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Research Paper

Frailty increases the risk of hospitalization for atrial fibrillation in older adults: a population-based cohort study

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ABSTRACT

Background and aims: Atrial fibrillation (AF) is more common with increasing age and older adults have greater prevalence of frailty, multimorbidity and polypharmacy, which may impact clinical outcomes. The present study aims to investigate the relationship between frailty and the risk of hospitalization for AF in older adults, and second, the possible interaction of multimorbidity in this association.

Methods and results: Data from the Progetto Veneto Anziani (Pro.V.A.), an observational cohort study in north-eastern Italy, were utilised. The analyses included 2909 individuals aged ≥65 years without AF at baseline, assessed between 1995 and 1997, with follow-ups at 4.4 and 7 years. Frailty was defined according to Fried's criteria, and multimorbidity as the number of chronic diseases. AF-related hospitalizations and deaths were recorded up to December 31, 2018. Multi-adjusted mixed-effects Cox regressions were performed to test associations.

Over the follow-up period, 318 (10.9 %) participants experienced AF-related hospitalizations. Compared to robust participants, the hazard ratio (HR) of hospitalizations due to AF was 1.42 (95 % Confidence Interval (95 % CI): 1.04–1.95) in pre-frail and 1.98 (95 %CI: 1.21–3.26) in frail individuals, even after adjusting for multimorbidity. The number of chronic diseases was only marginally and not significantly associated with AF-related hospitalizations (HR 1.07, 95 %CI: 0.99–1.15), but did not significantly interact with frailty in the association with AF-related hospitalizations.

Conclusion: Older adults with frailty present with higher hazards of AF-related hospitalizations, irrespective of the presence of multimorbidity. Further studies are needed to evaluate whether reducing frailty may prevent AF development and improve health outcomes in older adults.

1. Introduction

Atrial fibrillation (AF) is common in older adults, and increasing age is more associated with frailty, multimorbidity and polypharmacy, which may impact clinical outcomes and healthcare costs [1]. In recent years, frailty, which is a geriatric syndrome encountered mainly among older persons, characterized by reduced individual resilience, has been increasingly studied in relation to AF, given the aging general population. Several studies have reported that approximately 40 % of older adults with AF were frail [2,3] and these patients were associated with a higher mortality and risks of thromboembolism and of hemorrhagic complications from anticoagulant prescription [2,4,5].

Although the relationship between frailty and AF outcomes is relatively consistent, there is less evidence thus far concerning the possible effect of frailty on the onset of AF. Indeed, an association of frailty with incident AF has been observed by a few studies only in women and patients with hypertension [6,7], with other studies reporting no association [8,9], leaving this issue insufficiently explored.

Older adults with frailty may have a higher risk of AF, supported by the fact that some features of frailty predispose individuals to AF. For instance, low physical activity, slowness, weakness, and exhaustion, which characterize frailty phenotype, are risk factors for the onset of cardiovascular diseases, including AF, in advanced age [10–15]. From a pathophysiological point of view, frailty is linked to a gradual deterioration of systems and organs, leading to an accumulation of deficits and diseases [13,16] and the development of multimorbidity [17]. These deficits and diseases include somatic, psychological, and functional factors associated with an increased risk of AF [18,19]. Therefore, considering the close relationship between frailty and multimorbidity [17], it may be interesting to explore how these conditions interplay in the development of AF.

The aim of the present study was two-fold, first, to assess the longitudinal association between frailty and the risk of hospitalization for AF in older individuals and second, to evaluate the possible influence of multimorbidity on this relationship.

2. Methods

The present study is part of the "Atrial fibrillation integrated approach in frail, multimorbid and polymedicated older people" (AFFIRMO) project, funded by the European Union (Horizon 2020, Grant Agreement No. 899871) [20]. The overall goal of the project is to optimize the management of older adults with AF and multiple chronic conditions by extending the current evidence from observational studies and evaluating the effectiveness of an integrated approach in clinical settings.

