Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Cumulative Frailty Burden and Cardiovascular Outcomes in Atrial Fibrillation: Retrospective Analysis of UK Biobank

Qian Wu
South China University of Technology
Jun Huang
Guangdong Provincial People's Hospital
Endong Liu
Guangdong Provincial People's Hospital
Chuqi Xiang
Guangdong Provincial People's Hospital
Chenxuan Gao
Guangdong Provincial People's Hospital
Xinxin Jiang
Guangdong Provincial People's Hospital
Caibai Lin
Guangdong Provincial People's Hospital
Yunjiu Cheng
Guangdong Provincial People's Hospital
Junrong Jiang
Guangdong Provincial People's Hospital
Yumei Xue
xymgdci@163.com

South China University of Technology

Research Article

Keywords: Atrial fibrillation, Frailty index, Cumulative burden, Cardiovascular mortality, Older adults

Posted Date: September 8th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10579124/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Frailty is increasingly recognized as a dynamic clinical state, yet most frailty assessments rely on single time-point measurements that may miss important temporal information. The prognostic value of cumulative frailty burden—reflecting both the persistence and severity of frailty over time—remains unclear in older adults with atrial fibrillation (AF). We aimed to determine whether quantifying cumulative frailty burden using longitudinal area under the curve (AUC) provides superior prognostic information compared with single-point frailty assessments in older patients with AF.

Methods

We included 15,302 adults aged ≥ 60 years with AF from the UK Biobank and calculated their electronic Frailty Index (eFI) over 3 years after AF diagnosis. Cumulative frailty burden was quantified as the AUC of eFI measurements at years 1, 2, and 3. A landmark analysis that excluded participants who experienced the outcome of interest during the exposure period was used to minimize reverse causality, yielding 4,657 participants for the analysis of major adverse cardiovascular events (MACEs) and 6,116 for the mortality analyses, with follow-up starting at the landmark time point. Participants were stratified into quartiles of cumulative frailty burden, and associations with outcomes were assessed using Cox proportional hazards models with sequential adjustment.

Results

Compared with the lowest quartile, the highest quartile of cumulative frailty burden was associated with a 92% higher risk of MACEs (hazard ratio [HR] 1.92, 95% confidence interval [CI] 1.62–2.28; P < 0.001), a 110% higher risk of all-cause mortality (HR 2.10, 95% CI 1.72–2.57; P < 0.001), and a 114% higher risk of cardiovascular mortality (HR 2.14, 95% CI 1.46–3.15; P < 0.001), with significant dose-response trends across quartiles. A model incorporating cumulative frailty burden together with baseline frailty improved risk discrimination beyond baseline frailty alone (AUC increased from 0.638 to 0.671 for MACEs and from 0.623 to 0.700 for all-cause mortality).

Conclusions

Cumulative frailty burden during the first 3 years after AF diagnosis was independently associated with an approximately 2-fold increased risk of adverse cardiovascular outcomes and mortality, and provided incremental prognostic value beyond single-point assessments. Longitudinal frailty assessment may complement risk stratification in older patients with AF.

Background

Atrial fibrillation (AF) is a major driver of mortality, stroke, heart failure, and bleeding complications[1]. Older adults with AF frequently manage multiple comorbidities and complex polypharmacy[2–4]. These conditions exacerbate their susceptibility to frailty, leading to significantly higher rates of mortality, complications, and readmissions. In this context, frailty has emerged as a more robust indicator than chronological age for comprehensively assessing the overall health status of this population[5, 6].

While extensive research has established the relationship between AF prognosis and baseline frailty status, the association between cumulative frailty burden and long-term outcomes remains poorly understood. Crucially, frailty is increasingly recognized as a dynamic clinical state rather than a static baseline characteristic[7–9]. We hypothesize that a higher cumulative frailty burden, representing the temporal evolution of health deficits, significantly increases the risk of long-term MACE and mortality. To test this hypothesis, this study examined the relationship between cumulative frailty burden and AF prognosis using a longitudinal dataset spanning 3 years.

METHODS

Study Design and Data Source

This study analyzed data from the UK Biobank (UKB), a large, population-based prospective database. The UKB comprises comprehensive phenotypic and genotypic data from over 500,000 participants aged 40–69 years at recruitment (2006–2010)[10]. Notably, this represents an earlier period in AF management compared to contemporary practice, which should be considered when interpreting the generalizability of our findings. The study was conducted under the UKB application number 121022, and ethical approval was granted by the North West Multi-centre Research Ethics Committee. All participants provided electronic informed consent. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study Population and AF Identification

From the UK Biobank, we identified participants with AF (ICD-10: I48) who were aged ≥ 60 years (i.e., a minimum age of 60 years) using validated algorithms. After excluding individuals with valvular heart disease and addressing missing covariates through multiple imputation, cumulative frailty burden was quantified over a 3-year exposure assessment period following AF diagnosis (Figure S1-2). To ensure complete exposure assessment and minimize reverse causality, a landmark analysis was implemented; participants who died or experienced the outcome of interest during the 3-year exposure period were excluded. This yielded 4,657 participants for the MACE analysis and 6,116 for the mortality analyses, with follow-up commencing at the end of the 3-year assessment period (landmark time point). This 3-year exposure period was chosen to align with the landmark time point and ensure methodological consistency in our exposure assessment.

