**ORIGINAL RESEARCH**

# Existence of Geriatric Conditions Serves As a Prognostic Indicator for Significant Adverse Outcomes in Elderly Individuals with Atrial Fibrillation

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## ABSTRACT

**Background:** In elderly individuals with Atrial Fibrillation (AF), physical, psychosocial, and cognitive impairments are commonly observed. The prognostic significance of these conditions regarding the occurrence of major bleeding remains ambiguous. The objective of this research was to ascertain if geriatric conditions are linked prospectively to significant bleeding in elderly individuals with atrial fibrillation who are undergoing anticoagulation therapy. **Material and Methods**: Multicenter cohort study conducted over a three-year period from January 2013 to December 2015 within the Department of General Medicine at Rama Medical College, Hospital & Research Centre, Kanpur and Hapur, U.P., India The study included participants diagnosed with atrial fibrillation (AF), aged 65 years or older, possessing a CHA2DS2-VASc score of 2 or higher, and undergoing oral anticoagulant therapy (n=1,284). A total of 1,624 participants underwent screening. A comprehensive geriatric assessment comprising six components: frailty, cognitive function, social support, depressive symptoms, visual acuity, and auditory function. The primary outcome was significant hemorrhage as determined by a panel of physicians. **Result:** At baseline, the participants exhibited an average age of 76.5 years, with 48% being female. The average HASBLED score was 3.5, while the mean CHA2DS2-VASC score was 4.8. Over a three-year follow-up period, 140 participants (10.9%) experienced an episode of significant bleeding. Following adjustments for essential covariates and consideration of mortality as a competing risk, cognitive impairment (hazard ratio [HR] 1.63, 95% confidence interval [CI]: 1.01-2.54) and frailty (HR 2.78, 95% CI 1.36-5.59) were found to be significantly associated with the onset of major bleeding. **Conclusions:** In elderly individuals with Atrial Fibrillation who are receiving anticoagulant therapy, cognitive impairment and frailty were found to be independently linked to an increased risk of major bleeding.

**Keywords:** Atrial Fibrillation, Psychosocial Impairments, Geriatric Conditions



## INTRODUCTION

Atrial fibrillation (AF) represents the most prevalent cardiac arrhythmia among the elderly population and is correlated with an elevated risk of stroke and heart failure. Advanced age constitutes the most significant risk factor for atrial fibrillation (AF), as evidenced by data from 2010,[1] which indicates that over 80 percent of adults diagnosed with AF in the United States were aged 65 years or older. As the demographic profile of the Indian population continues to age, it is projected that the burden of atrial fibrillation (AF) will correspondingly increase

[2]. Among the elderly demographic afflicted with cardiovascular conditions,[3] there is a prevalent incidence of physical, cognitive, and psychosocial impairments [4]. In previous reports, it was documented that up to 15 percent of older ambulatory adults with atrial fibrillation were classified as frail, 30 percent exhibited symptoms of depression, and 40% demonstrated cognitive impairments. These impairments present challenges in the daily lives of patients and have been correlated with adverse clinical outcomes in isolated reports [5]. Nevertheless, the prognostic significance of these factors for major hemorrhagic events has not been investigated within a contemporary cohort of older patients diagnosed with atrial fibrillation (AF). Given the increasing treatment of older patients with atrial fibrillation (AF) using direct oral anticoagulants (DOACs), the efficacy of current bleeding risk prediction tools is limited, thus constraining their practical application [6]. The current study investigates the prognostic significance of geriatric conditions over a three-year follow-up period concerning physician-adjudicated clinical outcomes. Furthermore, we explored the potential for geriatric conditions to enhance the existing framework of bleeding risk stratification and to inform the discourse regarding the risks and benefits of anticoagulant prescription in elderly patients with atrial fibrillation.

