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Influence of frailty on anticoagulant prescription and clinical outcomes after 1-year follow-up in hospitalised older patients with atrial fibrillation

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Abstract

Frailty is an important prognostic factor in older adults with cardiovascular diseases. We aim to describe the characteristics of elderly hospitalised frail patients with non-valvular atrial fibrillation (NVAF) and to assess the influence of frailty, along with other functional and health status variables on anticoagulation prescription, 1-year all-cause mortality, and the incidence of ischemic and bleeding complications. An observational, prospective multicentre study was carried out on patients with NVAF over the age of 75, who were admitted to the Internal Medicine departments in Spain. A total of 615 patients were evaluated (mean age 85.23 ± 5.16 years, 54.3% females, 48.3% frail). Frail patients had higher CHA2DS2-VASc and HAS-BLED scores, more comorbidities and worse functional status and cognitive impairment compared to non-frail. During hospitalisation, 58 (9.4%) patients died (12.5% frail, 6.6% non-frail, $p = 0.01$). Among the participants discharged, 69.8% received anticoagulants, 13% anti-platelets only and 16.9% no anti-thrombotics, with no difference by frailty status. Frailty is not a predictor of anticoagulant prescription at discharge (OR 0.93, 95% CI 0.55–1.57), while functional dependency remains significantly associated (OR for severe dependency 0.44, 95% CI 0.23–0.82). After the 1-year follow-up, frail patients have a higher risk of death (HR 1.99, 95% CI 1.43–2.76). Among patients taking anticoagulants, the incidence of stroke and major bleeding is similar between frailty groups. In our study, frailty is related to worse global health status. It has no impact on antithrombotic prescription, nor is a predictor of AF complications, even though frail subjects have a higher mortality during hospitalisation and after 1-year follow-up.

Keywords Atrial fibrillation · Anticoagulants · Aged · Frailty · Elderly · Antithrombotic therapy

Introduction

The ageing of the world population increases the prevalence and clinical importance of problems such as frailty and atrial fibrillation (AF) [1].

Frailty is an important prognostic factor in older adults, which is associated with fractures, incident disabilities, hospitalisations, and mortality [2]. It is defined as a biological state of increased vulnerability to health stressors resulting from a decline in reserve and function of multiple physiological systems [3].

A relationship between frailty and cardiovascular disease has been demonstrated in several studies [4]. In particular, frailty is associated with poor outcomes in older patients with heart failure [5], myocardial infarction [6], and AF [7]. Due to its potential reversibility, with appropriate therapeutic

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interventions, its screening and early detection are of great importance for the prognosis of heart diseases.

AF is the most common dysrhythmia, and its prevalence increases with age, reaching 31% in subjects over 70 years hospitalised for any cause in Spain [8].

The major consequences of AF in older patients are a two-fold increased risk of mortality and a five-fold increased risk of stroke [9]. Although oral anticoagulation therapy (OAT) has been shown to be effective for the prevention of cardio-embolic stroke in this population, it is widely underused, particularly in the oldest, who are paradoxically those who could benefit the most [10].

Lately, several studies have evaluated the patterns of antithrombotic use among older hospitalised patients with AF. Severe functional impairment, high comorbidity or polypharmacy have been identified as predictors of OAT underuse [11, 12]. Frailty has also been related to non-prescription of OAT, although frail patients present higher thrombotic risk and mortality [13, 14].

None of these studies evaluated frailty simultaneously with the assessment of functional, cognitive and comorbidity status to clarify which condition is more relevant for the anticoagulant prescription.

The principal aims of this study are to describe the characteristics of hospitalised frail patients aged ≥ 75 years with non-valvular AF (NVAF), and to assess the influence of frailty and other functional and health status variables on the anticoagulation prescription at discharge. Second, we aim to investigate the impact of frailty on 1-year follow-up outcomes, including all-cause mortality and the incidence of bleeding and thrombotic complications.

Methods

The NONAVASC registry is an observational, prospective, multicentre study, conducted in the Internal Medicine departments of 64 hospitals from all the Spanish regions. Investigators were required to include at least ten consecutive patients older than 75 years, hospitalised for any reason, with previous NVAF diagnosis or incident AF at admission, who gave their written informed consent to participate in the registry.

This study has been described previously [15]. Briefly, inclusion was conducted between October 2014 and May 2015. NVAF is defined as those cases in which the dysrhythmia appeared in the absence of moderate-to-severe rheumatic mitral stenosis or valvular prosthesis [16]. Thrombotic and haemorrhagic risk stratifications were performed using the CHA2DS2-VASc [17] and the HAS-BLED scores [18].

