ESC HEART FAILURE
ESC Heart Failure 2025; **12**: 1893–1904
Published online 13 January 2025 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.15196

ORIGINAL ARTICLE

Pro-adrenomedullin as an independent predictive biomarker for heart failure in atrial fibrillation and flutter

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Abstract

Aims This study aimed to investigate potential biomarkers for predicting incident heart failure (HF) in patients with atrial fibrillation and flutter (AF and AFL), utilizing proteomic data from the UK Biobank Pharma Proteomics Project (UKB-PPP).

Methods This study analysed data from AF and AFL patients, split into discovery (n = 1050) and replication (n = 305) cohorts. Plasma biomarkers were screened using a multivariable-adjusted Cox proportional hazards model. Kaplan–Meier survival analysis and area under the receiver operating characteristic (ROC) curve assessments were conducted to evaluate predictive performance.

Results Over a follow-up of 14.2 years, 222 cases (21.1%) of HF were documented in the discovery cohort, while 117 cases (38.4%) occurred over 13.8 years in the replication cohort. Out of 2923 proteins measured, only pro-adrenomedullin (pro-ADM) consistently showed a significant association with incident HF in both cohorts. In the discovery cohort, each unit increase in pro-ADM was linked to an increased risk of HF (HR = 2.78, 95% CI 1.64–4.71, $P < 0.001$, FDR = 0.026), which was confirmed in the replication cohort (HR = 3.95, 95% CI 1.97–7.94, $P < 0.001$, FDR = 0.012). Kaplan–Meier analysis demonstrated that patients with higher pro-ADM levels had significantly shorter time to HF onset, with median times ranging from 2306 to 3183 days across quartiles ($P < 0.001$). The cumulative incidence of HF ranged from 15.3% to 42.7% across quartiles of pro-ADM (log-rank $P < 0.001$). Adding pro-ADM to a model with traditional risk factors, including NT-proBNP, significantly improved predictive accuracy for 3-year (AUC = 0.783; integrated discrimination improvement [IDI] = 0.010 and net reclassification index [NRI] = 0.206, both P = 0.002) and 5-year (AUC = 0.749, IDI = 0.013, NRI = 0.179, P = 0.001) risk of HF. In sensitivity analyses, the association between pro-ADM and incident HF remained consistent after excluding participants with self-reported AF and AFL, with each unit increase in pro-ADM being associated with an increased risk of HF (HR = 1.77, 95% CI 1.02–3.04, P = 0.041) and across subgroups of paroxysmal AF (HR = 2.80, 95% CI 1.11–7.07, P = 0.029) and persistent AF (HR = 4.36, 95% CI 1.41–13.43, P = 0.010).

Conclusions Pro-ADM is identified as an independent biomarker for predicting incident HF in AF and AFL patients. Its inclusion in risk prediction models enhances the ability to stratify HF risk beyond traditional biomarkers, demonstrating its potential utility in clinical practice.

Keywords Atrial fibrillation; Heart failure; Proteomics; Biomarker; Prediction; UK Biobank

Received: 15 August 2024; Revised: 16 October 2024; Accepted: 10 December 2024
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Introduction

Atrial fibrillation (AF) and flutter (AFL) are the most prevalent arrhythmia globally, contributing to a disability-adjusted life years (DALY) rate of 102.9 per 100 000 individuals that has consistently increased over the years.[1] Notably, one of the gravest consequences of AF/AFL are the occurrence of heart failure (HF).[2] Long-term follow-up from large community-

based studies indicates that individuals with AF exhibited a hazard ratio (HR) for incident HF that was nearly three to five times greater compared to those without AF.[3,4] While stroke prevention strategies associated with AF/AFL have been extensively studied, research on risk stratification—a crucial early prevention strategy—for HF related to AF/AFL remains limited.[5]

Early identification of high-risk AF/AFL patients for HF and implementing timely preventive measures is critical to reducing the incidence of HF. Circulating biomarkers not only provide insights into the underlying pathophysiological processes but also act as important indicators or biomarkers for specific diseases.[6,7] The N-terminal fragment of B-type natriuretic peptide (NT-proBNP) serves as a widely recognized plasma biomarker for predicting and stratifying various cardiovascular diseases (CVD).[8] Elevated NT-proBNP levels, which reflect cardiac remodelling, are indicative of incident AF and the associated risk of stroke.[9,10] Nevertheless, there is a notable lack of emphasis on identifying biomarkers for incident HF in individuals with AF. Although NT-proBNP is considered a stronger marker for both prevalent and incident AF compared to HF, its diagnostic utility in AF patients for detecting heart failure with preserved ejection fraction (HFpEF) remains notably limited.[11] There is a pressing need for further research to uncover new biomarkers for accurately assessing the risk of HF development in patients with AF. This would not only enhance our comprehension of the underlying mechanisms driving AF progression but also enable more tailored and effective management strategies for this population.

In this study, we employed plasma proteomics data sourced from the UK Biobank Pharma Proteomics Project (UKB-PPP). The project provided extensive long-term follow-up data, and participants' baseline blood samples underwent large-scale proteomic analysis. The primary objective of our study was to identify new biomarkers with predictive potential for incident HF in patients with AF.

Methods

Data source

The UK Biobank (UKB) is a comprehensive biomedical resource containing anonymized health information from approximately 500 000 participants, aged 40–69, designed for long-term follow-up. Biological samples were collected at recruitment, and their medical records are continuously linked through national health databases. This infrastructure supports large-scale, prospective studies, enabling the exploration of associations between various factors and disease outcomes.

The UKB-PPP specifically focused on profiling the plasma proteome of UKB participants. Between April 2021 and February 2022, over 50 000 plasma samples were analysed, yielding measurements for 2923 protein biomarkers. The study designated individuals from a randomly selected subset of the UKB-PPP as the discovery cohort, representing the larger UKB cohort.[12] Participants from the UKB-PPP Consortium pre-selection were assigned to the replication cohort.

The resulting dataset, made publicly available in October 2023, was collected following written informed consent from all participants and with ethical approval from the National Research Ethics Service Committee (reference number 11/NW/0382). All procedures complied with the Declaration of Helsinki. This study utilized UKB data under an approved project (application number 103736).