## MATERIALS AND METHODS

The particulars of the SAGE (Systematic Assessment of Geriatric Elements) - AF study have been delineated in prior literature [3,4,7]. The inclusion criteria encompassed the following: (1) individuals aged 65 years or older; (2) those attending an ambulatory visit at Rama Medical College, Hospital & Research Centre Kanpur, U.P., (3) the presence of atrial fibrillation established through an electrocardiogram or Holter monitor, or documented in any clinic note or hospital record; and (4) a CHA2DS2VASC (congestive heart failure; hypertension [8]; age ≥75 years; diabetes mellitus; history of stroke, transient ischemic attack, or thromboembolism; vascular disease; age between 65 and 74 years; female sex) risk score ≥2. The exclusion criteria encompassed if participants possessed an absolute contraindication to oral anticoagulation or had an indication for oral anticoagulation for reasons other than atrial fibrillation (e. g., the presence of a mechanical heart valve). Additionally, individuals unable to provide informed consent, those not proficient in the Hindi or English language, subjects with scheduled invasive procedures carrying a high bleeding risk, incarcerated individuals, or those unwilling or unable to attend planned follow-up visits were excluded from participation.

A total of 6,507 individuals underwent the screening process. In the current analysis, the sample was restricted to participants who were administering an oral anticoagulant (n=1,064) at the time of their enrollment in the study. The flow chart illustrating the enrollment process is presented in **Supplementary Figure S1**.

All participants furnished informed written consent. The study protocols received approval from the Institutional Research Committee and the Ethical Committee at Rama Medical College, Hospital and Research Centre, in Kanpur, Uttar Pradesh.

### Data Collection and Assessment of Geriatric Conditions

Staff members that had received certification extracted clinical data, socio-demographic information, and relevant laboratory information from the medical record for their own use. At the baseline period of January 2013 to December 2015, six geriatric conditions were evaluated using measures that had been confirmed. These conditions were cognitive dysfunction, frailty, social support, depressive symptoms, hearing impairment and vision impairment. The frailty scale included in the Cardiovascular Health Survey was used to evaluate frailty [9]. Each aspect is assigned a score of one point, and the range of the scale is from zero to five, with zero indicating that the individual is not frail, one to two indicating that the individual is prefrail, and three or more indicating that the individual is frail. Cognition was measured using the Montreal Cognitive Assessment Battery (MoCA) [10]. The Social Support Scale and the Social Network Scale were both utilized to evaluate the social support that was provided [11]. Patient Health Questionnaire was used to assess the symptoms of depression [12]. Self-reported responses to visual and hearing impairment were reported as yes or no, respectively. In the Supplementary material, you will find details regarding the assessment of geriatric diseases.

### Assessment of Outcome

An adjudication committee made up of physicians analyzed the medical records and death certificates in order to determine the occurrence of bleeding and death events throughout the 3-year follow-up period. The International Society on Thrombosis and Hemostasis scale was used to assign ratings to bleeding events based on their severity. Major bleeding was defined as fatal bleeding, symptomatic bleeding in a vital region or organ (such as intracranial, ocular, spinal, pericardial, retroperitoneal, arthritic, or intramuscular with compartment syndrome), or bleeding that caused a decrease in hemoglobin of ≥2 g/dL or that required ≥2 units of whole blood to be donated.

### Statistical Analysis

The baseline characteristics were analyzed in relation to the occurrence of the composite clinical endpoints, encompassing both significant hemorrhagic incidents and mortality, utilizing analysis of variance for continuous variables and the chi-square test for

categorical variables. The primary outcome of the study was the incidence of major bleeding. The secondary outcome encompassed a composite measure that included all-cause mortality, incidents of stroke, and major bleeding events. The relationship between the six geriatric conditions and the study outcomes was analyzed utilizing Cox regression, controlling for variables such as age, gender, insurance status, heart failure, history of major bleeding, coronary artery disease, peripheral arterial disease, diabetes, renal disease, hypertension, liver disease, and antiplatelet use [14,15]. The variables adjusted for within the model were determined based on their clinical importance and statistical significance as evidenced by the results presented in Table 1. The three-year survival rate of participants following major bleeding events was estimated through Kaplan-Meier survival analysis and subsequently compared utilizing the log-rank test. In the analysis of major bleeding as the primary outcome of interest, the competing risk associated with death was addressed by determining the cause-specific hazard ratios.

