Atrial fibrillation and frailty

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Abstract

Both the prevalence of atrial fibrillation (AF) and frailty are increasing with age, and they often occur simultaneously, leading them to become the central concerns in this aging society. The incidence of frailty in patients with AF is highly variable, ranging from 4.4% to 75.4%, depending on different evaluating instruments used. Moreover, the incidence of frailty among patients with AF is on the rise, which indicated that patients with AF are more prone to frailty compared to patients without AF. The relationship between AF and frailty is complicated. Frailty elevates the risk of stroke and mortality in AF patients and is also associated with longer hospitalizations. On the other hand, it may reduce the appropriate anticoagulation in AF patients. However, the evidence of the effects of frailty on anti-arrhythmic and interventional therapy in patients with AF is scarce. Frailty affects both the management and the prognosis of AF in the geriatric population. Vice versa, AF could worsen the frail state and may represent a marker of frailty. However, there are still questions need to be resolved, for example, the impact of frailty on the interventional therapy of patients with AF. Therefore, the geriatric assessment of frailty should be considered when planning individualized management of AF in older patients.

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1 Introduction

The concept of frailty has emerged as a geriatric vital sign beyond chronological age and comorbidities. Frailty is an age-related condition characterized by reduced physiological reserve, increased risk of disability, loss of resistance and greater vulnerability to adverse events, as manifested by increased morbidity and mortality.[1,2] Frailty is frequent in adults aged 65 years and older, with a prevalence ranging from 4% to 16%.[3,4] It is the most problematic expression of population aging, which gets a growing concern recently. Atrial fibrillation (AF) is often regarded as a “geriatric condition”, and its prevalence increases with age. As the population of elderly patients is growing, AF has become an important public health issue.[5] It is suggested that frailty is more common in individuals with AF.[5,6] On the other hand, the management of AF might be in turn affected by the frail state.[7–9] Many published studies have demonstrated that frail patients have an increased prevalence of AF, lower use of oral anticoagulation, a higher risk of bleeding complications from oral anticoagulation, and a higher risk of stroke and mortality.[6,7,9–12] The relationship between AF and frailty is complicated. In this article, we systematically review the association between AF and frailty.

2 Epidemiology of frailty in AF

The reported incidence of frailty in AF is highly variable, ranging from 4.4% to 75.4%.[10] It might be heavily influenced by the diagnostic test used, thus limiting direct comparisons between different studies.[8,9,13] Blodgett, et al.[13] reported that the prevalence of frailty had been shown to range from 3.6% to 34% in the same cohort of patients, depending on the measurement scale used. Perera, et al.[14] conducted a single-center prospective study of 220 hospitalized adults in Australia and found that 64% of subjects were frail. Nguyen, et al.[15] found that 52% of subjects were frail in their prospective observational study. Both of them evaluated the frail status using the Reported Edmonton Frail Scale (REFS).[16] The incidence was much lower in the study of Lefebvre, et al.[8] by using the Canadian Study of Health and Aging Clinical Frailty Scale (CFS), which found that 25% of subjects were frail.[8,17] Oqab, et al.[9] conducted...
a meta-analysis and concluded that the mean prevalence of frailty in patients with AF was 39%. In particular, the frailty of female patients with AF was higher than that of male patients.\(^{[18]}\) Regardless of the heterogeneity of data among these studies, the prevalence of frailty is still high in subjects with AF.

Moreover, the incidence of frailty among patients with AF is on the rise.\(^{[19]}\) One possible explanation might be that patients with AF are more prone to frailty compared to patients without AF, as reported previously.\(^{[7,20]}\) In the study of Madhavan, patients with frailty were more likely to have persistent or permanent AF than those without frailty (54.1% vs. 44.2%).\(^{[7]}\) This might suggest a worsening of the frail state due to AF.

### 3 Frailty evaluation

Although there is still a lack of consensual clinical assessment tools evaluating frailty, several instruments have been proposed for the diagnosis of frailty and it could be evaluated in many ways.\(^{[21,22]}\) Each instrument has its advantages and disadvantages. A better understanding of the content of the frailty instruments could help researchers as well as clinicians to make a better choice in the frailty evaluation in a specific situation for specific sub-populations of frail elderly.