Assessment of Frailty and Construction of Frailty Burden

Frailty was operationalized using an electronic Frailty Index (eFI), following the validated methodology[11]. While many UK Biobank studies rely on self-reported frailty measures from the baseline assessment, we utilized longitudinal electronic health records (EHR) to capture frailty. This approach is grounded in the well-established deficit accumulation model [5], which has been extensively validated within the UK Biobank population using various data sources [10, 12]. By mapping 36 clinical deficits to primary care (Read codes) and hospital records (ICD-10), our eFI provides a continuous, clinical-grade assessment of frailty. A summary of the 36 deficits and their corresponding ICD-10 codes used in this study is provided in Table S1. This record-based implementation is particularly suited for our study, as it enables the dynamic quantification of cumulative frailty burden over time—a feature not feasible with static, baseline-only self-reported measures.

Cumulative frailty burden was calculated using the area under the curve (AUC) method over a 3-year exposure period from 1 year to 3 years after AF diagnosis. The trapezoidal rule was applied to calculate AUC values: AUC = (eFI1y + eFI2y)/2 + (eFI2y + eFI3y)/2, where eFI1y, eFI2y, and eFI3y represent eFI scores at years 1, 2, and 3 after AF diagnosis, respectively. For the primary analysis, continuous 3-year eFI AUC values were categorized into quartiles (Q1-Q4) to examine potential prognostic gradients and dose-response relationships with clinical outcomes, with Q1 serving as the reference group (lowest burden).

Study Outcomes

The primary outcome was a composite of MACEs, defined as the first occurrence of heart failure, stroke or transient ischemic attack (TIA), clinically significant major bleeding, or cardiovascular death. Secondary outcomes were analyzed individually and included all-cause mortality and cardiovascular death.

All clinical outcomes were ascertained through linkage to the National Health Service (NHS) Digital death registries and hospital admission records (Hospital Episode Statistics, HES). Events were identified primarily using International Classification of Diseases, 10th Revision (ICD-10) codes. All clinical codes, including the ICD-10 and Read codes used to define baseline comorbidities, and all clinical outcomes, are detailed in Table S2.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) for normally distributed data, or median (interquartile range, IQR) for non-normally distributed data. Categorical variables are presented as frequencies (%). Trends across quartiles were assessed using linear regression for continuous variables and logistic regression for binary variables, treating the quartile as an ordinal variable. To mitigate reverse causality and ensure complete exposure assessment, a 3-year landmark analysis was

employed. Cumulative incidence of clinical outcomes was visualized via Kaplan-Meier curves and compared using log-rank tests.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models with 4 sequential levels of adjustment: Model 1 (unadjusted); Model 2 (adjusted for age, sex, and BMI); Model 3 (Model 2 + smoking status and alcohol consumption); Model 4 (fully adjusted: Model 3 + comorbidities).

The dataset was randomly split into the training set, internal validation set, and testing set at proportions of 6:2:2. Multiple machine learning models were trained and validated using frailty burden and other clinically relevant risk factors to predict AF-related adverse outcomes, and the model with optimal predictive performance was selected. Using the selected model, we further quantified and compared the incremental prognostic value of frailty burden versus baseline frailty, to determine whether incorporating longitudinal cumulative frailty information improves risk prediction beyond a single time-point frailty assessment.

The proportional hazards assumption was confirmed using Schoenfeld residuals. Subgroup analyses and interaction tests (multiplicative terms) were conducted across demographics and clinical strata. To ensure robustness, we performed sensitivity analyses to assess predictive stability. Differences in ROC curves among different models were compared by the DeLong test. Incremental predictive value was quantified using NRI and IDI. All analyses were conducted in R (version 4.4.3) with two-sided $P < 0.05$ as the threshold for significance.

Results

Study Population and Frailty Burden

Among 15,302 older adults with AF in whom 3-year eFI AUC was calculated, 4,657 participants were available for MACE analysis and 6,116 for mortality analyses after implementing a 3-year landmark analysis to exclude participants who experienced events during the exposure assessment period. Baseline characteristics were assessed across quartiles of cumulative frailty burden. Participants with higher cumulative frailty burden (Q3-Q4) were younger and consumed less alcohol, yet had higher BMI and a higher prevalence of smoking (Table 1). Increasing frailty burden was significantly associated with a higher prevalence of heart failure, diabetes, hypertension, COPD, and prior stroke, alongside elevated CHA2DS2-VA scores and higher rates of anticoagulation (all P for trend < 0.001). Furthermore, the distribution of cumulative frailty burden (AUC) showed a progressive increase across baseline frailty index quartiles, with significantly higher variability observed in the highest quartile.

Table 1
Baseline characteristics of participants according to quartiles of cumulative frailty burden

Characteristic	Overall (n = 15,302)	Q1 (n = 3,826)	Q2 (n = 3,826)	Q3 (n = 3,825)	Q4 (n = 3,825)	P value	P for trend
Age	69.26 ± 5.40	69.56 ± 5.52	69.74 ± 5.70	69.41 ± 5.40	68.33 ± 4.82	< 0.001	< 0.001
BMI	28.81 ± 5.18	27.71 ± 4.63	28.66 ± 5.14	28.99 ± 5.31	29.88 ± 5.38	< 0.001	< 0.001
Male	9260 (60.5%)	2279 (59.6%)	2337 (61.1%)	2260 (59.1%)	2384 (62.3%)	0.015	0.075
Smoking	8315 (54.3%)	1879 (49.1%)	1998 (52.2%)	2120 (55.4%)	2318 (60.6%)	< 0.001	< 0.001
Alcohol consumption	8970 (58.6%)	2465 (64.4%)	2310 (60.4%)	2183 (57.1%)	2012 (52.6%)	< 0.001	< 0.001
Hypertension	1557 (10.2%)	87 (2.3%)	182 (4.8%)	358 (9.4%)	930 (24.3%)	< 0.001	< 0.001
Heart failure	743 (4.9%)	31 (0.8%)	82 (2.1%)	186 (4.9%)	444 (11.6%)	< 0.001	< 0.001
Diabetes mellitus	631 (4.1%)	32 (0.8%)	48 (1.3%)	123 (3.2%)	428 (11.2%)	< 0.001	< 0.001
COPD	546 (3.6%)	34 (0.9%)	63 (1.6%)	125 (3.3%)	324 (8.5%)	< 0.001	< 0.001
Previous stroke	387 (2.5%)	30 (0.8%)	75 (2.0%)	97 (2.5%)	185 (4.8%)	< 0.001	< 0.001