Due to the comparatively reduced risk of stroke and bleeding associated with direct oral anticoagulants (DOACs) relative to warfarin, stratified analyses contrasting DOACs with warfarin were undertaken [16]. Within the warfarin subgroup, the time spent within the therapeutic range was further accounted for as an indicator of International Normalized Ratio (INR) stability. The stability of the International Normalized Ratio (INR) was evaluated through the metric of time within the therapeutic range. In the four weeks preceding enrollment, a maximum of 12 International Normalized Ratios (INRs) were collected. The assessment was conducted at the baseline and was not employed as a time-varying covariate. In order to enhance the assessment of the prognostic significance of frailty and cognitive impairment, the concordance statistic (C-statistic) of the HAS-BLED score was computed for major bleeding incidents and subsequently compared to the C-statistic outcomes of the HAS-BLED score augmented with geriatric conditions. The Mann–Whitney test was employed to conduct a comparative analysis of the areas under the receiver operating characteristic curves [17]. The continuous net reclassification index (NRI) was employed to assess the predictive enhancement achieved by incorporating frailty and cognitive impairment into the HAS-BLED score. This evaluation aimed to ascertain whether there was a potential augmentation in the predicted risks for outcome events, along with a concomitant reduction in the predicted risks for nonevents. The following formula was employed for the calculation of event and nonevent NRIs. The net reclassification improvement (NRI) for major bleeding events is calculated as the quotient of the difference between the number of events with an increased predicted risk and the number of events with a decreased predicted risk, and the total number of events. The Nonevent Net Reclassification Improvement (NRI) is calculated as follows: it is the difference between the number of nonevents with decreased predicted risk and the number of nonevents with increased predicted risk, divided by the total number of nonevents. The comprehensive Net Reclassification Improvement (NRI) is equivalent to the aggregate of the event NRI and the nonevent NRI [18]. All statistical analyses were conducted utilizing SAS 9. 4 (SAS Institute, Inc., Cary, NC). A two-tailed *p-value* of <0. 05 was deemed to represent statistical significance.

## RESULT

A total of 1,624 individuals were enlisted from January 2013 to December 2015. Among these, 1,284 individuals were using oral anticoagulants and were included in the study. At baseline, the average age of participants was 76.5 (SD±5.5) years; 48 percent were women. Those who experienced major bleeding (n= 140, 10.9%) were older than those who did not experience this complication. They had a greater burden of comorbidities, which included a history of major bleeding, ischemic heart disease, heart failure, peripheral artery disease, stroke, diabetes, and renal disease compared to individuals who did not experience major bleeding. They were also more likely to state that they were taking aspirin. Their HAS-BLED and CHA2DS2VASC scores were elevated as compared to those who did not experience major bleeding (Details are provided in Table No. 1).

**Table No. 1: Baseline Characteristics by Major Bleeding During Follow-up**

| Characteristic | Major bleeding | | *p*-value |
|---|---|---|---|
| | Yes (n=140) | No (n=1144) | |
| Age, mean (SD) | 76.5 (5.5) year | 78.5 (8.5) | 0.05 |
| 66-75 years | 64 (45.7%) | 540 (47.2%) | 0.22 |
| 76-85 years | 63 (45.0%) | 408 (35.6%) | |
| ≥85 years | 22 (15.7%) | 170 (11.7%) | |
| Females | 54 (38.5%) | 580 (50.6%) | 0.02 |
| EDUCATION | | | |
| Intermediate | 16 (11.4%) | 116 (10.1%) | 0.12 |
| Graduate | 83 (59.2%) | 613 (53.5%) | 0.21 |
| Post graduate or above | 12 (8.5%) | 131 (11.4%) | 0.13 |
| INCOME | | | |