2.1. Study population

Data from the Progetto Veneto Anziani (Pro.V.A.), an observational cohort study conducted in two cities of the Veneto region (north-eastern Italy), were analyzed, as described in detail elsewhere [21]. Briefly, the study was based on a random sample of 3099 adults aged ≥65 years, including both community-dwelling and institutionalized individuals, selected using a multistage stratified sampling method. Baseline assessment was conducted between 1995 and 1997, while the two active follow-up assessments were conducted after a mean of 4.4 (standard deviation (SD 0.5) and 7 years (SD 0.5) from the baseline. Information on participants' vital status and hospitalizations up to December 31, 2018, was obtained using administrative data from the regional archives. The study protocol was approved by the Ethics Committees of the University of Padova, the Local Health Units n. 15 and 18 of the Veneto Region, and the province of Padova center. All participants signed an informed consent form. The study complied with the principles of the Declaration of Helsinki.

[1] The complete list of the AFFIRMO Consortium can be found in the Acknowledgements.
[a] These authors equally contributed to the study.

2.2. Participant assessments

At baseline, face-to-face interviews, medical records evaluation, standardized questionnaires, and physical examinations were performed by trained physicians and nurses. Collected sociodemographic information pertained to age, gender, living arrangements (living with somebody vs. living alone vs. living in a nursing home), educational level (categorized as <5 vs ≥ 5 years), smoking habits (never, former or current smoker) and alcohol consumption (defined as no/occasional, light to moderate with <7 units of alcohol [UA]/week for women and <14 UA/week for men, and heavy with ≥7 UA/week for women and ≥14 UA/week for men). Body weight and height were measured with individuals wearing light indoor clothing and no shoes, and body mass index (BMI) was calculated as the ratio between body weight and height squared. Depressive symptoms were measured using the 30-item Geriatric Depression Scale (GDS), a validated scale to assess depressive mood in older adults, including those with mild to moderate dementia. The GDS score ranges from 0 (no depressive symptoms) to 30 (depressive symptoms), with a cutoff of 11 indicating clinically significant depressive symptoms [22]. Medical conditions assessed by physicians based on physical examination, medical records, questionnaires, drugs taken, and biochemical analyses included: congestive heart failure, coronary artery diseases (angina and myocardial infarction), peripheral artery disease, osteoporosis, history of hip fracture, osteoarthritis (at hand, knee or hip), disc disease, stroke, Parkinson Disease, congenital cognitive deficits, diabetes, hypertension, orthostatic hypotension, anemia, dyslipidemia, chronic kidney disease, chronic obstructive pulmonary disease (COPD), cancer, urinary and fecal incontinence. The total number of chronic diseases for each participant was calculated as an indicator of multimorbidity. Chronic joint pain was assessed by physicians by asking participants whether they had experienced pain in the back, hands/wrists, shoulders, knees or ankles/feet during the preceding month. Systolic and diastolic blood pressure was measured in participants in supine position. The average systolic and diastolic values of three measurements was taken into consideration for the analysis. From the list of chronically used medications, we derived the use of analgesics, diuretics, ACE inhibitors, and cardiovascular drugs (including beta-blockers, calcium channel blockers, centrally acting antihypertensive drugs, vasodilators, nitrates, antyarrthimics, digoxin, vasoprotective drugs, sympathomimetic drugs). Biochemical examinations were performed at baseline on venous blood samples collected from the study participants after an overnight fast. Samples were centrifuged, stored at −80 °C, and then analyzed at the laboratory of the University Hospital of Padua (Italy), following standard procedures and quality controls. In particular, for the purpose of this study, we considered serum creatinine and total cholesterol levels (both expressed as mg/dL).

Cognitive status was evaluated using the Mini-Mental State Examination (MMSE) score [23]. Functional status was measured through the Activities of Daily Living (ADL) scale, including assessment of self-sufficiency in bathing, dressing, transferring, toileting, continence, and feeding [24].

2.3. Exposures

Frailty status at baseline and the first follow-up was assessed using the criteria proposed by Fried et al. [13], which include weakness, exhaustion, weight loss, low physical activity, and low walking speed. In particular, robustness, pre-frailty, and frailty were defined based on the presence of none, 1–2, and ≥3 criteria mentioned above, respectively. The assessment methods of each frailty criterion are briefly described below.

