Ageing Research Reviews

Frailty Prevalence and Impact on Outcomes in Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis of 1,187,000 Patients

--Manuscript Draft--

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	Matteo Cesari
Abstract:	Frailty is a clinical syndrome characterized by a reduced physiologic reserve, increased vulnerability to stressors and an increased risk of adverse outcomes. People with atrial fibrillation (AF) are often burdened by frailty due to biological, clinical, and social factors. The prevalence of frailty, its management and association with major outcomes in AF patients are still not well quantified. We systematically searched PubMed and EMBASE, from inception to September 13 th , 2021, for studies reporting the prevalence of frailty in AF patients. The study was registered in PROSPERO (CRD42021235854). 33 studies were included in the systematic review (n=1,187,651 patients). The frailty pooled prevalence was 39.7% (95%CI=29.9%-50.5%, I 2 =100%), while meta-regression analyses showed it is influenced by age, history of stroke, and geographical location. Meta-regression analyses showed that OAC prescription was influenced by study-level mean age, baseline thromboembolic risk, and study setting. Frail AF patients were associated with a higher risk of all-cause death (OR=5.56, 95%CI=3.46-8.94), ischemic stroke (OR=1.59, 95%CI=1.00-2.52), and bleeding (OR=1.64, 95%CI=1.11-2.41), when compared to robust individuals. In this systematic review and meta-analysis, the prevalence of frailty was high in patients with AF. Frailty may influence the prognosis and management of AF patients, thus requiring person-tailored interventions in a holistic or integrated approach to AF care.
Suggested Reviewers:	Marco Canevelli marco.canevelli@uniroma1.it
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	Gheoghe Andrei Dan andrei.dan@gadan.ro
Opposed Reviewers:	Nicola Veronese nicola.veronese@unipa.it Dr. Veronese rejected the paper as Associate Editor of Age & Ageing in a previous submission
Response to Reviewers:	RESPONSES TO REVIEWERS COMMENTS

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UNIVERSITÀ DEGLI STUDI DI MILANO

Istituti Clinici Scientifici Maugeri

Milan, 26th February 2022

To Prof. Claudio Franceschi
Editor-in-Chief
Ageing Research Reviews

Dear Prof. Franceschi

RE: **Frailty Prevalence and Impact on Outcomes in Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis of 1,187,000 Patients**

Following our previous e-mail exchange, we are pleased to submit our paper, "*Frailty Prevalence and Impact on Outcomes in Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis of 1,187,000 Patients*" for consideration in **Ageing Research Reviews**.

Frailty is medical syndrome characterised by a reduced physiological reserve. Over the past twenty years, the concept of frailty initially raised from the geriatric medicine field, started to spread to other specialist disciplines.
Accumulating evidence in the recent years has indicated how atrial fibrillation (AF) is strongly characterized by a high level of multimorbidity and clinical complexity. Notwithstanding, evidence regarding the association between frailty and atrial fibrillation, and its epidemiology, is limited and sparse.

In this paper we provided a systematic review and meta-analysis about the impact of frailty among patients with atrial fibrillation (AF). First, we found that 40% of AF patients were found frail, with 3 out of 4 AF patients with a certain degree of frailty if we consider also prefrailty. Frail AF patients were more likely females, older and with a higher prevalence of all the main clinical characteristics associated with AF. Ultimately, frail AF patients have a higher burden of both thromboembolic risk and burden of multimorbidity. Also, presence of frailty can influence the prescription of OAC, according to the clinical setting.

Lastly, frailty was found to bring a significant higher risk for all the main clinical outcomes associated with AF, all-cause death, stroke and major bleeding.

In the light of clinical impact of the results described in this paper, we believe that this could be of great interest to the readers of **Ageing Research Reviews.**

We confirm the following: 1) the paper is not under consideration elsewhere, 2) none of the paper's contents have been previously published, 3) all authors had access to all the study data, take responsibility for the accuracy of the analysis, had authority

over manuscript preparation and the decision to submit the manuscript for publication and 4) have read and approved the manuscript; 4) the full disclosure of any potential conflict of interest has been made; 5) the manuscript has been adequately revised according to the reviewers' comments and to the Mayo Clinic Proceedings' journal style.

Yours sincerely

Marco Proietti MD PhD FESC FEHRA

Assistant Professor in Geriatric Medicine
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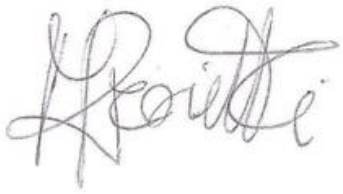

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Frailty Prevalence and Impact on Outcomes in Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis of 1,187,000 Patients

Running Title: Frailty in AF Patients

Marco Proietti[1,2,3]* MD PhD, Giulio Francesco Romiti[4]* MD, Valeria Raparelli[5,6,7] MD PhD, Igor Diemberger[8] MD PhD, Giuseppe Boriani[9] MD PhD, Laura Adelaide Dalla Vecchia[10] MD, Giuseppe Bellelli[11,12] MD, Emanuele Marzetti[13,14] MD PhD, Gregory YH Lip[3,15]† MD, Matteo Cesari[1,2]† MD PhD

[1]Geriatric Unit, IRCCS Istituti Clinici Scientifici Maugeri, Milan, Italy; [2]Department of Clinical Sciences and Community Health, University of Milan, Italy; [3]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; [4]Department of Translational and Precision Medicine, Sapienza – University of Rome, Italy; [5]Department of Translational Medicine, University of Ferrara, Italy; [6]University Center for Studies on Gender Medicine, University of Ferrara, Italy; [7]University of Alberta, Faculty of Nursing, Edmonton, Alberta, Canada; [8]Department of Experimental, Diagnostic and Specialty Medicine, Institute of Cardiology, University of Bologna, Policlinico S. Orsola-Malpighi, Bologna, Italy; [9]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Italy; [10]Department of Cardiology, IRCCS Istituti Clinici Scientifici Maugeri, Milan, Italy; [11]School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy; [12]Acute Geriatrics Unit, San Gerardo Hospital ASST Monza, Monza, Italy; [13]Università Cattolica del Sacro Cuore, Department of Geriatrics and Orthopedics, Rome, Italy; [14]Center for Geriatric Medicine (Ce.M.I.), Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS, Rome, Italy; [15]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

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†Joint senior authors

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ABSTRACT

Frailty is a clinical syndrome characterized by a reduced physiologic reserve, increased vulnerability to stressors and an increased risk of adverse outcomes. People with atrial fibrillation (AF) are often burdened by frailty due to biological, clinical, and social factors. The prevalence of frailty, its management and association with major outcomes in AF patients are still not well quantified. We systematically searched PubMed and EMBASE, from inception to September 13th, 2021, for studies reporting the prevalence of frailty in AF patients. The study was registered in PROSPERO (CRD42021235854). 33 studies were included in the systematic review (n=1,187,651 patients). The frailty pooled prevalence was 39.7% (95%CI=29.9%-50.5%, I^2=100%), while meta-regression analyses showed it is influenced by age, history of stroke, and geographical location. Meta-regression analyses showed that OAC prescription was influenced by study-level mean age, baseline thromboembolic risk, and study setting. Frail AF patients were associated with a higher risk of all-cause death (OR=5.56, 95%CI=3.46-8.94), ischemic stroke (OR=1.59, 95%CI=1.00-2.52), and bleeding (OR=1.64, 95%CI=1.11-2.41), when compared to robust individuals. In this systematic review and meta-analysis, the prevalence of frailty was high in patients with AF. Frailty may influence the prognosis and management of AF patients, thus requiring person-tailored interventions in a holistic or integrated approach to AF care.

KEYWORDS: atrial fibrillation; frailty; epidemiology; mortality; stroke.

1. INTRODUCTION

Frailty is a clinical syndrome characterized by reduced physiologic reserve and increased vulnerability to stressors; it represents a risk factor for negative health-related outcomes, including dependency and death(Morley et al., 2013) and is highly prevalent in the general population (~15%)(Collard et al., 2012). Frailty is today considered a public health priority, and its complexity requires specific managing strategies(Cesari et al., 2016). The relevance of frailty is also recognized in cardiovascular medicine(Aprahamian et al., 2018; Ida et al., 2019).

Atrial fibrillation (AF) is a highly prevalent condition in older persons, often in association with multimorbidity which complicates its clinical management(Hindricks et al., 2021; Proietti et al., 2019). However, the prevalence of frailty and associated factors in people with AF, as well as the impact of frailty on AF management and outcomes are not completely understood(Proietti and Cesari, 2021; Wilkinson et al., 2019). While the prevalence of frailty ranges between 1.6% and 56%, various studies show an association between presence of frailty and risk of all-cause death, although the extent of the association varied across studies(Proietti and Cesari, 2021). Furthermore, the impact of frailty on other outcomes in AF patients (such as stroke and major bleeding) has not been clearly elucidated(Proietti and Cesari, 2021). Moreover, previous studies have shown that frailty may be associated with an underuse of oral anticoagulant (OAC), based on the inclusion of very few cohorts(He et al., 2022; Oqab et al., 2018).

The aims of this study were the following: i) to report the cumulative prevalence of frailty in patients with AF; ii) to examine the associations between frailty and AF-

associated risk factors and comorbidities; iii) to describe prescriptions of OAC drugs in patients with AF and frailty; and iv) to analyse the impact of frailty on clinical outcomes in AF patients.

2. METHODS

This systematic review was performed according to the 'Meta-analysis Of Observational Studies in Epidemiology' (MOOSE) guidelines(Stroup et al., 2000) and reported according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines(Page et al., 2021). The protocol was registered on the international prospective register of systematic reviews (PROSPERO), N. CRD42021235854.

2.1 Search Strategy

A systematic and comprehensive literature search was performed on MEDLINE (accessed through PubMed) and EMBASE databases, from inception to September 13th, 2021. Relevant key terms were combined in the search strategy, including 'frailty', 'frail' and 'atrial fibrillation'. The full search strategy is reported in detail in the Supplementary Materials (Table S1).

2.1 Studies Selection

All articles retrieved from the literature search were systematically, sequentially, and independently screened for eligibility by two authors (MP and GFR). Each article included after the first screening phase focused on titles and abstracts was then evaluated considering the full text. Disagreements were resolved by collegial discussion.

2.2 Inclusion and Exclusion Criteria

Studies reporting data about the evaluation of frailty, irrespective of the tool used for its assessment, in AF patients were included. On the other side, studies on highly

selected cohorts of patients with AF, articles not in English, conference abstracts, letters, comments, editorials, case reports, systematic reviews, and/or meta-analysis were excluded. In the case of two or more studies based on the same cohort of patients, the study with the highest number of patients, the most complete data and/or the most recently published was considered.

2.3 Data Extraction and Quality Assessment

Data from the studies included were independently extracted by two authors (MP and GFR), through a standardized electronic form. We also extracted data on sample size, numbers of patients with prefrailty and frailty, age, proportion of women, prevalence of several comorbidities (including hypertension, diabetes mellitus, coronary artery disease (CAD), previous cerebrovascular disease, chronic heart failure (CHF), peripheral vascular disease (PVD)), CHA_2DS_2-VASc score, Charlson Comorbidity Index (CCI), proportion of patients prescribed with OAC and type of OAC prescribed, for each included study when available. Additionally, we extracted data on clinical outcomes (i.e., all cause death, stroke, major bleeding) according to the presence of frailty, when available.

All the included studies were independently evaluated by two authors (MP and GFR) to assess the risk of bias. We evaluated the risk of bias separately for each outcome of the study. We evaluated the risk of bias for studies reporting frailty prevalence using a customized version of the Newcastle-Ottawa Scale (NOS) for cross-sectional studies. The NOS is composed of 5 items organized into three domains (i.e., Selection, Comparability, Outcome), with a maximum score of 5 points (Table S2). Studies with a score ≤3 were considered at high risk of bias. For studies reporting on

outcomes according to the presence of frailty, we evaluated the risk of bias using a customized version of the NOS for population-based studies,(Viswanathan et al., 2012) composed of 8 items and three domains (i.e., Selection, Comparability, Outcome), with a maximum score of 9 points (Table S3). Each study with a NOS ≤6 was considered as at high risk of bias.