Study population

Study participants were selected based on self-reported or medically documented diagnosis of atrial fibrillation (AF) and atrial flutter (AFL). Only 24 cases of self-reported AF and AFL were verified during nurse interviews at the time of admission (accounting for 1.77% of the total cohort of 1355 participants). These participants' medical conditions were linked to national health systems using their National Health Service (NHS) number (for England and Wales) or Community Health Index (CHI) number (for Scotland). AF and AFL diagnoses were identified through the use of International Classification of Diseases-10 (ICD-10) codes from hospital records (I48.0, I48.1, I48.2, I48.3, I48.4 and I48.9). Additionally, Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS-4) codes were employed to track AF catheter ablation (K62.1, K62.2, K62.3 and K62.4).

Due to the data collection design of the UKB, AF and AFL events were recorded together. Therefore, all AF event data in this study include both AF and AFL events, as represented by ICD-10 code I48, which corresponds to 'atrial fibrillation and flutter'. Individuals were classified as having medically recorded AF and AFL if their first documented AF/AFL instance occurred before their enrolment in the UKB. Out of the baseline cohort of 1355 AF and AFL patients, 240 patients (17.7%) were classified as having paroxysmal AF, and 65 patients (4.8%) were diagnosed with persistent AF. The remaining participants did not have a clearly defined phenotype (77.5%). Additionally, individuals with a history of HF were excluded from the study. The definition of HF history was based on both self-reported and medically recorded instances (with only four self-reported HF cases, accounting for 0.30% of the total cohort). Further details on the HF definition are provided below. The flowchart illustrating the enrolment process of the study population is displayed in *Figure* S1.

Proteomics measurement procedure

A comprehensive account of the UKB-PPP data generation has been previously documented.[12] In brief, the Olink™ Explore platform was used to process all blood samples using the proximity extension assay (PEA) technique. This analysis involved the use of four distinct protein panels—cardiometabolic, inflammation, neurology and oncology—to measure 2941 protein analytes, representing 2923 unique proteins. Further details regarding the protein processing and measurement procedures are provided in the Supporting Information.

Study outcome and variables

The primary endpoint of this study was the time to incident HF. HF diagnoses were identified using the corresponding ICD-10 codes (I50.0, I50.1 and I50.9), which were extracted from medical records, including death registries, primary care records, and hospital admission data. The variables selected for inclusion in this study encompassed demographic details, lifestyle factors, anthropometric data, medical history elements and laboratory test results. A concise overview of these variables is available on the UKB website (https://biobank.ndph.ox.ac.uk/showcase/) and in previously published studies.[13,14]

Statistical analysis

The continuous variables presented as mean ± standard deviation or median with interquartile range (IQR) and categorical variables expressed as percentages. Statistical comparisons for continuous data with normal distribution were conducted using Student's *t*-test, while the Mann–Whitney U-test were applied for non-normally distributed data. One-way ANOVA (normally distributed data) or Kruskal–Wallis test (non-normally distributed data) were utilized to compare continuous variables across three or more groups, and pairwise comparisons were performed using the Bonferroni correction. The chi-square test was used to compare categorical data.

The potential biomarkers for predicting incident HF in AF patients were initially screened using a multivariable-adjusted Cox proportional hazards model in both the discovery and replication cohorts. The model was adjusted for confounding factors, including age, sex, British background, smoking and drinking status, medical histories (hypertension, diabetes, ischaemic heart disease, cardiomyopathy and sleep apnoea), anthropometric data (systolic and diastolic blood pressure and body mass index) and laboratory results (haemoglobin, creatinine, non-high-density lipoprotein, glycosylated haemoglobin, C-reactive protein and insulin-like growth factor 1). The false discovery rate (FDR) was set as the statistical significance threshold during the biomarker screening process.

The correlation between the identified biomarkers and clinical risk factors was assessed using Spearman correlation analysis. Additionally, the continuous relationship between biomarkers and the risk of incident HF was analysed using restricted cubic splines (RCS). The Cox regression model fitted with RCS was adjusted for the same variables used during screening. Kaplan–Meier estimation, with the log-rank test, was employed to evaluate the time to incident HF, stratified by the quartiles of pro-adrenomedullin (pro-ADM) levels. Subgroup analysis was conducted to assess the relationship between the identified biomarkers and HF occurrence.

To evaluate the clinical value of the identified proteins as biomarkers for incident HF, the area under the receiver operating characteristic curve (AUROC) at 3 and 5 years was calculated. Age and sex were considered fundamental elements of the predictive model, and NT-proBNP was incorporated into the model as a baseline. The predictive performance of the identified biomarkers was compared to the baseline model using DeLong's test. Furthermore, the novel biomarker-incorporated model was compared to the baseline model using integrated discrimination improvement (IDI) and net reclassification index (NRI).[15] The model's fit was assessed using the Hosmer–Lemeshow test, with a *P*-value exceeding 0.05 suggesting a well-fitted model.

Several sensitivity analyses were performed to validate the findings. First, in a dataset comprising 1705 individuals (1304 for the discovery cohort and 401 for the replication cohort), random forest methods were employed to impute missing data for race, anthropometrics and laboratory tests. The biomarker screening process was then repeated. Second, to account for potential overlap in clinical presentations and risk factors between AF and HF, individuals diagnosed with HF within 1 year of enrolment were excluded (leaving 1340 individuals after exclusion; 1042 for the discovery and 298 for the replication cohort). After completing the biomarker screening, revalidation of the association between identified proteins and incident HF was conducted to address potential bias arising from death events or HF related to ischaemic heart disease (IHD). This approach involved excluding individuals with a history of IHD at enrollment. Fine–Gray subdistribution hazard models were then applied, treating death and IHD as competing risks in the combined discovery and replication cohorts (n = 1028 after exclusion). To further ensure the robustness of our findings, we conducted a multivariable Cox regression analysis excluding participants with only self-reported AF, evaluating the HR for incident HF with pro-ADM as both a continuous and categorical variable. We performed a multivariable Cox regression analysis specifically for participants with paroxysmal AF (n = 240) and persistent AF (n = 65), exploring the relationship between each unit increase in pro-ADM and the risk of HF.