| | | | |
|---|---|---|---|
| Low income | 63 (45.0%) | 612 (53.5%) | 0.01 |
| Middle income | 42 (30.0%) | 388 (33.9%) | 0.14 |
| High income | 35 (25.0%) | 144 (12.5%) | 0.01 |
| HEALTH INSURANCE | | | |
| Commercial insurance | 28 (20.0%) | 308 (26.9%) | 0.01 |
| Personal insurance | 13 (9.2%) | 118 (10.3%) | 0.14 |
| Government insurance | 8 (5.7%) | 210 (18.3%) | 0.01 |
| CHA2DS2-VASC Score, mean (SD) | 4.8 (1.8) | 4.6 (1.5) | 0.02 |
| HAS-BLED score, mean (SD) | 3.5 (1.2) | 3.1 (1.1) | <0.01 |
| SMOKING HABIT | | | |
| Never smoker | 58 (41.4%) | 598 (52.3%) | 0.05 |
| Former smoker | 74 (52.8%) | 612 (53.4%) | 0.13 |
| Current smoker | 9 (6.4%) | 26 (2.3%) | 0.14 |
| HISTORY OF MAJOR BLEEDING | 48 (34.3%) | 205 (17.9%) | 0.01 |
| Bleeding requiring transfusion | 13 (9.5%) | 43 (3.7%) | |
| Gastrointestinal bleed | 32 (22.8%) | 122 (10.7%) | |
| Intracranial hemorrhage | 1 (0.7%) | 18 (1.6%) | |
| MEDICAL HISTORY | | | |
| Heart failure | 72 (51.4%) | 448 (39.1%) | 0.02 |
| Ischemic heart disease | 58 (41.4%) | 352 (30.7%) | 0.01 |
| Peripheral vascular disease | 32 (22.8%) | 163 (14.2%) | 0.02 |
| Hypertension | 128 (91.4%) | 1042 (91.0%) | 0.09 |
| Diabetes | 59 (42.1%) | 308 (26.9%) | 0.03 |
| Hypelipidemia | 121 (86.4%) | 902 (78.8%) | 0.25 |
| Stroke | 22 (15.7%) | 132 (11.5%) | 0.02 |
| Alcohol abuse/dependency | 37 (26.4%) | 398 (34.7%) | 0.23 |
| Anemia | 57 (40.7%) | 398 (34.7%) | 0.12 |
| Asthma/COPD | 35 (25.0%) | 243 (21.2%) | 0.78 |
| Renal disease | 59 (42.1%) | 381 (33.4%) | <0.01 |
| Implantable cardiac device | 53 (37.8%) | 330 (28.8%) | 0.05 |
| Creatinine (mg/dL) | 1.2 (SD 0.6) | 1.0 (SD 0.5) | <0.01 |
| Hemoglobin (g/dL) | 12.5 (SD 2.2) | 13.4 (SD 1.9) | 0.1 |
| Platelet (x $10^9$ per liter) | 196.3 (SD 62.2) | 212.3 (SD 68.4) | 0.08 |
| Systolic blood pressure (mmHg) | 129.3 (SD 18.2) | 132.3 (SD 20.4) | 0.21 |
| Baseline visit heart rate (bpm) | 57 (40.7%) | 329 (28.8%) | 0.01 |
| Aspirin | 13 (9.2%) | 62 (5.4%) | 0.08 |
| Clopidogrel | 2 (1.4%) | 3 (0.2%) | |
| Direct oral anticoagulant | 52 (37.1%) | 411 (35.9%) | 0.14 |
| Warfarin | 92 (65.7%) | 632 (55.2%) | |

At baseline, cognitive, psychosocial and physical impairments were prevalent: frailty (n= 176, 13.7%), social isolation (n=155, 12.1%), cognitive impairment (n=528, 41.1%), hearing impairment (n=453, 35.2%), depressive symptoms (n=359, 27.1%) and visual impairment (n=424, 33.0%) were all commonly occurring comorbidities. During average follow-up of three years (standard deviation 0.5), 97 (7.5%) individuals died. Major bleeding occurred in 140 (10.9%) individuals. There were 18 (1.4%) individuals who developed stroke.

**Table No 2: Hazard Ratios of Experiencing a Major Bleeding Episode over three years by Geriatric Conditions**

| | | Hazard ratio (95%CI) | |
|---|---|---|---|
| | | **Unadjusted** | **Model I** |
| Cognitive impairment | Yes<br>No | 1.96 (1.30-2.96)<br>Reference | 1.63 (1.01-2.54) |
| Depression | Yes<br>No | 1.33 (0.87-2.03)<br>Reference | 1.27 (0.79-2.03) |
| Frailty | Frail<br>Prefrail<br>No | 3.37 (1.79-6.34)<br>1.96 (1.14-3.38)<br>Reference | 2.78 (1.36-5.59)<br>1.76 (0.98-3.06) |
| Hearing impairment | Yes | 1.49 (0.97-2.24) | 1.29 (0.83-2.06) |

| | | | |
|---|---|---|---|
| | No | Reference | |
| Social isolation | Yes<br>No | 1.01 (0.56-1.86)<br>Reference | 1.08 (0.59-1.99) |
| Vision impairment | Yes<br>No | 1.12 (0.73-1.68)<br>Reference | 0.97 (0.65-1.49) |