2.4 Definition of Outcomes

Prevalence of pre-frailty and frailty were defined irrespective of the assessment tool used in each study. Cut-off values to define the presence of pre-frailty and frailty were established according to the original studies, considering the usual practice or the authors' classification. We also investigated the management of patients with AF according to the presence of frailty (i.e., rates and type of OAC drugs prescription). Further, we investigated the impact of frailty on the risks of all-cause death, stroke, and major bleeding.

2.5 Statistical Analysis

The prevalence of frailty reported in the included studies was pooled with a generalized linear mixed model (i.e., random intercept logistic regression model)(Stijnen et al., 2010). The number of patients prescribed with OAC, the number of events, and the total number of patients according to the frailty status were pooled and compared using random-effects models. For continuous outcomes, mean, standard deviation (SD), and total number in each group were pooled and compared with inverse variance method.

Pooled estimates were reported as Odds Ratios (OR) and 95% confidence intervals (CI), or mean difference and 95% CI for continuous variables. The inconsistency index (I^2) was calculated to measure heterogeneity, with low heterogeneity defined as an I^2 of <25%, moderate heterogeneity when I^2 falls between 25 and 75%, and high heterogeneity when I^2 was >75%, as per previously pre-specified cut-offs.(Higgins et al., 2003)

For each outcome, a sensitivity analysis was performed with a "leave-one-out" approach, in which all studies are removed one at a time to analyse their influence on the primary analysis. We also performed a sensitivity analysis for the prevalence of frailty using the inverse variance method and two different transformations of the prevalence (i.e., logit transformation and Freeman-Tukey double arcsine).

To account for potential sources of heterogeneity in the pooled prevalence of frailty and OAC prescription, we performed several subgroup analyses, according to relevant study-level characteristics. We also performed meta-regression analyses, according to mean age, sex, geographic location, and comorbidities. Multivariable meta-regressions were also performed with the variables significantly associated at univariate level.

Publication bias was assessed for studies reporting outcomes according to the frailty status, with the use of funnel plots, which were visually inspected for asymmetricity. Egger's test was also performed. All the statistical analyses were performed using R version 4.0.3 (R Core Team, 2021, Vienna, Austria).

3. RESULTS

Among 1,350 records identified from the literature search (333 from PubMed, 1017 from EMBASE), 33 studies (a total of 1,187,651 persons with AF) were eventually included (Table 1) after removal of duplicates, title and abstract screening, and full-text assessment [Figure S1]. Sixteen studies were conducted in Europe; 7 in Asia; 6 in North America; and 4 in other geographical regions, including multinational cohorts. Fifteen were observational single-centre studies; 9 were observational multicentre studies; 5 were based on electronical medical records; and 3 were population-based studies. Four studies enrolled only patients with AF and a high thromboembolic risk. Finally, 14 studies were conducted in a hospital-based setting; 10 in community-based setting; and 9 in other settings, including mixed and unclear settings.

As for the type of frailty assessment tool used in the original studies, 8 cohorts used the frailty index proposed by Rockwood and Mitnitski; 6 were based on the Edmonton frail scale; 5 on the clinical frailty scale (CFS); 4 on the frailty phenotype designed by Fried and colleagues; 3 on the FRAIL tool; 2 on a claim frailty index (CFI); 2 on the Tilburg frailty index (TFI); and 3 on other methods. Finally, 13 studies were found to be at high risk of bias for the prevalence of frailty, while 2 studies were at high risk of bias among those reporting clinical outcomes according to frailty (Table S4 and S5, respectively).

3.1 Prevalence of Frailty and Pre-Frailty in patients with AF

Based on 33 studies including 1,187,651 patients with AF, the prevalence of frailty was 39.7% (95%CI: 29.9-50.5%), with high heterogeneity between studies (Figure

1). The pre-specified leave-one-out analysis showed little to no influence of individual studies on pooled estimates or heterogeneity (Figure S2 in supplementary materials). Sensitivity analyses according to the inverse variance methods were largely consistent with the main analysis [Table S6].

Thirteen studies reported data on the prevalence of pre-frailty, with a pooled prevalence of 35.0% (95%CI: 26.1-45.1%), and a high heterogeneity between studies [Figure S3]. The pre-specified leave-one-out sensitivity analysis showed little influence of individual studies on pooled prevalence or heterogeneity [Figure S4].

The results of the subgroup analysis for the prevalence of frailty are reported in Figure 2. Significant interactions were found according to geographical location, tool used for the assessment of frailty, study design, and risk of bias. The prevalence of frailty was found to be higher in European-based cohorts, and in the studies that used CFS or TFI, while the lowest prevalence of frailty was observed in studies using the frailty phenotype. A higher proportion of patients with AF were found to be frail in observational single-centres studies, while a lower prevalence was reported in population-based studies, randomized controlled trials, and studies with low risk of bias. Finally, the prevalence of frailty was lower in studies conducted in community-based settings, and higher in studies from hospital settings. Heterogeneity was found to be high in most of the analyzed subgroups.

3.2 Univariate and Multivariable Meta-Regression Analysis

To explore the potential sources of heterogeneity in our estimates for the prevalence of frailty, we performed univariate and multivariable meta-regression analyses

according to several study-level characteristics. On univariate analyses, mean age, geographical location, study setting, risk of bias, and proportion of patients with hypertension or history of stroke were found significantly associated with frailty (Table S7 in Supplementary Materials). Particularly, studies with higher mean age and higher proportion of patients with history of cerebrovascular accidents showed increased prevalence of frailty. Conversely, studies based on Asian cohorts, those conducted in a community-based setting, and those at low risk of bias were associated with a lower prevalence of frailty, consistent with the results of subgroup analyses. A non-significant trend was also observed between prevalence of hypertension and frailty. Figure 3 shows a graphical representation of the relationship between mean age, proportion of patients with history of stroke, and prevalence of frailty.

In a multivariable meta-regression analysis, including the study-level characteristics that were significantly associated with the prevalence of frailty at univariate analysis, a model including mean age, prevalence of history of stroke, geographical location, study setting, and risk of bias explained a relevant proportion of the observed heterogeneity (R^2=67.7%, Table S7), although none of the variables was independently associated with the prevalence of frailty in the final model.

3.3 Comorbidities and Clinical Characteristics Associated with Frailty

Overall, 13 studies reported data on clinical characteristics and comorbidities in frail and robust patients. All studies reported data about sex; 12 reported information on history of stroke; 11 on hypertension, diabetes or congestive heart failure (CHF); 10 studies reported data on mean age; 7 on CHA_2DS_2-VASc score; 6 on peripheral

vascular disease; and 4 on Charlson Comorbidity Index (CCI). Frailty was associated with female sex and with all the main investigated comorbidities [Figure S5, Panel A]. Frail patients were older and with higher CHA_2DS_2-VASc and CCI scores [Figure S5, panel B]. High heterogeneity was found for all comparisons.

3.4 OAC Prescription According to Frailty Status

To evaluate OAC prescription across different degrees of frailty, we compared the rates of OAC prescription among frail, pre-frail, and robust patients.

After excluding studies in which all patients were already receiving OAC, we identified 17 studies that reported the number of patients prescribed with OAC according to frailty status. We performed one primary comparison (frail vs. robust patients), and 3 additional comparisons (frail vs. pre-frail/robust, frail vs. pre-frail, and pre-frail vs. robust subjects) [Figure 4]. None of the analyses showed significant differences in OAC prescription across frailty status categories, although there was a trend towards lower OAC prescription in frail persons. High heterogeneity was observed for all the comparisons.

The results of the sensitivity analyses according to the leave-one-out approach are reported in Figure S6. The exclusion of the study by Jankowska-Polanska et al(Jankowska-Polańska et al., 2020) showed a significant lower OAC prescription in frail vs. pre-frail/robust patients (OR 0.78, 95%CI 0.62-0.97) [Figure S6, Panel B], while the omission of the study of Pilotto et al.(Pilotto et al., 2016) showed a significant higher OAC prescription for pre-frail vs. robust subjects (OR 1.22, 95%CI 1.06-1.43) [Figure S6, Panel D]. No significant influence of individual studies was found for the other analyses.

We performed three subgroup analyses for our primary comparison (i.e., frail vs. robust patients), according to study design, thromboembolic risk of patients enrolled, and study setting [Figure S7]. We found significant interaction by study type and in OAC prescription in frail vs. robust patients. Frail patients enrolled in observational multicentre cohorts and in the studies based on electronic medical records were less likely to be prescribed with OAC, while the opposite was found in the two population-based studies included. Frail persons were 28% less prescribed with OAC in studies that included patients irrespective of baseline thromboembolic risk (OR: 0.72, 95%CI: 0.54-0.97), while a trend towards higher rates of prescription was found in cohorts that enrolled only patients with high thromboembolic risk. Finally, significant differences were found across study settings, with a 48% less OAC prescription in frail patients enrolled in hospital-based studies, compared with non-significant differences between frail and robust patients in community-based studies and studies conducted in other settings.

To identify other possible causes of between-studies variability, we also performed meta-regression analyses. Among the study-level characteristics investigated, only mean age was significantly and inversely associated with the probability of OAC prescription in frail patients compared with non-frail individuals (R^2=37.4%; Table S8 in supplementary materials); non-significant trends were also observed for study setting, with lower OAC prescription in hospital-based studies. A graphical representation of the relationship between mean age of the included studies and the OR for OAC prescription in frail patients is reported in Figure S8. In frail patients ≥80 years OAC was significantly less prescribed.

Finally, we compared frail vs. non-frail patients for the probability of receiving Non-Vitamin K Antagonist OACs (NOACs) when anticoagulation is prescribed. In the 7 studies that reported available data for the comparison(Gugganig et al., 2021; Gullón et al., 2019; Mostaza et al., 2018; Saczynski et al., 2020; Sanghai et al., 2021; Sławuta et al., 2020; Son et al., 2019), we did not find any difference in the probability of NOACs prescription between frail and robust patients [Figure S9].

3.5 Risk of Outcomes according to Frailty Status in patients with AF

To analyse the impact of frailty on the risk of all-cause mortality, stroke, and bleeding, we compared frail vs. robust patients. We also compared frail vs. pre-frail/robust, frail vs. pre-frail, and pre-frail vs. robust patients.

In the main comparison, frail patients had an increased risk of all outcomes, compared with robust patients, with a 5.6-fold higher risk of all-cause mortality, and roughly 60% increased risk of stroke and bleeding [Figure 5, Panels A to C, respectively]. Heterogeneity was high for all comparisons. Similar results were found for all other comparisons, with a higher risk of all-cause mortality according to any worse frailty status [Figure S10-S12]. A sensitivity analysis on the risk of all-cause mortality according to the study setting did not show any difference according to study in the community, hospital, and other mixed settings [Figure S13].

3.6 Publication Bias

Assessment of publication bias was performed only for the studies reporting outcomes according to the frailty status. Due to the low number of studies available

for the comparison of pre-frail patients, we only assessed publication bias for frail vs. robust and frail vs. pre-frail/robust comparisons. There was no significant publication bias across the outcomes investigated [Figure S14].

