Original Article

L-shaped association between gamma-glutamyl transferase-to-albumin ratio and dabigatran-related bleeding in non-valvular atrial fibrillation patients: a multicenter cohort study

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Background: The correlation between the gamma-glutamyl transferase-to-albumin ratio (GAR) and the risk of bleeding in patients with non-valvular atrial fibrillation (NVAF) undergoing treatment with the dabigatran anticoagulant is poorly understood. This study aims to explore whether GAR is associated with bleeding events among patients with NVAF receiving dabigatran anticoagulant therapy.

Methods: We conducted a multicenter, observational cohort study in 12 Chinese hospitals from six provinces, including Beijing, Shanghai and Guangzhou, to evaluate the effectiveness and safety of dabigatran (110 mg) treatment in NVAF patients who were consecutively enrolled during February 2015 and December 2017. All patients had completed a 3-month follow-up period. The baseline variable of interest was the GAR, and the outcome variable was the occurrence of bleeding events. Both univariate and multivariate Cox proportional hazard models were used to evaluate the relationship between GAR and bleeding outcome.

Results: This prospective cohort study included a total of 834 patients (mean age 65.6±11.1 years; 56.8% male). Overall, 82 subjects experienced bleeding. The patients were categorized based on the tertiles of the GAR. Participants in tertile 2 (0.59–1.03) [hazard ratio (HR): 0.28; 95% confidence interval (CI): 0.14–0.55; P<0.001] and tertile 3 (≥1.04) (HR: 0.47; 95% CI: 0.25–0.89; P=0.02) exhibited a lower rate of bleeding compared to the reference group (T1: ≤0.58). Multivariable models with restricted cubic splines demonstrated a nonlinear relationship between GAR and bleeding outcome, with a GAR inflection point of 0.68. The HR (95% CI) was 0.05 (0.01–0.31) (P=0.002) for GAR values <0.68 and 0.96 (0.70–1.31) (P=0.78) for GAR values ≥0.68. Moreover, the correlation between decreased GAR and an increase in bleeding events remained consistent across various subgroups.

Conclusions: GAR is a prevalent, independent predictor of dabigatran-related bleeding in NVAF patients. Moreover, a significant L-shaped association between GAR and bleeding events has been observed.

Keywords: Gamma-glutamyl transferase-to-albumin ratio (GAR); bleeding; non-valvular atrial fibrillation (NVAF); dabigatran

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Introduction

Stroke prevention is the primary goal of managing atrial fibrillation (AF) patients, and oral anticoagulant therapy has demonstrated a significant reduction in stroke incidence. Extensive research has substantiated the efficacy of dabigatran, a novel oral anticoagulant medication, in reducing the incidence of events rates of ischemic stroke and thromboembolic in cases with non-valvular atrial fibrillation (NVAF) (1). The latest American College of Cardiology (ACC)/American Heart Association (AHA) AF guidelines indicate that anticoagulation is recommended to prevent strokes and systemic thromboembolism (I, A) in patients with AF and thromboembolic 2% yearly risk (equivalent to undergo a CHA_2DS_2-VASc score of 2, while women are recommended a score of 3) (2). Simultaneously, significant emphasis is placed on the safety concerns associated with dabigatran administration. It is critical to assess the potential risks of bleeding when starting antithrombotic therapy. A study reported an 11.5% incidence of bleeding following a three-month follow-up period of dabigatran therapy (3). Moreover, Asian patients have a higher risk of hemorrhagic stroke during anticoagulant therapy compared to non-Asian patients (4). Research into the identification of early warning indicators for bleeding remains limited.

Both serum gamma-glutamyl transferase (GGT) and albumin have been identified as short- and long-term prognostic markers for patients with cardiovascular conditions (5-8). Moreover, according to previous studies, the gamma-glutamyl transferase-to-albumin ratio (GAR) can be a novel predictor for bleeding events after percutaneous coronary interventions (9,10). However, the potential association between GAR and bleeding risk in NVAF patients with treatment of dabigatran is not yet clear.

The purpose of this study is to investigate the potential of GAR as an independent biochemical marker for predicting bleeding risk in NVAF patients undergoing dabigatran therapy. We present this article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-258/rc).

Highlight box

Key findings

- A distinct exposure-response relationship in the shape of an 'L' was detected between gamma-glutamyl transferase-to-albumin ratio (GAR) and the risk of bleeding events.

What is known and what is new?