The analysis was performed using R version 4.3.1, developed by The R Foundation for Statistical Computing in Vienna, Austria. The 'mice' R package was used for multiple imputation, the 'rms' R package was employed for RCS evaluation and visualization, and the 'cmprsk' R package was used for analysing competing risk data. To assess the predictive performance of the models, the 'pROC' and 'survIDINRI' R packages were utilized. A significance threshold of $P < 0.05$ was applied for all two-sided tests.

Results

Baseline characteristics

The primary analysis included 1050 participants in the discovery cohort and 305 participants in the replication cohort. The average age in the discovery cohort was slightly lower compared to the replication cohort. While the proportion of female participants was similar across both cohorts, a higher prevalence of individuals with a British background was noted in the discovery cohort. The replication cohort displayed a more complex medical history, with a greater prevalence of comorbidities. Additionally, participants in the replication cohort exhibited higher levels of inflammation, as indicated by elevated C-reactive protein levels when compared to the discovery cohort. In contrast, the discovery cohort showed more favourable markers for kidney function and lipid metabolism (see *Table 1*).

Identification of biomarkers as predictors for incident HF

During a 14.2-year follow-up in the discovery cohort, 222 cases (21.1%) of incident HF were documented, while the 13.8-year follow-up in the replication cohort identified 117 cases (38.4%) of incident HF. The multivariable-adjusted Cox regression model identified 24 plasma proteins as predictors for incident HF in the discovery cohort and 68 proteins in the replication cohort (see *Table S1* and *Table S2*). Three proteins —pro-ADM (pro-adrenomedullin), ANGPTL4 (angiopoietin-like protein 4) and ACVRL1 (serine/threonine-protein kinase receptor R3)—were consistently identified across both cohorts.

To further validate the screening process, we conducted two sensitivity analyses. First, we applied missing data imputation to the dataset ($n = 1705$). The second analysis excluded individuals who had been diagnosed with HF within 1 year of enrolment. Both analyses confirmed that pro-ADM remained the sole biomarker strongly associated with incident HF, as demonstrated in *Figure 1A*.

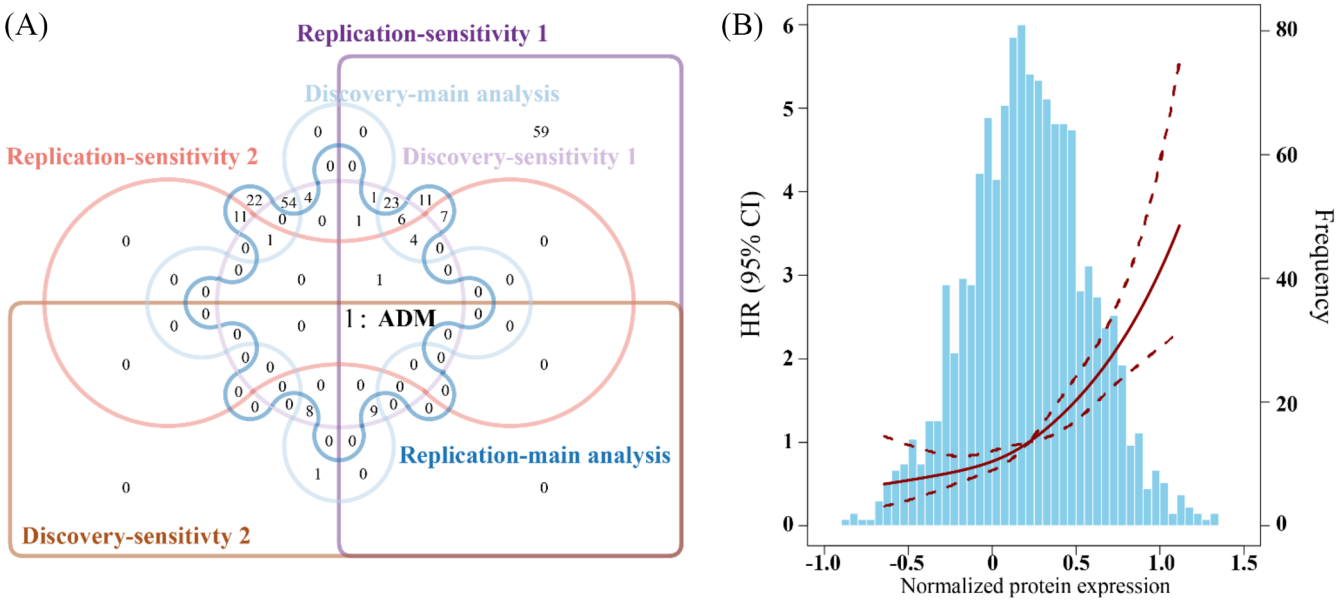
In the primary analysis, each unit increase in pro-ADM was associated with a 1.78-fold increased risk of incident HF in the discovery cohort (HR = 2.78, 95% CI 1.64–4.71, FDR = 0.026). This risk was even greater in the replication cohort (HR = 3.95, 95% CI 1.97–7.94, FDR = 0.012). The non-linear relationship between pro-ADM levels and incident HF risk is depicted in *Figure 1B* using the pro-ADM data from the combined discovery and replication cohorts. Baseline comparisons of pro-ADM expression levels showed that nor-