4. DISCUSSION

In this systematic review and meta-analysis of 1,187,651 persons with AF, approximately 40% were frail, with confidence intervals pointing towards a range of prevalence from 30% to 50%. Frail patients were older, more often women, and with higher prevalence of comorbidities. Frail AF patients had also a higher overall burden of multimorbidity, as well as of thromboembolic risk, but we did not find significant differences in OAC prescription in frail or pre-frail persons. While a differential influence on OAC prescription was found according to the study design, we observed a significant impact of mean age, with frail older persons (i.e., age ≥80) being less likely prescribed. When considering general AF cohorts (i.e., excluding those cohorts enrolling only patients with high thromboembolic risk), frail patients had a 30% lower chance to receive an OAC compared to robust ones. Finally, frail patients were at higher risk of all major adverse outcomes, and frailty was positively associated with all-cause death

In the last 20 years, the issue of frailty has increasingly been raised by geriatricians, underlining the significant impact on patients and health services, clinical care and research(Cesari et al., 2016; Vellas et al., 2012). Recent estimates suggest that the worldwide prevalence of frailty is about 18%, with a prevalence of pre-frailty of about 45%, irrespective of clinical setting(O'Caoimh et al., 2021). While a significant link between AF and frailty has already been described(Proietti and Cesari, 2021), our paper provides a solid estimate of the prevalence of frailty in patients with AF, documenting that approximately 4 out of 10 patients with AF are frail and 35% are pre-frail. These findings indicate that up to 75% of patients with AF have some degree of frailty, in contrast to 63% in the general population(O'Caoimh et al., 2021).

Based on subgroup analyses, we identified an overall prevalence of frailty of 17% in AF patients in the community, which is higher than previous estimates in general community cohorts showing a 12% prevalence, irrespective of frailty tools(Collard et al., 2012). Furthermore, there was a higher prevalence of frailty compared with pre-frailty, different from what was previously reported in general population(O'Caoimh et al., 2021). Our estimates, which on some extent can be considered even too high (and influenced by the overall high mean age of patients included in this analysis), are supported by similar projects exploring the prevalence of frailty in other cardiovascular diseases(Denfeld et al., 2017; Liperoti et al., 2021; Palmer et al., 2019). Indeed, in these studies the extent of frailty burden was reported up to 70% of the patients included in the studies, even though the overall mean ages of the patients included in those meta-analyses were lower than our(Denfeld et al., 2017; Liperoti et al., 2021; Palmer et al., 2019). Moreover, data from the subgroup analysis about frailty assessment tools (i.e., frailty phenotype reporting the lower prevalence) showed that, when frailty is multidimensionally assessed and/or via a functional approach, its prevalence tends to be significantly higher (O'Caoimh et al., 2021).

In AF, multimorbidity is associated with a higher burden of thromboembolic and bleeding risks, under-prescription and lower quality of OAC treatment, and a higher risk of all major AF-related negative outcomes(Jani et al., 2018; Proietti et al., 2021, 2019). While multimorbidity represents a significant health construct in influencing patients' lives and the natural history of disease, it does not adequately capture the individual's overall capacity and physiological reserve. The evaluation of frailty provides a deeper insight into the entire spectrum of phenomena influencing patient care(Cesari et al., 2016; Morley et al., 2013). While agreement exists regarding the

theoretical construct of frailty(Morley et al., 2013), a large number of tools are used for its assessment (Proietti and Cesari, 2020). Of these, the frailty phenotype evaluates the residual physiological reserve on the basis of the phenotypic manifestation of different physical signs and symptoms(Fried et al., 2001), while the frailty index provides an overall evaluation of health deficits(Mitnitski et al., 2001).

Prior studies have provided a limited analysis of the relationship between frailty and OAC prescription as well as of the impact of frailty on major negative outcomes(Proietti and Cesari, 2021; Villani et al., 2018; Wilkinson et al., 2019). Hence, our work provides a solid estimate of the prevalence of frailty and pre-frailty in patients with AF. The evidence that 3 out of 4 AF patients show a certain degree of frailty - with almost half of them frail – has major implications for their management. Indeed, in recent years there has been a shift towards a more holistic or integrated approach to AF care. Given the role of multimorbidity in AF, the need for a more comprehensive assessment, characterisation, and personalized management of patients with AF has emerged(Bhat et al., 2021; Potpara et al., 2020). This approach has been advocated in clinical guidelines(Hindricks et al., 2021), promoting the 'Atrial Fibrillation Better Care' (ABC) pathway(Lip, 2017) wherein adherence to such an approach is associated with a significant reduction of major negative outcomes(Romiti et al., 2021b). Such an integrated care approach has also been advocated for other chronic conditions(Field et al., 2021; Lip and Ntaios, 2021).

Frailty in the general population has been associated with an increased risk of all-cause death, regardless the assessment tool used(Chang and Lin, 2015; Kojima et

al., 2018). In the general population, the presence of frailty (according to the frailty phenotype) was associated with a 2-fold and 1.5-fold risk of all-cause death relative to robust and pre-frail persons, respectively(Chang and Lin, 2015). Our estimates provide evidence that frail patients with AF have up to a 5-fold higher risk of dying compared with robust ones and an almost 3-fold higher risk compared to those who are pre-frail. Furthermore, the risk of all-cause death was not significantly different according to the study setting, even though the low number of studies considered suggests caution in interpretation. In a recent study enrolling long-term care residents with AF, the presence of geriatric conditions (e.g., recent fall, functional dependency, cognitive impairment, mobility impairment) did not affect the risk of stroke or bleeding (Kapoor et al., 2022). In contrast, our findings indicate that frailty may influence the onset of adverse outcomes in AF patients.

In recent years several researchers put significant efforts in defining the concept of 'inflammageing', defined as a low-grade systemic inflammatory status contributing to the development of ageing-related diseases and conditions(Ferrucci and Fabbri, 2018; Franceschi et al., 2018). Such pro-inflammatory status has been associated to the development and perpetuation of frailty(Kanapuru and Ershler, 2009; Van Epps et al., 2016) which is associated with increased systemic inflammatory markers(Soysal et al., 2016). Similarly, inflammation has a significant role in initiating, determining and perpetuating AF(Boriani et al., 2021; Brundel et al., 2022; Korantzopoulos et al., 2018). From this perspective, even if not supported by specific data we can postulate that the increased inflammatory burden firstly ignites AF and subsequently, with other inflammatory stimuli related to AF itself, characterise AF along with the high burden of risk factors and multimorbidity which characterize

AF(Boriani et al., 2021), determines the occurrence of frailty. The epidemiological evidence linking AF and frailty, which interplay could amplify the inflammatory state, and the high risk of several relevant clinical events related to AF(Odutayo et al., 2016), that become less manageable for a frail individual, can suggest the possible mechanism entailing the higher risk of outcomes.

Hence, a formal evaluation of frailty should be conducted in every older person with AF to aid personalized interventions. In patients with frailty, a comprehensive geriatric assessment followed by a personalized intervention effectively reduces the burden of frailty itself and provides a significant improvement in clinical outcomes(Cesari et al., 2015; Ellis et al., 2017). A more formal assessment of frailty to identify those in need of comprehensive geriatric assessment (and the consequent personalization of care) could reduce the risk of negative outcomes.

Although we did not find a significant reduction in the overall population, the presence of frailty can negatively affect the prescription of OAC, modulated by increasing age, study setting, and baseline thromboembolic risk. This suggests that chronological age may be considered more important than the biological age (captured by frailty) in the clinical decision process (as observed in other cohorts(Fumagalli et al., 2015; Marzona et al., 2019)). Conversely, in patients at high thromboembolic risk, the increased clinical complexity (i.e., higher risk of outcomes) related to frailty shows a trend towards higher OAC prescription. Indeed, the differences we found - with observational studies characterized by lower prescription, and population-based studies showing a higher rate of prescription - underline the differential way to consider the presence of frailty. In observational studies, when

frailty is explicitly assessed, its presence may discourage OAC prescriptions, which might relate to the fear of adverse events (i.e., major, or intracranial bleeding) or to the assumption that OAC would be unable to substantially reduce the risk of adverse events in frail patients. In population-based studies, the higher risk profile of frail patients with AF might drive more OAC prescriptions. Regarding the prescription of VKA and NOACs in frail patients, our data did not show any difference, highlighting the limited evidence regarding the effectiveness and safety of NOACs in this specific patient subgroup(Grymonprez et al., 2020). Notwithstanding, recent findings provide reassuring data regarding the use of apixaban in patients with AF and frailty(Kim et al., 2021; Lip et al., 2021). On the other side, there is currently limited data on the efficacy of novel approach for thromboembolic risk preventions, such as left atrial appendage occlusion, which may represent an interesting alternative for frail patients who are deemed not candidate to OAC.(Volgman et al., 2022) Further studies are needed to shed light on these perspectives.

Our work has important implications in terms of clinical and public health implications. On the clinical point of view, the assessment of frailty and the consequential personalization of offered care could reduce the burden of adverse clinical events by allocating person-tailored interventions, in conjunction with an integrated AF care approach. Benefits are not limited to the patient-level, but may also positively impact the public health, given the costs associated to both conditions(Burdett and Lip, 2020; Hoogendijk et al., 2019). Projecting our findings on the growing prevalence and burden of AF, it might be conceivable to decentralize services, privileging primary care models to traditional hospital-based ones. Indeed, recommendations coming also from the World Health Organization support the

strengthening of primary care for the preventive, multidisciplinary, and integrated management of older persons, especially the most vulnerable ones(World Health Organisation, 2017). In this context, it is foreseeable the need to reorient primary care services to better allow them the management of patients with AF, in particular when frailty is simultaneously present(Cesari et al., 2016).

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Lastly, we also advocate the need for specific studies which will test how the evaluation of frailty and the integrated care approach now recommended for AF patients could have a positive impact on clinical outcomes (Hindricks et al., 2021)(Chao et al., 2021).

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4.1 Limitations and Strengths

The main limitation to this systematic review is the high heterogeneity reported in our pooled estimates. Furthermore, it is possible that some cohorts were not included, despite our best efforts to include any relevant study, due to not being captured by our search strategy.

Nonetheless, our paper has important strengths. First, we performed specific analyses to evaluate heterogeneity, including the multivariable meta-regression, which accounts for roughly 65% of the observed heterogeneity in the pooled estimate for frailty prevalence. Notwithstanding, high heterogeneity is a common concern in epidemiological meta-analyses exploring the prevalence of conditions which could vary consistently across studies and is nowadays largely accepted, when proper study of heterogeneity is performed(Colditz et al., 1995; Odutayo et al.,

2016; Romiti et al., 2021a). Second, we included 33 studies and over a million of AF patients, thus providing robust data for the estimates reported in this analysis.

5. CONCLUSIONS

In this systematic review and meta-analysis, the prevalence of frailty was high (approximately 40%, with 95% confidence intervals ranging between 30-50%) in patients with AF. Frailty influences the prognosis and management of AF patients, thus requiring person-tailored interventions in a holistic or integrated approach to AF care.

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COMPETING INTEREST

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FIGURE LEGENDS

Graphical Abstract – Frailty in Atrial Fibrillation (Created with Biorender.com)

Legend: CI= Confidence Interval; OR= Odds Ratio.

Figure 1 – Prevalence of Frailty in patients with Atrial Fibrillation.

Legend: CI= Confidence Interval; GLMM= General Linear Mixed Model.

Figure 2 – Subgroup Analyses for the Prevalence of Frailty.

Legend: CFI= Claim Frailty Index; CFS= Clinical Frailty Scale; CI= Confidence Interval; GLMM= Generalised Linear Mixed Model; RCT= Randomised Controlled Trial; TFI= Tilburg Frailty Index.

Figure 3 – Univariable meta-regressions for the prevalence of Frailty according to study-level characteristics

Legend: Panel A: Mean Age; Panel B: Prevalence of History of Stroke

Figure 4 – OAC Prescription according to Frailty status

Legend: CI= Confidence Interval; OR= Odds Ratio.

Figure 5 – Risk of All-Cause Death, Stroke and Bleeding in Frail vs. Robust subjects.

Legend: Panel A: All-Cause Death; Panel B: Stroke; Panel C: Bleeding; CI= Confidence Interval; MH= Mantel-Haenszel; OR= Odds Ratio.