- Weakness was evaluated by handgrip strength, considering our population's lowest sex- and BMI-specific 20th percentile as a cutoff [13]. Handgrip strength was measured using a dynamometer, with two trials per hand, and the best value (expressed in kg) was taken into account for the analysis. Participants with missing data on handgrip strength were considered weak if they reported an inability to eat autonomously based on the specific ADL item, as this implies a lack of grip strength, which is essential for feeding ability [24].
- Exhaustion was assessed using GDS [22]; participants were considered exhausted if they did not feel full of energy and scored 11 or more points on the GDS.
- Weight loss was defined as a self-reported loss of 5 kg or more in the last year.
- Low physical activity was determined by calculating estimated energy expenditure for daily activities, collected through a structured questionnaire, and using the lowest sex-specific 20th percentile as a cutoff [13].
- Low walking speed was assessed by measuring the time to walk 4 m at the usual pace, using the lowest sex- and height-specific 20th percentile as a cut-off [13]. If walking speed data were missing, participants were considered to have a low walking speed if they reported being unable to move around autonomously (use of walking aids was allowed).

2.4. Outcome

Hospitalizations for AF over the first 10 years of observation were obtained through linkage from regional registers, considering the ICD-9 codes reported at discharge as primary or secondary diagnosis. In particular, the following ICD-9 codes were considered as indicators of AF-related hospitalization: 427.3 (Atrial Fibrillation), 427.31 (Atrial Fibrillation), and 427.32 (Atrial flutter). Deaths during the observation period were derived from regional registers. Two time periods were considered for these analyses: (i) from baseline to the first follow-up (mean duration 4.3 ± 0.5 years), and (ii) from the first follow-up to 10 years (mean duration 6 ± 0.6 years).

2.5. Statistical analysis

The baseline characteristics of the study participants are presented as mean (standard deviation (SD)) for quantitative variables and count (percentage) for qualitative variables. Participants with AF diagnosis at baseline were excluded from these models. Comparisons of baseline characteristics among robust, pre-frail, and frail individuals, as well as the number of morbidities (0–2, first quartile of the distribution; 3–4, second quartile; 5+, third and fourth quartiles) were conducted using Student's t-test and the Fisher or Chi-squared test.

The association between frailty and the risk of AF-related hospitalization was evaluated considering mixed-effects Cox regressions over two time periods (from baseline to the first follow-up, and from the first follow-up to 10 years), considering the presence of repeated measures for each individual. The model intercept was set as random to take into account multiple observations for each participant. In the analysis, we considered time to the first AF-related hospitalization or, for those who did not experience any event, time to death or the end of observation as appropriate. Analyses were run first adjusted only for age and sex (model 1) and, then adjusting also for other potential confounders (living arrangements, education, smoking habits, alcohol consumption, number of chronic diseases, MMSE score, GDS score, BMI; model 2). The multiplicative interaction between frailty and multimorbidity was also evaluated. Models were re-run adjusting for specific diseases (cardiovascular diseases, osteoarticular diseases, neuropsychiatric diseases, diabetes mellitus, cancer, chronic obstructive pulmonary disease, hypertension, dyslipidemia, chronic kidney disease, depression, low vision, and hearing loss).

Missing values were not imputed in the primary analysis. Sensitivity analyses were conducted using multiple imputations for confounders with missing data, considering the fully conditional specification method [25]. A total of ten imputed data sets were created and combined using Proc MI Analyze.

Further sensitivity analyses were performed using mixed-effects competing risks Cox regression models. The data were obtained by duplicating the dataset, giving each subject a separate observation for each outcome (AF-related hospitalization, and mortality), as described by Lunn and McNeil [26]. Additional sensitivity analyses included mixed-effects Cox regression models further adjusted for systolic and diastolic blood pressure, total cholesterol, creatinine levels, and the use of cardiovascular medications, as well as diuretics and ACE inhibitors. All statistical tests were two-tailed, and statistical significance was assumed for a p-value <0.05. All analyses were performed using SAS 9.4 and SAS OnDemand for Academics.

