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Research article

Predictive value of neutrophil-to-apolipoprotein A1 ratio in all-cause and cardiovascular death in elderly non-valvular atrial fibrillation patients

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ABSTRACT

Neutrophil-to-apolipoprotein AI ratio's (NAR's) predictive value for the elderly non-valvular atrial fibrillation (NVAF) patients' death has not been fully recognized. We consecutively enrolled 1224 elderly patients with NVAF (≥75 years). With an average follow-up of 733.35 ± 271.39 days, 222 all-cause deaths were identified. Among these, 101 were caused by cardiovascular diseases. Cox regression showed that after correcting for potential confounders, patients in the Q4 group had an increased all-cause (hazard ratio [HR] = 1.90, 95% confidence interval [CI]: 1.20–2.99) and cardiovascular death (HR = 2.59, 95% CI: 1.30–5.15) risk compared to those in the lowest NAR quartile. Kaplan–Meier analysis indicated that all-cause and cardiovascular death were higher in the high NAR than those in the lowest NAR category (log rank, all, $P < 0.001$). A nonlinear association was observed between death and NAR. NAR may be a promising predictive biomarker for identifying elderly NVAF patients with poor clinical prognoses.

1. Introduction

The prevalence of atrial fibrillation (AF) is increases with age [1]; its overall prevalence in the population is approximately 2% and increases to 10–12% in people aged >80 years [2]. AF patients show an aging trend, and elderly patients with AF are ≥75 years old [3,4]. More importantly, aging (≥75 years) and heart failure (HF) are considered death predictors in AF patients [5,6,7]. Compared with all ages, the mortality rate of elderly AF patients (≥75 years old) is as high as 10.4–23.7% [8]. The increased death risk in elderly AF patients suggests that understanding the patient prognosis and strengthening disease management have important public health

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significance for better medical resources allocation and mortality reduction.

Studies have shown that AF's increased morbidity and mortality rates are related to oxidative stress and inflammatory processes [9]. Conversely, apolipoprotein A1 (apoA1), the major apolipoprotein component of high-density lipoprotein cholesterol (HDL-C), has anti-inflammatory and antioxidant properties [10]. High levels of apoA1 are protective factors for mortality in AF patients, reducing all-cause and cardiovascular death risk by 20% [11]. The neutrophil-to-apolipoprotein A1 (NAR) ratio is a composite inflammation and lipid metabolism marker that can exert anti-inflammatory and antithrombotic effects [12,13,14]. NAR can be used as a prognostic indicator of the five-year overall survival of nasopharyngeal carcinoma patients [15]. Nevertheless, the relationship between NAR and all-cause and cardiovascular mortality in elderly AF patients remains unclear. Therefore, the main objective of this study is to explore NAR's impact and predictive value on all-cause and cardiovascular deaths in elderly AF patients.

2. Methodology

2.1. Study design and participants

The ethics committee of the First Affiliated Hospital of Xinjiang Medical University approved this retrospective cohort study (ethics number: K202111-05). The committee agreed to waive the need for written informed consent owing to the retrospective study design. The study subjects were elderly patients with AF ($\geq$75 years old) admitted to each clinical department of the First Affiliated Hospital of Xinjiang Medical University from 1 January 2018 to 31 December 2019. The exclusion criteria were as follows: valvular AF, congenital heart diseases such as atrial septal defects, rheumatic and senile valvular disease, missing NAR and other vital data, refusal to participate in this study, and loss during follow-up. Finally, 1224 elderly non-valvular atrial fibrillation (NVAF) patients were collected in this study.

2.2. Data collection

Baseline data (age, sex, ethnicity, smoking history), medical history (HF, hypertension, diabetes, previous stroke, vascular disease history, and malignancy) and medication history (oral anticoagulants and lipid-lowering drugs) were acquired from the hospital's electronic medical record system. Fasting venous blood was collected within 24 h of hospitalisation. Triglyceride (TG), total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL-C), apoA1, platelet counts, mean platelet volume (MPV), neutrophil counts, haemoglobin, red cell distribution width (RDW), albumin, total bilirubin, and alanine transaminase (ALT) levels were measured using an automatic haematology analyser (Roche Cobas 8000, Sysmex XN-2000). According to the following scoring criteria, the CHA_2DS_2-VASc score was obtained: HF, hypertension, age 65–74, diabetes, vascular disease, and female sex each scored one point, whereas age over 75 years old and previous stroke/transient ischaemic attack/thromboembolism each scored two points. NAR = neutrophil count (10^9/L)/apoA1 (g/L).

2.3. Outcomes and follow-up

The study outcomes were all-cause and cardiovascular mortality during follow-up. All-cause death was defined as mortality from various causes, such as tumours, cardiovascular events, and respiratory infections. Cardiovascular mortality was defined as death from cardiovascular causes, including acute myocardial infarction, HF, stroke, and death from any other cardiovascular cause [16]. Patients regularly go to the hospital for re-examination because of the study's retrospective observational nature. Consequently, the outcomes were obtained through medical records or telephone interviews. The participants were followed-up from the first day of hospital discharge to outcome event occurrence or until June 30, 2021.

2.4. Statistical analysis

Based on NAR's quartiles, the subjects were divided into four groups (first quartile [Q1]: <2.50, second quartile [Q2]: 2.50–3.56, third quartile [Q3]: 3.56–5.22, and highest quartile [Q4] $\geq$ 5.22). The study cohort's baseline characteristics were described by NAR quartiles. If continuous variables followed normal distributions, mean $\pm$ standard deviation ($\overline{x} \pm S$) is provided, and one-way ANOVA was used for statistical tests; conversely, the differences between groups were compared utilizing the Kruskal–Wallis H test, and the median (interquartile interval) is given. Qualitative data are presented as frequencies (percentages) using chi-square (χ^2) tests to compare variances between groups. The Mantel–Haenszel χ^2 test was used to determine whether all-cause and cardiovascular deaths increased with an increase in the NAR level. Cox regression models were built to examine the relationship between NAR (as a categorical variable by quartiles) and all-cause and cardiovascular death risk, correcting for covariates such as CHA_2DS_2-VASc score, sex, and tumour. Three correction models were constructed. Model 1 was adjusted for age, sex, ethnicity, smoking, albumin level, and malignancy status. Model 2 was further adjusted for hypertension, diabetes, HF, previous stroke, vascular disease, oral anticoagulants, and statins, based on Model 1. Model 3 additionally corrected the CHA_2DS_2-VASc score, total bilirubin, ALT, TC, TG, HDL-C, LDL-C, RDW, platelet count, MPV, and haemoglobin level. The proportional hazards assumption was examined using Schoenfeld residuals [17]. The hazard ratio of no covariate was observed to change over time throughout the follow-up period. The cumulative incidence of all-cause and cardiovascular mortality in each NAR quartile was calculated utilizing the Kaplan–Meier (KM) method and log-rank tests. Subsequently, the KM curve was corrected using the inverse probability weighting (IPW) method. The C-index, net reclassification index (NRI), and integrated discrimination improvement (IDI) were calculated to evaluate NAR's discrimination in predicting death;