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1 **Table 1 – Main Characteristics of the Studies Included in the Systematic Review**

STUDY	YEAR	GEOGRAPHIC LOCATION	STUDY TYPE	SETTING	INCLUSION CRITERIA	FRAILTY ASSESSMENT	N	PREFRAIL	FRAIL	AGE (mean)	CHA_2DS_2-VASC (mean)	OAC (%)
Annoni(Annoni and Mazzola, 2016)	2016	Italy	Observational Single Centre	Hospital	AF ≥65 years	Robinson	403	115	231	84.6	N/A	N/A
Bo(Bo et al., 2017)	2017	Italy	Observational Multicentre	Hospital	AF ≥65 years	Groningen	452	N/A	341	81.6	N/A	49.8
Campitelli(Campitelli et al., 2021)	2021	Canada	Administrative Database	Other	AF ≥65 years	Frailty Index	36466	12985	17778	N/A	N/A	50.8
De Simone(De Simone et al., 2020)	2020	Italy	Observational Single Centre	Hospital	AF ≥80 years	Edmonton	731	N/A	300	85	N/A	100
Gugganig(Gugganig et al., 2021)	2021	Switzerland	Observational Multicentre	Other	AF ≥65 years	Frailty Index	2369	1436	252	73	3.5	90.4
Gullon(Gullón et al., 2019)	2019	Spain	Observational Multicentre	Hospital	AF ≥65 years	FRAIL	615	N/A	297	85.2	5.3	69.8
Hohmann(Hohmann et al., 2019)	2019	Germany	Administrative Database	Community	AF ≥18 years on OAC	CFI	70501	N/A	36267	74	3.7	100
Induruwa(Induruwa et al., 2017)	2017	UK	Observational Single Centre	Hospital	AF ≥75 years	CFS	419	N/A	282	85*	4*	48.7
Jankowska-Polanska(Jankowska-Polańska et al., 2020)	2021	Poland	Observational Single Centre	Other	AF ≥60 years	Edmonton	158	N/A	84	70.9	N/A	42.4
Kim(Kim et al., 2017)	2017	Korea	Observational Single Centre	Other	AF ≥65 years	Frailty Index	365	68	176	79.4	N/A	34.2
Koca(Koca et al., 2020)	2020	Turkey	Observational Single Centre	Community	AF ≥65 years	Fried	64	33	10	75.3	N/A	N/A

Lefebvre(Lefebvre et al., 2015)	2016	Canada	Observational Multicentre	Hospital	AF ≥80 years	CFS	682	N/A	558	86.4	N/A	69.6
Lip(Lip et al., 2021)	2021	US	Administrative Database	Community	AF ≥65 years on OAC	CFI	404798	N/A	150487	N/A	N/A	N/A
Liu(Liu et al., 2020)	2020	China	Observational Multicentre	Other	AF ≥65 years	CFS	500	N/A	201	75.2	4*	39.6
Madhavan(Madhavan et al., 2019)	2019	US	Observational Multicentre	Community	AF ≥18 years	Fried	9749	N/A	575	75*	4*	76.4
Mlynarska(Mlynarska et al., 2017)	2017	Poland	Observational Single Centre	Hospital	AF ≥60 years	TFI	132	N/A	79	72.7	4.3	N/A
Mostaza(Mostaza et al., 2018)	2018	Spain	Observational Multicentre	Other	AF ≥75 years on OAC	FRAIL	837	N/A	360	83	5	100
Nguyen(Nguyen et al., 2016)	2016	Australia	Observational Singe Centre	Hospital	AF ≥65 years	Edmonton	302	N/A	161	84.7	4.6	51.3
Ohta(Ohta et al., 2021)	2021	Japan	Observational Singe Centre	Hospital	AF on OAC	Fried	120	N/A	34	77.7	3.1	100
Perera(Perera et al., 2009)	2009	Australia	Observational Single Centre	Hospital	AF ≥70 years	Edmonton	220	N/A	140	82.7	N/A	40.1
Pilotto(Pilotto et al., 2016)	2016	Italy	Observational Multicentre	Community	AF ≥65 years	MPI	1827	634	488	84.4	3.8	43.7
Polidoro(Polidoro et al., 2013)	2013	Italy	Observational Single Centre	Hospital	AF	Frailty Index	70	N/A	62	79.3	N/A	N/A
Saczynski(Saczynski et al., 2020)	2020	US	Observational Multicentre	Community	AF ≥65 years with High TE Risk	Fried	1244	659	172	75.5	4*	85.5
Sanghai(Sanghai et al., 2021)	2021	US	Administrative Database	Other	AF w/ CHA_2DS_2-VASc ≥2	Frailty Index	308664	99185	109475	77.7	4.6	39.5
Slawuta(Sławuta et al., 2020)	2020	Poland	Observational Single Centre	Hospital	AF ≥60 years	Edmonton	158	16	84	70.4	N/A	100

Son(Son et al., 2019)	2019	Korea	Observational Single Centre	Community	AF ≥60 years on AT	FRAIL	298	143	53	72.1	N/A	63.8
Uchmanowicz(Uchmanowicz et al., 2020)	2020	Poland	Observational Single Centre	Hospital	AF ≥65 years w/out CI	TFI	100	N/A	67	70.3	N/A	N/A
Wilkinson(Wilkinson et al., 2020)	2020	Multinational	RCT	Other	AF ≥21 years	Frailty Index	20867	12326	4082	N/A	N/A	100
Wilkinson 2(Wilkinson et al., 2021)	2020	UK	Population-Based	Community	AF ≥65 years	Frailty Index	61177	20352	34382	79.7	3.8	53.1
Wojszel(Wojszel et al., 2019)	2019	Poland	Observational Single Centre	Hospital	AF	CFS	98	N/A	65	84*	N/A	N/A
Yamamoto(Yamamoto et al., 2019)	2019	Japan	Administrative Database	Other	AF on NOACs	CFS	240	N/A	120	76.1	4*	100
Yang MT(M. T. Yang et al., 2020)	2020	Taiwan	Population-Based	Community	AF ≥65 years	Edmonton	38	N/A	2	73.5	N/A	N/A
Yang PS(P. S. Yang et al., 2020)	2020	Korea	Population-Based	Community	AF ≥18 years CHA_2DS_2-VASc ≥1	Frailty Index	262987	37341	4104	58*	1.8	100

Legend: *median values; AF= Atrial Fibrillation; CFI= Claim Frailty Index; CFS= Clinical Frailty Scale; CI= Cognitive Impairment; MPI= Multidimensional Prognostic Index; N/A= Not Available; NOACs= Non-Vitamin K Antagonist Oral Anticoagulants; OAC= Oral Anticoagulant; RCT= Randomised Controlled Trial; TFI= Tilburg Frailty Indicator; UK= United Kingdom; US= United States.

HIGHLIGHTS

- Frailty is increasingly reported in AF patients, but solid data are still lacking
- In this systematic review, we found up to 40% of AF patients being frail
- OAC prescription in frail AF patients is influenced by several characteristics
- Frail AF patients were at higher risk of all-cause death, stroke, and bleeding

FRAILTY IN ATRIAL FIBRILLATION

A Systematic Review and Meta-Analysis

PREVALENCE OF FRAILTY: 39.7% (95%CI: 29.9-50.5%)
Across **33 studies** and **1,187,651 AF** patients (I^2=100%)

PREVALENCE OF PREFRAILTY: 35.0% (95%CI: 26.1-45.1%)
Across **13 studies** and **696,889 AF** patients (I^2=100%)

FRAIL PATIENTS SHOWED A TREND TOWARDS
OAC UNDERPRESCRIPTION
Frail vs. Robust: OR 0.84 (95% CI: 0.64-1.10)
Frail vs. Pre-Frail: OR 0.93 (95% CI: 0.78-1.12)
Frail vs. Pre-Frail/Robust: OR: 0.83 (95%CI: 0.64-1.06)

MEAN AGE, THROMBOEMBOLIC RISK AND **STUDY SETTING**
MAY INFLUENCE **OAC PRESCRIPTION** IN FRAIL PATIENTS

FRAIL AF PATIENTS AT **HIGHER RISK OF MAJOR OUTCOMES**
COMPARED TO ROBUST SUBJECTS

ALL-CAUSE DEATH
OR: 5.56 (95%CI: 3.46-8.94)

STROKE
OR: 1.59 (95%CI: 1.00-2.52)

BLEEDING
OR: 1.64 (95%CI: 1.11-2.41)