3. Results

From the initial study population of 3099 older adults, we excluded 190 individuals (6.1 %) with AF at baseline. Excluded participants were significantly older, had a higher mean number of comorbidities and a lower MMSE score, and were more frequently frail or pre-frail than those included in the analysis (Supplementary Table 1).

The final sample cohort consisted of 2909 individuals; of these, 267 (9.2 %) were frail, and 1333 (45.8 %) were pre-frail (Table 1). The mean age of the participants was 76.2 years (SD 7.8), about 60 % were female, and around half reported ≥5 years of schooling. Most lived in the community, with only 3.8 % residing in nursing homes. The total sample had on average five chronic conditions, a mean MMSE score of 22.9 (SD 6.6), and a relatively high level of self-sufficiency in ADL.

Frail participants were significantly older, more frequently females, reported lower education and higher percentages of institutionalization than pre-frail or robust individuals. Compared with non-frail individuals, they had a higher mean number of diseases, worse MMSE scores, and lower independency in ADL. Similar characteristics were observed for the participants with a higher number of diseases (Supplementary Table 2).

At least one AF-related hospitalization was reported by 155 individuals (5.3 %) from the baseline to the first follow-up, and by 163 (6.8 %) from the first follow-up to the end of the observation period (Supplementary Table 3). Participants hospitalized for AF were more likely to be older, less educated, frail, multimorbid, and have worse cognitive and functional status than those with no AF-related hospitalization (Table 2), with no significant sex differences. Overall, 1519 individuals died during the follow-up.

In a mixed-effects Cox regression model adjusted for potential confounders, including the number of chronic diseases, frailty was significantly associated with AF-related hospitalization, with a hazar ratio (HR) 1.42 for pre-frail and 1.98 for frail individuals (Table 3).

The number of chronic diseases showed a borderline significant association with AF-related hospitalization (HR = 1.07, 95 %CI: 0.99–1.15; Fig. 1). A non-significant interaction between frailty and the number of chronic diseases was found (p = 0.410). The association with frailty and the borderline association with the number of chronic diseases were confirmed when analyses were repeated after multiple imputation for missing data for the confounders (HR = 1.45, 95 % CI: 1.06–1.97; HR = 2.06, 95 % CI: 1.30–3.24, and HR = 1.06, 95 % CI: 0.997–1.13, for pre-frailty, frailty and the number of chronic diseases, respectively).

In sensitivity analyses, when adjusting models for specific diseases, frailty remained significantly associated with AF-related hospitalization (Supplementary Table 4, HR 1.45, 95 % CI 1.08–1.94 for pre-frailty, and HR 2.02, 95 % CI 1.32–3.08 for frailty). Considering the competing risk of death, sensitivity analyses confirmed the association between frailty and AF-related hospitalization (Supplementary Table 5: HR 1.29, 95 % CI 0.99–1.67 for pre-frailty; HR 1.50, 95 % CI 1.07–2.09 for frailty). Adjusting for systolic and diastolic blood pressure, total cholesterol, creatinine, and for diuretics, ACE inhibitors and cardiovascular drugs use, the association of frailty with AF-related hospitalization remained significant (HR = 2.05, 95 % CI 1.20–3.51, Supplementary Table 6).

Table 1
Baseline characteristics by frailty status.