The social, functional and cognitive status at admission were assessed through a personal interview with the patient or primary caregiver.

The five-item FRAIL Questionnaire was used for screening for frailty, according to the phenotype approach, which evaluates a combination of five conditions: fatigue, resistance, aerobic activity, illnesses and loss of weight [19]. This questionnaire is a simple and rapid screening test validated in several geriatric scenarios [1, 20, 21]. We consider the results as frail (3–5 points), pre-frail (1–2 points) and robust (0 points) health status.

The comorbidity grade was evaluated through the Charlson Comorbidity index [22]. We consider high comorbidity when the score is ≥ 3 points. The functional status was evaluated according to the Barthel index (BI) (range from 0 to 100) regarding the level of independence for the realisation of basic activities of daily living (BADL) [23]. We establish four categories: total (BI ≤ 20), severe (BI = 21–40), moderate (BI = 41–60) and mild functional impairment (BI = 61–99). The cognitive status was evaluated with the Short Portable Mental Status Questionnaire (Pfeiffer) [24]. The categories of cognitive impairment are: severe (8–10 mistakes), mild–moderate (3–7 mistakes), normal (0–2 mistakes). Sarcopenia was evaluated through the SARC-F questionnaire [25]. Scores greater than 4 points are predictive of sarcopenia.

The estimated glomerular filtration rate (eGFR) was calculated with the CKD-EPI Equation and measured in ml/min. The serum albumin concentration was measured in g/dL. Both measures were obtained from a blood extraction performed on admission according to usual clinical practise.

For the purpose of this present study, and since the main objective is the evaluation of the impact of frailty on the anticoagulant prescription, we include only the patients from the initial NONAVASC sample with frailty evaluation and recorded treatment at discharge (Fig. 1 Study flow chart).

After 1-year follow-up, the clinical outcomes evaluated are all-cause mortality, and incidence of haemorrhagic and thrombotic events. Major bleeding is defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria as clinically overt bleeding requiring transfusion of at least two units of packed red cells, occurring at a critical site (intracranial, intraocular, intraspinal, intra-articular, intramuscular with compartment syndrome, pericardial or retroperitoneal), or resulting in death [26]. Thrombotic events include acute transient ischaemic attack, thrombotic stroke, cardio-embolic stroke, undetermined stroke and peripheral embolism. Patients lost to follow-up were included in the analyses of prescription patterns but excluded from the 1-year outcome analyses.

The study is approved by the Ethics Committee for Clinical Research (CEIC) of the University Hospital of La Princesa (Madrid). It is sponsored by the Spanish Foundation of Internal Medicine and the Spanish Society of Internal Medicine.