concurrently, by plotting the calibration graph, the indicator calibration can be obtained. To further explore the potential modification effects of anticoagulants, lipid-lowering drugs, sex, and type of AF on NAR, subgroup analyses were conducted based on sex, type of AF (paroxysmal, and non-paroxysmal), and receipt of anticoagulants and lipid-lowering drugs after admission. The multiplicative interaction effects between stratification variables and NAR were estimated using the Wald test. We further examined the potential nonlinear relationship between NAR and all-cause and cardiovascular death risk using a restricted cubic spline (RCS) model with four knots at the 5th, 35th, 65th, and 95th percentiles.

Sensitivity analysis was performed to test the robustness of the results. First, we excluded patients with a history of malignant tumours. Subsequently, we performed Cox regression to avoid the influence of malignancy on the causal relationship of NAR and all-cause mortality. Additionally, to prevent hypoalbuminemia from affecting the causal relationship between NAR and all-cause and cardiovascular death, hypoalbuminemia patients were excluded, and a Cox regression analysis was conducted. Because hyperlipidaemia may affect the level of blood lipids and inflammation, we conducted sensitive analysis in patients with hyperlipidaemia. All statistical analyses were performed utilizing SPSS 21.0 (SPSS Inc., Chicago, IL, USA) and R software (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria). In this study, $\alpha = 0.05$ was used for all the statistical test standards.

3. Results

3.1. Baseline characteristics

One thousand two hundred and twenty-four NVAF patients, including 535 women and 689 men, were finally included in the study. Fig. 1 shows a flowchart of patient inclusion. Table 1 shows the general baseline characteristics of the participants grouped by NAR quartiles. The higher the NAR, the lower the proportion of females, Han Chinese, and anticoagulants and lipid-lowering drug use, and the higher the likelihood of smoking, heart failure, and malignant tumours (all $P < 0.05$). There was no difference in the composition of the new oral anticoagulants (NOAC) and warfarin in the four groups. Patients with higher NAR had lower albumin, TC, HDL-C, and apoA-1 levels but were more likely to have higher ALT, platelet, and neutrophil levels (all $P < 0.05$).

The NAR and malignant tumours and RDW percentages in the all-cause death group were higher than those in the survival group. Conversely, haemoglobin and albumin concentrations and the patient proportion treated with anticoagulants and lipid-lowering drugs were lower (Table S1). There was no difference in baseline characteristics between patients who were lost to follow-up and patients

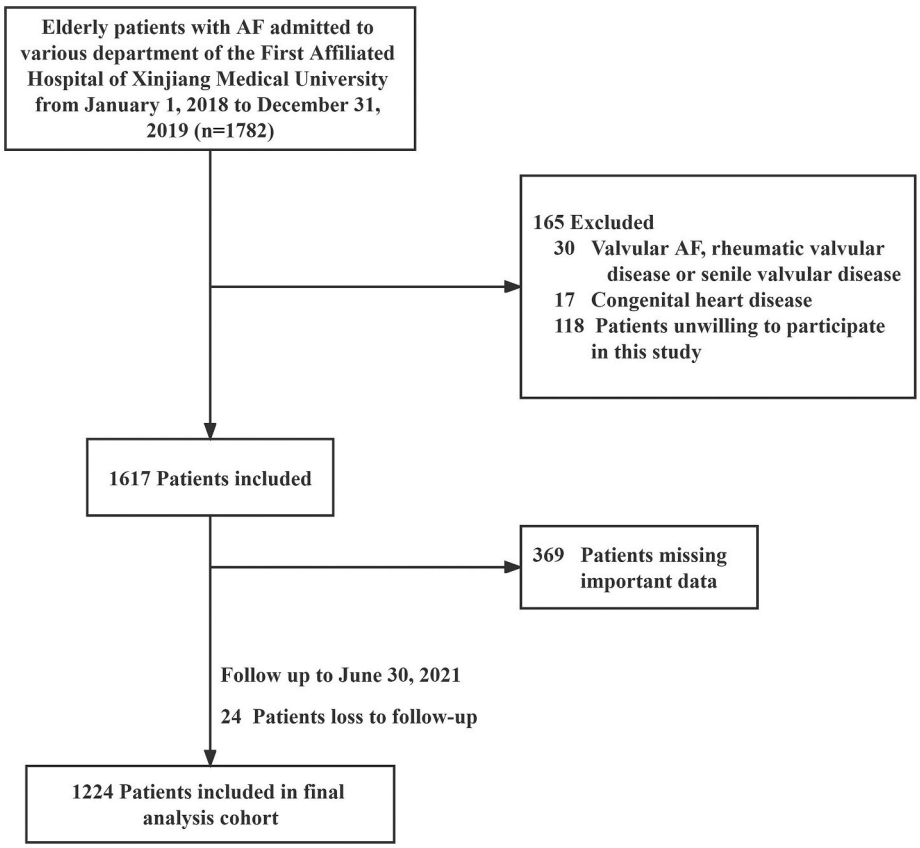

Fig. 1. Flow chart for selecting patients. AF, atrial fibrillation.

Table 1
Baseline characteristics of the cohort per quartiles of the NAR ratio.