Table 1 Baseline characteristics

	UKB-PPP	Discovery	Replication	*P*-value[a]
Participants	53 021	1050	305	
Age, years	57 ± 8	62 ± 6	63 ± 6	0.004
Female, *n* (%)	28 584 (53.9)	407 (38.8)	122 (40.0)	0.696
British, *n* (%)	46 291 (87.5)	988 (94.1)	274 (89.8)	0.010
Current smoker, *n* (%)	5601 (10.6)	104 (9.9)	28 (9.2)	0.707
Current drinker, *n* (%)	48 313 (91.4)	953 (90.8)	264 (86.6)	0.033
SBP, mmHg	140 ± 20	142 ± 20	143 ± 21	0.352
DBP, mmHg	82 ± 11	82 ± 11	82 ± 12	0.585
BMI, kg/m^2	27.5 ± 4.8	28.6 ± 5.1	29.1 ± 5.6	0.175
Medical history, *n* (%)				
HTN	15 525 (29.3)	527 (50.2)	194 (63.6)	<0.001
DM	5181 (9.8)	203 (19.3)	75 (24.6)	0.045
Obesity	12 962 (24.4)	352 (33.5)	104 (34.1)	0.852
IHD	3317 (6.3)	221 (21.0)	106 (34.8)	<0.001
Cardiomyopathy	24 (0.0005)	2 (0.2)	3 (1.0)	0.044
Sleep apnoea	1261 (2.4)	45 (4.3)	18 (5.9)	0.238
Laboratory				
Haemoglobin, g/dL	14.1 ± 1.3	14.3 ± 1.3	14.2 ± 1.4	0.177
Creatinine, mmol/L	73.1 ± 20.2	78.2 ± 19.4	86.1 ± 33.9	<0.001
Non-HDL, mmol/L	4.12 ± 1.48	3.99 ± 1.18	3.77 ± 1.09	0.003
HbA1c, mmol/mol	35.3 (32.9–38.1)	36.5 (34.1–39.4)	36.9 (34.2–41.0)	0.051
CRP, mg/L	1.4 (0.7–2.8)	1.7 (0.8–3.3)	2.2 (1.0–4.5)	0.002

BMI, body mass index; CRP, C-response protein; DBP, diastolic blood pressure; DM, diabetes mellitus; HbA1c, glycosylated haemoglobin; HTN, hypertension; IHD, ischaemic heart diseases; non-HDL, non-high density lipoprotein; SBP, systolic blood pressure.
[a]Comparison of variables between the identified discovery and replication cohorts.

Figure 1 The identification of proteins linked to incident heart failure in atrial fibrillation cohorts. Panel (A) features a Venn diagram showcasing the interrelationships between various analysis procedures: sensitivity 1 depicts the sensitivity analysis utilizing missing data with multiple imputation, while sensitivity 2 showcases the sensitivity analysis using data that excludes participants diagnosed with heart failure within 1 year. Panel (B) presents the distribution of normalized plasma protein expression levels of pro-adrenomedullin (pro-ADM) and its correlation with incident heart failure. The Cox regression model was utilized to calculate age- and sex-adjusted hazard ratios (HR) along with confidence intervals (CI) within the complete cohort of individuals diagnosed with atrial fibrillation but without heart failure (n = 1329). The solid red line symbolizes HR, with the red dashed line indicating the 95% CI.



malized protein expression (NPX) of pro-ADM was lowest in individuals without AF and highest in those with both AF and HF (*Figure S3A*). Pro-ADM levels were positively correlated with age, BMI, CRP, creatinine and HbA1c, as indicated by significant Spearman correlations ($P < 0.001$) (*Figure S3B*). The baseline characteristics stratified by pro-ADM quartiles are provided in *Table S3*.

Association between circulating pro-adrenomedullin and incident HF

We explored the relationship between pro-ADM levels and the incidence of HF by categorizing participants into four groups based on the interquartile range of pro-ADM. The results showed a positive correlation between higher pro-ADM levels and increased HF events. The cumulative incidence ranged from 15.3% to 42.7%, with a significant difference (log-rank $P < 0.001$) as shown in *Figure 2*. Pro-ADM consistently demonstrated a strong association with HF occurrence across three adjustment models (*Table 2*). In the final Model 3, each unit increase in pro-ADM was associated with a 107% higher risk of incident HF (HR = 2.07, 95% CI 1.33–3.23, P = 0.001). Even after excluding participants with self-reported AF in discovery cohort, the association between each unit increase in pro-ADM and the higher risk of incident HF remained consistent across all three adjustment models (Model 1: HR = 3.98, 95% CI 2.60–6.08, $P < 0.001$; Model 2: HR = 2.95, 95% CI 1.88–4.64, $P < 0.001$; Model 3: HR = 1.77, 95% CI 1.02–3.04, P = 0.041), with detailed results presented in *Table S4*.

Individuals in the highest quartile of pro-ADM levels had a 51% higher risk of incident HF compared to those in the lowest quartile (HR = 1.51, 95% CI 1.01–2.27, P = 0.046) in Model 3 (*Table 2*). In the cohort of 1705 participants, patients in Quartile 1 of pro-ADM had 64 cases of HF, with a median onset time of 3137 days (IQR 2512–3856). Quartile 2 had 79 cases with a median onset time of 2670 days (IQR 1570–3913). Quartile 3 had 99 cases, with a median onset time of 3183 days (IQR 1465–4380). In Quartile 4, 178 patients developed HF, with a median onset time of 2306 days (IQR 1149–3626). A significant difference in the time to HF onset was observed across the quartiles (*chi-squared* = 17.071, $P < 0.001$), with patients in Quartile 4 having a significantly shorter time to HF onset compared to Quartile 1 (P = 0.004).

As a continuous variable, pro-ADM demonstrated a consistent association with a higher risk of incident HF across various subgroups (*Figure 3*). Notably, individuals with a non-British background (n = 93) showed neutral findings (HR = 0.94, 95% CI 0.17–5.06). In a sensitivity analysis accounting for competing risks of death and IHD, the

DOI: 10.1002/ehf2.15196

Figure 2 The cumulative incidence of heart failure in patients with atrial fibrillation categorized based on various pro-adrenomedullin levels. The pro-adrenomedullin values were divided into four quartiles according to their interquartile range.