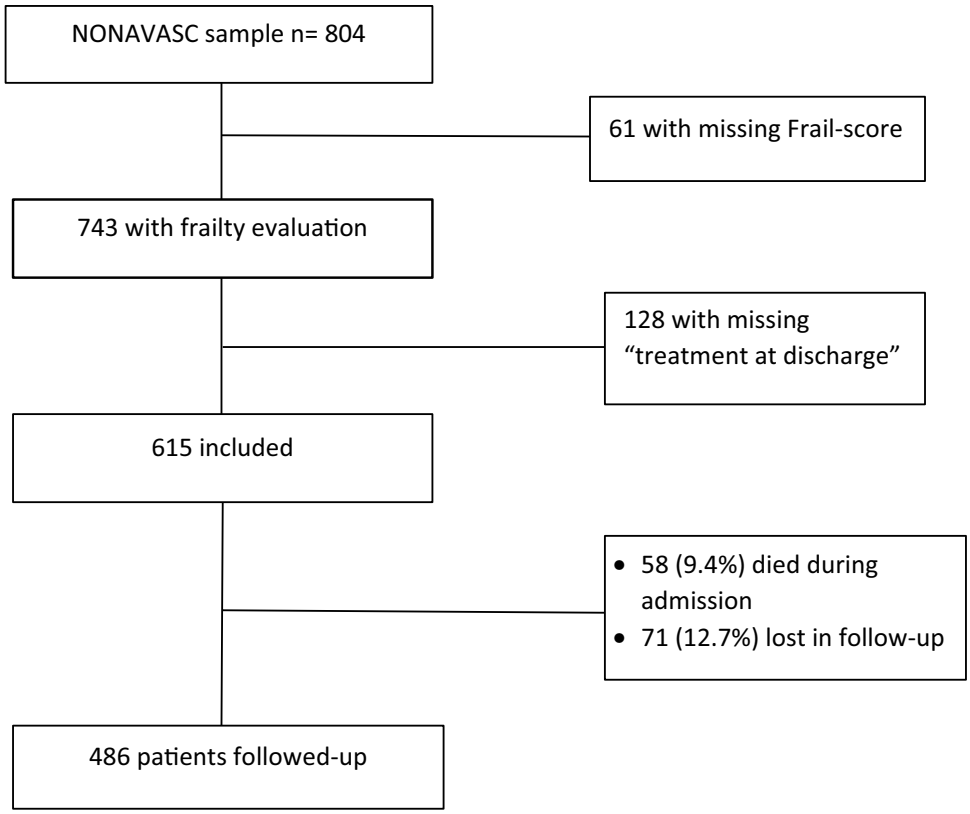

Fig. 1 Study flow chart for patient inclusion

In some patients with relevant cognitive impairment, the informed consent was obtained from their main caregiver or legal guardian.

Data analysis

Normally distributed continuous variables are reported as mean ± standard deviation or median and interquartile range (IQR). Categorical variables are reported as absolute frequencies and percentages. The Student's *t* test is used to compare continuous variables, following the performance of Levene's test for equality of variances. We use the Chi-square statistic and the Fisher's exact test for the comparison between categorical variables. To maximise the statistical power the frailty variable is analysed dichotomized (frail/non-frail). Multivariate logistic regression analyses were performed to identify factors associated with anticoagulant prescription at discharge, including vitamin K antagonist (VKA), direct oral anticoagulants (DOACs) or low molecular weight heparins (LMWH) versus no prescription of anticoagulants (including together those subjects prescribed with anti-platelets and without thromboprophylaxis). Odds ratio (OR) and 95% confidence interval (CI) were calculated. The variables include in the model were age, gender, frailty, Charlson comorbidity index (according to previous knowledge) and the baseline clinical variables with a p value < 0.10 in the univariate analysis. We twice performed the same model, first including the BI as a quantitative variable and then as a categorical one. We also performed, as a sensitivity analysis, a logistic regression evaluating the association of the different stages of frailty status and the anticoagulant prescription, considering the robust category as the reference group. The Kaplan–Meier and log-rank tests were performed to compute the survival curves of the frail and non-frail subjects. Statistical significance is accepted for a two-sided p value < 0.05. All analyses were performed with SPSS programme, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 615 patients are included in the study. The excluded patients from the initial NONAVASC sample do not present relevant differences in the clinical or baseline functional variables in comparison to the included subjects. The mean age is 85.23 ± 5.16 years (range 75–101), 54.3% female, and in most cases (89.2%) community-dwelling. The prevalence of frailty is 48.3%; 42% of patients are classified as pre-frail, and 9.8% as robust. NVAF had been diagnosed before admission in 572 (93%) patients. Hypertension is the most prevalent comorbidity (88.3%), followed by heart failure (67.2%) and chronic kidney disease (CKD) (45.2%).

Table 1 shows the comparison of baseline characteristics between frail and non-frail subjects. Frail patients have higher CHA2DS2-VASc and HAS-BLED scores compared to non-frail. They also have a higher prevalence of all cardiovascular comorbidities. In particular, the prevalence of diabetes, heart failure, stroke, peripheral vascular disease and CKD are significantly higher.

Global geriatric assessment at admission shows that, compared with non-frail, frail participants have higher comorbidities, history of more frequent of falls, lower BI scores, and more cognitive impairment and sarcopenia.

Cardiovascular pathologies and infections are the main causes that led to hospitalisation. The most frequent diagnoses at admission are heart failure (44.7%), acute renal failure (40.6%) and respiratory tract infection (37.1%). Urinary tract infection and acute renal failure are more prevalent among frail patients: 12.7% frail vs 6.1% non-frail ($p=0.002$) and 45.6% frail vs 36% non-frail ($p=0.017$), respectively, with no differences found in the rest of causes for admission.

Prescription of antithrombotic and other cardiovascular-related medications

On admission, considering only the participants with previously diagnosed AF, 87.8% were prescribed with any antithrombotic treatment: 69.8% anticoagulants [80.6% vitamin K antagonist (VKA), 14.9% direct oral anticoagulants (DOACs), and 4.5% low molecular weight heparins (LMWH)], 17.9% anti-platelets (APT) only and 9.5% double therapy (anticoagulants and APT). No differences in the antithrombotic prescription rates exist between frail and non-frail participants, although frail patients receive a significantly higher number of medications per day (Table 2). Differences are also not found in the prescription of other cardiovascular-related medications (including beta-blockers, renin–angiotensin–aldosterone system blockers, calcium antagonist, diuretics, statins, amiodarone, digoxin, and nitrates).