Characteristics	NAR quartiles				χ^2/H	*P* value
	Q1 (n = 306)	Q2 (n = 306)	Q3 (n = 306)	Q4 (n = 306)		
Range of NAR quartile	<2.50	[2.50, 3.56)	[3.56,5.22)	≥5.22		
Age, year	80.00 (77.00, 82.25)	79.00 (77.00, 82.00)	79.00 (77.00, 83.00)	79.00 (77.00, 83.00)	1.42	0.702
Sex, n (%)					25.83	<0.001
Women	170 (55.56)	133 (43.46)[a]	116 (37.91)[b]	116 (37.90)[c]		
Men	136 (44.44)	173 (56.54)[a]	190 (62.09)[b]	190 (62.10)[c]		
Ethnicity, n (%)					16.52	<0.001
Other	28 (9.15)	38 (12.42)	59 (19.28)[b,d]	55 (17.97)[c]		
Han	278 (90.85)	268 (87.58)	247 (80.72)[b,d]	251 (82.03)[c]		
Smoking, n (%)					16.00	0.014
Never	261 (85.29)	236 (77.12)[a]	229 (74.84)[b]	225 (73.53)[c]		
Current	10 (3.27)	18 (5.88)	23 (7.52)[b]	19 (6.21)		
Former	35 (11.44)	52 (16.99)[a]	54 (17.65)[b]	62 (20.26)[c]		
Heart failure, n (%)	153 (50.00)	176 (57.52)	188 (61.44)[b]	166 (54.25)	8.78	0.032
Hypertension, n (%)	195 (63.73)	215 (70.26)	226 (73.86)	214 (69.93)	7.65	0.054
Diabetes mellitus, n (%)	67 (21.90)	79 (25.82)	84 (27.45)	88 (28.76)	4.23	0.238
Stroke, n (%)	107 (34.97)	99 (32.35)	108 (35.29)	94 (30.72)	1.97	0.579
Vascular disease, n (%)	71 (23.20)	76 (24.84)	72 (23.53)	74 (24.18)	0.27	0.967
Malignant tumour, n (%)	15 (4.90)	21 (6.86)	20 (6.54)	33 (10.78)[c]	8.47	0.037
CHA_2DS_2-VASc score	4.00 (3.00, 5.00)	4.00 (3.00, 5.00)	4.00 (3.00, 5.00)	4.00 (3.00, 5.00)	0.93	0.818
Albumin, g/L	38.70 (36.18, 41.93)	38.90 (35.58, 42.10)	38.60 (35.30, 41.70)	34.80 (30.98, 38.70)[c,e,f]	118.69	<0.001
Total bilirubin, umol/L	14.20 (10.58, 19.20)	14.80 (10.70, 19.13)	14.22 (11.41, 19.08)	16.00 (11.20, 22.90)	7.54	0.057
ALT, u/L	15.00 (11.18, 22.03)	16.20 (11.58, 24.63)	16.29 (11.65, 24.10)	19.95 (12.78, 32.88)[c,e,f]	34.30	<0.001
TC, mmol/L	3.41 (2.87, 3.98)	3.26 (2.73, 3.93)	3.27 (2.71, 3.83)	3.00 (2.55, 3.64)[c,e]	24.50	<0.001
TG, mmol/L	0.94 (0.73, 1.29)	1.05 (0.78, 1.44)	1.12 (0.79, 1.46)[b]	1.01 (0.79, 1.43)	13.68	<0.001
LDL-C, mmol/L	2.04 (1.54, 2.49)	2.06 (1.58, 2.68)	1.99 (1.53, 2.53)	1.93 (1.52, 2.51)	3.58	0.310
HDL-C, mmol/L	1.23 (1.04, 1.52)	1.10 (0.91, 1.29)[a]	1.05 (0.88, 1.26)[b]	0.90 (0.72, 1.11)[c,e,f]	167.39	<0.001
ApoA1, g/L	1.23 (1.09, 1.42)	1.12 (1.00, 1.27)[a]	1.07 (0.95, 1.20)[b,d]	0.89 (0.74, 1.04)[c,e,f]	296.16	<0.001
Platelet count, 10^9/L	165.00 (131.00, 201.00)	178.50 (142.00, 211.00)	189.00 (156.75, 233.25)[d]	196.00 (147.75, 256.25)[c,e,f]	47.50	<0.001
Neutrophil count,10^9/L	2.44 (2.04, 2.82)	3.41 (2.97, 3.85)[a]	4.52 (3.96, 5.17)[b,d]	6.65 (5.31, 8.94)[c,e,f]	913.04	<0.001
Haemoglobin, g/L	127.00 (113.75, 138.00)	131.00 (119.00, 142.00)[a]	135.00 (120.00, 146.25)[b]	126.50 (109.00,141.25)[e,f]	31.05	<0.001
RDW, %	13.50 (12.90, 14.30)	13.30 (12.80, 14.10)	13.40 (12.90, 14.20)	13.70 (13.00, 15.00)[e,f]	19.32	<0.001
MPV, fL	10.65 (9.90, 11.50)	10.70 (10.00, 11.40)	10.50 (9.90, 11.23)	10.65 (9.90, 11.50)	5.66	0.129
Medication use in hospital						
Anticoagulants, n (%)	204 (66.67)	204 (66.67)	183 (59.80)	159 (51.96)[c,e]	18.96	<0.001
NOAC	175 (85.78)	177 (86.76)	152 (83.06)	140 (88.05)	1.95	0.583
Warfarin	29 (14.22)	27 (13.24)	31 (16.94)	19 (11.95)		
Statins, n (%)	163 (53.27)	172 (56.21)	155 (50.65)	129 (42.16)[c,e]	13.45	<0.001

Abbreviations: ApoA1, apolipoprotein A1; NAR, neutrophil-to-apolipoprotein A1; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; ALT, alanine aminotransferase; RDW, red-cell distribution width; MPV, mean platelet volume; NOAC, new oral anticoagulants.

[a] Indicates a significant difference between Q1 and Q2;
[b] Indicates a significant difference between Q1 and Q3;
[c] Indicates a significant difference between Q1 and Q4;
[d] Indicates a significant difference between Q2 and Q3;
[e] Indicates a significant difference between Q2 and Q4;
[f] Indicates a significant difference between Q3 and Q4.

who were not lost to follow-up (Table S2).

3.2. Association of NAR with all-cause and cardiovascular mortality

With an average follow-up of 733.35 ± 271.39 days, 222 all-cause deaths were identified. Among these, 101 were caused by cardiovascular disease. The Cox regression analysis results for the NAR and all-cause mortality are presented in Table 2. The trend χ^2 test results showed that the number of all-cause deaths gradually increased with increasing NAR concentration ($P < 0.001$). The hazard ratio (HR) of NAR's highest quartile (Q4) was 3.24 (95% CI: 2.21–4.74) (*P* for trend <0.001) compared to that of the Q1 group. Compared to the reference group (Q1), all models suggested that patients in Q4 had an increased all-cause death risk after correction for confounding factors. In the fully corrected model, the HR of Q4 was 1.90 (95% CI: 1.20–2.99) compared to the Q1 group.