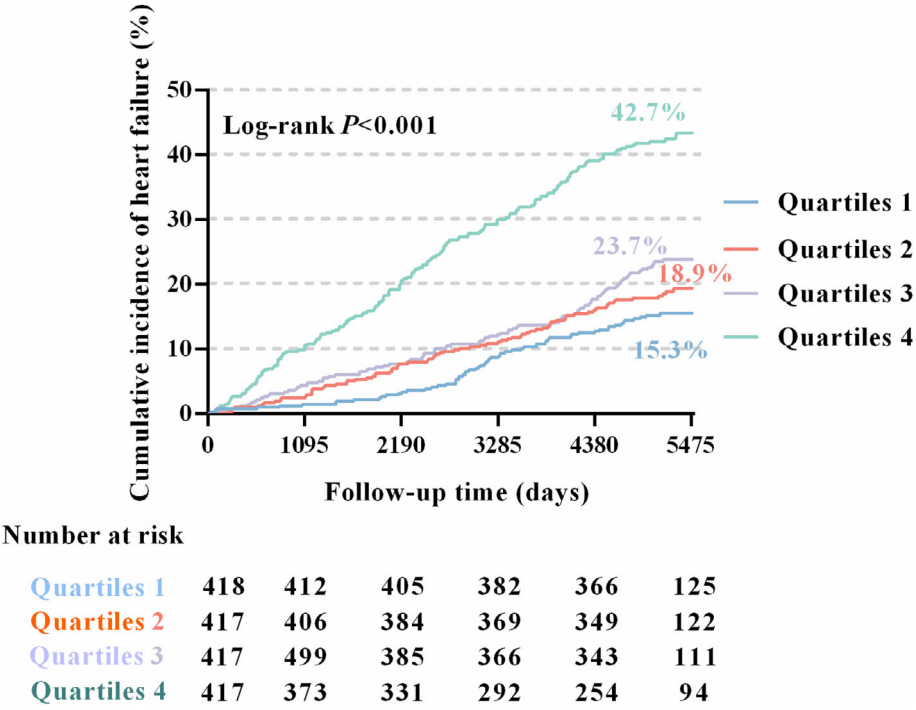


Table 2 Association of plasma pro-adrenomedullin with incident heart failure in entire cohort

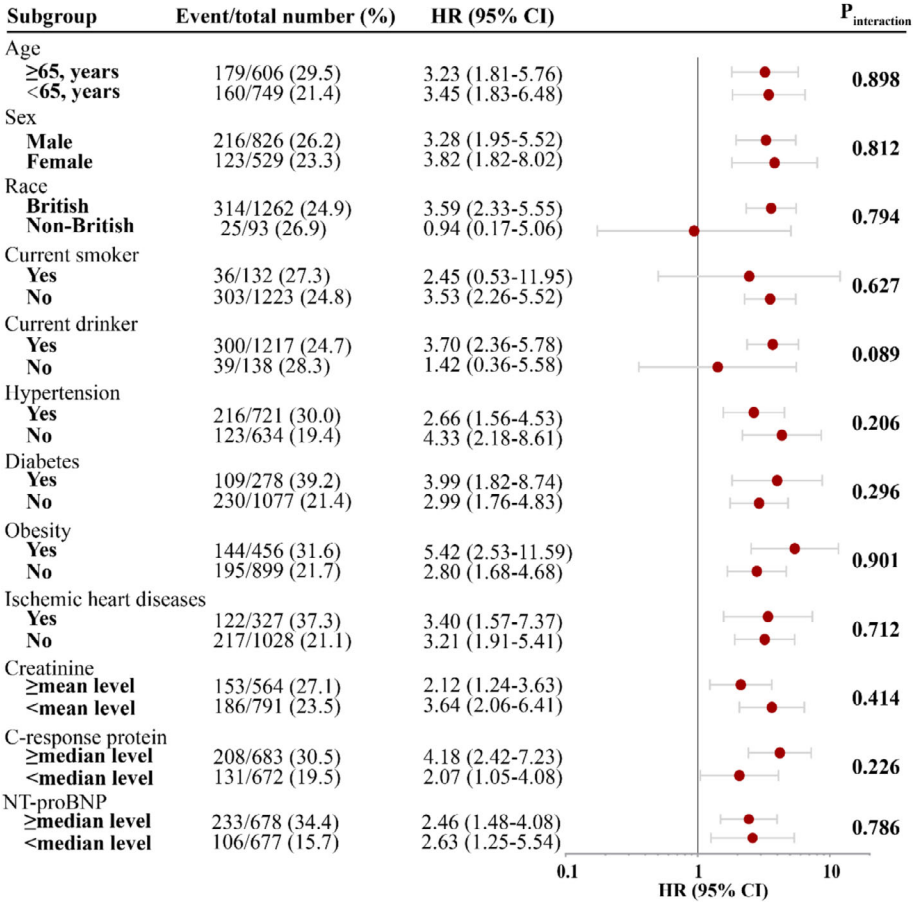
	Model 1			Model 2			Model 3		
Variables	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Continuous	3.60	2.62–4.95	<0.001	3.03	2.16–4.26	<0.001	2.07	1.33–3.23	0.001
Categorical									
Quartiles 1	Ref	Ref		Ref	Ref		Ref	Ref	
Quartiles 2	1.12	0.77–1.63	0.542	1.05	0.72–1.53	0.819	0.92	0.62–1.35	0.655
Quartiles 3	1.64	1.16–2.33	0.005	1.41	0.98–2.02	0.063	1.03	0.70–1.51	0.896
Quartiles 4	2.83	2.03–3.94	<0.001	2.36	1.65–3.36	<0.001	1.51	1.01–2.27	0.046
P for trend			<0.001			<0.001			0.016

The pro-adrenomedullin plasma expression level was characterized both as a continuous and categorical variable based on its interquartile range (n = 1355). To assess its correlation with the occurrence of heart failure, a Cox regression model was employed, accounting for various confounding factors through adjustments. Model 1 included age, sex, British, systolic blood pressure, smoke and alcohol status. Model 2 included Molde1 and medical history (hypertension, diabetes, obesity (BMI > =30), ischaemic heart diseases, cardiomyopathy and sleep apnoea). Model 3 included Model 2, haemoglobin, creatinine, non-high density lipoprotein, glycosylated haemoglobin, C-response protein and insulin-like growth factor 1 as well as NT-proBNP assessed using the Olink platform.

cumulative incidence before incident HF was 40.0%, with 411 events out of 1028 individuals (see *Figure S2*). During follow-up, 91 cases of incident HF were documented, and the multivariable-adjusted subdistribution hazard ratio for plasma pro-ADM in relation to incident HF was 2.98 (95% CI 2.06–4.32, $P < 0.001$).

Due to limitations in the UKB-PPP dataset, detailed AF subtypes information (e.g. paroxysmal and persistent AF) was not available for all participants. However, we performed an analysis using the available AF subtype data. For participants with paroxysmal AF (n = 240), after adjusting for age, sex, British status, systolic blood pressure, smoking and alcohol status (Model 1), each unit increase in pro-ADM was associated with a 1.8-fold higher risk of HF (HR = 2.80, 95% CI 1.11–7.07, P = 0.029). For participants with persistent AF (n = 65), after adjusting for age and sex, each unit increase in pro-ADM was associated with a 3.36-fold higher risk of HF (HR = 4.36, 95% CI 1.41–13.43, P = 0.010). These results are consistent with our primary findings, demonstrating similar risk trends across AF subtypes.