Figure 2

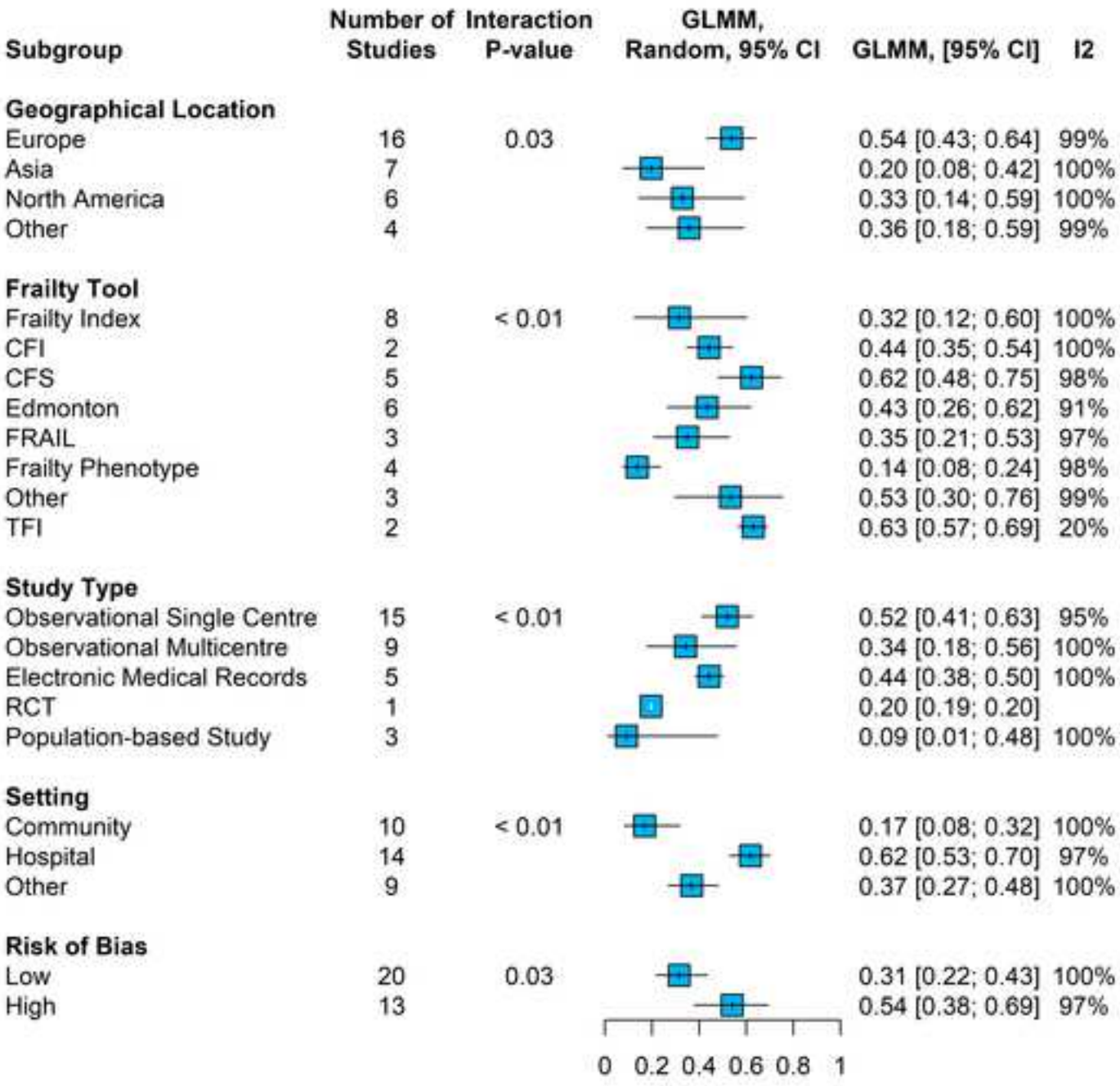


Figure 3

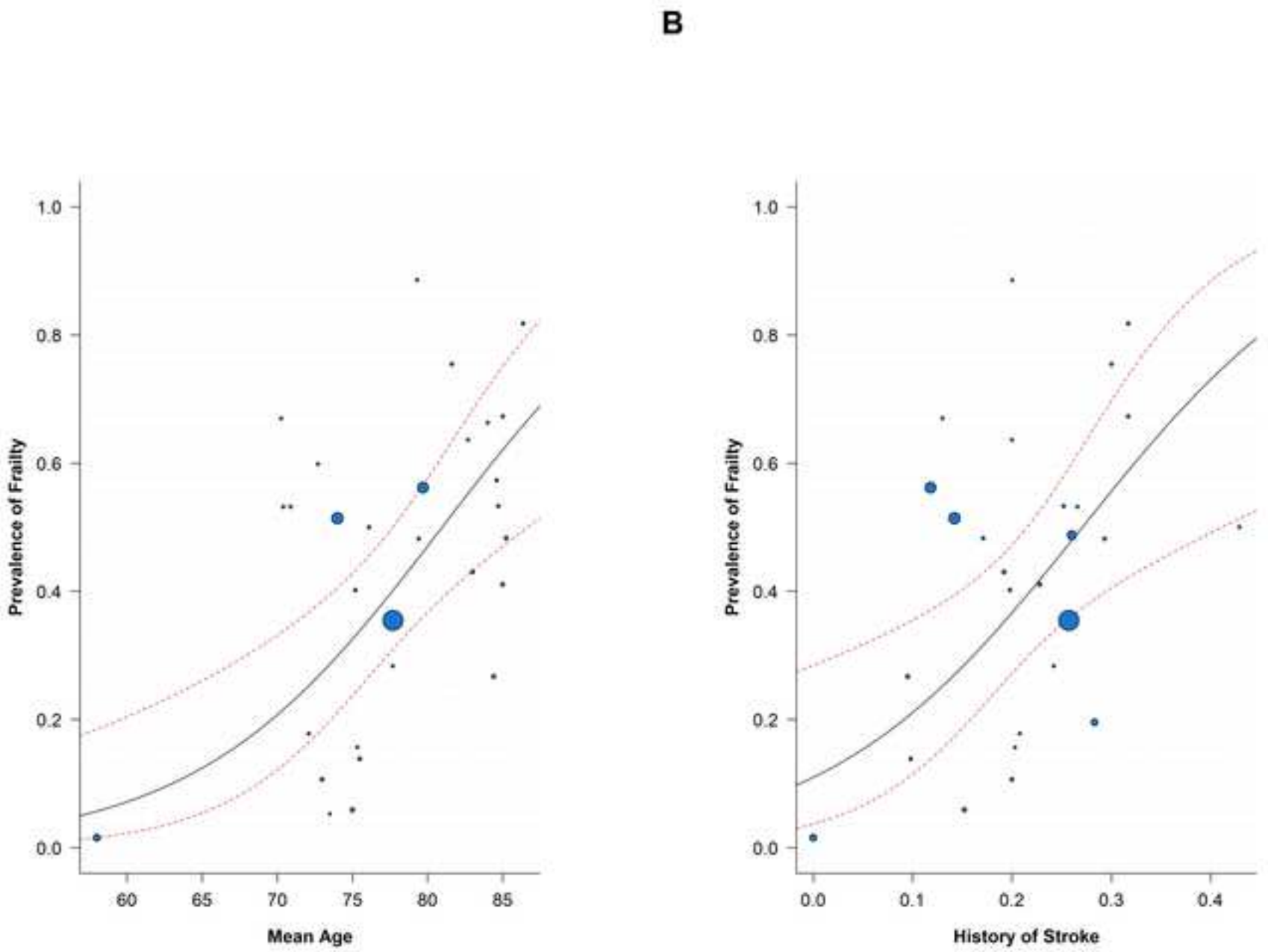


Figure 4

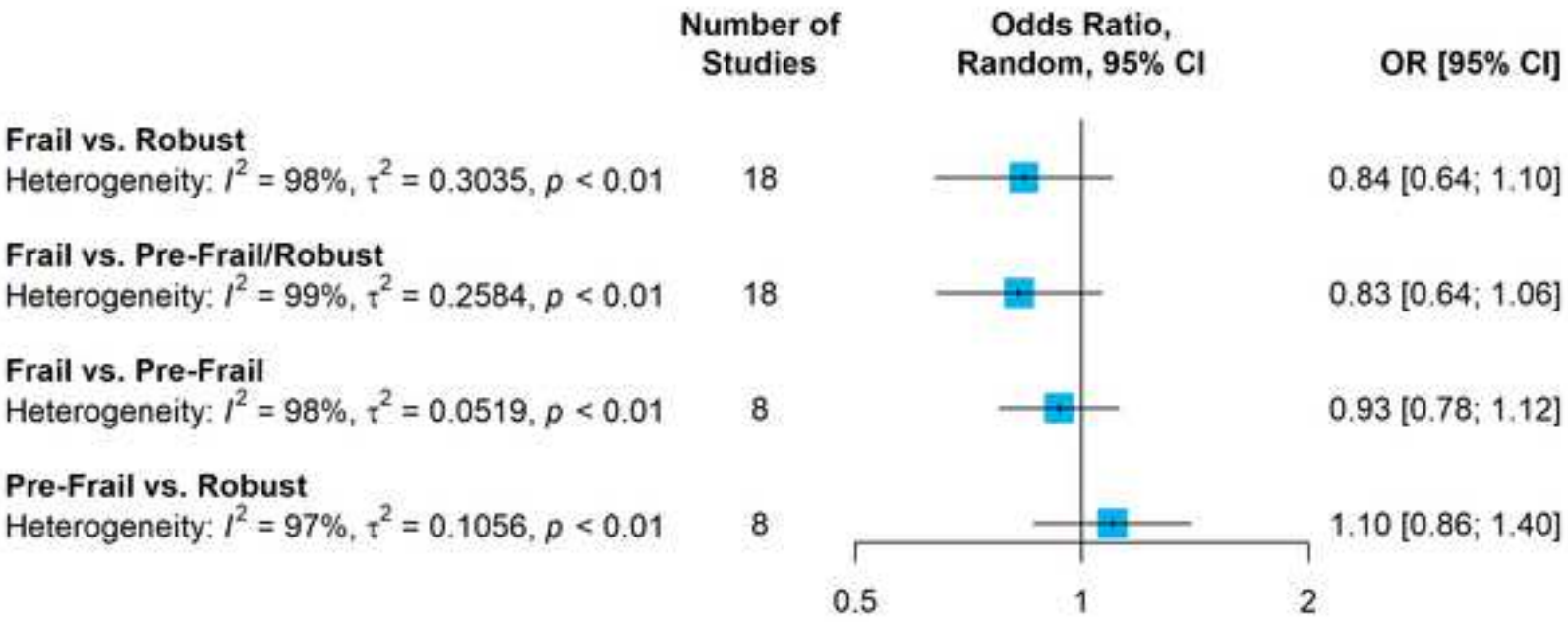
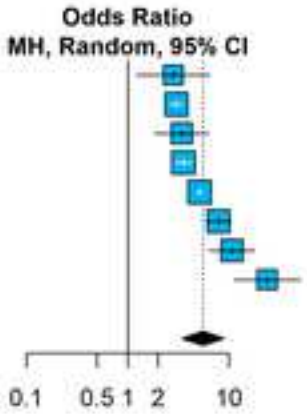


Figure 5

A

Study	Frail Events	Frail Total	Robust Events	Robust Total	Weight	Odds Ratio MH, Random, 95% CI
Perera	32	130	8	77	9.9%	2.82 [1.22; 6.48]
Wilkinson	792	4082	328	4459	14.1%	3.03 [2.64; 3.48]
Nguyen	49	161	16	141	11.5%	3.42 [1.84; 6.35]
Madhavan	182	575	1054	9147	14.0%	3.56 [2.95; 4.29]
Yang PS	1946	4104	32929	221542	14.2%	5.17 [4.85; 5.50]
Pilotto	418	488	303	705	13.5%	7.92 [5.91; 10.63]
Kim	98	176	24	229	12.2%	10.73 [6.40; 18.00]
Gugganig	56	252	8	681	10.5%	24.04 [11.27; 51.28]
Total (95% CI)	**9968**		**236981**		**100.0%**	**5.56 [3.46; 8.94]**

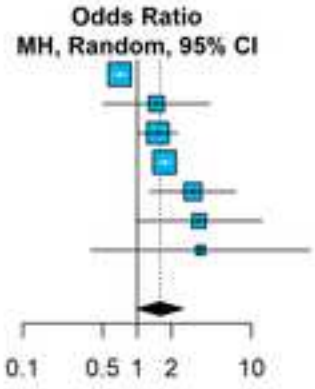
Heterogeneity: $Tau^2 = 0.4115$; $Chi^2 = 99.01$, df = 7 (P < 0.01); $I^2 = 93\%$



B

Study	Frail Events	Frail Total	Robust Events	Robust Total	Weight	Odds Ratio MH, Random, 95% CI
Yang PS	252	4104	18739	221542	22.6%	0.71 [0.62; 0.80]
Gullon	8	234	6	255	10.3%	1.47 [0.50; 4.30]
Madhavan	30	575	319	9147	19.8%	1.52 [1.04; 2.24]
Hohmann	648	36267	355	34234	22.5%	1.74 [1.52; 1.98]
Gugganig	11	252	10	681	12.7%	3.06 [1.28; 7.30]
Perera	16	130	3	77	8.4%	3.46 [0.97; 12.30]
Nguyen	4	161	1	141	3.7%	3.57 [0.39; 32.29]
Total (95% CI)	**41723**		**266077**		**100.0%**	**1.59 [1.00; 2.52]**

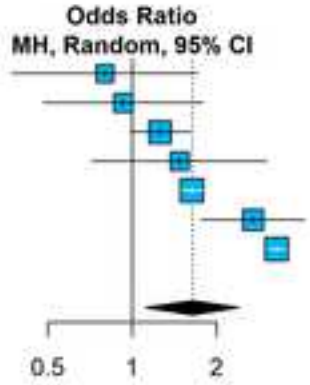
Heterogeneity: $Tau^2 = 0.2428$; $Chi^2 = 104.34$, df = 6 (P < 0.01); $I^2 = 94\%$



C

Study	Frail Events	Frail Total	Robust Events	Robust Total	Weight	Odds Ratio MH, Random, 95% CI
Nguyen	14	161	15	141	10.5%	0.80 [0.37; 1.72]
Gullon	18	234	21	255	11.8%	0.93 [0.48; 1.79]
Madhavan	78	575	1015	9147	16.7%	1.26 [0.98; 1.61]
Perera	30	130	13	77	11.0%	1.48 [0.72; 3.04]
Hohmann	1323	36267	775	34234	17.7%	1.63 [1.49; 1.79]
Gugganig	46	252	52	681	14.7%	2.70 [1.76; 4.14]
Yang PS	1074	4104	21587	221542	17.8%	3.28 [3.06; 3.52]
Total (95% CI)	**41723**		**266077**		**100.0%**	**1.64 [1.11; 2.41]**

Heterogeneity: $Tau^2 = 0.2156$; $Chi^2 = 189.10$, df = 6 (P < 0.01); $I^2 = 97\%$



Frailty Prevalence and Impact on Outcomes in Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis of 1,187,000 Patients

Running Title: Frailty in AF Patients

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ABSTRACT

Frailty is a clinical syndrome characterized by a reduced physiologic reserve, increased vulnerability to stressors and an increased risk of adverse outcomes. People with atrial fibrillation (AF) are often burdened by frailty due to biological, clinical, and social factors. The prevalence of frailty, its management and association with major outcomes in AF patients are still not well quantified. We systematically searched PubMed and EMBASE, from inception to September 13th, 2021, for studies reporting the prevalence of frailty in AF patients. The study was registered in PROSPERO (CRD42021235854). 33 studies were included in the systematic review (n=1,187,651 patients). The frailty pooled prevalence was 39.7% (95%CI=29.9%-50.5%, I^2=100%), while meta-regression analyses showed it is influenced by age, history of stroke, and geographical location. Meta-regression analyses showed that OAC prescription was influenced by study-level mean age, baseline thromboembolic risk, and study setting. Frail AF patients were associated with a higher risk of all-cause death (OR=5.56, 95%CI=3.46-8.94), ischemic stroke (OR=1.59, 95%CI=1.00-2.52), and bleeding (OR=1.64, 95%CI=1.11-2.41), when compared to robust individuals. In this systematic review and meta-analysis, the prevalence of frailty was high in patients with AF. Frailty may influence the prognosis and management of AF patients, thus requiring person-tailored interventions in a holistic or integrated approach to AF care.