	All (n = 2909)	Frailty			p-value
		Robust (n = 1309)	Pre-frail (n = 1333)	Frail (n = 267)	
Age, years, mean ± SD	76.2 ± 7.8	73.0 ± 6.2	78.2 ± 8.1	81.5 ± 7.1	<0.001
Sex, females, n (%)	1742 (59.9)	752 (57.5]	816 (61.2)	174 (65.2)	0.026
Education ≥5 years, n (%)	1501 (51.7)	799 (61.0]	597 (44.9)	105 (39.5)	<0.001
Living arrangements, n (%)					<0.001
Living with somebody	2304 (69.5)	1068 (81.6]	1040 (68.4)	196 (64.5)	
Living alone	486 (16.8)	237 (18.1]	201 (15.2)	48 (18.3)	
Living in nursing home	109 (3.8)	4 (0.3]	86 (6.5)	19 (6.2)	
Smoking habits, current smoker, n (%)	259 (8.9)	135 (10.3]	114 (8.6)	10 (3.8)	0.003
Alcohol consumption, heavy drinker, n (%)	349 (12.0)	191 (14.6]	149 (11.2)	9 (3.4)	<0.001
BMI, mean ± SD	27.6 ± 4.6	27.6 ± 4.3	27.4 ± 4.7	27.9 ± 5.4	0.183
N. chronic diseases, mean ± SD	4.9 ± 2.4	3.9 ± 1.9	5.5 ± 2.4	6.9 ± 2.4	<0.001
Mini-Mental State Examination, mean ± SD	22.9 ± 6.6	25.4 ± 4.0	21.1 ± 7.8	19.8 ± 6.0	<0.001
Geriatric Depression Scale, mean ± SD	8.8 ± 6.3	6.1 ± 4.6	10.3 ± 6.4	16.0 ± 5.7	<0.001
Activities of Daily Living, mean ± SD	4.7 ± 1.7	5.2 ± 1.1	4.2 ± 1.8	2.9 ± 2.0	<0.001
Chronic joint pain, n (%)	2007 (64.8)	878 (64.3)	885 (61.6)	244 (82.4)	<0.001
Analgesic drugs, n (%)	694 (27.0)	292 (27.4)	313 (25.2)	89 (34.1)	0.012
Cardiovascular drugs, n (%)	1408 (54.8)	506 (47.6)	741 (59.6)	161 (61.7)	<0.001
Diuretics, n (%)	1064 (41.4)	384 (36.1)	539 (43.4)	141 (54.0)	<0.001
ACE inhibitors, n (%)	736 (28.7)	303 (28.5)	357 (28.7)	76 (29.1)	0.977
Systolic blood pressure, mmHg, mean ± SD	153.4 ± 25.8	152.7 ± 20.8	153.8 ± 30	154.4 ± 24.7	0.674
Diastolic blood pressure, mmHg, mean ± SD	83.1 ± 12.2	84 ± 12.1	82.3 ± 12.1	82.8 ± 13.4	<0.001
Total cholesterol, mg/dL, mean ± SD	229.5 ± 45.3	233.7 ± 43.9	227.1 ± 45.6	222.1 ± 48.7	<0.001
Creatinine, mg/dL, median (IQR)	0.97 (0.85, 1.11)	0.95 (0.84, 1.09)	0.98 (0.85, 1.14)	1 (0.86, 1.14)	<0.001

Abbreviations: BMI, Body Mass Index; IQR, Interquartile range; SD, Standard Deviation.

4. Discussion

The present study investigated the association between frailty, multimorbidity, and the risk of hospitalizations for AF in a cohort of older adults. Our principal finding was that both pre-frailty and frailty were associated with AF-related hospitalizations even after adjustment for multiple confounders, including the number and type of comorbidities.

Our results support the important role of frailty in influencing the onset of cardiovascular diseases in the older population. In particular, the risk of AF-related hospitalizations gradually increased from pre-frail to frail individuals, the latter having a nearly two fold higher risk

Table 2
Baseline characteristics by hospitalization for AF hospitalizations.