Figure 3 Subgroup analysis examining the relationship between plasma pro-adrenomedullin and incident heart failure in patients with atrial fibrillation. Hazard ratios (HR) and corresponding confidence intervals (CI) were determined using a Cox proportional hazards model, stratified by factors such as age, sex, British race, smoking and drinking habits, history of hypertension, diabetes, obesity and ischaemic heart diseases. Additionally, the analysis considered subgroups based on plasma levels of creatinine and C-response protein, along with the interaction between pro-adrenomedullin and the respective subgroup variable. The average creatinine level was 80 mmol/L, while the median C-response protein level was 1.77 mg/L.



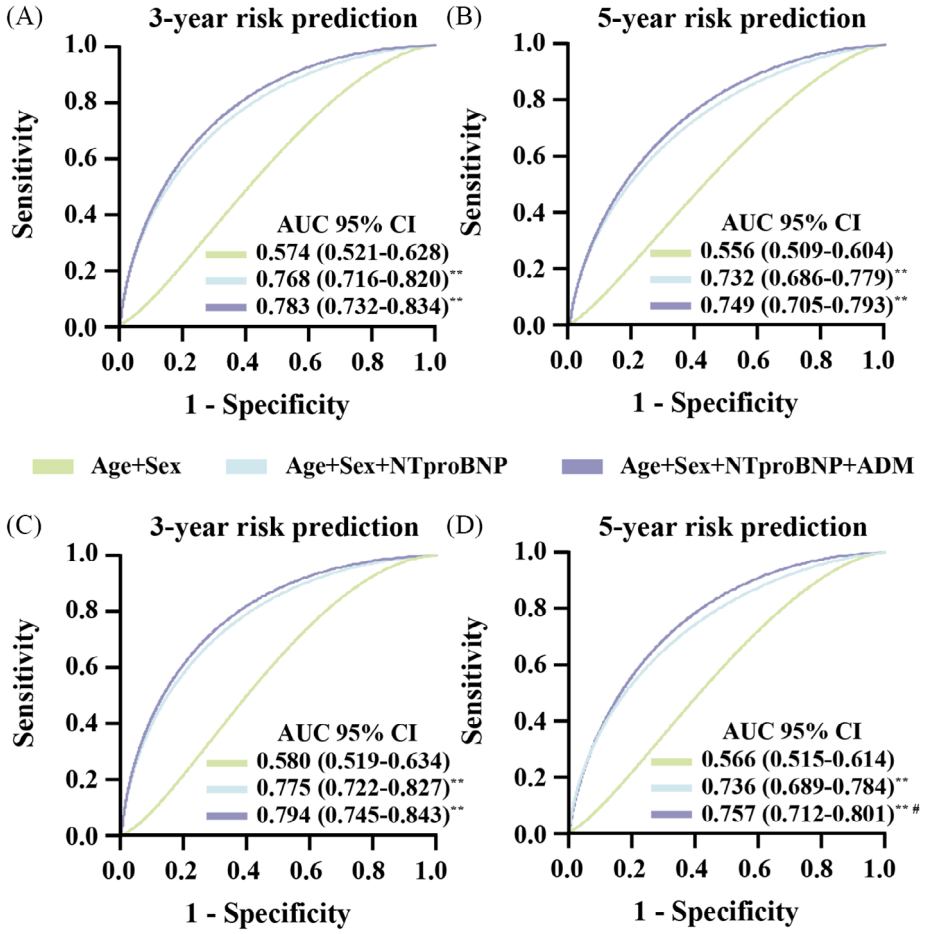
Predictive performance of pro-adrenomedullin in anticipating the incident HF

There was no significant difference in the AUC between the NT-proBNP and pro-ADM models for predicting 3-year (AUC 0.762 vs. 0.720, P = 0.199) and 5-year (AUC 0.728 vs. 0.700, P = 0.280) risks in the combined discovery and replication cohort (entire cohort). To assess the clinical utility of pro-ADM as a predictive marker, we constructed a fundamental model based on age and sex, and a basic model incorporating NT-proBNP. In this analysis, involving individuals with complete data for both NT-proBNP and pro-ADM (n = 1,641), the fundamental model had an AUC of 0.574 for 3-year risk prediction and 0.556 for 5-year risk prediction in the entire cohort. Adding NT-proBNP significantly enhanced predictive performance, resulting in AUC of 0.768 at 3 years and 0.732 at 5 years (both $P < 0.001$ compared to the fundamental model) for the entire cohort (*Figure 4A,B*).

Although the addition of pro-ADM to the basic model did not enhance the overall prediction of incident HF in the entire cohort for 3-year risk (P = 0.235 compared to the basic model) and 5-year risk (P = 0.113), this experimental model showed significant improvements in 3-year risk prediction based on IDI (0.01, 95% CI 0.003–0.021, P = 0.002) and NRI (0.206, 95% CI 0.084–0.315, P = 0.002). Similarly, for 5-year risk prediction, the experimental model demonstrated improved performance relative to the basic model, as indicated by IDI (0.013, 95% CI 0.004–0.026, P = 0.001) and NRI (0.179, 95% CI 0.074–0.265, P = 0.001). The calibration of the experimental model based on pro-ADM showed a good fit, as supported by the Hosmer–Lemeshow test result (P = 0.818).

We stratified the study cohort by British background, focusing on the predictive performance of pro-ADM in the British subgroup without missing data for NT-proBNP and pro-ADM (n = 1526) (*Figure 4C,D*). The pro-ADM-inclusive model outperformed the NT-proBNP-based basic model in predicting 5-year incident HF risk (AUC 0.757 vs. 0.736) with

Figure 4 The area under the receiver operating characteristic curve for predicting incident heart failure in patients with atrial fibrillation at both 3 and 5 years in the British population. Panels (A) and (B) represent the entire population (n = 1641), panels (C) and (D) represent the British population (n = 1526). **Comparison of AUC with prediction model 1 (age and sex), DeLong's test $P < 0.001$. # Comparison of AUC between prediction model 2 (age, sex and NT-proBNP) and prediction model 3 (age, sex, NT-proBNP and ADM), DeLong's test $P = 0.0509$.



a borderline *P*-value of 0.0509 (Hosmer–Lemeshow test P = 0.841). In contrast, in the non-British subgroup (n = 114), the experimental model (AUC 0.620) appeared relatively inferior to the basic model (AUC 0.669) for 5-year risk, though the difference was not statistically significant (P = 0.507) (Hosmer–Lemeshow test P = 0.445).