The Cox regression analysis results for NAR and cardiovascular mortality are shown in Table 3. The cardiovascular death rate gradually increased as the NAR level increased (trend χ^2, $P < 0.001$). Univariate Cox regression analysis showed cardiovascular death risk in the highest NAR quartile was 2.51-fold higher than that in Q1 (HR = 3.51, 95% CI: 1.96–6.29) (*P* for trend <0.001). The

Table 2
Multivariable adjusted hazard ratios (95% confidence intervals) of NAR quartile for incident all-cause mortality.

NAR	Events, n (%)	Crude model		Model 1		Model 2		Model 3	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Q1 (<2.50)	36/306 (11.76)	1.00		1.00		1.00		1.00	
Q2 [2.50, 3.56)	37/306 (12.09)	1.03 (0.65, 1.63)	0.897	0.92 (0.58, 1.45)	0.712	0.92 (0.58, 1.46)	0.725	0.94 (0.58, 1.50)	0.781
Q3 [3.56,5.22)	49/306 (16.01)	1.42 (0.92, 2.18)	0.113	1.25 (0.81, 1.93)	0.321	1.18 (0.76, 1.84)	0.455	1.24 (0.78, 1.96)	0.365
Q4 (≥5.22)	100/306 (32.68)	3.24 (2.21, 4.74)	<0.001	2.01 (1.34, 3.00)	0.001	1.95 (1.31, 2.93)	0.001	1.90 (1.20, 2.99)	0.006
P for trend	<0.001*	<0.001		<0.001		<0.001		0.003	

Abbreviations: NAR, neutrophil-to-apolipoprotein A1; HR, hazard ratio; 95% CI, 95% confidence interval
Model 1: adjusted for sex, age, ethnicity, smoke, albumin, and malignancy; Model 2: adjusted for model 1 + anticoagulants, statins, hypertension, diabetes mellitus, heart failure, stroke, and vascular disease; Model 3: adjusted for model 2 + CHA_2DS_2-VASc, total bilirubin, alanine aminotransferase, triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, red-cell distribution width, platelet count, mean platelet volume, and haemoglobin.
*Mantel–Haenszel χ^2 test.

Table 3
Multivariable adjusted hazard ratios (95% confidence intervals) of NAR quartile for incident cardiovascular mortality.

NAR	Events, n (%)	Crude model		Model 1		Model 2		Model 3	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Q1 (<2.50)	15/306 (4.90)	1.00		1.00		1.00		1.00	
Q2 [2.50, 3.56)	18/306 (5.88)	1.20 (0.61, 2.39)	0.599	1.14 (0.57, 2.26)	0.716	1.21 (0.61, 2.42)	0.585	1.27 (0.62, 2.59)	0.513
Q3 [3.56,5.22)	23/306 (7.52)	1.60 (0.83, 3.06)	0.160	1.42 (0.74, 2.75)	0.293	1.40 (0.72,2.72)	0.321	1.57 (0.79, 3.14)	0.198
Q4 (≥5.22)	45/306 (14.71)	3.51 (1.96, 6.29)	<0.001	2.45 (1.33, 4.50)	0.004	2.62 (1.42, 4.84)	0.002	2.59 (1.30, 5.15)	0.007
P for trend	<0.001*	<0.001		0.006		0.003		0.024	

Abbreviations: NAR, neutrophil-to-apolipoprotein A1; HR, hazard ratio; 95% CI, 95% confidence interval.
Model 1: adjusted for sex, age, ethnicity, smoke, albumin, and malignancy; Model 2: adjusted for model 1 + anticoagulants, statins, hypertension, diabetes mellitus, heart failure, stroke, and vascular disease; Model 3: adjusted for model 2 + CHA_2DS_2-VASc, total bilirubin, alanine aminotransferase, triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, red-cell distribution width, platelet count, mean platelet volume, and haemoglobin.
* Mantel–Haenszel χ^2 test.

cardiovascular death risk in Q4 was consistently higher than that in Q1 in all three adjusted models.

KM curves showed that compared with low-level NAR (Q1, <2.50), higher NAR (Q4, ≥5.22) had significantly increased all-cause (log-rank $P < 0.001$) and cardiovascular mortality (log-rank $P < 0.001$) (Fig. 2A and B). KM analysis corrected by the IPW method indicated the same trends (Fig. 2C and D). The NAR's C-index predicting all-cause and cardiovascular death was 0.68 (95% CI: 0.63–0.73) and 0.69 (95% CI: 0.62–0.76), respectively. After correction for multiple factors, NAR's predictive power was significantly improved (both C statistic >0.73, $P < 0.001$, Table 4). NAR remarkably improved the correct reclassification rate of all-cause death compared with the CHA_2DS_2-VASc score (category-free NRI: 49.33% for 1 year, 44.25% for 2 years, and 41.93% for 3 years) (Table S3). Furthermore, the NRI of NAR was >0, indicating that NAR's ability to predict all-cause mortality was improved compared with that of the CHA_2DS_2-VASc score (IDI: 3.5% for 1 year, 4.5% for 2 years, and 5.9% for 3 years, all $P < 0.001$). Likewise, NAR has good predictive power for cardiovascular death (Table S4).

NAR's calibration plot predicting all-cause death (Figure S1) and cardiovascular death (Figure S2) showed that the calibration curve and reference line almost entirely coincided, indicating that the survival rate predicted by the indicator was close to the actual value and had high accuracy.

3.3. Subgroup analysis of NAR and all-cause mortality

As shown in Fig. 3, the subgroup analysis of all-cause death was stratified by sex, anticoagulant use, lipid-lowering drug use, and type of AF. Compared with females, high NAR was strongly associated with all-cause death in male patients with NVAF (HR = 1.96, 95% CI: 1.06–3.64). We also identified a positive relationship between a high NAR and all-cause death in patients treated with lipid-lowering drugs. Patients with paroxysmal AF had a higher risk of all-cause death in the high NAR group (HR: 3.15, 95% CI: 1.40–7.09). Moreover, we found that NAR had no significant multiplicative interaction with sex, anticoagulants, lipid-lowering drugs, or type of AF (P for interaction > 0.05).