The comparison of antithrombotic strategies at admission between the patients who died during hospitalisation and those discharged alive by frailty status is shown in the supplementary material (Table S1).

During hospitalisation, 58 (9.4%) patients died (12.5% frail vs 6.6% non-frail, $p=0.01$), leaving 557 participants discharged. Among those patients, 69.8% received anticoagulants (67.9% VKA, 21.1% DOACs and 11% LMWH), 13.3% APT only and 9.7% double therapy. The percentage of patients with no thromboprophylaxis increased to 16.9%, due to the decrease of anti-platelet prescription (Table 2).

The prevalence of VKA prescription on discharge is lower in frail patients: 42.7% vs 51.5% (OR 0.70, 95% CI 0.50–0.98, $p=0.037$). There are no differences between frail and non-frail in the prescription of other antithrombotic choices, including anti-platelets only (OR 1.32, 95% CI 0.80–2.15), or even the non-prescription of any thromboprophylaxis (OR 1.23, 95% CI 0.79–1.92).

The antithrombotic strategies prescribed at discharge in the subgroup of subjects whose NVAF was diagnosed during the admission are shown in the supplementary material (Table S2).

Factors associated with anticoagulant prescription upon discharge (Table 3)

On the univariate statistical analysis, age, paroxysmal AF, the history of acute coronary syndrome, and the CHADS2-VASC and HAS-BLED scores are significantly associated with anticoagulant prescription. Among the variables included in the geriatric global assessment, lower Barthel scores, higher Pfeiffer index scores, and sarcopenia are associated with a decreased likelihood of anticoagulant prescription.

However, in the multivariate analysis, cognitive impairment (Pfeiffer index) and sarcopenia are no longer significant. We decided to adjust the model by Charlson index, according to previous reports [12, 14], even though we did not find differences in the univariate analysis. The BI is the only functioning parameter that remains as an independent predictor of anticoagulant prescription. The OR for severe-total dependency is 0.44 (95% CI 0.23–0.82, $p=0.01$).

Frailty is not a significant predictor of anticoagulant prescription at discharge on the univariate analysis (OR 0.74, 95% CI 0.51–1.07), nor on the multivariate analysis (aOR 0.93, 95% CI 0.55–1.57). However, the probability of receiving anticoagulants at discharge decreases d 0.89 (95% CI 0.77–1.03) times for each increase of one point in the FRAIL score. We also evaluated, as a sensitivity analysis, the relationship between the anticoagulant prescription at discharge and frailty as a scale of three categories (frail, pre-frail and robust), being robust the reference group, with similar results. The OR for the pre-frail category is 1.17 (95% CI 0.65–2.12), while the OR for the frail category is 0.75 (95% CI 0.42–1.34).

Among patients with a previous diagnosis of AF, anticoagulated on admission, who do not die during the hospitalisation, 11.2% (39) were discharged without anticoagulant therapy. Frailty is not significantly associated with the discontinuation of the anticoagulation. Differences in the prevalence of frailty between subjects who remained anticoagulated compared with those who withdrew anticoagulation are not statistically significant (43.5% vs 53.8%, $p=0.221$).

Among patients non-anticoagulated on admission, 57 (33.5%) started anticoagulation at discharge. The prevalence of frailty is similar between those who started anticoagulant therapy and those who remained without it (47.4% vs 51.3%, $p=0.481$).