Discussion

Our findings suggest that pro-ADM may serve as an independent predictor for incident HF in the AF and AFL population. In this study, we utilized proteomic data from the UKB-PPP to identify potential biomarkers linked to incident HF in AF and AFL patients. We employed two cohorts—one for exploration, representing the overall UK Biobank population, and another for result verification. Among the 2923 measured proteins, only pro-ADM consistently showed a connection to incident HF across both cohorts, even under varied analytic conditions. Subgroup analysis confirmed a stable association between pro-ADM levels and HF risk, even after excluding participants with solely self-reported AF. This association remained consistent across both the paroxysmal AF and persistent AF subgroups, with results closely aligning with the primary findings. When incorporated into the NT-proBNP-based predictive model for incident HF, pro-ADM significantly enhanced the model's discrimination.

Adrenomedullin (ADM), a gene located on chromosome 11p15.4, encodes pre-pro-adrenomedullin, which is further processed into pro-ADM. This precursor is cleaved into four peptides: ADM and pro-ADM N-terminal 20 peptide (PAMP), both of which exhibit biological activity, as well as mid-regional pro-ADM (MR-proADM) and C-terminal pro-ADM, which are inactive products following enzymatic amidation.[16] ADM functions primarily as a vasodilator, playing a key role in endothelial nitric oxide formation and water–sodium homeostasis.[17] Although initially identified in

the adrenal medulla, ADM is widely expressed in human tissues and can be detected in circulation. However, measuring plasma ADM is challenging due to its short half-life and the presence of binding proteins. In contrast, pro-ADM and MR-proADM, which are stable and inactive fragments from proteolytic cleavage, are reliably detectable in blood samples and are frequently used in clinical and research settings as indirect markers of ADM production.[18]

There is growing evidence that the ADM family—including bioactive ADM, its precursor pro-ADM and the stable fragment MR-proADM—acts as a predictive biomarker for HF across various disease settings and populations.[18–26] In patients with stable ischaemic heart disease and preserved left ventricular ejection fraction (LVEF), elevated baseline MR-proADM levels have been independently associated with an increased risk of cardiovascular mortality and HF, including both heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF), and these findings suggest that MR-proADM plays a significant prognostic role in identifying subclinical cardiovascular stress, which can contribute to the development of both HFpEF and HFrEF.[19]

In our subgroup analysis, individuals with a non-British background (n = 93) showed neutral results regarding the association between pro-ADM levels and incident HF, likely due to the limited sample size. Nevertheless, a comprehensive review of the literature supports a strong correlation between pro-ADM and its variants with incident HF across various non-British populations. For instance, Beer *et al*. found that elevated pro-ADM levels (OR 3.01, 95% CI 1.75–5.38, $P < 0.001$) were significant predictors of worsening heart failure (WHF), highlighting its prognostic utility in a German cohort of patients with acute heart failure.[20] Moreover, findings from the Gutenberg Health Study demonstrated that elevated MR-proADM levels were strongly associated with AF and HF, as well as systolic and diastolic dysfunction in non-British populations, which suggested elevated MR-proADM levels are linked to both HFpEF and HFrEF supporting its role in predicting HF across different subtypes.[21] Additionally, the Malmö Diet and Cancer Study suggested that the predictive ability of MR-proADM for incident AF and HF was influenced by interactions with other biomarkers, particularly natriuretic peptides, and also identified MR-proADM as an independent predictor of both HF and AF in a large, non-British, community-based cohort.[22] The RA-HF study from Portugal showed that elevated ADM levels were independently associated with a higher risk of HF in patients with rheumatoid arthritis (RA), validating ADM as a reliable biomarker for cardiovascular events.[23] Similarly, a study from Poland involving patients undergoing coronary artery bypass grafting (CABG) revealed that elevated pro-ADM levels predicted post-operative left ventricular dysfunction, reinforcing its prognostic relevance across European populations.[24] Furthermore, a comparative study from Singapore and New Zealand confirmed the diagnostic superiority of MR-proADM in identifying acute decompensated heart failure (ADHF), especially in AF patients, where it outperformed natriuretic peptides in predicting HF in non-British background.[25] This finding is further supported by a study conducted by Tan *et al*. in Singapore, which included 1099 participants with a diverse ethnic composition: Chinese (60.7%), Malay (27.4%), Indian (11.0%) and other (0.9%).[26] They found that MR-proADM concentrations were more strongly associated with HF hospitalization in AF patients (HR 3.92, 95% CI 1.67–9.17) compared to non-AF patients, underscoring its importance as a key biomarker for HF in AF patients.[26]

While these studies affirm that pro-ADM and its variants are robust biomarkers for HF in various non-British populations, potential genetic, environmental and healthcare-related factors could influence the strength of these associations.[23] Although our study did not find significant associations in the non-British subgroup, the extensive body of evidence supports ADM family as reliable predictor of HF across multiple populations. Future research should focus on larger non-British cohorts to verify whether the associations between pro-ADM and HF in AF patients remain consistent across diverse populations.