3.4. Subgroup analysis of NAR and cardiovascular mortality

The subgroup analysis of cardiovascular mortality was stratified by sex, anticoagulant use, lipid-lowering drug use, and type of AF (Fig. 4). Compared with females, high NAR was strongly associated with cardiovascular death in male NVAF patients (HR = 3.41, 95% CI: 1.30–8.90). A positive association between NAR and cardiovascular mortality was observed only in non-paroxysmal AF. The

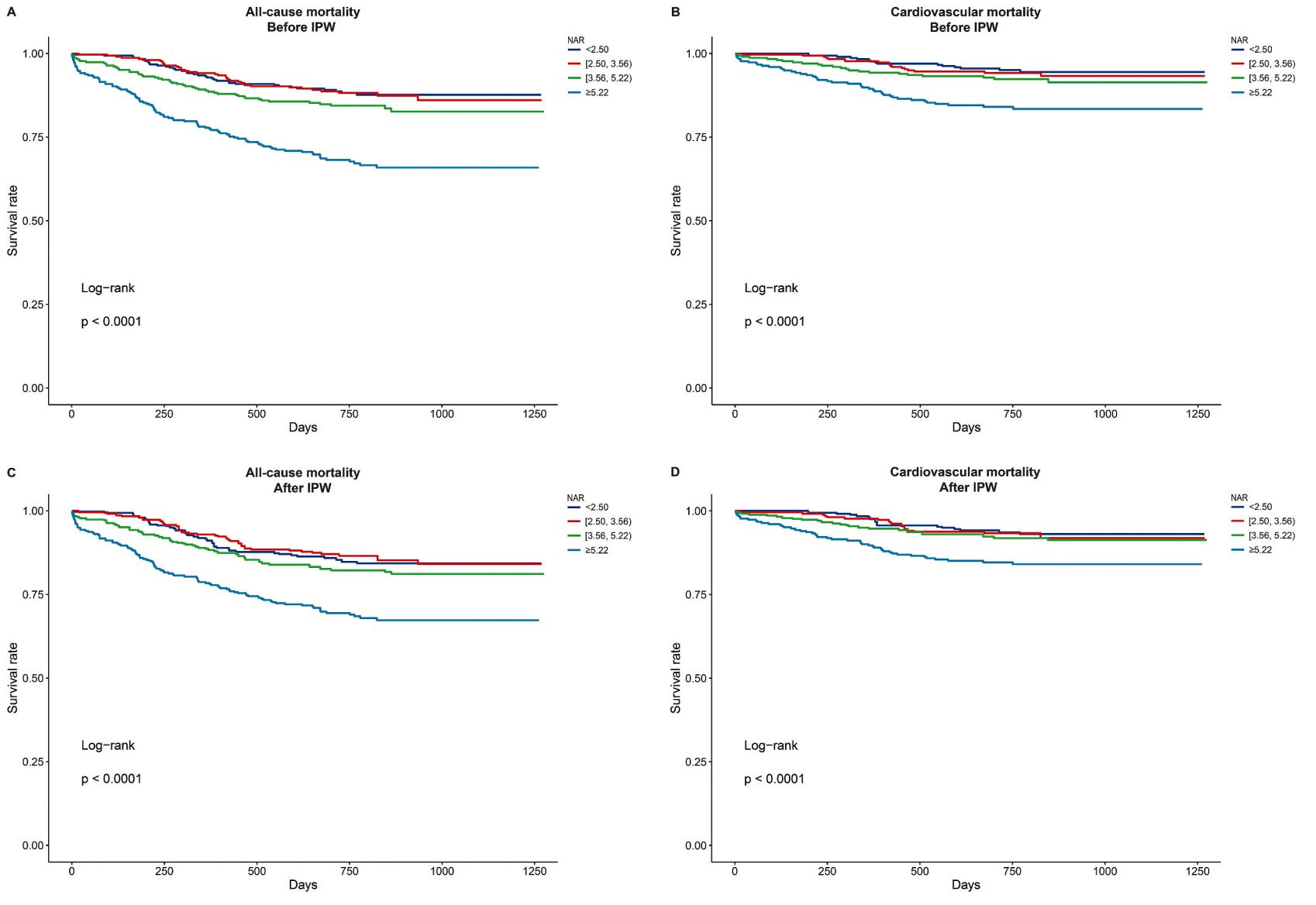

Fig. 2. An un-adjusted and adjusted Kaplan-Meier survival plot of NAR quartiles regarding all-cause and cardiovascular mortality. The inverse probability weighting (IPW) method was used to adjust for age, sex, race, smoke, albumin, and malignancy (C and D). NAR, neutrophil-to-apolipoprotein A1; IPW, inverse probability weighting.

Table 4
The C-index of NAR for all-cause mortality and cardiovascular mortality.

	All-cause mortality		Cardiovascular mortality	
	C statistics	*P*-value	C statistics	*P*-value
NAR	0.68 (0.63, 0.73)	Reference	0.69 (0.62, 0.76)	Reference
Model 1	0.74 (0.71, 0.77)	<0.001	0.73 (0.69, 0.78)	<0.001
Model 2	0.75 (0.72, 0.78)	<0.001	0.74 (0.70, 0.79)	<0.001
Model 3	0.76 (0.73, 0.79)	<0.001	0.76 (0.72, 0.81)	<0.001

Abbreviations: NAR, neutrophil-to-apolipoprotein A1.
Model 1: adjusted for sex, age, ethnicity, smoke, albumin, and malignancy; Model 2: adjusted for model 1 + anticoagulants, statins, hypertension, diabetes mellitus, heart failure, stroke, and vascular disease; Model 3: adjusted for model 2 + CHA_2DS_2-VASc, total bilirubin, alanine aminotransferase, triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, red-cell distribution width, platelet count, mean platelet volume, and haemoglobin.

relationship between NAR and cardiovascular death was not affected by anticoagulant or lipid-lowering drug use. No multiplicative interaction was observed between the stratification variables and NAR (*P* for interaction > 0.05).

3.5. Dose-response relationship between NAR and all-cause death

The NAR level and all-cause mortality risk were nonlinear and J-shaped (*P* for nonlinear < 0.001). The lowest point of all-cause death risk was 3.18. When NAR was higher than 3.18, all-cause death risk increased by 1.05-fold for each standard deviation (SD) increase in NAR (HR = 2.05; 95% CI: 1.53–2.75) (Figure S3).