	Hospitalization for AF					
	Time window 1 (from baseline to the first follow-up)			Time window 2 (from the first follow-up to 10 years)		
	No (n = 2753)	Yes (n = 155)	p-value	No (n = 677)	Yes (n = 153)	p-value
Age, years, mean ± SD	76.0 ± 7.8	79.4 ± 7.5	<0.001	78.2 ± 6.9	81.1 ± 7.4	<0.001
Sex, females, n (%)	1650 (59.9)	91 (58.7)	0.76	1359 (63.1)	91 (59.5)	0.37
Education ≥5 years, n (%)	1436 (52.2)	65 (42.2)	0.02	1196 (55.6)	65 (42.5)	0.002
Living arrangements, n (%)			0.15			0.51
Living with somebody	2191 (69.9)	113 (63.4)		817 (57.8)	68 (56.2)	
Living alone	451 (16.4)	34 (22.1)		419 (29.7)	41 (33.9)	
Institutionalized	102 (3.7)	7 (4.6)		177 (12.5)	12 (9.9)	
Current smoking habits, n (%)	250 (9.1)	9 (5.8)	0.16	132 (6.3)	8 (5.4)	0.33
High alcohol consumption, n (%)	327 (11.9)	22 (14.2)	0.39	256 (11.9)	18 (11.8)	0.97
BMI, mean ± SD	27.6 ± 4.6	26.9 ± 4.2	0.19	27.9 ± 4.8	28.1 ± 4.9	0.91
Frailty, n (%)			0.0002			0.004
Robust	1260 (45.8)	48 (31.0)		818 (55.4)	49 (41.5)	
Pre-frail	1251 (45.4)	82 (52.9)		543 (36.8)	52 (44.1)	
Frail	242 (8.8)	25 (16.1)		116 (6.9)	17 (14.4)	
N. chronic diseases, mean ± SD	4.9 ± 2.4	5.4 ± 2.4	0.007	4.6 ± 2.3	5.2 ± 2.5	0.004
MMSE, mean ± SD	23.0 ± 6.5	21.4 ± 7.4	0.002	22.5 ± 7.3	21.4 ± 6.4	0.001
GDS, mean ± SD	8.7 ± 6.3	9.7 ± 6.5	0.08	8.9 ± 6.3	8.7 ± 6.1	0.86
ADL, mean ± SD	4.7 ± 1.6	4.2 ± 1.9	0.006	4.8 ± 1.6	4.6 ± 1.6	0.036
Chronic joint pain, n (%)	1784 (64.8)	97 (62.6)	0.573	1454 (67.5)	106 (69.3)	0.650
Analgesic drugs, n (%)	636 (28.1)	25 (19.4)	0.031	505 (28.8)	35 (27.6)	0.761
Cardiovascular drugs, n (%)	1157 (51.1)	95 (73.6)	<0.001	849 (48.5)	75 (59.1)	0.021
Diuretics, n (%)	885 (39.1)	65 (50.4)	0.011	656 (37.4)	57 (44.9)	0.095
ACE inhibitors, n (%)	633 (28.0)	42 (32.6)	0.260	492 (28.1)	46 (36.2)	0.050
Systolic blood pressure, mmHg, mean ± SD	153.6 ± 26.1	153.7 ± 23.4	0.933	152.7 ± 21.3	159.6 ± 23.7	<0.001
Diastolic blood pressure, mmHg, mean ± SD	83.3 ± 12.0	81.9 ± 15.2	0.060	83.6 ± 11.6	84.7 ± 14.2	0.587
Total cholesterol, mg/dL, mean ± SD	231.1 ± 44.9	220.5 ± 45.1	0.005	234 ± 43.6	231.9 ± 46.6	0.485
Creatinine, mg/dL, median (IQR)	0.97 (0.84–1.11)	0.99 (0.86–1.16)	0.086	0.95 (0.84–1.09)	0.98 (0.87–1.10)	0.178

Abbreviations: ADL, Activities of Daily Living; BMI, Body Mass Index; GDS, Geriatric Depression Scale; IQR, Interquartile range; MMSE, Mini-Mental State Examination; SD, Standard Deviation. Notes. Time window 1 covers from baseline to the first follow-up (mean duration 4 year); Time window 2 covers from the first follow-up to 10 years (mean duration 6 years).

Table 3
Association between frailty, multimorbidity and the risk of atrial fibrillation-related hospitalizations.

	N. events person-years	Model 1 HR [95 % CI) p-value	Model 2 HR [95 % CI) p-value
Robust	202/20453	[ref]	[ref]
Pre-frail	243/14411	1.43 (1.10–1.88) p = 0.009	1.42 (1.04–1.95) p = 0.029
Frail	68/2538	1.94 (1.32–2.85) p = 0.001	1.98 (1.21–3.26) p = 0.007
Number of chronic diseases		–	1.07 (0.99–1.15) p = 0.051

Model 1 is adjusted for age and sex. Model 2 is adjusted also for living arrangements, education, smoking habits, alcohol consumption, number of chronic diseases, Mini-Mental State Examination, Geriatric Depression Scale, and Body Mass Index.