Models of frailty have been developed using three different domains: functional, biological, and deficit accumulation.\(^{[22–25]}\) They could be mainly divided into three categories: (1) Phenotype-based models: they often rely upon functional measures of physical performance, of which the Fried Scale is the most widely researched.\(^{[26,27]}\) It is a biological model of frailty including exhaustion (fatigue), weight loss, measured grip strength (weakness), walking speed, and low energy expenditure.\(^{[26]}\) However, the lack of standards for some of the measurements, the difficulty in performing these tests in frail older persons and the failure to exclude disability have limited its application in the general clinical practice.\(^{[28,29]}\) (2) Deficit accumulation models: it is another way to define frailty by summing the number of impairments. Among these instruments, the frailty index (FI) was the first to be systematically evaluated, which appeared to be predictive of death and institutionalization. It is a cumulative count of various clinical deficits—a combination of symptoms, diseases, conditions, and disability—derived from the Canadian Study of Health and Ageing Study.\(^{[21]}\) FI is easy to understand, however, it is time-consuming because it includes no fewer than 70 items. Thus, it is not practical for use in a busy clinic. Clinical Frailty Scale (CFS) is another instrument that simplifies the time consuming multiple assessment processes required by the FI.\(^{[17]}\) It is highly correlated with FI, which mixes items such as co-morbidity, cognitive impairment and disability.\(^{[17]}\) And (3) Combination of phenotype and deficit accumulation: the FRAIL scale was developed as a simple measure that combines components of functional, biological and deficit accumulation models.\(^{[22]}\) It comprises five factors: fatigue, resistance, ambulation, illness, and loss of weight, which predicts future disability and mortality.\(^{[21,28–31]}\) The FRAIL scale is an interview-only tool and is easily used in clinical practice.

### 4 Impact of frailty on the management of AF

Frailty might influence the management decisions in elderly patients with AF. The management of AF mainly involves three aspects: anticoagulation, rhythm control, and rate control. Researches about the impact of frailty on the management of AF mainly focus on the anticoagulation, with less evidence on the other two aspects.

#### 4.1 Frailty and anticoagulation

AF greatly increases the risk of ischemic stroke and is associated with increased mortality.\(^{[11,12]}\) To identify patients who will benefit most from anticoagulation, CHA\(_2\)DS\(_2\)-VASC score is recommended to estimate the risk of stroke in AF patients.\(^{[32,33]}\) Even old age is a risk factor for thromboembolic outcomes of AF, the rate of appropriate oral anticoagulation (OAC) decreases with age,\(^{[32,34–36]}\) which appears to be related to the fear of iatrogenic harm and frailty status in an older population.\(^{[8,14,36–39]}\)

There are increasing recognitions that frailty is a more useful approach to guide management decisions in an older population than chronological age. Studies demonstrated that AF patients who were frail had elevated risk of stroke and a higher mean CHA\(_2\)DS\(_2\)-VASC score than those who were non-frail.\(^{[6,7,14,15,40]}\) Nonetheless, the influence of frailty on the risk of bleeding is controversial. Requena Calleja, et al.\(^{[6]}\) found that frail patients had a higher bleeding risk reflected by HAS-BLED scores. Madhavan, et al.\(^{[7]}\) also identified an increased risk with both higher HAS-BLED and ORBIT scores. But other reports revealed that the risk of bleeding at baseline and the risk of hemorrhage after OAC have no significant differences between the frail and non-frail in AF patients.\(^{[14,15]}\) Additionally, evidence of the impact of frailty on OAC prescription is conflicting. The majority of researches implies that frailty reduces the appropriate OAC in AF patients.\(^{[6,7,14,41]}\) In a single-center prospective study of 220 hospitalized elder adults in Australia, Perera, et al.\(^{[14]}\) found that frail participants were signifi-
cantly less likely to receive warfarin than non-frail on admission and discharge. Lefebvre, et al.\textsuperscript{[8]} conducted a cross-sectional study in which frailty was evaluated by CFS and found that only severe frailty (CFS ≥ 7) related to the absence of OAC. However, in the research of Nguyen, et al.\textsuperscript{[15]} frailty decreased the likelihood of anticoagulant prescription on univariate analysis but not on multivariable analysis, thus they believed that frail status had little impact on OAC prescription. The same conclusion also demonstrated by Bo, et al.\textsuperscript{[42]} The discrepancy among different researches might attribute to the heterogeneity of subjects included. Wilkinson, et al.\textsuperscript{[40]} conducted a meta-analysis of the association between frailty and OAC prescription, they found that frailty in different cohorts had different impacts on the OAC. Besides, novel oral anticoagulants (NOACs) might be a more preferred choice for this kind of patients than Vitamin K antagonists (VKAs) because of a significant reduction in severe bleeding and mortality.\textsuperscript{[43,44]} Left atrial appendage closure might another useful solution for frail elderly individuals with AF, however, the evidence related to this field is scarce.\textsuperscript{[44]} Owing to a lack of evidence to guide optimal care, anticoagulation is still a challenge in patients with both AF and frailty in clinic.