3.6. Dose-response relationship between NAR and cardiovascular death

The dose-response curve between NAR and cardiovascular mortality risk is illustrated in Figure S4. There was a nonlinear relationship between NAR and cardiovascular death (*P* for nonlinear <0.001). With a NAR of 3.18 as the reference point (lowest cardiovascular death risk), for each SD increase in NAR, cardiovascular mortality risk on the right side of the reference point increased by 93% (HR = 1.93; 95% CI: 1.26–2.97).

3.7. Sensitivity analysis

To avoid the influence of tumour history on the causal relationship between NAR and all-cause death, we excluded subjects with a malignant tumour history, and the sensitivity analysis results did not change (Table S5). Additionally, the increasing trend of all-cause and cardiovascular death risk with NAR levels elevations remained unchanged after excluding subjects with hypoalbuminemia (Tables S6 and S7, respectively). In patients with hyperlipidaemia, there was no significant relationship between NAR and all-cause and cardiovascular death of AF (Tables S8 and S9).

4. Discussion

This study is the first to explore NAR's prognostic value on the clinical outcomes of elderly patients with NVAF. First, higher NAR levels were positively correlated with all-cause and cardiovascular risk of death after adjusting for confounding factors such as albumin and malignant tumours. The corrected KM curves suggested that patients' long-term survival rate in the highest NAR quartile was significantly reduced. Additionally, RCS illustrated a nonlinear association between NAR and all-cause and cardiovascular deaths. An increasing trend in all-cause and cardiovascular mortality risk was observed when the NAR was >3.18.

Serum lipoprotein level is a powerful death predictor in the older population [18]. Compared to HDL-C, apoA1 has a closer relationship with cardiovascular events, indicating that apoA1 is a better adverse cardiovascular events predictor than HDL-C [19,20]. Among subjects in different age groups, low apoA1 (<1.28 g/L) was consistently related to higher all-cause and cardiovascular deaths [21]. High apoA1 levels are related to a lower death risk in AF patients receiving anticoagulant therapy [11]. Nevertheless, the underlying mechanism by which apoA1 reduces death risk in AF patients remains unclear. ApoA1's ability to transport excess cholesterol from extrahepatic tissues to the liver has a cardioprotective function [22], which may be one of the potential mechanisms by which apoA1 reduces the death risk. ApoA1 nanoparticles (n-apoA1) are complexes composed of human apoA1 and phosphatidylcholine [23]. After intravenous injection, n-apoA1 can enter ischaemic and inflammatory heart tissues, exert anti-inflammatory effects through interactions with leukocytes, protect myocardial tissue, and improve cardiac function in ischaemic-reperfusion mice [23]. A clinical transformation study indicated that the number of neutrophils in the blood circulation of patients with type 2 diabetes mellitus was reduced 72 h after intravenous n-apoA1 injection [23]. Additionally, lipid-lowering therapy increases apoA1 levels [24,25,26]. Whether elevated apoA-1 can further reduce cardiovascular diseases risk remains controversial [24,27]. More prospective studies are required to support the clinical benefits of lipid-lowering therapy. Therefore, the above results highlighted the importance of detecting lipoproteins in elderly AF patients who may benefit from lipid reduction and circulating apoA1 level increase.

The neutrophil number is positively correlated with all-cause death risk [28]. Neutrophils have a higher predictive value compared