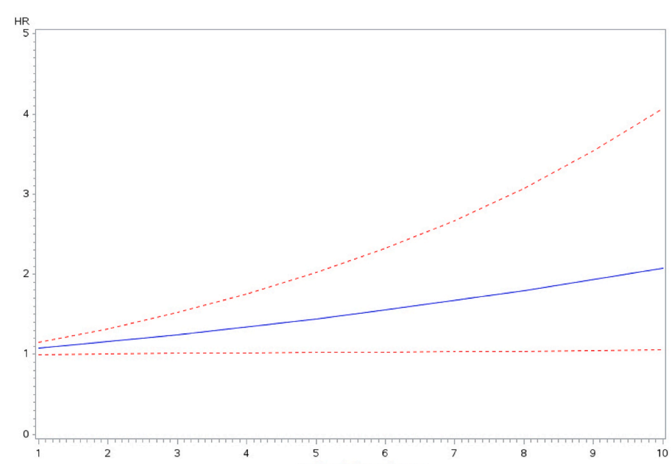

Fig. 1. Hazard Ratio (HR, solid blu line) and 95 % Confidence Interval (CI, dotted red lines) related to the number of chronic diseases from the model adjusted for confounders. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

compared to robust counterparts. This suggests that during frailty progression, even before the overt manifestation of this syndrome, older adults who may be more vulnerable to adverse cardiovascular outcomes, such as AF.

Frailty awareness has grown significantly in recent decades, making its assessment crucial not only in geriatrics but also in other medical fields, such as cardiology [27]. In particular, frailty has been linked to increased cardiovascular morbidity and mortality, both in patients with existing cardiovascular diseases and in those without prior diagnoses [28–36]. Therefore, frailty evaluation could help cardiologists assess prognosis, evaluate procedural risks, and tailor treatments for optimal patient-centered care [5].

In the context of AF, we found that both pre-frailty and frailty were associated with an increased risk of hospitalizations for AF. The mechanisms supporting these results may be multifaceted. First, frailty can exacerbate some aging-related processes including chronic inflammation, mitochondrial dysfunction, alterations in the autonomic nervous system, and hormonal dysregulations. Overall, this can lead to more severe clinical presentations of the diseases, such as AF, and a higher risk of hospitalizations [37–39], which may significantly contribute to the progression of cardiac diseases including AF. Second, from a clinical perspective, frailty may contribute to a more severe initial presentation of the disease. Indeed, the observed results may be related to the fact that only cases of AF leading to hospital admissions were considered, which usually are those that are more symptomatic. Given the complex interplay between frailty and AF, public health interventions aimed at preventing or mitigating frailty in older adults could play a vital role. Preventive strategies such as structured exercise programs, nutritional support, and community-based health monitoring may not only improve robustness but also help reduce hospitalizations and healthcare costs due to cardiovascular diseases.

Notably, the number of chronic conditions did not significantly modify the effect of frailty on the risk of hospitalization for AF, highlighting that frailty is strongly associated with AF regardless of the presence of multimorbidity. This result may appear counterintuitive, as multimorbidity and frailty have a bidirectional relationship [17,40]. Nevertheless, this suggests that frailty and multimorbidity may have independent effects on the risk of hospitalization for AF. While frailty can lead to the development of chronic conditions that, in turn, contribute to the onset of AF, there are likely to be other mechanisms through which frailty impacts AF independently of multimorbidity [41]. On the other hand, it is also possible that multimorbidity precedes the development of frailty, suggesting that the latter may, in fact, represent an expression of the presence of multiple comorbidities. For this reason, a clear interaction between these two conditions may not have emerged in our study.