Table 1 Patient characteristics

	All	Frail	Non-frail	*P*
n (%)	615	297 (48.3)	318 (51.7)	
Age (years) (mean ± SD)	85.23 ± 5.16	85.46 ± 5.05	85.01 ± 5.26	0.282
Female	334 (54.3)	181 (60.9)	153 (48.1)	0.001
Previous AF diagnosis	572 (93)	278 (93.6)	294 (92.5)	0.576
AF type				0.450
Permanent	427 (77.4)	212 (78.5)	215 (76.2)	0.523
Persistent	33 (6)	18 (6.7)	15 (5.3)	0.253
Paroxysmal	92 (16.7)	40 (14.8)	52 (18.4)	0.504
CHA2DS2-VASC Score	5.26 ± 1.37	5.62 ± 1.41	4.93 ± 1.24	< 0.0001
HAS- BLED Score	2.64 ± 1.19	2.88 ± 1.20	2.41 ± 1.14	< 0.0001
Cardiovascular diseases and risk factors				
Hypertension	543 (88.3)	266 (89.6)	277 (87.1)	0.344
Diabetes	234 (38)	126 (42.4)	108 (34)	0.031
Dyslipidaemia	252 (41.1)	125 (42.4)	127 (39.9)	0.540
Active smoking	21 (3.6)	11 (3.9)	10 (3.2)	0.324
Ischaemic heart disease	140 (23.3)	68 (23.6)	72 (23.1)	0.877
Heart failure	413 (67.2)	215 (72.4)	198 (62.3)	0.008
Cerebrovascular disease	143 (23.3)	88 (29.6)	55 (17.3)	< 0.0001
Stroke	105 (17.1)	65 (21.9)	40 (12.6)	0.002
TIA	53 (8.6)	34 (11.4)	19 (6)	0.016
Peripheral embolism	34 (5.7)	22 (7.6)	12 (3.9)	0.047
Peripheral vascular disease	83 (13.6)	51 (17.3)	32 (10.1)	0.009
History of bleeding	87 (14.1)	48 (16.2)	39 (12.3)	0.166
Chronic renal insufficiency[a]	276 (45.2)	155 (52.7)	121 (38.3)	< 0.0001
VTE	33 (5.4)	18 (6.1)	15 (4.7)	0.465
Charlson index score	3.94 ± 2.58	4.67 ± 2.71	3.27 ± 2.26	< 0.0001
Charlson classification[b]				< 0.0001
High comorbidity	420 (68.4)	228 (77)	192 (60.4)	< 0.0001
No comorbidity	106 (17.3)	29 (9.8)	77 (24.2)	< 0.0001
History of falls	268 (27.8)	98 (33.8)	70 (22.2)	0.001
Number of falls last year	2.43 ± 2.03	2.52 ± 1.95	2.32 ± 2.14	0.554
Barthel index score	66.00 ± 31.58	53.14 ± 30.07	77.94 ± 28.11	< 0.0001
Barthel categories[c]				< 0.0001
Total-severe dependency	152 (24.8)	106 (35.9%)	46 (14.5%)	< 0.0001
Moderate dependency	88 (14.4)	61 (21.7%)	24 (7.5%)	< 0.0001
Mild or no dependency	373 (60.8)	125 (42.4%)	248 (78%)	< 0.0001
Pfeiffer score	3.51 ± 3.03	4.06 ± 3.04	2.99 ± 2.93	< 0.0001
Pfeiffer categories[c]				< 0.0001
Severe cognitive impairment	77 (13.4)	43 (15.4%)	34 (11.4%)	0.162
Mild–moderate cognitive impairment	238 (41.3)	135 (48.4%)	103 (34.7%)	0.001
No cognitive impairment	261 (45.3)	101 (36.2%)	160 (53.9%)	< 0.0001
Sarcopenia[d]	299 (49.8)	207 (72.4%)	92 (29.3%)	< 0.0001
Serum albumin (g/dL)	3.47 ± 0.61	3.42 ± 0.67	3.51 ± 0.55	0.098
Exitus during admission	58 (9.4)	37 (12.5%)	21 (6.6%)	0.013

SD standard deviation, *AF* atrial fibrillation, *TIA* transient ischemic attack, *VTE* venous thromboembolism

[a]eGFR < 60 ml/min

[b]Charlson index categories: high comorbidities (≥ 3 points). No comorbidities (0–1 points)

[c]Barthel index categories: total-severe (BI ≤ 40), moderate (BI = 41–60) and mild or no dependency (BI = 61–99)

[c]Pfeiffer score categories: severe (8–10 mistakes), mild–moderate (3–7 mistakes), normal (0–2 mistakes)

[d]SARC-F scale > 4 points

Table 2 Distribution of the antithrombotic strategies on admission and discharge

	All	Frail	Non-frail	*P*
Admission[a]				
n (%)	547	263 (48.1)	284 (51.9)	
No. active ingredients per day	8.54 ± 3.47	9.06 ± 3.54	8.05 ± 3.34	0.001
No. pills per day	9.67 ± 4.55	10.51 ± 4.81	8.91 ± 4.16	< 0.0001
Antithrombotic therapy	480 (87.8)	229 (87.1)	251 (88.4)	0.641
Anti-platelet therapy only	98 (17.9)	51 (19.4)	47 (16.5)	0.386
Anticoagulants	382 (69.8)	178 (67.7)	204 (71.8)	0.310
VKA	308 (56.3)	141 (53.6)	167 (58.8)	0.221
DOACs	57 (10.4)	26 (9.9)	31 (10.9)	0.694
LMWH	17 (3.1)	11 (4.2)	6 (2.1)	0.163
Double therapy[b]	52 (9.5)	25 (9.5)	27 (9.5)	1.000
No thromboprophylaxis	67 (12.2)	34 (12.9)	33 (11.6)	0.641
Discharge				
n (%)	557	260 (46.7)	297 (53.3)	
No. active ingredients per day	8.95 ± 3.34	9.42 ± 3.36	8.53 ± 3.27	**0.002**
No. pills per day	10.33 ± 4.45	11.08 ± 4.53	9.67 ± 4.27	**< 0.0001**
Antithrombotic therapy	463 (83.1)	212 (81.5)	251 (84.5)	0.350
Anti-platelet therapy only	74 (13.3)	39 (15)	35 (11.8)	0.265
Anticoagulants	389 (69.8)	173 (66.5)	216 (72.7)	0.112
VKA	**264 (47.4)**	**111 (42.7)**	**153 (51.5)**	**0.037**
DOACs	82 (14.7)	40 (15.4)	42 (14.1)	0.680
LMWH	43 (7.7)	22 (8.4)	21 (9.7)	0.735
Double therapy	54 (9.7)	21 (8.1)	33 (7)	0.227
No thromboprophylaxis	94 (16.9)	48 (18.5)	46 (15.5)	0.350