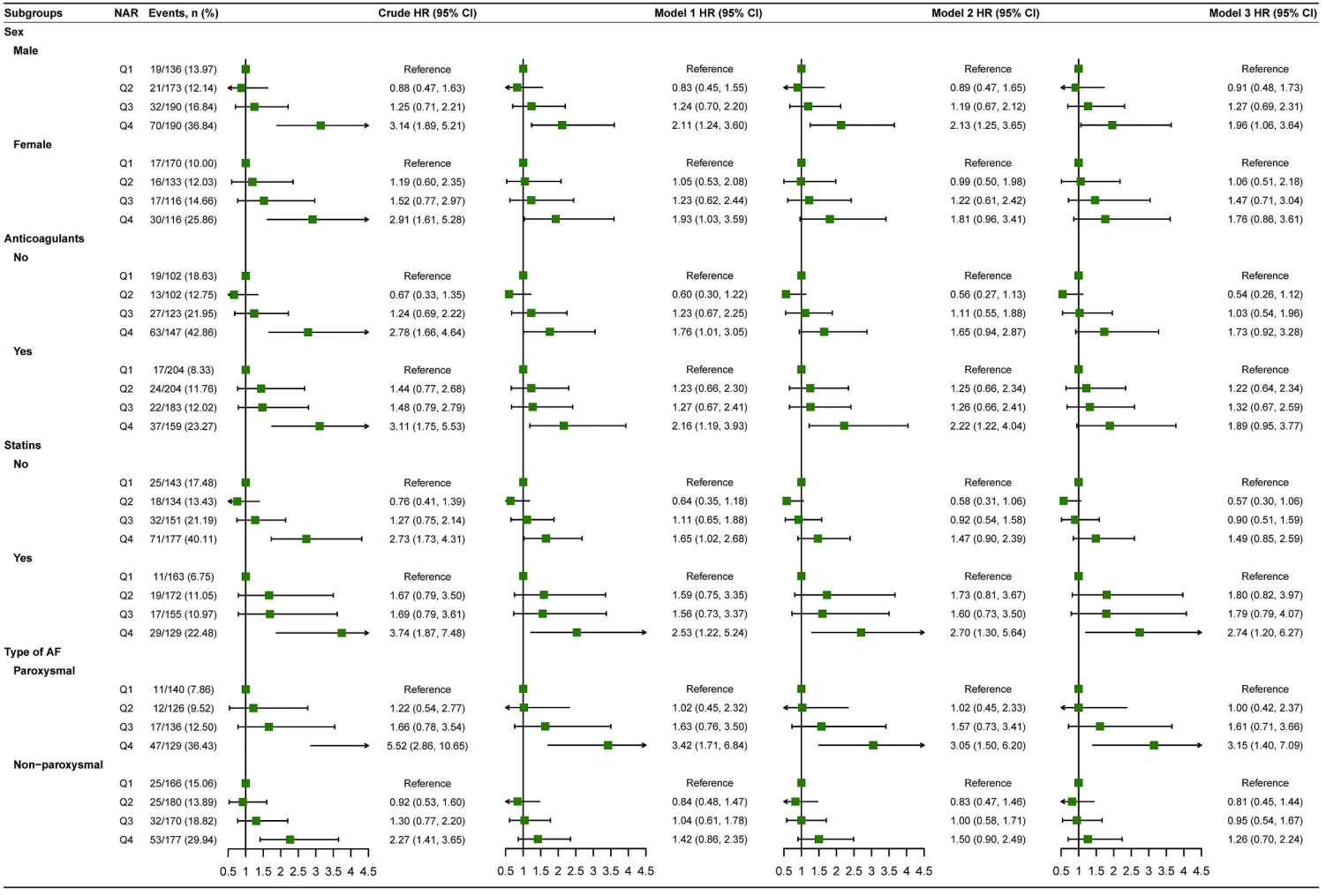

Fig. 3. Subgroup analysis of NAR on all-cause mortality. Note: The *P* values for interactions were 0.777, 0.338, 0.667, and 0.074 for sex, anticoagulants, statins, and type of AF, respectively (in crude model); The *P* values for interactions were 0.926, 0.406, 0.285, and 0.154 for sex, anticoagulants, statins, and type of AF, respectively (in model 1); The *P* values for interactions were 0.958, 0.394, 0.178, and 0.374 for sex, anticoagulants, and statins, and type of AF, (in model 2); The *P* values for interactions were 0.969, 0.404, 0.162, and 0.346 for sex, anticoagulants, statins, and type of AF, respectively (in model 3). AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; NAR, neutrophil-to-apolipoprotein A1. Model 1: adjusted for sex, age, ethnicity, smoke, albumin, and malignancy; Model 2: adjusted for model 1 + anticoagulants, statins, hypertension, diabetes mellitus, heart failure, stroke, and vascular disease; Model 3: adjusted for model 2 + CHA_2DS_2-VASc, total bilirubin, alanine aminotransferase, triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, red-cell distribution width, platelet count, mean platelet volume, and haemoglobin. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

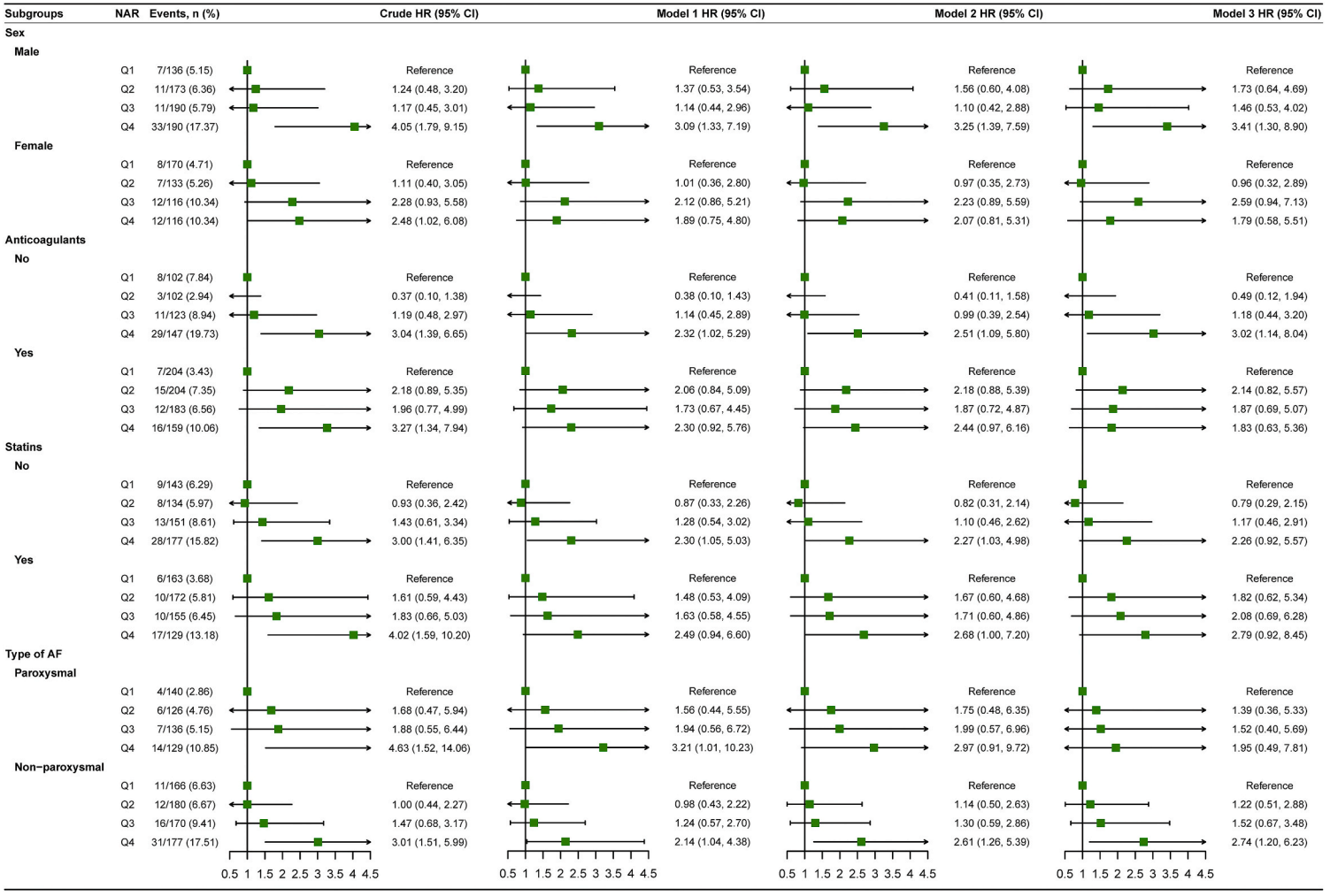

Fig. 4. Subgroup analysis of NAR on cardiovascular mortality. Note: The *P* values for interactions were 0.206, 0.083, 0.894, and 0.902 for sex, anticoagulants, statins, and type of AF, respectively (in crude model); The *P* values for interactions were 0.145, 0.113, 0.874, and 0.944 for sex, anticoagulants, statins, and type of AF, respectively (in model 1); The *P* values for interactions were 0.123, 0.110, 0.788, and 0.940 for sex, anticoagulants, statins, and type of AF, respectively (in model 2); The *P* values for interactions were 0.179, 0.143, 0.765, and 0.960 for sex, anticoagulants, statins, and type of AF, respectively (in model 3). AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; NAR, neutrophil-to-apolipoprotein A1. Model 1: adjusted for sex, age, ethnicity, smoke, albumin, and malignancy; Model 2: adjusted for model 1 + anticoagulants, statins, hypertension, diabetes mellitus, heart failure, stroke, and vascular disease; Model 3: adjusted for model 2 + CHA_2DS_2-VASc, total bilirubin, alanine aminotransferase, triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, red-cell distribution width, platelet count, mean platelet volume, and haemoglobin. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