Our study explores this relationship and suggests that, although the number of chronic conditions is associated with the risk of AF, frailty has a more significant effect, likely capturing mechanisms closely involved in the development of AF. In this sense, physiological changes associated with frailty, such as reduced physiological reserve and impaired homeostasis, could have a principal role in increasing vulnerability to AF and its complications. Undoubtedly, the mechanisms through which frailty elevates the risk of hospitalization for AF—such as inflammation, oxidative stress, and cardiovascular remodeling—may overlap with those of chronic diseases. However, our clinical study suggests that the accumulation of further chronic conditions may not significantly increase the risk of AF-related hospitalizations beyond that linked to frailty. This vulnerable population may require specific interventions to counteract frailty, as part of the overall holistic or integrated care approach to AF management, which is now recommended in guidelines globally [42–44]. Implementation of such integrated care management may offer potential benefits for cardiovascular outcomes [45,46].

The issue of oral anticoagulation in frail older adults with atrial fibrillation warrants careful consideration, especially given the growing prevalence of both conditions in the aging population. While frailty is often associated with increased vulnerability to adverse events, including bleeding and renal function decline, it should not be considered a contraindication per se to anticoagulation. Rather, it represents a condition that necessitates a personalized approach, integrating clinical judgment, patient values, and comprehensive geriatric assessment. Evidence suggests that, when appropriately managed, frail patients may still benefit from DOACs, provided that treatment is tailored with attention to dosing, drug interactions, renal function monitoring, and fall risk [47]. Shared decision-making, combined with regular follow-up, remains crucial to ensure safety and therapeutic efficacy in this complex clinical scenario.

4.1. Strengths and limitations

The strengths of this study include the large sample size, the prospective study design, and the comprehensive assessment of the frailty phenotype and multimorbidity. However, among the limitations, the observational nature of the study precludes establishing causality between frailty and AF, and the potential for residual confounding cannot be entirely excluded. Another limitation of this study is the potential underestimation of the onset of AF. Given that only hospitalized cases were analyzed, it is likely that predominantly symptomatic patients were included, while those with asymptomatic forms of the condition may have been overlooked. Furthermore, reliance on administrative data to record AF-related hospitalizations and mortality may affect the accuracy of our conclusions, although such data are generally considered reliable. This combination of factors could lead to an underestimation of the true incidence of AF in the analyzed population. A limitation of the study is also the incomplete availability of handgrip strength measurements, a key component of the Fried frailty phenotype. In participants without this measure, we used limitations in ADLs as a surrogate for physical weakness. Although this proxy has been supported in previous geriatric research, it may lead to misclassification and should be interpreted with caution when evaluating frailty status [48]. Moreover, the limited assessment of chronic pain—focused solely on joint-related pain in specific anatomical sites and lacking information on pain intensity or other relevant types such as neuropathic or visceral pain—may have resulted in an underestimation of the overall pain burden and its potential impact on health outcomes. This under-recognition is particularly relevant given the well-established association between chronic pain and frailty [49]. Chronic pain may contribute to sustained sympathetic nervous system activation, which in turn could be linked to the occurrence of recurrent paroxysmal AF or to an increased ventricular rate in patients with persistent or permanent AF. Finally, the lack of echocardiographic and detailed electrocardiographic data prevents us from assessing the potential influence of structural cardiac remodeling—such as left atrial enlargement—on atrial fibrillation occurrence. This absence may limit the ability to fully disentangle the role of frailty from underlying subclinical cardiovascular changes.

4.2. Conclusions

Our study reveals that frailty is independently associated with AF-related hospitalizations in older adults, regardless of multimorbidity. These findings underscore the need to integrate frailty assessment into routine clinical practice to effectively identify at-risk pre-frail or frail individuals.

Contributors

CT and MN conceived and planned the study. MN performed the analyses. CC, CT and MN wrote the manuscript. DLV, MP, GYHL, IB, MDR, GS and SM contributed to the data interpretation and critically revised the manuscript. All authors approved the final version of the manuscript.

Ethical approval

The study protocol was approved by the Ethics committees from the University of Padova, the Local Health Units no.15 and 18 of the Veneto Region, and the province of Padova center. All participants signed informed consent. The study complies with the principles of the Declaration of Helsinki.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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