KEYWORDS: atrial fibrillation; frailty; epidemiology; mortality; stroke.

1. INTRODUCTION

Frailty is a clinical syndrome characterized by reduced physiologic reserve and increased vulnerability to stressors; it represents a risk factor for negative health-related outcomes, including dependency and death(Morley et al., 2013) and is highly prevalent in the general population (~15%)(Collard et al., 2012). Frailty is today considered a public health priority, and its complexity requires specific managing strategies(Cesari et al., 2016). The relevance of frailty is also recognized in cardiovascular medicine(Aprahamian et al., 2018; Ida et al., 2019).

Atrial fibrillation (AF) is a highly prevalent condition in older persons, often in association with multimorbidity which complicates its clinical management(Hindricks et al., 2021; Proietti et al., 2019). However, the prevalence of frailty and associated factors in people with AF, as well as the impact of frailty on AF management and outcomes are not completely understood(Proietti and Cesari, 2021; Wilkinson et al., 2019). While the prevalence of frailty ranges between 1.6% and 56%, various studies show an association between presence of frailty and risk of all-cause death, although the extent of the association varied across studies(Proietti and Cesari, 2021). Furthermore, the impact of frailty on other outcomes in AF patients (such as stroke and major bleeding) has not been clearly elucidated(Proietti and Cesari, 2021). Moreover, previous studies have shown that frailty may be associated with an underuse of oral anticoagulant (OAC), based on the inclusion of very few cohorts(He et al., 2022; Oqab et al., 2018).

The aims of this study were the following: i) to report the cumulative prevalence of frailty in patients with AF; ii) to examine the associations between frailty and AF-

associated risk factors and comorbidities; iii) to describe prescriptions of OAC drugs in patients with AF and frailty; and iv) to analyse the impact of frailty on clinical outcomes in AF patients.

2. METHODS

This systematic review was performed according to the 'Meta-analysis Of Observational Studies in Epidemiology' (MOOSE) guidelines(Stroup et al., 2000) and reported according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines(Page et al., 2021). The protocol was registered on the international prospective register of systematic reviews (PROSPERO), N. CRD42021235854.

2.1 Search Strategy

A systematic and comprehensive literature search was performed on MEDLINE (accessed through PubMed) and EMBASE databases, from inception to September 13th, 2021. Relevant key terms were combined in the search strategy, including 'frailty', 'frail' and 'atrial fibrillation'. The full search strategy is reported in detail in the Supplementary Materials (Table S1).

2.2 Studies Selection

All articles retrieved from the literature search were systematically, sequentially, and independently screened for eligibility by two authors (MP and GFR). Each article included after the first screening phase focused on titles and abstracts was then evaluated considering the full text. Disagreements were resolved by collegial discussion.

2.3 Inclusion and Exclusion Criteria

Studies reporting data about the evaluation of frailty, irrespective of the tool used for its assessment, in AF patients were included. On the other side, studies on highly

selected cohorts of patients with AF, articles not in English, conference abstracts, letters, comments, editorials, case reports, systematic reviews, and/or meta-analysis were excluded. In the case of two or more studies based on the same cohort of patients, the study with the highest number of patients, the most complete data and/or the most recently published was considered.

2.4 Data Extraction and Quality Assessment

Data from the studies included were independently extracted by two authors (MP and GFR), through a standardized electronic form. We also extracted data on sample size, numbers of patients with prefrailty and frailty, age, proportion of women, prevalence of several comorbidities (including hypertension, diabetes mellitus, coronary artery disease (CAD), previous cerebrovascular disease, chronic heart failure (CHF), peripheral vascular disease (PVD)), CHA_2DS_2-VASc score, Charlson Comorbidity Index (CCI), proportion of patients prescribed with OAC and type of OAC prescribed, for each included study when available. Additionally, we extracted data on clinical outcomes (i.e., all cause death, stroke, major bleeding) according to the presence of frailty, when available.

All the included studies were independently evaluated by two authors (MP and GFR) to assess the risk of bias. We evaluated the risk of bias separately for each outcome of the study. We evaluated the risk of bias for studies reporting frailty prevalence using a customized version of the Newcastle-Ottawa Scale (NOS) for cross-sectional studies. The NOS is composed of 5 items organized into three domains (i.e., Selection, Comparability, Outcome), with a maximum score of 5 points (Table S2). Studies with a score ≤3 were considered at high risk of bias. For studies reporting on

outcomes according to the presence of frailty, we evaluated the risk of bias using a customized version of the NOS for population-based studies,(Viswanathan et al., 2012) composed of 8 items and three domains (i.e., Selection, Comparability, Outcome), with a maximum score of 9 points (Table S3). Each study with a NOS ≤6 was considered as at high risk of bias.

2.5 Definition of Outcomes

Prevalence of pre-frailty and frailty were defined irrespective of the assessment tool used in each study. Cut-off values to define the presence of pre-frailty and frailty were established according to the original studies, considering the usual practice or the authors' classification. We also investigated the management of patients with AF according to the presence of frailty (i.e., rates and type of OAC drugs prescription). Further, we investigated the impact of frailty on the risks of all-cause death, stroke, and major bleeding.

2.6 Statistical Analysis

The prevalence of frailty reported in the included studies was pooled with a generalized linear mixed model (i.e., random intercept logistic regression model)(Stijnen et al., 2010). The number of patients prescribed with OAC, the number of events, and the total number of patients according to the frailty status were pooled and compared using random-effects models. For continuous outcomes, mean, standard deviation (SD), and total number in each group were pooled and compared with inverse variance method.

Pooled estimates were reported as Odds Ratios (OR) and 95% confidence intervals (CI), or mean difference and 95% CI for continuous variables. The inconsistency index (I^2) was calculated to measure heterogeneity, with low heterogeneity defined as an I^2 of <25%, moderate heterogeneity when I^2 falls between 25 and 75%, and high heterogeneity when I^2 was >75%, as per previously pre-specified cut-offs.(Higgins et al., 2003)

For each outcome, a sensitivity analysis was performed with a “leave-one-out” approach, in which all studies are removed one at a time to analyse their influence on the primary analysis. We also performed a sensitivity analysis for the prevalence of frailty using the inverse variance method and two different transformations of the prevalence (i.e., logit transformation and Freeman-Tukey double arcsine).

To account for potential sources of heterogeneity in the pooled prevalence of frailty and OAC prescription, we performed several subgroup analyses, according to relevant study-level characteristics. We also performed meta-regression analyses, according to mean age, sex, geographic location, and comorbidities. Multivariable meta-regressions were also performed with the variables significantly associated at univariate level.

Publication bias was assessed for studies reporting outcomes according to the frailty status, with the use of funnel plots, which were visually inspected for asymmetricity. Egger’s test was also performed. All the statistical analyses were performed using R version 4.0.3 (R Core Team, 2021, Vienna, Austria).

3. RESULTS

Among 1,350 records identified from the literature search (333 from PubMed, 1017 from EMBASE), 33 studies (a total of 1,187,651 persons with AF) were eventually included (Table 1) after removal of duplicates, title and abstract screening, and full-text assessment [Figure S1]. Sixteen studies were conducted in Europe; 7 in Asia; 6 in North America; and 4 in other geographical regions, including multinational cohorts. Fifteen were observational single-centre studies; 9 were observational multicentre studies; 5 were based on electronical medical records; and 3 were population-based studies. Four studies enrolled only patients with AF and a high thromboembolic risk. Finally, 14 studies were conducted in a hospital-based setting; 10 in community-based setting; and 9 in other settings, including mixed and unclear settings.

As for the type of frailty assessment tool used in the original studies, 8 cohorts used the frailty index proposed by Rockwood and Mitnitski; 6 were based on the Edmonton frail scale; 5 on the clinical frailty scale (CFS); 4 on the frailty phenotype designed by Fried and colleagues; 3 on the FRAIL tool; 2 on a claim frailty index (CFI); 2 on the Tilburg frailty index (TFI); and 3 on other methods. Finally, 13 studies were found to be at high risk of bias for the prevalence of frailty, while 2 studies were at high risk of bias among those reporting clinical outcomes according to frailty (Table S4 and S5, respectively).

3.1 Prevalence of Frailty and Pre-Frailty in patients with AF

Based on 33 studies including 1,187,651 patients with AF, the prevalence of frailty was 39.7% (95%CI: 29.9-50.5%), with high heterogeneity between studies (Figure

1). The pre-specified leave-one-out analysis showed little to no influence of individual studies on pooled estimates or heterogeneity (Figure S2 in supplementary materials). Sensitivity analyses according to the inverse variance methods were largely consistent with the main analysis [Table S6].

Thirteen studies reported data on the prevalence of pre-frailty, with a pooled prevalence of 35.0% (95%CI: 26.1-45.1%), and a high heterogeneity between studies [Figure S3]. The pre-specified leave-one-out sensitivity analysis showed little influence of individual studies on pooled prevalence or heterogeneity [Figure S4].

The results of the subgroup analysis for the prevalence of frailty are reported in Figure 2. Significant interactions were found according to geographical location, tool used for the assessment of frailty, study design, and risk of bias. The prevalence of frailty was found to be higher in European-based cohorts, and in the studies that used CFS or TFI, while the lowest prevalence of frailty was observed in studies using the frailty phenotype. A higher proportion of patients with AF were found to be frail in observational single-centres studies, while a lower prevalence was reported in population-based studies, randomized controlled trials, and studies with low risk of bias. Finally, the prevalence of frailty was lower in studies conducted in community-based settings, and higher in studies from hospital settings. Heterogeneity was found to be high in most of the analyzed subgroups.

3.2 Univariate and Multivariable Meta-Regression Analysis

To explore the potential sources of heterogeneity in our estimates for the prevalence of frailty, we performed univariate and multivariable meta-regression analyses

according to several study-level characteristics. On univariate analyses, mean age, geographical location, study setting, risk of bias, and proportion of patients with hypertension or history of stroke were found significantly associated with frailty (Table S7 in Supplementary Materials). Particularly, studies with higher mean age and higher proportion of patients with history of cerebrovascular accidents showed increased prevalence of frailty. Conversely, studies based on Asian cohorts, those conducted in a community-based setting, and those at low risk of bias were associated with a lower prevalence of frailty, consistent with the results of subgroup analyses. A non-significant trend was also observed between prevalence of hypertension and frailty. Figure 3 shows a graphical representation of the relationship between mean age, proportion of patients with history of stroke, and prevalence of frailty.

In a multivariable meta-regression analysis, including the study-level characteristics that were significantly associated with the prevalence of frailty at univariate analysis, a model including mean age, prevalence of history of stroke, geographical location, study setting, and risk of bias explained a relevant proportion of the observed heterogeneity (R^2=67.7%, Table S7), although none of the variables was independently associated with the prevalence of frailty in the final model.