VKA vitamin K antagonists, *DOACs* direct oral anticoagulants, *LMWH* low molecular weight heparins

[a]Evaluated in patients with previous diagnose of AF

[b]Anticoagulant and anti-platelet therapies

Table 3 Factors associated with anticoagulant prescription upon discharge

Variables	Anticoagulants	No anticoagulants	Univariate		Multivariate	
			OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Male sex	184 (47.3)	68 (40.5)	1.32 (0.91–1.90)	0.137	1.45 (0.85–2.48)	NS
Age	84.58 ± 5.03	86.35 ± 5.34	0.93 (0.90–0.97)	< 0.001	0.95 (0.91–0.99)	0.049
Paroxysmal AF	49 (13.8)	43 (23.1)	1.76 (1.11–2.7)	0.014	0.41 (0.22–0.74)	0.003
ACS	80 (26.6)	14 (8.5)	2.80 (1.53–5.10)	0.001	2.20 (1.08–4.48)	0.029
CHADS2-VASC score	5.35 ± 1.39	5.11 ± 1.33	1.13 (0.99–1.29)	0.065	1.45 (1.16–1.81)	0.001
HAS-BLED score	2.54 ± 1.19	2.77 ± 1.17	0.84 (0.73–0.98)	0.034	0.74 (0.60–0.91)	0.005
Charlson index	3.94 ± 2.60	3.85 ± 2.57	1.01 (0.94–1.08)	0.682	0.90 (0.81–1.00)	NS
Barthel index	72.25 ± 28.40	56.58 ± 33.93	1.17 (1.10–1.24)*	<0.001	1.17 (1.05–1.31)*	0.005
Pfeiffer index	2.95 ± 2.70	4.12 ± 3.27	0.87 (0.82–0.93)	<0.001	0.98 (0.89–1.08)	NS
Frailty	173 (44.5)	87 (51.8)	0.74 (0.51–1.07)	0.112	0.93 (0.55–1.57)	NS
Sarcopenia	164 (42.8)	96 (60)	0.49 (0.34–0.72)	<0.001	0.92 (0.54–1.49)	NS
History of falls	112 (29.5)	49 (31.6)	0.90 (0.60–1.35)	0.625	–	–

AF atrial fibrillation, *ACS* acute coronary syndrome, *OR* odds ratio, *aOR* adjusted OR, *NS* non-significant

*OR calculated for each ten-point variation in Barthel index score

Outcomes over a 1-year follow-up

Seventy-one participants (12.7%) went missing during the follow-up period (frail 40.8%). Data were available in 486 subjects. The lost patients do not present differences in any of the clinical or functional variables studied compared to the patients with follow-up.

Overall, there are 19 (4.1%) thrombotic complications: ten cardio-embolic strokes, three thrombotic strokes, three undetermined strokes and three transient ischaemic attacks. The incidence of stroke in patients taking anticoagulants is 3%, with no differences between frail and non-frail (2.7% vs 3.2%, $p=0.79$).

There were also 55 bleeding events (11.8%), 65.5% that occurred in patients taking anticoagulants, and 70.9% are considered to be major bleeds. Among those taking anticoagulants, the incidence of major bleeding is 7.9%, with no significant differences between frail and non-frail (7.5% vs 8.1%, $p=0.84$).

During the follow-up year, 161 patients died (33.1%). The Kaplan–Meier survival function indicates that frail participants have a higher probability of dying compared to non-frail (log-rank Mantel–Cox 17.79, 1 df, $p<0.001$) (Fig. 2). Univariate Cox regression analysis shows that frail patients have a nearly two-fold higher risk of all-cause death over 1 year (HR 1.99, 95% CI 1.43–2.76).