**Major Bleeding and Geriatric Conditions**

Of the six geriatric conditions examined, cognitive impairment and frailty exhibited a significant association with major bleeding during the follow-up period (Table No. 2). Kaplan–Meier estimates of freedom from significant bleeding, stratified by the presence of cognitive impairment at baseline. After adjusting for age, gender, bleeding history, insurance, heart failure, peripheral arterial disease, coronary artery disease, hypertension, diabetes, renal disease, chronic obstructive pulmonary disease, liver disease, and antiplatelet medication use, as well as considering the competing risk of mortality, individuals with cognitive impairment exhibited a markedly elevated risk of experiencing significant bleeding (hazard ratio [HR] 1.63, 95% confidence interval [CI]: 1.01-2.54) compared to those without cognitive impairment. Kaplan–Meier estimates of freedom from major bleeding, stratified by baseline frailty status, revealed that, after controlling for various demographic and clinical factors and accounting for the competing risk of death, patients classified as frail had a significantly higher risk of major bleeding (HR 2.78, 95% CI 1.36-5.59) compared to those not identified as frail.

**Table No 3: Hazard Ratios of Experiencing a Major Bleeding, Stroke or Death over three years follow-up by Geriatric Conditions**

| | | Hazard ratio (95%CI) | |
|---|---|---|---|
| | | **Unadjusted** | **Adjusted** |
| Cognitive impairment | Yes<br>No | 2.01 (1.34-2.76)<br>Reference | 1.43 (1.03-2.04) |
| Depression | Yes<br>No | 1.73 (1.07-2.43)<br>Reference | 1.72 (1.19-2.43) |
| Frailty | Frail<br>Prefrail<br>No | 3.87 (2.49-6.24)<br>2.26 (1.44-3.39)<br>Reference | 2.38 (1.39-3.95)<br>1.68 (1.09-2.56) |
| Hearing impairment | Yes<br>No | 1.42 (1.03-1.89)<br>Reference | 1.19 (0.85-1.56) |
| Social isolation | Yes<br>No | 1.09 (0.72-1.69)<br>Reference | 1.24 (0.79-1.92) |
| Vision impairment | Yes<br>No | 1.23 (0.93-1.69)<br>Reference | 1.07 (0.78-1.46) |

The prognostic significance of cognitive impairment and frailty for major bleeding was not significantly different among people on warfarin or DOAC. The C-statistic of HAS-BLED for predicting major bleeding was 0.58, which rose to 0.65 with the inclusion of frailty and cognitive impairment ($p$=0.05). The continuous net reclassification index (NRI) for including frailty and cognitive impairment to HAS BLED was 0.42 (95% confidence interval 0.20–0.63; event NRI= 0.17 and non-event NRI=0.28).

**Geriatric Conditions and the Composite of Death, Major Bleeding, and Stroke**

Frailty (HR 2.38, 95%CI: 1.39-3.95), Cognitive impairment (HR 1.43, 95% CI: 1.03-2.04), and depression (HR 1.72, 95% CI: 1.19-2.43) were significantly associated with the composite of major bleeding, death, and stroke after controlling for age, gender, insurance, bleeding history, coronary artery disease, heart failure, peripheral arterial disease, diabetes, hypertension, chronic obstructive lung disease, liver disease, renal disease and antiplatelet use (Table No.3).

**DISCUSSION**

In a modern cohort of elderly patients receiving anticoagulation for atrial fibrillation, impairments in various clinically significant and readily evaluable geriatric conditions were frequently observed and served as predictors of negative clinical outcomes. Cognitive impairment and frailty were found to be prospectively correlated with a markedly elevated risk of major bleeding during the 3-year follow-up period. The relationships among cognitive impairment, frailty, and significant bleeding exhibited no statistically significant differences between individuals taking warfarin or a direct oral anticoagulant (DOAC). Moreover, the inclusion of frailty and cognitive impairment in the HAS-BLED score markedly enhanced its predictive capability for major bleeding. Anticoagulation represents the primary treatment approach for the prevention of stroke in the context of atrial fibrillation (AF) management. Notwithstanding the adverse effect of hemorrhage, anticoagulation is considered to offer clinical advantages, particularly among very elderly individuals with atrial fibrillation [19-21]. Analogous