3.3 Comorbidities and Clinical Characteristics Associated with Frailty

Overall, 13 studies reported data on clinical characteristics and comorbidities in frail and robust patients. All studies reported data about sex; 12 reported information on history of stroke; 11 on hypertension, diabetes or congestive heart failure (CHF); 10 studies reported data on mean age; 7 on CHA_2DS_2-VASc score; 6 on peripheral

vascular disease; and 4 on Charlson Comorbidity Index (CCI). Frailty was associated with female sex and with all the main investigated comorbidities [Figure S5, Panel A]. Frail patients were older and with higher CHA_2DS_2-VASc and CCI scores [Figure S5, panel B]. High heterogeneity was found for all comparisons.

3.4 OAC Prescription According to Frailty Status

To evaluate OAC prescription across different degrees of frailty, we compared the rates of OAC prescription among frail, pre-frail, and robust patients.

After excluding studies in which all patients were already receiving OAC, we identified 17 studies that reported the number of patients prescribed with OAC according to frailty status. We performed one primary comparison (frail vs. robust patients), and 3 additional comparisons (frail vs. pre-frail/robust, frail vs. pre-frail, and pre-frail vs. robust subjects) [Figure 4]. None of the analyses showed significant differences in OAC prescription across frailty status categories, although there was a trend towards lower OAC prescription in frail persons. High heterogeneity was observed for all the comparisons.

The results of the sensitivity analyses according to the leave-one-out approach are reported in Figure S6. The exclusion of the study by Jankowska-Polanska et al(Jankowska-Polańska et al., 2020) showed a significant lower OAC prescription in frail vs. pre-frail/robust patients (OR 0.78, 95%CI 0.62-0.97) [Figure S6, Panel B], while the omission of the study of Pilotto et al.(Pilotto et al., 2016) showed a significant higher OAC prescription for pre-frail vs. robust subjects (OR 1.22, 95%CI 1.06-1.43) [Figure S6, Panel D]. No significant influence of individual studies was found for the other analyses.

We performed three subgroup analyses for our primary comparison (i.e., frail vs. robust patients), according to study design, thromboembolic risk of patients enrolled, and study setting [Figure S7]. We found significant interaction by study type and in OAC prescription in frail vs. robust patients. Frail patients enrolled in observational multicentre cohorts and in the studies based on electronic medical records were less likely to be prescribed with OAC, while the opposite was found in the two population-based studies included. Frail persons were 28% less prescribed with OAC in studies that included patients irrespective of baseline thromboembolic risk (OR: 0.72, 95%CI: 0.54-0.97), while a trend towards higher rates of prescription was found in cohorts that enrolled only patients with high thromboembolic risk. Finally, significant differences were found across study settings, with a 48% less OAC prescription in frail patients enrolled in hospital-based studies, compared with non-significant differences between frail and robust patients in community-based studies and studies conducted in other settings.

To identify other possible causes of between-studies variability, we also performed meta-regression analyses. Among the study-level characteristics investigated, only mean age was significantly and inversely associated with the probability of OAC prescription in frail patients compared with non-frail individuals (R^2=37.4%; Table S8 in supplementary materials); non-significant trends were also observed for study setting, with lower OAC prescription in hospital-based studies. A graphical representation of the relationship between mean age of the included studies and the OR for OAC prescription in frail patients is reported in Figure S8. In frail patients ≥80 years OAC was significantly less prescribed.

Finally, we compared frail vs. non-frail patients for the probability of receiving Non-Vitamin K Antagonist OACs (NOACs) when anticoagulation is prescribed. In the 7 studies that reported available data for the comparison(Gugganig et al., 2021; Gullón et al., 2019; Mostaza et al., 2018; Saczynski et al., 2020; Sanghai et al., 2021; Sławuta et al., 2020; Son et al., 2019), we did not find any difference in the probability of NOACs prescription between frail and robust patients [Figure S9].

3.5 Risk of Outcomes according to Frailty Status in patients with AF

To analyse the impact of frailty on the risk of all-cause mortality, stroke, and bleeding, we compared frail vs. robust patients. We also compared frail vs. pre-frail/robust, frail vs. pre-frail, and pre-frail vs. robust patients.

In the main comparison, frail patients had an increased risk of all outcomes, compared with robust patients, with a 5.6-fold higher risk of all-cause mortality, and roughly 60% increased risk of stroke and bleeding [Figure 5, Panels A to C, respectively]. Heterogeneity was high for all comparisons. Similar results were found for all other comparisons, with a higher risk of all-cause mortality according to any worse frailty status [Figure S10-S12]. A sensitivity analysis on the risk of all-cause mortality according to the study setting did not show any difference according to study in the community, hospital, and other mixed settings [Figure S13].

3.6 Publication Bias

Assessment of publication bias was performed only for the studies reporting outcomes according to the frailty status. Due to the low number of studies available

for the comparison of pre-frail patients, we only assessed publication bias for frail vs. robust and frail vs. pre-frail/robust comparisons. There was no significant publication bias across the outcomes investigated [Figure S14].

4. DISCUSSION

In this systematic review and meta-analysis of 1,187,651 persons with AF, approximately 40% were frail, with confidence intervals pointing towards a range of prevalence from 30% to 50%. Frail patients were older, more often women, and with higher prevalence of comorbidities. Frail AF patients had also a higher overall burden of multimorbidity, as well as of thromboembolic risk, but we did not find significant differences in OAC prescription in frail or pre-frail persons. While a differential influence on OAC prescription was found according to the study design, we observed a significant impact of mean age, with frail older persons (i.e., age ≥80) being less likely prescribed. When considering general AF cohorts (i.e., excluding those cohorts enrolling only patients with high thromboembolic risk), frail patients had a 30% lower chance to receive an OAC compared to robust ones. Finally, frail patients were at higher risk of all major adverse outcomes, and frailty was positively associated with all-cause death

In the last 20 years, the issue of frailty has increasingly been raised by geriatricians, underlining the significant impact on patients and health services, clinical care and research(Cesari et al., 2016; Vellas et al., 2012). Recent estimates suggest that the worldwide prevalence of frailty is about 18%, with a prevalence of pre-frailty of about 45%, irrespective of clinical setting(O'Caoimh et al., 2021). While a significant link between AF and frailty has already been described(Proietti and Cesari, 2021), our paper provides a solid estimate of the prevalence of frailty in patients with AF, documenting that approximately 4 out of 10 patients with AF are frail and 35% are pre-frail. These findings indicate that up to 75% of patients with AF have some degree of frailty, in contrast to 63% in the general population(O'Caoimh et al., 2021).

Based on subgroup analyses, we identified an overall prevalence of frailty of 17% in AF patients in the community, which is higher than previous estimates in general community cohorts showing a 12% prevalence, irrespective of frailty tools(Collard et al., 2012). Furthermore, there was a higher prevalence of frailty compared with pre-frailty, different from what was previously reported in general population(O'Caoimh et al., 2021). Our estimates, which on some extent can be considered even too high (and influenced by the overall high mean age of patients included in this analysis), are supported by similar projects exploring the prevalence of frailty in other cardiovascular diseases(Denfeld et al., 2017; Liperoti et al., 2021; Palmer et al., 2019). Indeed, in these studies the extent of frailty burden was reported up to 70% of the patients included in the studies, even though the overall mean ages of the patients included in those meta-analyses were lower than our(Denfeld et al., 2017; Liperoti et al., 2021; Palmer et al., 2019). Moreover, data from the subgroup analysis about frailty assessment tools (i.e., frailty phenotype reporting the lower prevalence) showed that, when frailty is multidimensionally assessed and/or via a functional approach, its prevalence tends to be significantly higher (O'Caoimh et al., 2021).

In AF, multimorbidity is associated with a higher burden of thromboembolic and bleeding risks, under-prescription and lower quality of OAC treatment, and a higher risk of all major AF-related negative outcomes(Jani et al., 2018; Proietti et al., 2021, 2019). While multimorbidity represents a significant health construct in influencing patients' lives and the natural history of disease, it does not adequately capture the individual's overall capacity and physiological reserve. The evaluation of frailty provides a deeper insight into the entire spectrum of phenomena influencing patient care(Cesari et al., 2016; Morley et al., 2013). While agreement exists regarding the

theoretical construct of frailty(Morley et al., 2013), a large number of tools are used for its assessment (Proietti and Cesari, 2020). Of these, the frailty phenotype evaluates the residual physiological reserve on the basis of the phenotypic manifestation of different physical signs and symptoms(Fried et al., 2001), while the frailty index provides an overall evaluation of health deficits(Mitnitski et al., 2001).

Prior studies have provided a limited analysis of the relationship between frailty and OAC prescription as well as of the impact of frailty on major negative outcomes(Proietti and Cesari, 2021; Villani et al., 2018; Wilkinson et al., 2019). Hence, our work provides a solid estimate of the prevalence of frailty and pre-frailty in patients with AF. The evidence that 3 out of 4 AF patients show a certain degree of frailty - with almost half of them frail – has major implications for their management. Indeed, in recent years there has been a shift towards a more holistic or integrated approach to AF care. Given the role of multimorbidity in AF, the need for a more comprehensive assessment, characterisation, and personalized management of patients with AF has emerged(Bhat et al., 2021; Potpara et al., 2020). This approach has been advocated in clinical guidelines(Hindricks et al., 2021), promoting the 'Atrial Fibrillation Better Care' (ABC) pathway(Lip, 2017) wherein adherence to such an approach is associated with a significant reduction of major negative outcomes(Romiti et al., 2021b). Such an integrated care approach has also been advocated for other chronic conditions(Field et al., 2021; Lip and Ntaios, 2021).

Frailty in the general population has been associated with an increased risk of all-cause death, regardless the assessment tool used(Chang and Lin, 2015; Kojima et

al., 2018). In the general population, the presence of frailty (according to the frailty phenotype) was associated with a 2-fold and 1.5-fold risk of all-cause death relative to robust and pre-frail persons, respectively(Chang and Lin, 2015). Our estimates provide evidence that frail patients with AF have up to a 5-fold higher risk of dying compared with robust ones and an almost 3-fold higher risk compared to those who are pre-frail. Furthermore, the risk of all-cause death was not significantly different according to the study setting, even though the low number of studies considered suggests caution in interpretation. In a recent study enrolling long-term care residents with AF, the presence of geriatric conditions (e.g., recent fall, functional dependency, cognitive impairment, mobility impairment) did not affect the risk of stroke or bleeding (Kapoor et al., 2022). In contrast, our findings indicate that frailty may influence the onset of adverse outcomes in AF patients.

In recent years several researchers put significant efforts in defining the concept of 'inflammageing', defined as a low-grade systemic inflammatory status contributing to the development of ageing-related diseases and conditions(Ferrucci and Fabbri, 2018; Franceschi et al., 2018). Such pro-inflammatory status has been associated to the development and perpetuation of frailty(Kanapuru and Ershler, 2009; Van Epps et al., 2016) which is associated with increased systemic inflammatory markers(Soysal et al., 2016). Similarly, inflammation has a significant role in initiating, determining and perpetuating AF(Boriani et al., 2021; Brundel et al., 2022; Korantzopoulos et al., 2018). From this perspective, even if not supported by specific data we can postulate that the increased inflammatory burden firstly ignites AF and subsequently, with other inflammatory stimuli related to AF itself, characterise AF along with the high burden of risk factors and multimorbidity which characterize

AF(Boriani et al., 2021), determines the occurrence of frailty. The epidemiological evidence linking AF and frailty, which interplay could amplify the inflammatory state, and the high risk of several relevant clinical events related to AF(Odutayo et al., 2016), that become less manageable for a frail individual, can suggest the possible mechanism entailing the higher risk of outcomes.

Hence, a formal evaluation of frailty should be conducted in every older person with AF to aid personalized interventions. In patients with frailty, a comprehensive geriatric assessment followed by a personalized intervention effectively reduces the burden of frailty itself and provides a significant improvement in clinical outcomes(Cesari et al., 2015; Ellis et al., 2017). A more formal assessment of frailty to identify those in need of comprehensive geriatric assessment (and the consequent personalization of care) could reduce the risk of negative outcomes.

