CI) unadjusted	p-value	HR (95% CI) adjusted	p-value
Any unplanned hospitalization								
non- frail	135 / 681	1273	10.6		Ref.		Ref.	
pre- frail	488 / 1436	2267	21.5	0.29	2.00 (1.65 - 2.42)	<0.001	1.82 (1.49 - 2.22)	<0.001
frail	139 / 252	309	45.0	0.13	4.10 (3.23 - 5.19)	<0.001	3.59 (2.78 - 4.63)	<0.001
First cardiovascular hospitalization								
non- frail	41 / 681	1393	3.0		Ref.		Ref.	
pre- frail	213 / 1436	2630	8.1	0.40	2.70 (1.93 - 3.77)	<0.001	2.51 (1.77 - 3.55)	<0.001
frail	68 / 252	409	16.6	0.17	5.44 (3.69 - 8.02)	<0.001	4.96 (3.28 - 7.49)	<0.001
First non-cardiovascular hospitalization								
non- frail	103 / 681	1333	7.7		Ref.		Ref.	
pre- frail	329 / 1436	2512	13.1	0.20	1.70 (1.36 - 2.12)	<0.001	1.48 (1.17 - 1.87)	0.001
frail	91 / 252	363	25.1	0.11	3.24 (2.45 - 4.30)	<0.001	2.67 (1.97 - 3.62)	<0.001

Data are presented as Hazard ratio (HR) with 95% confidence intervals (CI), reference value is non- frail (frailty index ≤ 0.1)

Model adjusted for age, sex, type of oral anticoagulation, any antiplatelet therapy, type of atrial fibrillation, education, smoking

Table 4. Cox Regression for the association between frailty and all-cause mortality, all stroke and any bleeding

Level of frailty	Events/no. at risk	Person-years	Incidence rate per 100 person-years	Population attributable risk	HR (95% CI) unadjusted	p-value	HR (95% CI) adjusted	p-value
All-cause mortality								
non- frail	8 / 681	1463	0.6		Ref.		Ref.	
pre- frail	95 / 1436	2931	3.2	0.48	5.98 (2.91 - 12.31)	<0.001	5.07 (2.43 - 10.59)	<0.001
frail	56 / 252	484	11.6	0.33	21.51 (10.25 - 45.14)	<0.001	16.72 (7.75 - 36.05)	<0.001
Stroke								
non- frail	10 / 681	1447	0.7		Ref.		Ref.	
pre- frail	29 / 1436	2904	1.0	0.17	1.47 (0.72 - 3.02)	0.3	1.43 (0.67 - 3.06)	0.35
frail	11 / 252	476	2.3	0.15	3.48 (1.48 - 8.20)	0.004	3.29 (1.29 - 8.39)	0.01
Bleeding								
non- frail	52 / 681	1389	3.7		Ref.		Ref.	
pre- frail	175 / 1436	2730	6.4	0.22	1.71 (1.26 - 2.34)	<0.001	1.53 (1.11 - 2.13)	0.01
frail	46 / 252	438	10.5	0.10	2.82 (1.90 - 4.20)	<0.001	2.46 (1.61 - 3.77)	<0.001

Data are presented as Hazard ratio (HR) with 95% confidence intervals (CI), reference value is non- frail (frailty index ≤ 0.1)

Model adjusted for age, sex, type of oral anticoagulation, any antiplatelet therapy, type of atrial fibrillation, education, smoking

Figure 1. Cumulative incidence of unplanned hospitalizations (a), all-cause mortality (b), any bleeding (c) and all stroke (d) stratified by levels of frailty.