to AF, the prevalence of cognitive impairment and frailty increases with advancing age. Intuitively, these conditions ought to impart an elevated risk of hemorrhage in elderly individuals with atrial fibrillation [22,23]. In this context, our research tackled this clinically significant inquiry through the systematic assessment of geriatric conditions, prospective monitoring, and thorough adjudication of outcomes. The research regarding the prognostic significance of diverse geriatric conditions in individuals with atrial fibrillation is constrained. For instance, depression has been linked to elevated all-cause mortality in patients with atrial fibrillation who also have concomitant heart failure [5] and are managed within the primary care environment [24]. Frailty is correlated with a higher risk of mortality and readmission following atrial fibrillation (AF) ablation [25]. Nevertheless, the conclusions drawn from earlier research are constrained by several factors: (1) the investigations were performed prior to the introduction of direct oral anticoagulants (DOACs), resulting in all participants being treated with warfarin, which does not represent the contemporary prescription trends of anticoagulants [26]; (2) the exposures of interest, such as frailty or cognitive impairment, were evaluated via International Classification of Diseases (ICD) or clinical documentation codes [27] rather than validated instruments, potentially leading to under-reporting and misclassification; and [25] (3) the bleeding outcomes were not subject to central adjudication by a panel of physicians but were instead based on billing codes [26]. We noted a significant incidence of bleeding (9% major bleeding, 26% clinically relevant but non-major bleeding over a 3-year period), which surpassed the rates reported in the pivotal trials of direct oral anticoagulant (DOAC) therapy in atrial fibrillation (AF). In the ARISTOTLE trial, which evaluated apixaban against warfarin for stroke prevention in individuals with atrial fibrillation (median age 70 years, interquartile range 63–76 years, presence of at least one additional risk factor for stroke, mean CHADS2 score 2.1), the annual incidence of major bleeding was 2.1% in the apixaban cohort and 3.1% in the warfarin cohort [20]. In the ROCKET-AF study, rivaroxaban was evaluated against warfarin in individuals with nonvalvular atrial fibrillation (median age 73 years, interquartile range 65–78 years, mean CHADS2 score 3.5), revealing a clinically significant bleeding rate of approximately 14% per year in both treatment groups. The advanced age and increased prevalence of comorbidities among patients in our cohort may account for the disparities noted between our research and earlier clinical trials [19]. The perceived net clinical advantage between stroke prevention and hemorrhagic complications may not be as advantageous in real-world clinical practice as it is in controlled clinical trials. This consideration should be evaluated in the risk/benefit analysis of anticoagulation prescriptions and underscores the significance of enhancing bleeding risk stratification in individuals with atrial fibrillation.

Our discovery enhances the predictive significance of frailty for adverse clinical outcomes in older populations with conditions distinct from atrial fibrillation [28]. Frailty was evaluated independently of biological age or the number of comorbidities. Alternatively, the evaluation emphasized functional status, encompassing weight loss, fatigue, reduced physical activity, decreased gait speed, and diminished strength. The evaluation of these symptoms has not constituted an essential component of clinical visits for atrial fibrillation (AF), and our results should motivate healthcare providers to evaluate these symptoms when caring for elderly patients with AF. The ramifications of this research are dual in nature. Firstly, individuals identified as high-risk for stroke are typically also classified as high-risk for bleeding, owing to the interrelated elements of the CHA2DS2VASC and HASBLED scoring systems. Our results indicate that the absence of frailty and cognitive impairment may enhance clinicians' confidence in administering anticoagulation to these patients. Secondly, the implementation of bleeding risk scores is recommended by the management guidelines in the care of atrial fibrillation [29,30]. Consequently, our results emphasize the necessity for future research aimed at developing and validating risk calculators that incorporate assessments of cognitive function and frailty in elderly patient populations.

## CONCLUSION

In summary, among elderly individuals with atrial fibrillation who face a heightened risk of stroke and are undergoing anticoagulation, cognitive impairment and frailty represent significant and emerging risk factors for major bleeding. Cognitive and physical functional status ought to be taken into account during the shared decision-making process concerning anticoagulation for individuals with atrial fibrillation.

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