Data are presented as mean ± SD for continuous variables and n (%) for categorical variables. Q1–Q4, quartiles of cumulative frailty burden; BMI, body mass index; COPD, chronic obstructive pulmonary disease; SD, standard deviation. P value was calculated by analysis of variance for continuous variables and the chi-square test for categorical variables. P for trend was calculated across quartiles of cumulative frailty burden.

During median follow-up of 8.3 years for both MACE and mortality analyses, 1,321 MACE events and 1,510 deaths (including 458 cardiovascular deaths) were recorded among the study population.

Frailty Burden and the Risk of MACEs

In the landmark analysis of 4,657 participants who were event-free during the 3-year exposure period, a clear graded association was observed between cumulative frailty burden and MACEs. Crude incidence rates escalated markedly from 18.7% in Q1 to 36.8% in Q4 (Table S4). In fully adjusted Cox models, patients in the highest quartile (Q4) had a 92% higher risk of MACEs compared to the lowest quartile (Q1) (HR: 1.92, 95% CI: 1.62–2.28; P < 0.001; Fig. 1). A significant dose-response relationship was

observed across quartiles (P for trend < 0.001). Cumulative incidence curves further confirmed these differences across quartiles (Log-rank test, χ^2=130.45, P < 0.001; Fig. 2).

Frailty Burden and Mortality Outcomes

Among 6,116 participants in the mortality analysis, cumulative frailty burden exhibited a robust, graded association with all-cause mortality. The cumulative incidence curves demonstrated significant and early separation across quartiles (Log-rank test, χ^2=200.2, P < 0.001), with mortality rates rising sharply from 12.1% in Q1 to 34.3% in Q4. Multivariable Cox regression models confirmed this dose-response relationship. In the fully adjusted model (Model 4), patients in the highest quartile (Q4) faced a substantially elevated mortality risk compared to the reference group (Q1) (HR: 2.10, 95% CI: 1.72–2.57; P < 0.001; Fig. 1). Similarly, frailty burden was a significant predictor for cardiovascular (CV) mortality. Patients in the highest quartile (Q4) had a 114% increased risk of CV mortality compared to Q1 (HR: 2.14, 95% CI: 1.46–3.15; P < 0.001; Fig. 1). Significant positive trends were observed for all mortality outcomes (P for trend < 0.001 for all; Fig. 1). Detailed model estimates are provided in the supplementary materials (Table S4).

Machine Learning-Based Prediction and Incremental Value

Several machine learning models including XGBoost, logistic regression, and random forest were developed to predict the prognosis based on frailty burden, and XGBoost generally provided the best overall predictive performance (Figure S3). Model performance was further compared across three incremental frameworks: (1) Baseline Model (age, sex, and baseline frailty); (2) Burden Model (age, sex, and frailty burden); and (3) Comprehensive Model (age, sex, baseline frailty, and frailty burden).

On the testing set, the comprehensive model, which incorporated both baseline frailty and cumulative frailty burden, generally showed better discrimination than the baseline model. For MACEs, the AUC was 0.638 (95% CI 0.607–0.669) with the baseline model, 0.664 (95% CI 0.633–0.694) with the burden model (P = 0.088 vs baseline), and 0.671 (95% CI 0.641–0.702) with the comprehensive model (P = 0.008 vs baseline; Figs. 3A and 4). The predictive gain from cumulative frailty burden was most evident for all-cause mortality: the AUC increased from 0.623 (95% CI 0.589–0.656) with the baseline model to 0.700 (95% CI 0.668–0.732) with both the burden and comprehensive models (P < 0.001; Fig. 3B). For cardiovascular mortality, the AUC was 0.670 (95% CI 0.607–0.732) with the baseline model, 0.695 (95% CI 0.634–0.756) with the burden model (P = 0.341), and 0.710 (95% CI 0.650–0.769) with the comprehensive model (P = 0.066; Fig. 3C). Notably, adding baseline frailty to the burden model did not yield substantial additional gain for mortality, suggesting that the incremental prognostic information of baseline frailty may be largely captured by cumulative frailty burden.

Beyond model discrimination, we evaluated clinical utility by comparing the comprehensive model against the baseline model (Table S3). For MACEs, the addition of cumulative frailty burden improved model discrimination (IDI = 0.016; NRI = 0.404) and reclassification. Improvements were also observed

for all-cause mortality (IDI = 0.015; NRI = 0.415) and cardiovascular mortality (IDI = 0.007; NRI = 0.469), supporting the value of combining cumulative frailty burden with baseline frailty for risk refinement.

Subgroup and Interaction Analyses

Stratified analyses confirmed a consistent dose-response relationship between frailty burden and outcomes across most subgroups. Significant interactions were observed for hypertension and anticoagulation (all P for interaction < 0.001; Table S5; Figure S4). Specifically, the risk associated with the highest frailty burden (Q4 vs. Q1) was more pronounced in non-hypertensive patients (HR 4.67; 95% CI 3.71–5.88) than in those with hypertension (HR 1.87; 95% CI 1.03–3.40). Similarly, frailty-associated risk of MACEs was markedly higher in patients not receiving oral anticoagulants (HR 4.98) compared to those on therapy (HR 1.88). No other interactions (age, diabetes, or heart failure) reached statistical significance (all P for interaction > 0.05).