Bio-active ADM plays a crucial role in stabilizing vascular endothelial cells and inducing vasodilation by regulating vascular smooth muscle cells.[17] Consequently, bio-active ADM may serve as an indicator of the compensatory state in HF, where endothelial dysfunction leads to vascular leakage and fluid retention, making it a surrogate marker for congestion. In the BIOSTAT-CHF study, plasma bio-active ADM was associated with signs of systemic and pulmonary congestion in patients with de novo or worsening HF.[27] Additionally, in patients with advanced heart failure with reduced ejection fraction (HFrEF) undergoing right heart catheterization, bio-active ADM demonstrated a positive correlation with pulmonary capillary wedge pressure (PCWP), mean right atrial pressure and NT-proBNP, although the strength of the association was moderate.[28] The association between MR-proADM and both arterial vascular remodelling and pulmonary haemodynamics abnormalities has also been confirmed in individuals with HFpEF.[29]

In individuals with chronic HF and a median LVEF of 31%, the efficacy of MR-proADM in predicting 1-year mortality has been established.[30] Notably, MR-proADM showed greater prognostic efficacy compared to NT-proBNP in improving the performance of the baseline predictive model.[31] The long-term prognostic value of MR-proADM was further demonstrated in stable outpatients with HF, where elevated MR-proADM levels predicted an increased risk of mortality in patients discharged after de novo or worsening HF.[31] In HFrEF patients, MR-proADM outperformed NT-proBNP with a C-statistic of 0.771, indicating robust predictive performance for major adverse cardiac events.[32] However, in HFrEF

patients with moderate anaemia, MR-proADM did not enhance the clinical prediction model for HF hospitalization or cardiovascular death, despite a significant adjusted HR of 2.28 (95% CI 1.83–2.84) for observed events.[33]

Limited data exist regarding the prognostic role of the ADM family in AF. Previous studies indicated that MR-proADM could predict hospitalization events in patients with recurrent AF and provided superior discrimination of acute HF compared to NT-proBNP and troponin in AF.[25,34] However, the predictive value of the ADM family for incident HF—a critical complication of AF—has not been documented, and the underlying mechanisms remain unclear. Considering biological function of ADM as a potential 'fireman' protecting the heart from injuries leading to fibrosis and oedema, it may help counteract the pathophysiological processes of HF.[17] Notably, this hypothesis is further supported by ADM's potential as a therapeutic target. Previous research demonstrated improvements in cardiac structure and function following the administration of exogenous ADM (via inhalation).[35] An ongoing trial (NCT04252937) is currently recruiting patients with acute HF to evaluate the safety and efficacy of adrecizumab, an ADM-binding antibody designed to extend its half-life and facilitate redistribution in circulation.

Limitations

Several limitations in the current study warrant acknowledgment. Firstly, neutral results were observed among patients with non-British backgrounds. This can be attributed to the fact that our study data were derived from the UKB, where the majority of participants are of British descent, with only a small proportion of non-British individuals (n = 93). The limited sample size of the non-British cohort may have contributed to these neutral findings. Although previous studies in non-British populations have demonstrated a strong association between the ADM family and HF risk, it is important to consider potential racial variations in the association between pro-ADM and incident HF in AF patients.

Secondly, due to the data collection characteristics of the UKB, only a very small portion of AF (n = 24) and HF (n = 4) cases were solely self-reported by patients. Although these self-reported diagnoses may lead to potential underdiagnosis or exclusion of some AF patients, they were subsequently verified through nurse interviews to ensure accuracy. Sensitivity analyses excluding participants with self-reported AF yielded consistent results across all models. The vast majority of AF and HF cases in our cohort were confirmed through medical records or a combination of self-reported diagnoses, inpatient diagnosis codes and procedure codes, enhancing the validity of the diagnoses. Although direct validation within the UKB was not available, this method for defining AF has been widely accepted and validated in an external dataset of approximately 7 million individuals, showing a high positive predictive value of 92%.[36,37]

Thirdly, a limitation exists in obtaining comprehensive details regarding LVEF during the diagnosis of HF, which prevented further classification into HFrEF and HFpEF. This is due to the nature of the UKB-PPP dataset, which defines HF using ICD-10 codes (I50.0: Congestive heart failure, I50.1: Left ventricular failure, I50.9: Heart failure, unspecified) without distinguishing between HFrEF and HFpEF.

Lastly, the measurement of pro-ADM protein expression relied on the Olink platform without additional validation from alternative testing methods or commercial kits. This highlights the need for further investigations to substantiate these findings.

Conclusions

In this study using the UKB-PPP data, pro-ADM was identified as an independent predictor of incident HF in patients with AF and AFL. This association persisted after adjusting for traditional risk factors, including NT-proBNP. Importantly, adding pro-ADM to existing prediction models significantly improved their performance, highlighting its potential utility in risk stratification for HF among AF and AFL patients.

Acknowledgements

Gratitude is extended to all participants and staff members of the UK Biobank for their dedicated efforts.

Conflict of interest

All authors declare no competing interests related to this study.

Funding

This work was supported by the National Key Research and Development Program of China (grant number 2022YFC3601300) and the National Natural Science Foundation of China (grant numbers 82103904, 82270316 and 82100326) and Beijing Postdoctoral Research Foundation.

Data availability statement

Data and materials are available via UK Biobank at http://www.ukbiobank.ac.uk/.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Association of plasma proteins with incident heart failure in the discovery cohort following multivariable adjustments.

Table S2. Association of plasma proteins with incident heart failure in the replication cohort following multivariable adjustments.

Table S3. Baseline characteristics by the interquartile range of pro-adrenomedullin.

Table S4. Association of pro-ADM with Incident HF in Discovery Cohort Excluding Self-Reported AF Patients.

Figure S1. Study population enrollment flowchart. AF, atrial fibrillation; HF, heart failure; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HbA1c, glycosylated hemoglobin; Non-HDL, non-high density lipoprotein; Hb, hemoglobin; Current smoke, Current alcohol miss data excluded in 1,705 participants.

Figure S2. Incidence of heart failure compared with the competing risk (death or ischemic heart diseases before heart failure). IHD: ischemic heart diseases, HF: heart failure.

Figure S3. The variations in the expression levels of pro-adrenomedullin and its correlogram in relation to physical and laboratory indicators. Panel (A) The violin plot depicts the baseline distinctions in plasma pro-adrenomedullin (ADM) levels across cohorts based on their history of atrial fibrillation and heart failure. Notably, individuals with both atrial fibrillation and heart failure (n = 226) exhibited the highest pro-ADM levels, while those without a history of atrial fibrillation had the lowest levels (n = 50,064). Panel (B) The correlation matrix, calculated using Spearman Correlation, is presented (n = 1,030). The size of each dot reflects the strength of the correlation, with larger dots indicating higher Spearman correlation values. The colour of each dot indicates the direction of the correlation, with green representing positive correlations and pink representing negative correlations.

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