Although we did not find a significant reduction in the overall population, the presence of frailty can negatively affect the prescription of OAC, modulated by increasing age, study setting, and baseline thromboembolic risk. This suggests that chronological age may be considered more important than the biological age (captured by frailty) in the clinical decision process (as observed in other cohorts(Fumagalli et al., 2015; Marzona et al., 2019)). Conversely, in patients at high thromboembolic risk, the increased clinical complexity (i.e., higher risk of outcomes) related to frailty shows a trend towards higher OAC prescription. Indeed, the differences we found - with observational studies characterized by lower prescription, and population-based studies showing a higher rate of prescription - underline the differential way to consider the presence of frailty. In observational studies, when

frailty is explicitly assessed, its presence may discourage OAC prescriptions, which might relate to the fear of adverse events (i.e., major, or intracranial bleeding) or to the assumption that OAC would be unable to substantially reduce the risk of adverse events in frail patients. In population-based studies, the higher risk profile of frail patients with AF might drive more OAC prescriptions. Regarding the prescription of VKA and NOACs in frail patients, our data did not show any difference, highlighting the limited evidence regarding the effectiveness and safety of NOACs in this specific patient subgroup(Grymonprez et al., 2020). Notwithstanding, recent findings provide reassuring data regarding the use of apixaban in patients with AF and frailty(Kim et al., 2021; Lip et al., 2021). On the other side, there is currently limited data on the efficacy of novel approach for thromboembolic risk preventions, such as left atrial appendage occlusion, which may represent an interesting alternative for frail patients who are deemed not candidate to OAC.(Volgman et al., 2022) Further studies are needed to shed light on these perspectives.

Our work has important implications in terms of clinical and public health implications. On the clinical point of view, the assessment of frailty and the consequential personalization of offered care could reduce the burden of adverse clinical events by allocating person-tailored interventions, in conjunction with an integrated AF care approach. Benefits are not limited to the patient-level, but may also positively impact the public health, given the costs associated to both conditions(Burdett and Lip, 2020; Hoogendijk et al., 2019). Projecting our findings on the growing prevalence and burden of AF, it might be conceivable to decentralize services, privileging primary care models to traditional hospital-based ones. Indeed, recommendations coming also from the World Health Organization support the

strengthening of primary care for the preventive, multidisciplinary, and integrated management of older persons, especially the most vulnerable ones(World Health Organisation, 2017). In this context, it is foreseeable the need to reorient primary care services to better allow them the management of patients with AF, in particular when frailty is simultaneously present(Cesari et al., 2016).

Lastly, we also advocate the need for specific studies which will test how the evaluation of frailty and the integrated care approach now recommended for AF patients could have a positive impact on clinical outcomes (Hindricks et al., 2021)(Chao et al., 2021).

4.1 Limitations and Strengths

The main limitation to this systematic review is the high heterogeneity reported in our pooled estimates. Furthermore, it is possible that some cohorts were not included, despite our best efforts to include any relevant study, due to not being captured by our search strategy.

Nonetheless, our paper has important strengths. First, we performed specific analyses to evaluate heterogeneity, including the multivariable meta-regression, which accounts for roughly 65% of the observed heterogeneity in the pooled estimate for frailty prevalence. Notwithstanding, high heterogeneity is a common concern in epidemiological meta-analyses exploring the prevalence of conditions which could vary consistently across studies and is nowadays largely accepted, when proper study of heterogeneity is performed(Colditz et al., 1995; Odutayo et al.,

2016; Romiti et al., 2021a). Second, we included 33 studies and over a million of AF patients, thus providing robust data for the estimates reported in this analysis.

5. CONCLUSIONS

In this systematic review and meta-analysis, the prevalence of frailty was high (approximately 40%, with 95% confidence intervals ranging between 30-50%) in patients with AF. Frailty influences the prognosis and management of AF patients, thus requiring person-tailored interventions in a holistic or integrated approach to AF care.

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FIGURE LEGENDS

Graphical Abstract – Frailty in Atrial Fibrillation (Created with Biorender.com)

Legend: CI= Confidence Interval; OR= Odds Ratio.

Figure 1 – Prevalence of Frailty in patients with Atrial Fibrillation.

Legend: CI= Confidence Interval; GLMM= General Linear Mixed Model.

Figure 2 – Subgroup Analyses for the Prevalence of Frailty.

Legend: CFI= Claim Frailty Index; CFS= Clinical Frailty Scale; CI= Confidence Interval; GLMM= Generalised Linear Mixed Model; RCT= Randomised Controlled Trial; TFI= Tilburg Frailty Index.

Figure 3 – Univariable meta-regressions for the prevalence of Frailty according to study-level characteristics

Legend: Panel A: Mean Age; Panel B: Prevalence of History of Stroke

Figure 4 – OAC Prescription according to Frailty status

Legend: CI= Confidence Interval; OR= Odds Ratio.

Figure 5 – Risk of All-Cause Death, Stroke and Bleeding in Frail vs. Robust subjects.

Legend: Panel A: All-Cause Death; Panel B: Stroke; Panel C: Bleeding; CI= Confidence Interval; MH= Mantel-Haenszel; OR= Odds Ratio.

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1 Table 1 – Main Characteristics of the Studies Included in the Systematic Review

STUDY	YEAR	GEOGRAPHIC LOCATION	STUDY TYPE	SETTING	INCLUSION CRITERIA	FRAILTY ASSESSMENT	N	PREFRAIL	FRAIL	AGE (mean)	CHA_2DS_2-VASC (mean)	OAC (%)
Annoni(Annoni and Mazzola, 2016)	2016	Italy	Observational Single Centre	Hospital	AF ≥65 years	Robinson	403	115	231	84.6	N/A	N/A
Bo(Bo et al., 2017)	2017	Italy	Observational Multicentre	Hospital	AF ≥65 years	Groningen	452	N/A	341	81.6	N/A	49.8
Campitelli(Campitelli et al., 2021)	2021	Canada	Administrative Database	Other	AF ≥65 years	Frailty Index	36466	12985	17778	N/A	N/A	50.8
De Simone(De Simone et al., 2020)	2020	Italy	Observational Single Centre	Hospital	AF ≥80 years	Edmonton	731	N/A	300	85	N/A	100
Gugganig(Gugganig et al., 2021)	2021	Switzerland	Observational Multicentre	Other	AF ≥65 years	Frailty Index	2369	1436	252	73	3.5	90.4
Gullon(Gullón et al., 2019)	2019	Spain	Observational Multicentre	Hospital	AF ≥65 years	FRAIL	615	N/A	297	85.2	5.3	69.8
Hohmann(Hohmann et al., 2019)	2019	Germany	Administrative Database	Community	AF ≥18 years on OAC	CFI	70501	N/A	36267	74	3.7	100
Induruwa(Induruwa et al., 2017)	2017	UK	Observational Single Centre	Hospital	AF ≥75 years	CFS	419	N/A	282	85*	4*	48.7
Jankowska-Polanska(Jankowska-Polańska et al., 2020)	2021	Poland	Observational Single Centre	Other	AF ≥60 years	Edmonton	158	N/A	84	70.9	N/A	42.4
Kim(Kim et al., 2017)	2017	Korea	Observational Single Centre	Other	AF ≥65 years	Frailty Index	365	68	176	79.4	N/A	34.2
Koca(Koca et al., 2020)	2020	Turkey	Observational Single Centre	Community	AF ≥65 years	Fried	64	33	10	75.3	N/A	N/A

Lefebvre(Lefebvre et al., 2015)	2016	Canada	Observational Multicentre	Hospital	AF ≥80 years	CFS	682	N/A	558	86.4	N/A	69.6
Lip(Lip et al., 2021)	2021	US	Administrative Database	Community	AF ≥65 years on OAC	CFI	404798	N/A	150487	N/A	N/A	N/A
Liu(Liu et al., 2020)	2020	China	Observational Multicentre	Other	AF ≥65 years	CFS	500	N/A	201	75.2	4*	39.6
Madhavan(Madhavan et al., 2019)	2019	US	Observational Multicentre	Community	AF ≥18 years	Fried	9749	N/A	575	75*	4*	76.4
MIynarska(Mlynarska et al., 2017)	2017	Poland	Observational Single Centre	Hospital	AF ≥60 years	TFI	132	N/A	79	72.7	4.3	N/A
Mostaza(Mostaza et al., 2018)	2018	Spain	Observational Multicentre	Other	AF ≥75 years on OAC	FRAIL	837	N/A	360	83	5	100
Nguyen(Nguyen et al., 2016)	2016	Australia	Observational Singe Centre	Hospital	AF ≥65 years	Edmonton	302	N/A	161	84.7	4.6	51.3
Ohta(Ohta et al., 2021)	2021	Japan	Observational Singe Centre	Hospital	AF on OAC	Fried	120	N/A	34	77.7	3.1	100
Perera(Perera et al., 2009)	2009	Australia	Observational Single Centre	Hospital	AF ≥70 years	Edmonton	220	N/A	140	82.7	N/A	40.1
Pilotto(Pilotto et al., 2016)	2016	Italy	Observational Multicentre	Community	AF ≥65 years	MPI	1827	634	488	84.4	3.8	43.7
Polidoro(Polidoro et al., 2013)	2013	Italy	Observational Single Centre	Hospital	AF	Frailty Index	70	N/A	62	79.3	N/A	N/A
Saczynski(Saczynski et al., 2020)	2020	US	Observational Multicentre	Community	AF ≥65 years with High TE Risk	Fried	1244	659	172	75.5	4*	85.5
Sanghai(Sanghai et al., 2021)	2021	US	Administrative Database	Other	AF w/ CHA_2DS_2-VASc ≥2	Frailty Index	308664	99185	109475	77.7	4.6	39.5
Slawuta(Sławuta et al., 2020)	2020	Poland	Observational Single Centre	Hospital	AF ≥60 years	Edmonton	158	16	84	70.4	N/A	100

Son(Son et al., 2019)	2019	Korea	Observational Single Centre	Community	AF ≥60 years on AT	FRAIL	298	143	53	72.1	N/A	63.8
Uchmanowicz(Uchmanowicz et al., 2020)	2020	Poland	Observational Single Centre	Hospital	AF ≥65 years w/out CI	TFI	100	N/A	67	70.3	N/A	N/A
Wilkinson(Wilkinson et al., 2020)	2020	Multinational	RCT	Other	AF ≥21 years	Frailty Index	20867	12326	4082	N/A	N/A	100
Wilkinson 2(Wilkinson et al., 2021)	2020	UK	Population-Based	Community	AF ≥65 years	Frailty Index	61177	20352	34382	79.7	3.8	53.1
Wojszel(Wojszel et al., 2019)	2019	Poland	Observational Single Centre	Hospital	AF	CFS	98	N/A	65	84*	N/A	N/A
Yamamoto(Yamamoto et al., 2019)	2019	Japan	Administrative Database	Other	AF on NOACs	CFS	240	N/A	120	76.1	4*	100
Yang MT(M. T. Yang et al., 2020)	2020	Taiwan	Population-Based	Community	AF ≥65 years	Edmonton	38	N/A	2	73.5	N/A	N/A
Yang PS(P. S. Yang et al., 2020)	2020	Korea	Population-Based	Community	AF ≥18 years CHA_2DS_2-VASc ≥1	Frailty Index	262987	37341	4104	58*	1.8	100

Legend: *median values; AF= Atrial Fibrillation; CFI= Claim Frailty Index; CFS= Clinical Frailty Scale; CI= Cognitive Impairment; MPI= Multidimensional Prognostic Index; N/A= Not Available; NOACs= Non-Vitamin K Antagonist Oral Anticoagulants; OAC= Oral Anticoagulant; RCT= Randomised Controlled Trial; TFI= Tilburg Frailty Indicator; UK= United Kingdom; US= United States.

Frailty Prevalence and Impact on Outcomes in Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis of 1,187,000 Patients

Running Title: Frailty in AF Patients

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