The stratified analysis by anticoagulant prescription shows that this association between frailty and mortality is particularly relevant in patients who are anticoagulated (35.7 vs 20.1%, log-rank Mantel–Cox 17.54, 1 df, $p<0.001$), meanwhile in the group of non-anticoagulated, the differences in the survival rates are not statistically significant (53.2 vs 40.9%, log-rank Mantel–Cox 2.07, 1 df, $p=0.150$).

Discussion

In this multicentre study of hospitalised older patients with NVAF, we find frailty to be present in almost half of the sample. Frail patients have more comorbidities and a higher risk of stroke and bleeding according to CHAD2S2-VASC and HAS-BLED scores. Their functional and cognitive status are worse compared to non-frail with 36% of severe-total dependency and 15.4% of severe cognitive impairment. These findings are in agreement with previous studies, in which frailty has been associated with increased comorbidities, higher thrombotic risk, and institutionalization [13, 14, 27].

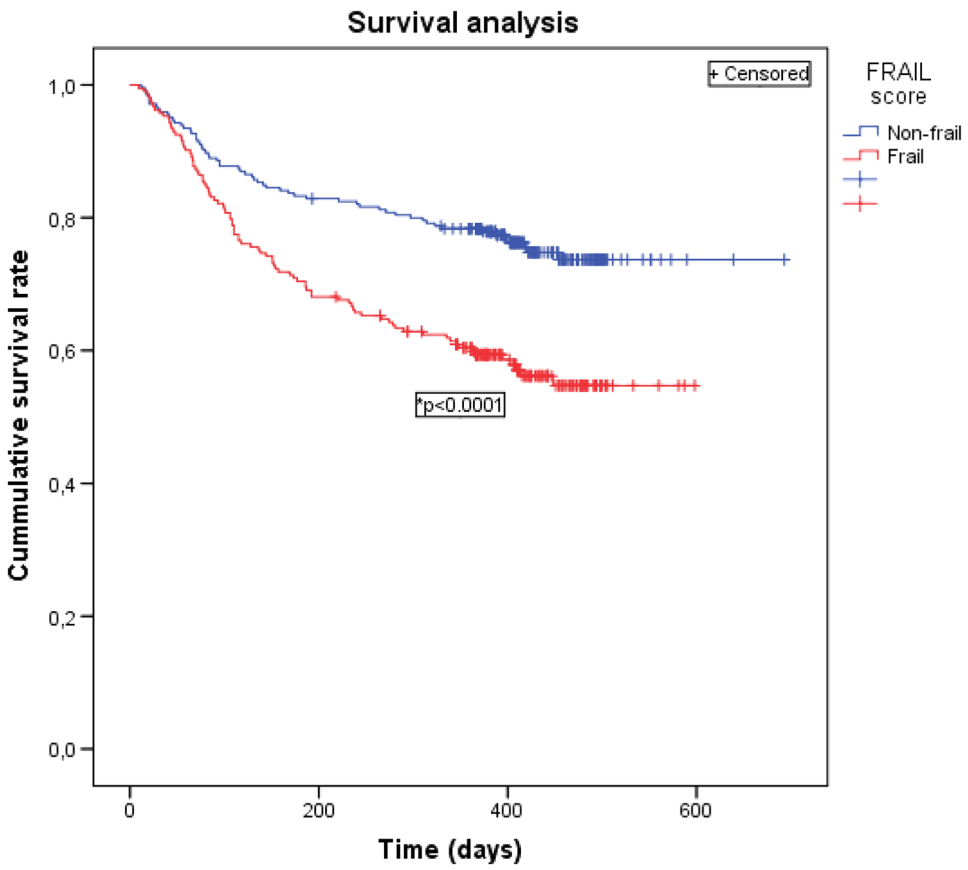

Fig. 2 The Kaplan–Meier survival curves in frail and non-frail participants

We find that 66% of the participants were prescribed with oral anticoagulants on admission, and that this percentage decreases to 62% at discharge. Published data on OAT prescription rates in older patients vary between 32 and 59% [28, 29]. Our rate is slightly higher, but similar to that found in other studies performed in hospitalised patients [11, 14].

In the univariate analysis, frail patients are less likely to be prescribed with VKA upon discharge. However, this association is not confirmed in the multivariate analysis. The factors that are identified as independent predictors of a decreased likelihood of anticoagulant prescription are: age, higher HAS-BLED scores, paroxysmal AF and functional dependency, while higher CHAD2S2-VASC scores and the history of ACS increase it.