These results remained consistent in sensitivity analyses. After excluding 632 individuals with large health fluctuations, the graded link between frailty burden and MACEs persisted. Additionally, in analyses not employing landmark design, the association between frailty burden and outcomes remained significant, though the magnitude of effect estimates was attenuated, suggesting that survivor bias may have modestly influenced our primary findings.

The graded association between frailty burden and outcomes remained robust across other clinical subgroups, including BMI categories, age groups, and sex. In all subgroups examined, higher cumulative frailty burden was associated with increased risk of adverse outcomes, with significant dose-response relationships observed across all stratification variables. The consistency of these findings across diverse clinical subgroups supports the generalizability of our results and underscores the broad clinical relevance of cumulative frailty burden assessment in older AF patients.

Discussion

In this study, we analyzed the association between cumulative frailty burden and the risk of adverse outcomes using 3-year longitudinal data from the UK Biobank. Our principal findings are as follows. First, the cumulative frailty burden showed a robust graded association with the risk of MACEs and mortality, where higher quartiles of accumulated frailty corresponded to significantly increased likelihood of adverse outcomes across all endpoints examined. Second, this longitudinal measure provided additional prognostic information beyond traditional single-point assessments, as demonstrated by our machine learning analyses showing improved risk discrimination when incorporating cumulative frailty burden into predictive models. This suggests that the duration and severity of frailty accumulation over time are relevant considerations in cardiovascular risk stratification. Third, the association remained consistent across major clinical subgroups, supporting the generalizability of our findings.

Our study represents a significant methodological advancement by introducing the concept of cumulative frailty burden assessment through 3-year area under the curve calculation. This approach

captures both the magnitude and temporal duration of frailty exposure, addressing limitations of traditional cross-sectional frailty assessments. The landmark analysis design ensures methodological consistency by aligning the 3-year exposure period with the 3-year landmark time point, addressing temporal sequence concerns and minimizing reverse causality bias. By utilizing the trapezoidal rule to calculate eFI AUC from annual measurements during the 3-year exposure period, we quantify the cumulative "burden" in a way that integrates intermediate fluctuations—which may be less visible in studies comparing only baseline and follow-up scores. This approach offers a detailed perspective on a patient's gradual physiological decline over time.

To our knowledge, longitudinal evidence regarding the prognostic impact of cumulative frailty burden in patients with AF remains relatively limited. A recent study offered valuable insights into frailty dynamics over a 3-year period in older patients with AF receiving anticoagulants[12]. While that research identified important factors influencing changes in frailty status, our study aims to complement these findings by examining frailty accumulation over a longer period in a broader population. Using data from the UK Biobank, we observed individuals across a wider range of health statuses with an extended follow-up duration. Our analysis suggests that cumulative frailty burden is associated with the risk of MACEs and mortality, even when considering baseline frailty and other clinical factors.

The prognostic value of longitudinal frailty assessment demonstrated in our study suggests that incorporating cumulative frailty burden into risk assessment models may improve risk stratification for AF patients. Future research should evaluate whether interventions aimed at slowing frailty progression can improve cardiovascular outcomes in this population. Clinical implementation of longitudinal frailty monitoring would require further validation and consideration of practical feasibility.

Recent studies have further demonstrated the prognostic value of longitudinal frailty assessment in cardiovascular populations. For instance, long-term changes in frailty have been associated with the development of atrial fibrillation, heart failure, coronary heart disease, and stroke [15]. These findings collectively support the concept that frailty is a dynamic rather than static clinical characteristic, underscoring the need for approaches that capture its temporal evolution.

Building on these findings, our study explores a different methodological approach to capture frailty trajectories. Current evidence highlights differing but complementary clinical emphases. For instance, prior study has shown that the baseline frailty level is a primary predictor of mortality[13]. Another line of research emphasizes the prognostic significance of its longitudinal trajectory[14]. Rather than being contradictory, these perspectives together provide a more comprehensive understanding of frailty-related risk. They collectively suggest that observing both current severity and long-term changes may be beneficial for patient assessment[15–17].

Finally, our machine learning analysis indicates that combining cumulative frailty burden with baseline frailty provides incremental prognostic information for risk stratification, particularly for MACEs and all-cause mortality. This suggests that longitudinal frailty assessment may serve as a valuable adjunct to traditional risk stratification approaches in older AF patients.

In our subgroup analyses, the association between cumulative frailty burden and adverse outcomes remained robust across most clinical strata, although the magnitude of the association differed according to hypertension status and anticoagulant use, with significant interactions for both (all P for interaction < 0.001). The observed dose-response relationship across all subgroups indicates that cumulative frailty burden represents a fundamental risk factor that operates independently of traditional clinical stratification variables.

Limitations

Survivor Bias from Landmark Design

Our landmark analysis excluded participants who died or experienced primary outcomes during the 3-year exposure assessment period. This design choice introduces survivor bias, as excluded participants likely had higher baseline frailty and greater disease severity. Consequently, our estimates may underestimate the true association between cumulative frailty burden and adverse outcomes.

Study Population and Generalizability

The UK Biobank cohort primarily consists of community-dwelling individuals with relatively low frailty burden, which may limit the generalizability of our findings to institutionalized or severely frail populations. This reflects both the healthy volunteer nature of UK Biobank participants and the specific inclusion criteria of our study.