to monocytes and lymphocytes in all-cause and cardiovascular mortality [29,30,31]. As immune cells involved in the first line of defence against the inflammatory response, neutrophils have antibacterial effects and secrete cytokines and other inflammatory factors [32]. Activated neutrophils release neutrophil extracellular traps (NETs) into the extracellular space, and NET accumulation can cause vascular obstruction, tissue damage, and inflammation [33]. Neutrophil elastase (NE) was considered to be one of the most specific quantitative methods for monitoring NETs [34]. Elevated NE levels were independently correlated with an increased all-cause and cardiovascular death risk in AF patients [34]. Besides, AF patients with high NE levels are more likely to have cardiovascular diseases such as hypertension and HF; thus, they are more likely to reach the inflammatory threshold of cardiovascular adverse events [34].

NAR has a predictive value for long-term tumour disease prognosis [15,35]. However, data on NAR's impact on the long-term prognosis of AF patients are limited. The multivariate Cox regression of this study demonstrated that NAR was an independent death predictor in elderly AF patients, implying that NAR may affect the disease prognosis in some aspects. The possible mechanisms by which NAR affects NVAF patient prognosis are as follows. First, inflammation and oxidative stress are potential mechanisms of cardiovascular death in AF [36]. Neutrophils are involved in the inflammatory response, whereas apoA1 exerts an anti-inflammatory effect [37]. Consequently, we believe that high NAR may be closely related to inflammation. High NAR may be due to the enhanced inflammatory neutrophil response and the reduction of the anti-inflammatory and antithrombotic apoA1 properties, which breaks the body's balance. Moreover, when the body is in a continuous inflammatory activation state, NET release from neutrophils is unbalanced, intensifying inflammation and tissue damage, affecting the disease prognosis [33]. Second, apoA1 is degraded by neutrophil protease released by activated neutrophils [38], and 25% of apoA1 recovers its integrity after applying a protease inhibitor. In vivo and in vitro experiments have shown that apoA1 inhibits activated neutrophil function [39], and apoA1 mimetic peptide has a dose-dependent rescue effect on the N-terminal-mediated histone H4 cytotoxicity released by activated neutrophils, preventing further damage to organs and tissues [40]. Consequently, we speculated that high NAR might represent enhanced apoA1 degradation by neutrophils, and apoA1's ability to inhibit neutrophil function is attenuated, reflecting an inflammation and lipid metabolism imbalance. In summary, neutrophils and apoA1 interact with and influence each other. High NAR levels may lead to adverse cardiovascular events by upregulating the inflammatory response, downregulating anti-inflammatory properties, and eventually damaging tissues.

This study comprehensively analyzed the relationship between NAR and long-term survival of elderly NVAF patients and revealed a nonlinear dose–response relationship. The NAR's C-index for predicting all-cause and cardiovascular death were 0.68 and 0.69, respectively, suggesting that the indicator has a moderate predictive value. After correcting for confounders such as age, sex, and malignancy, the ability of NAR to predict death significantly improved, and the C-index was >0.73. Compared with the CHA_2DS_2-VASc score, NAR substantially improved all-cause and cardiovascular death risk stratification. Additionally, NAR is composed of routine blood test parameters that provide more prognostic information than single neutrophil and apoA1 values. Subgroup analysis revealed that the association between NAR and death was more robust in male patients, highlighting the importance of routine detection of this indicator in male NVAF patients, even if no interaction between sex and NAR was found. Although the proportion of patients with malignancy was higher in the group with high NAR, the sensitivity analysis results after excluding these patients still suggested that NAR was an independently predictive biomarker of all-cause death. Frailty has a high prevalence rate in older AF patients and increases death risk [41]. Because malnutrition represented by hypoalbuminemia is one of frailty's manifestations, we conducted a sensitivity analysis after excluding these patients to avoid hypoalbuminemia affecting the relationship between NAR and all-cause and cardiovascular death. Notwithstanding, it was indicated that high NAR was an independent predictor of death.

The study is the first to propose that NAR is a biomarker with good predictive value in elderly NVAF patients, which may provide an idea for comprehensive patient management, mortality reduction, and improvement in prognosis and quality of life.

5. Conclusion

The all-cause and cardiovascular death risk in elderly NVAF patients increased with increased NAR. This suggested that NAR may be a promising predictive biomarker for identifying elderly NVAF patients with poor prognoses.

6. Limitations of the study

This study has several limitations. First, reverse causality may have limited causal associations in this observational study. In the baseline data, participants in the group with the highest NAR received a lower proportion of oral anticoagulants and statins, suggesting that statins and anticoagulants are potential confounding factors that may affect the effect of NAR on outcomes. However, there was no difference in the composition of NOAC and warfarin in each group. Additionally, we controlled the effects of statins and anticoagulants on the risk of death as much as possible through multivariate adjusted regression and stratified analysis. Second, this study only included inpatients, and there was selection bias. Third, although several potential confounding factors were adjusted, possible residual confounding could not be ruled out. Fourth, the results of this study suggest that the NAR is a cost-effective biomarker to monitor the survival of elderly patients with NVAF. However, in primary hospitals, apoA1 may not be a routine measurement item. Considering that the application of this index has good clinical significance, primary medical units should be encouraged to include this index in routine examination items. Fifth, NAR was measured only at baseline. There were no follow-up data; thus, it was impossible to compare the impact of the dynamic NAR changes on the prognosis of elderly NVAF patients. Sixth, in vivo and in vitro studies of deeper molecular mechanisms were not conducted.

Author contribution statement

Xianhui Zhou, and Baopeng Tang: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.
Xiaoxue Zhang: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
Meng Wei: Performed the experiments; Analyzed and interpreted the data.
Yakun Bo, Jie Song, and Yaping Yu: Performed the experiments; Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e12918.

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