The impact of frailty on anticoagulant prescription is controversial. Some studies have shown an association between frailty and non-prescription of OAT [13, 14], while others have not [27, 30]. The variability in these results could be explained by the use of different tools to identify frailty, since there is no consensus on which tool should be used, and each one focuses on different aspects. Conversely, functional disability for BADL has been consistently related to non-prescription of OAT [11, 12, 31, 32].

The relationship between frailty and disability is noticeable. Severely frail patients typically have functional impairment, but not all frail individuals are necessarily disabled, since frailty usually precedes dependence [33]. In our study, the prevalence of frailty among those with severe-total dependency is 70%, while the prevalence of severe or total dependency among the frail participants is 35.9%.

Regarding the other factors identified, our results are in accordance with several previous studies in which the CHAD2DS2-VASc and the HAS-BLED scores have been highlighted as predictors of OAT prescription [11, 12, 14, 31].

Paroxysmal AF is identified as an independent predictor of a reduced likelihood of anticoagulant prescription. This association has been previously reported [12, 34]. This finding could be due to a false perception by the treating physicians of a lower thrombotic risk associated with this type of AF, although the stroke risk is considered equivalent between paroxysmal and permanent AF. The current guideline-based recommendations for anticoagulation explicitly indicate that prescriptions should be made based on risk factors regardless of AF type or duration [16].

Likewise, we find that chronological age is also an independent predictor of anticoagulant prescription. This finding is not novel in the literature [11, 12, 14]. Considering that the mean age of our sample is 85 years, this result indicates that the oldest patients with a consequent shorter life expectancy may not be considered optimal candidates for anticoagulant therapy.

Our results reflect the complex real-world experience of prescribing anticoagulants in older adults, in which several factors currently not included in common scoring systems, may play a relevant role in the physician's decision to prescribe OAC. Its use in the oldest, most vulnerable, severely frail and disabled patients could be understood as futile. For this reason, the current recommendations advice combines a comprehensive geriatric assessment with the traditional risk scores for the selection of the candidates [35, 36].

The use of non-OAT thromboprophylaxis observed in our study deserves some comments. The proportion of patients receiving APT decreases at discharge (17.9% at admission and 13.3% at discharge), while the use of DOAC and the proportion of participant with no therapy increases. Our data show similar or even lower rates of APT prescription, compared to previous studies conducted in Europe [8, 11, 12]. However, APT continues to be used frequently, despite proper indications against this practise [16].

Our results show that frailty is not associated with bleeding complications or higher incidence of stroke, among those patients with anticoagulants during follow-up. To our knowledge, only two studies had evaluated this aspect in hospitalised subjects, both with a follow-up of 6 months. Perera et al. report that frail participants have an RR of 3.5 for experiencing an embolic stroke, with a non-significant increase in the risk of haemorrhage [13]. Nguyen et al. find no significant differences between frailty groups in both items [27].

Finally, we observe that frailty is associated with higher mortality during admission and with a two-fold increased risk of death after 1 year. There is consistent evidence in the literature agreeing with our results [2, 5, 6]. This association seems particularly relevant in the frail patients who are anticoagulated. The lack of statistically significant differences in mortality by frailty among the non-anticoagulated subjects could be explained by a greater relative mortality risk of the non-frail participants due to the absence of the beneficial effects of the anticoagulation. Further studies should bring more information about the causes of death of the frail patients, considering that they do not seem to suffer more AF or antithrombotic treatment-related complications.

Our study has several limitations. The findings can only be extrapolated to a very old hospitalised population. Some information was obtained through interviews with the patients/caregivers and a retrospective review of medical records. Therefore, an information bias cannot be excluded. Our observational study design can provide evidence of predictive association but not of causality. Some data were missing and the 12% of participants lost in the follow-up is not insignificant. Despite these limitations, we believe that our study has important strengths. Based on its national multicentre study design and its broad inclusion criteria, we reached a significant sample size of very old and frail people who are often excluded

from studies [37]. Moreover, the methodology used allowed us to achieve the stated objectives.

In conclusion, in this real-world setting of older patients with NVAF, frailty correlates with greater comorbidities and worse global health status. However, it has no impact on the selection of the antithrombotic strategy nor is a predictor of AF complications among those anticoagulated, even though frail subjects have a higher mortality during hospitalisation and after 1-year follow-up.

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Compliance with ethical standards

Conflict of interest None of the authors have had any relationship with industry and financial associations that might pose a conflict of interest with the manuscript.

Statements on human and animal rights The study is approved by the appropriate institutional research ethics committee. All procedures performed in the study involving human participants are in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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