Methodological Considerations

Several methodological limitations should be acknowledged. First, machine learning analyses also utilized the 3-year cumulative frailty burden, computed consistently with the primary analyses. Second, the cumulative frailty burden effectively integrates overall exposure, but may not capture every granular trajectory fluctuation over the 3-year assessment period. Third, the absence of anticoagulation data in our subgroup analysis represents a limitation, as anticoagulant therapy may influence both frailty trajectories and cardiovascular outcomes.

Data Quality and Temporal Context

The UKB data were collected between 2006–2010, representing an earlier period in AF management compared to contemporary practice. During this period, anticoagulation rates were lower globally, and direct oral anticoagulants were not yet widely available. The accuracy of the eFI depends on the precision of clinical coding within administrative records. The use of ICD codes to assess frailty may lead to missing data or underestimation of frailty scores. However, even with these potential limitations, cumulative burden was able to differentiate risk levels in our population.

Conclusions

In conclusion, cumulative frailty burden, as measured by 3-year eFI AUC, is independently associated with nearly 2-fold increased risk of adverse cardiovascular outcomes and mortality in older AF patients. This longitudinal assessment provides incremental prognostic information beyond traditional single-point measurements, as evidenced by improved model performance in machine learning analyses. Our findings highlight the clinical relevance of monitoring frailty burden over time and suggest that longitudinal frailty assessment should be incorporated into routine risk stratification strategies for older AF patients. Future research should evaluate whether interventions aimed at slowing frailty progression can improve cardiovascular outcomes in this population.

Abbreviations

AF
atrial fibrillation
AUC
area under the curve
BMI
body mass index
CHA2DS2-VA
a thromboembolic risk score
CI
confidence interval
COPD
chronic obstructive pulmonary disease
CVD
cardiovascular death
eFI
electronic Frailty Index
HES
Hospital Episode Statistics
HR
hazard ratio
ICD-10
International Classification of Diseases,Tenth Revision
IDI
integrated discrimination improvement
MACEs
major adverse cardiovascular events
NHS
National Health Service
NRI

net reclassification improvement
OAC
oral anticoagulant
ROC
receiver operating characteristic
SD
standard deviation
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
TIA
transient ischaemic attack
UKB
UK Biobank.

Declarations

Ethics approval and consent to participate

This study was conducted under the UK Biobank application number 121022. Ethical approval was granted by the North West Multi-centre Research Ethics Committee, and all participants provided electronic informed consent.

Consent for publication

Not applicable. This study used de-identified data from the UK Biobank, and no individual person's data are presented.

Competing interests

The authors declare no competing interests.

Funding

No specific funding was received for this study.

Author Contribution

Q.W. and J.H. conceived and designed the study. Q.W., J.H., E.L., C.X., C.G., and Y.C. performed the statistical and machine learning analyses. X.J. and C.L. contributed to data curation and interpretation.

Q.W. and J.H. drafted the manuscript. E.L., C.X., C.G., X.J., C.L., and Y.C. critically revised the manuscript for important intellectual content. J.J. and Y.X. supervised the study and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to express their sincere gratitude to the participants and staff of the UK Biobank for their vital contributions to the data resource used in this research. This study was conducted under UK Biobank application number 121022. We also thank the members of our research team for their technical assistance during the data cleaning and statistical analysis process.

Data Availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

References

1. Dai H, et al. Global, regional, and national prevalence, incidence, mortality, and risk factors for atrial fibrillation, 1990–2017: results from the Global Burden of Disease Study 2017. Eur Heart J Qual Care Clin Outcomes. 2021;7(6):574–82.
2. Gullón A, et al. Influence of frailty on anticoagulant prescription and clinical outcomes after 1-year follow-up in hospitalised older patients with atrial fibrillation. Intern Emerg Med. 2019;14(1):59–69.
3. Madhavan M, et al. Association of frailty and cognitive impairment with benefits of oral anticoagulation in patients with atrial fibrillation. Am Heart J. 2019;211:77–89.
4. Wilkinson C, et al. Management of atrial fibrillation for older people with frailty: a systematic review and meta-analysis. Age Ageing. 2019;48(2):196–203.
5. Rockwood K, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489–95.
6. Clegg A, et al. Frailty in elderly people. lancet. 2013;381(9868):752–62.
7. Khan M, Nicholl BI, Hanlon P. Ethnicity and frailty: A systematic review of association with prevalence, incidence, trajectories and risks. Ageing Res Rev. 2025;109:102759.
8. Pandey A, et al. Frailty and Effects of Semaglutide in Obesity-Related HFpEF: Findings From the STEP-HFpEF Program. JACC Heart Fail. 2025;13(10):102610.
9. Lai HY, et al. The burden of frailty in heart failure: Prevalence, impacts on clinical outcomes and the role of heart failure medications. J Cachexia Sarcopenia Muscle. 2024;15(2):660–70.
10. Sudlow C, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.

11. Clegg A, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing. 2016;45(3):353–60.
12. Nakamaru R, et al. Trajectories of Frailty and Clinical Outcomes in Older Adults With Atrial Fibrillation: Insights From the Shizuoka Kokuho Database. Circ Cardiovasc Qual Outcomes. 2024;17(8):e010642.
13. Bai G, et al. Frailty trajectories in three longitudinal studies of aging: Is the level or the rate of change more predictive of mortality? Age Ageing. 2021;50(6):2174–82.
14. Kaufmann CC et al. Prognostic impact of frailty at admission and in-hospital changes of frailty status in elderly patients with acute heart failure. Eur J Heart Fail, 2025.
15. Cai L, et al. Long-term changes in frailty and incident atrial fibrillation, heart failure, coronary heart disease, and stroke: A prospective follow-up study. Heart Rhythm. 2025;22(12):3090–8.
16. Myers V, Drory Y, Gerber Y. Clinical relevance of frailty trajectory post myocardial infarction. Eur J Prev Cardiol. 2014;21(6):758–66.
17. Wang J, et al. The frailty risk trajectory associated with kidney and cardiovascular morbidities among patients with incident diabetes: A population-based study. Atherosclerosis. 2022;358:60–7.