4.2 Frailty and anti-arrhythmic therapy

Unlike anticoagulation, the evidence of the effects of frailty on anti-arrhythmic therapy is less reported. In a prospective observational study of AF patients aged ≥ 65 years, 52.6% received rate-control drugs, only 11.8% received rhythm-control drugs and 13.5% received both, additionally, 22.1% were not prescribed either, with no difference by frailty status.\textsuperscript{[15]} Thus, it indicated that frail status had little impact on anti-arrhythmic prescription.\textsuperscript{[15]} In another survey evaluating the influence of frailty on the clinical management of arrhythmias, European Heart Rhythm Association (EHRA) indicated that 40% of the centers included in the survey considered that a rate-control strategy was the unique approach for frail patients with AF, whereas 57.1% of the centers believed that both the rate-control and rhythm-control strategy could be chosen according to the clinical situation.\textsuperscript{[44]}

There are few reports associated with the impact of frailty on interventional therapy in AF patients such as radiofrequency catheter ablation. Some reports suggest that frailty predicts poor outcomes from interventions or procedures.\textsuperscript{[45-48]} In the study conducted by Ekerstad, et al.\textsuperscript{[46]} frailty was a strong negative predictor for the performance of coronary angiography. Another study indicated that frail individuals might benefit from less invasive procedures in surgical patients.\textsuperscript{[48]} However, the evidence relating to the frailty and radiofrequency catheter ablation is lack. Further studies are needed to explore this area.

5 Impact of frailty on the prognosis of AF

Frailty is associated with adverse clinical outcomes in patients with AF. Firstly, frailty was associated with increased stroke incidence as described above. Secondly, frail patients had higher mortality than non-frail patients with AF.\textsuperscript{[6,17,40]} Perera, et al.\textsuperscript{[14]} identified that patients with both AF and frailty were more likely to die compared with patients only with AF but not frailty. Nguyen, et al.\textsuperscript{[15]} indicated that frailty was independently associated with not only the mortality but also the length of hospital stay in AF patients. The same conclusion was obtained from a meta-analysis conducted by Wilkinson, et al.\textsuperscript{[41]} Thus, thirdly, frailty was also associated with longer hospitalizations.

Both the prevalence of AF and frailty are increasing with age, and they often occur simultaneously, leading them to become the central concerns in this aging society. Frailty affected both the management and the prognosis of AF in the geriatric population. Vice versa, AF could worsen the frailty state. Polidoro, et al.\textsuperscript{[20]} found that AF was strongly associated with frailty status independently of age, sex and some common diseases of elderly people, accordingly, they pointed out that having AF was associated with a greater chance of being frail. Furthermore, AF is associated with worse clinical outcomes in frail individuals. On this basis, AF may represent a marker of frailty.\textsuperscript{[49]} However, there are still some questions need to be resolved, for example, if frailty is a trigger of AF and the impact of frailty on the interventional therapy of AF. The relationship between AF and frailty is complicated. They are two related conditions in old populations, therefore, the geriatric assessment of frailty should be considered when planning individualized management of AF in older patients.

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