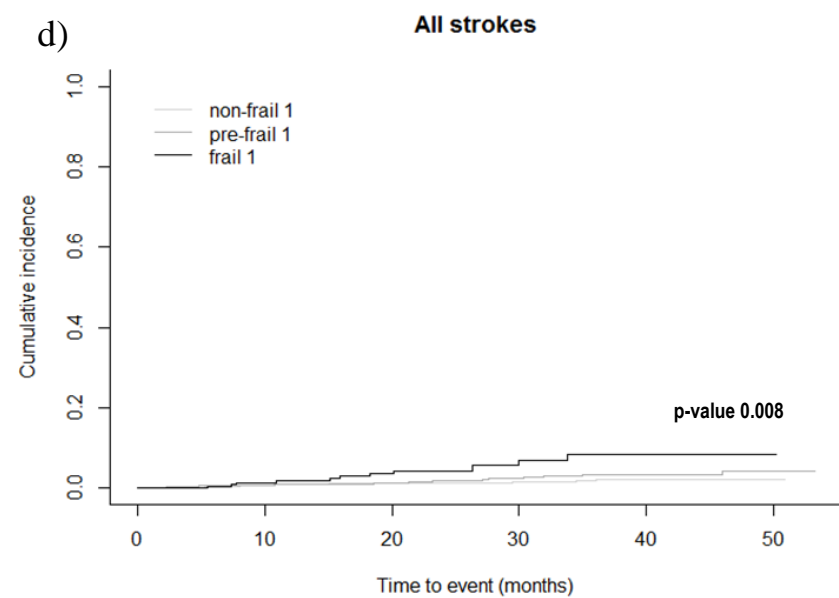
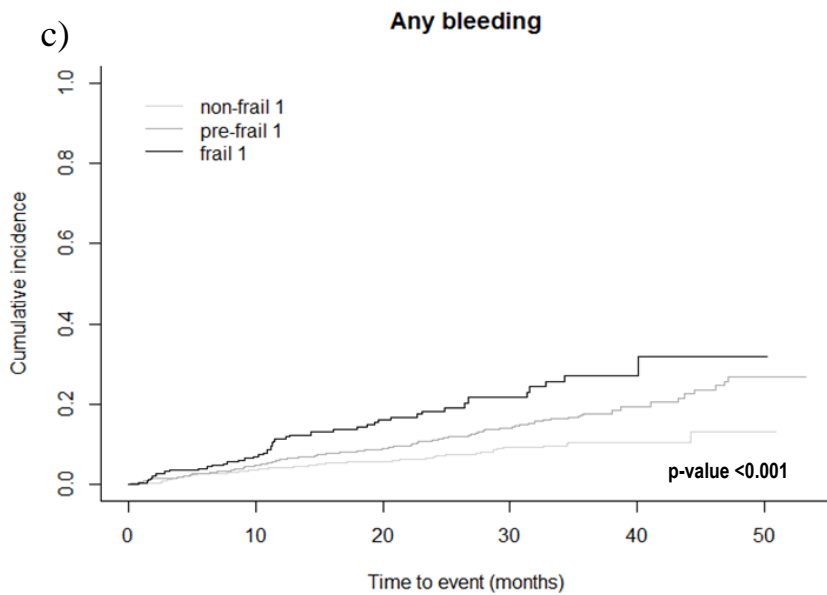
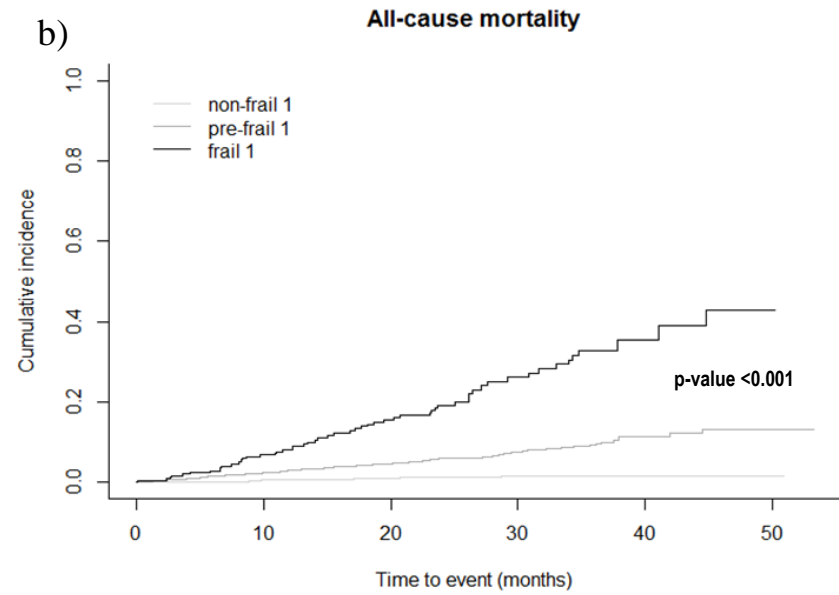
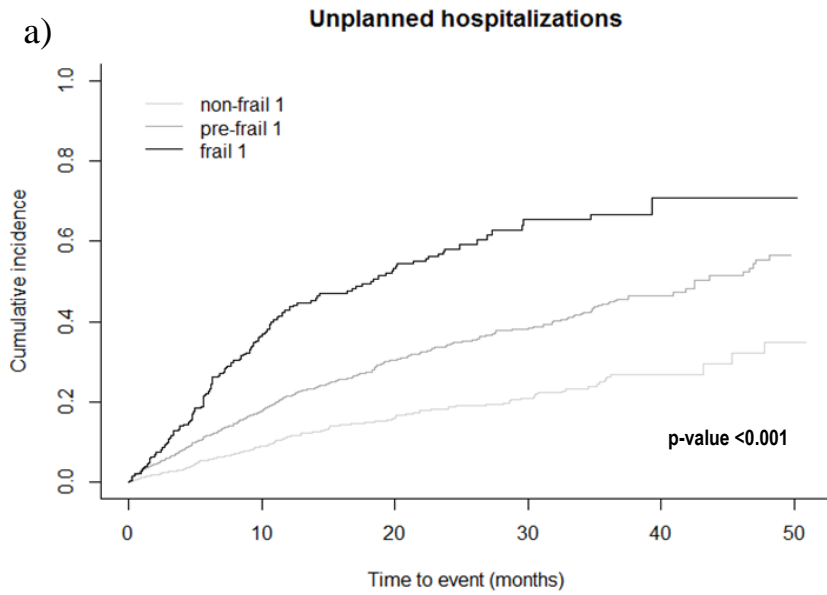
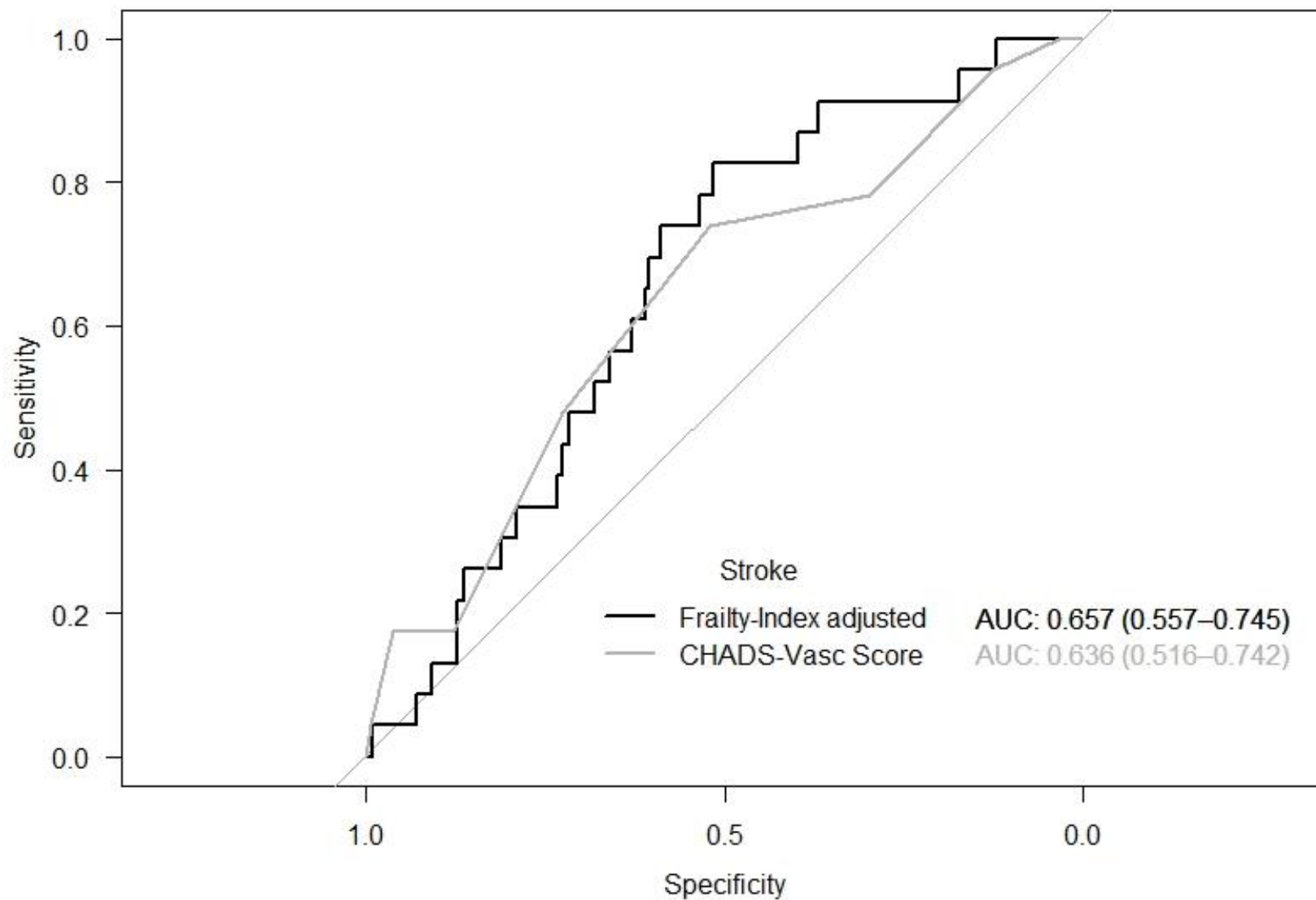


Figure 2. Receiver Operating Characteristic (ROC) curve of age and sex adjusted frailty index and CHA₂DS₂-VASc score for stroke



Take home figure. Prevalence and impact of frailty in patients with AF