Figures

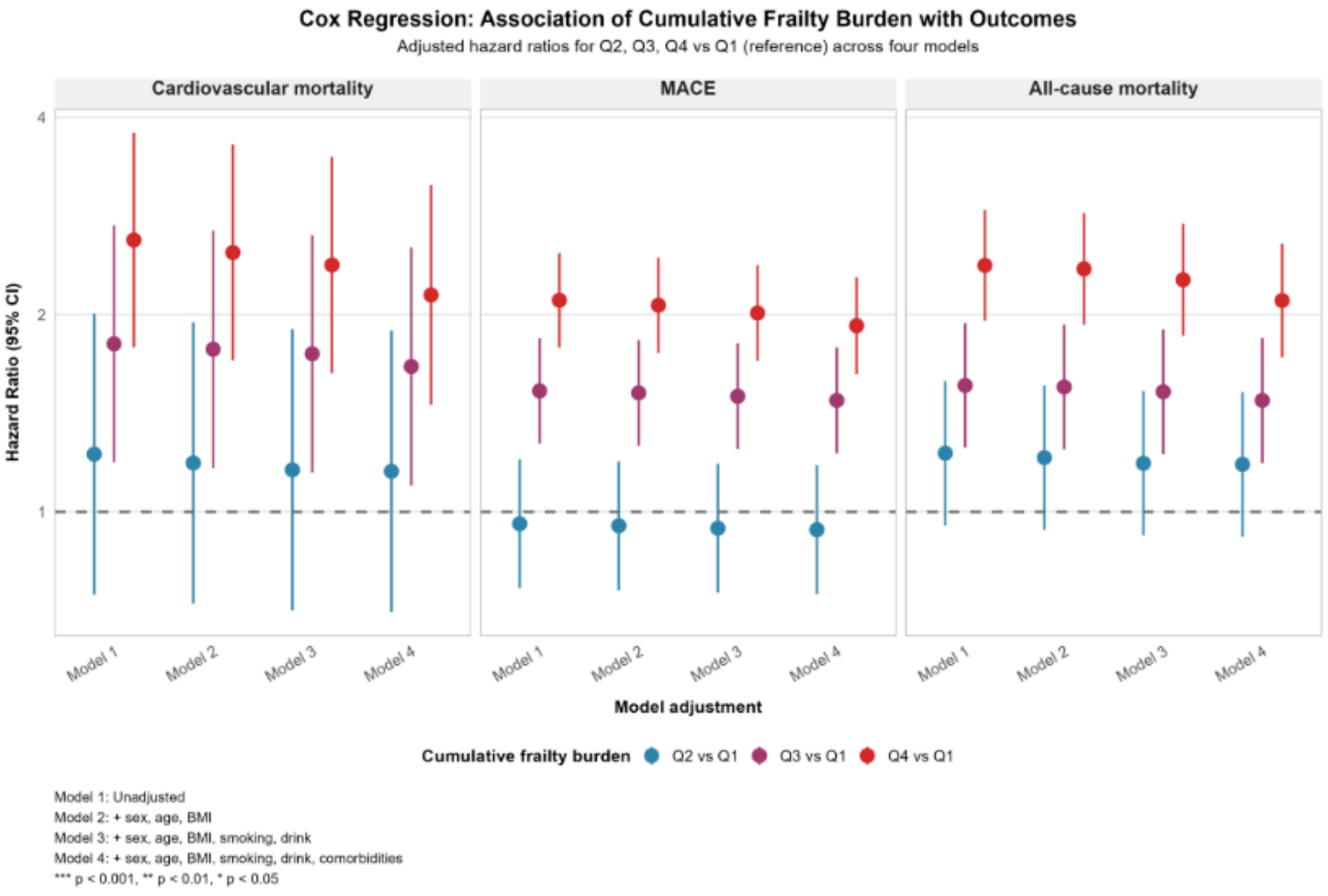


Figure 1

Association between cumulative frailty burden and clinical outcomes.

Forest plot showing adjusted hazard ratios (95% CI) for Q2, Q3, and Q4 versus Q1 (reference) across four sequentially adjusted Cox models for cardiovascular mortality, MACEs, and all-cause mortality. Abbreviations: MACEs, major adverse cardiovascular events; CI, confidence interval; HR, hazard ratio.

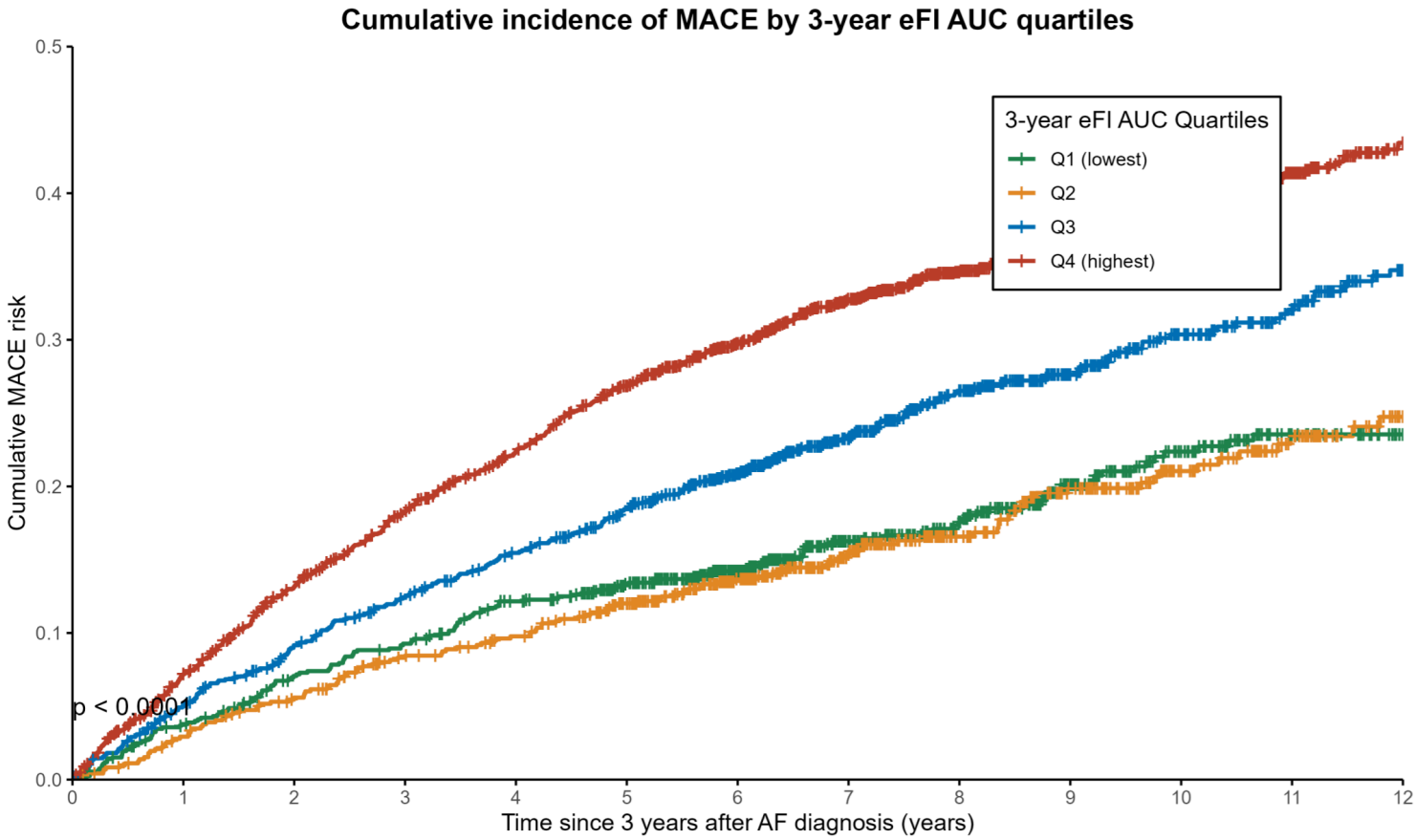


Figure 2

Risk curves for major adverse cardiovascular events (MACEs) according to quartiles of cumulative frailty burden.

Abbreviations: MACEs, major adverse cardiovascular events.

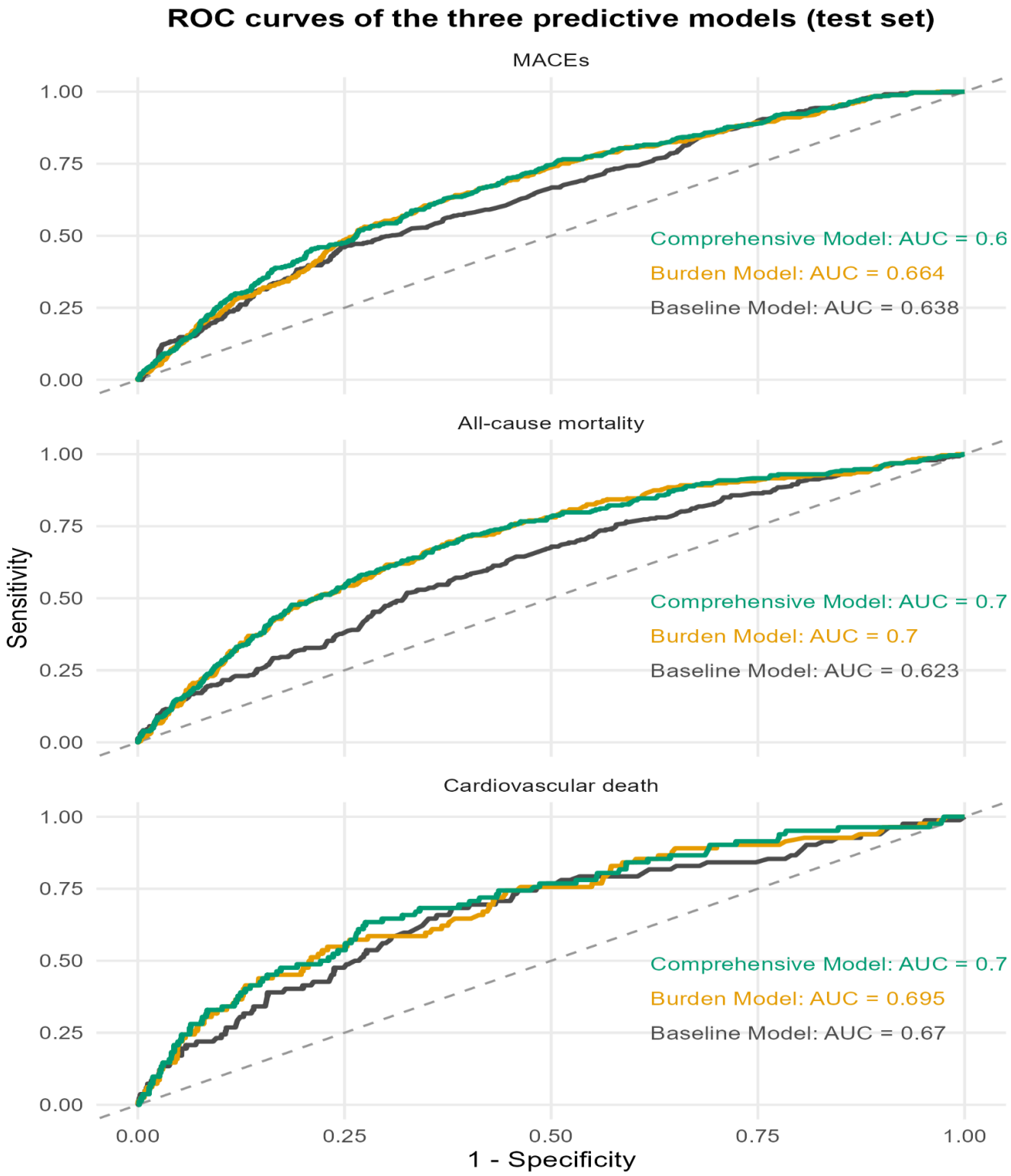


Figure 3

Predictive performance of models incorporating cumulative frailty burden for clinical outcomes

The predictive performance for (A) MACEs, (B) All-cause mortality, and (C) Cardiovascular death was compared across three models. The Baseline Model (blue line) includes Age, Sex, and Baseline Frailty; the Burden Model (yellow line) includes Age, Sex, and Frailty Burden; the Comprehensive Model (green

line) includes Age, Sex, Baseline Frailty, and Frailty Burden. Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; EFI, electronic Frailty Index; MACEs, major adverse cardiovascular events.

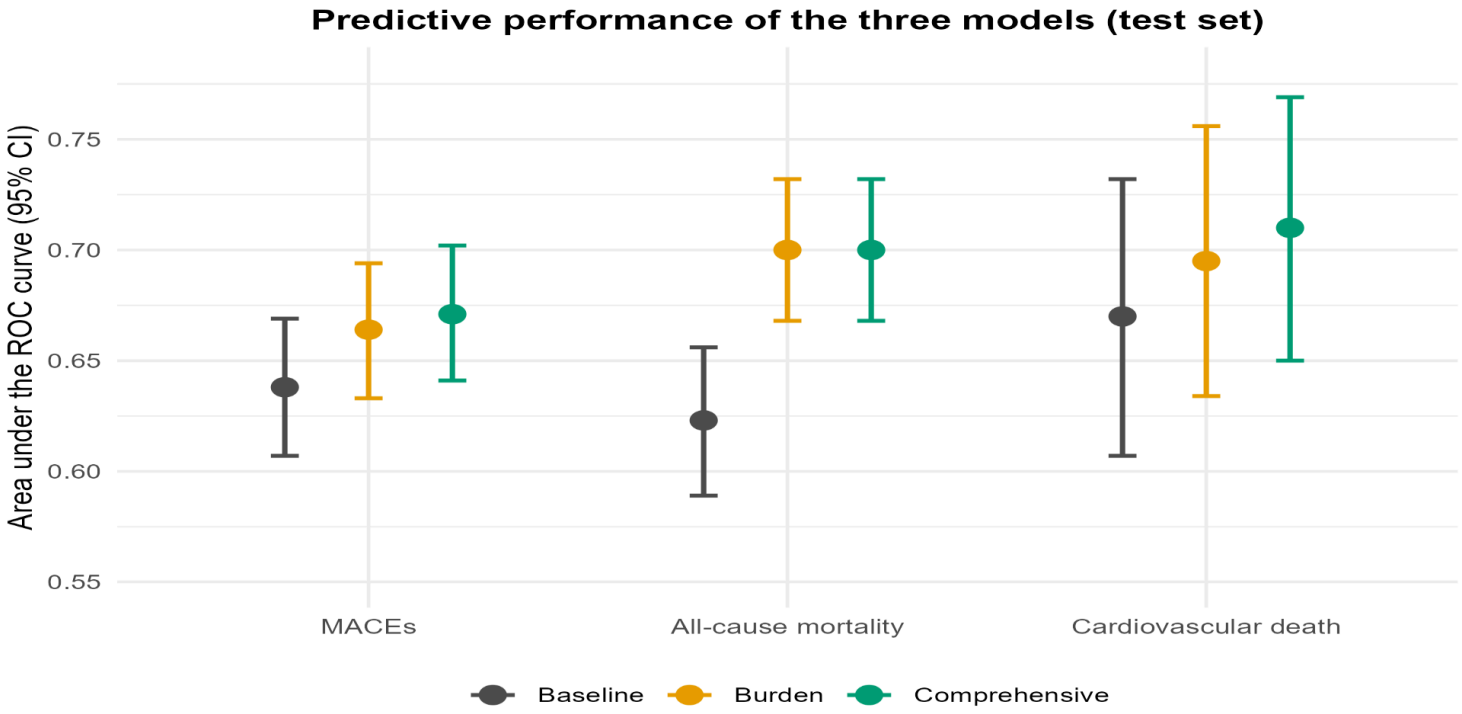


Figure 4

Comparison of predictive performance among the Baseline, Burden, and Comprehensive models.

Area under the ROC curve (AUC) values (95% CI) for MACEs, all-cause mortality, and cardiovascular death in the test set. *P < 0.05, **P < 0.01, ***P < 0.001 versus the Baseline model (DeLong test). Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; MACEs, major adverse cardiovascular events.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalFileforReviewfinalv2.docx