- GAR, as an indicator of the body's inflammatory status, is a novel predictive marker used in the diagnosis and prognosis of gliomas, liver tumors, and coronary artery disease.
- The association between GAR and bleeding risk in non-valvular atrial fibrillation (NVAF) patients treated with dabigatran remains unclear.

What is the implication, and what should change now?

- GAR is a novel and independent prognostic indicator for bleeding events in NVAF patients treated with anticoagulant dabigatran, which holds clinical significance for guiding the safe use of non-vitamin K antagonist oral anticoagulants.

Methods

Study design and populations

The data were obtained from the Monitor System for the Safety of Dabigatran Treatment Study (MISSION-AF) (registration No. NCT02414035), which has been previously reported (11-15). This was a national multicentre prospective observational cohort study supported by China's major new drug creation program (2014ZX09303305) (13) from the National Science and Technology Major Project, conducted in 12 Chinese hospitals between February 2015 and December 2017 (13). The purpose of this study was to assess the association between GAR and time to bleeding event of dabigatran anticoagulant therapy and to identify the factors influencing bleeding events. The inclusion criteria in this protocol were given below: (I) patients aged ≥18 years; (II) patients were diagnosed with NVAF (involves patients without mitral stenosis or artificial heart valves) (16); (III) CHA_2DS_2-VASc score of greater than or equal 1, or radiofrequency catheter ablation (RFCA) for AF; (IV) participation in the study requires written informed consent (17). Among the exclusion criteria were heart valve disorders (mitral stenosis or hemodynamically relevant valve disease that is expected to require surgical intervention during the course of the study) (18); stroke within the

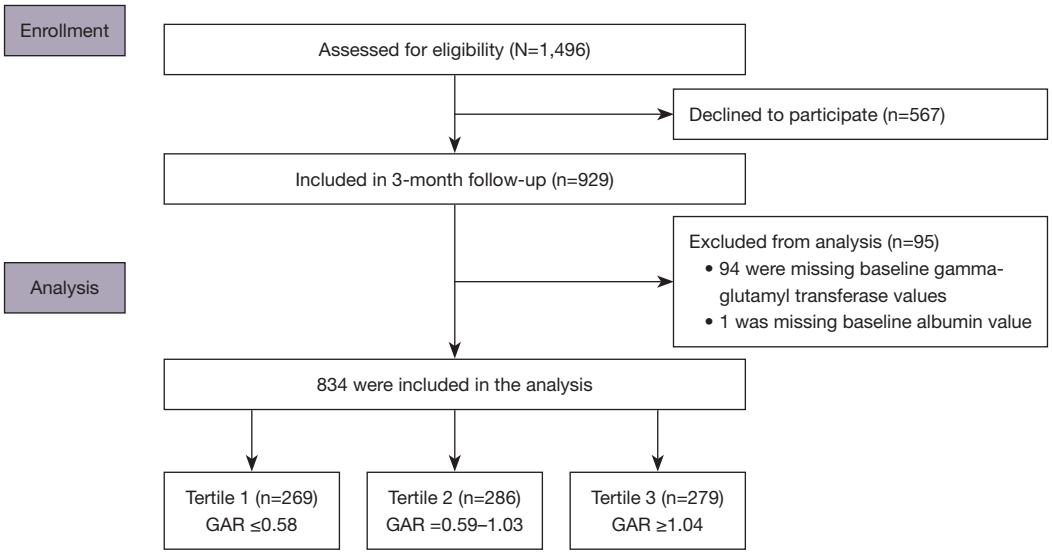

Figure 1 Study flow diagram. GAR, gamma-glutamyl transferase-to-albumin ratio.

previous 14 days; and a family history of coronary artery disease (17); patients with AF (or hematuria; severe renal impairment; severe liver dysfunction) who develop an acute coronary syndrome within a year (17); previous month's major surgery; the presence of bleeding intracranially, intraocularly, spinally, retroperitoneally, or intraarticularily caused by trauma; abuse of alcohol or drugs; hematuria or hemorrhage in the gastrointestinal tract; and involvement in any other investigational drug or medical device clinical trial. Participants were prescribed oral dabigatran (110 mg, once daily) and were scheduled for follow-up at 1 and 3 months. The follow-up was completed in May 2018. At each follow-up visit, trained researchers and physicians conducted in-person outpatient interviews to record vital signs study medication adherence, combination therapy use, laboratory tests, and outcomes. The outcome measure was the incidence of bleeding during the treatment period (from the time of the first dose to the time of the last dose). Results and follow-up data management were handled by specialized staff unaware of the results. The trial protocol was approved by all ethics committees of the participating 12 clinical centers in China. The related website (https://clinicaltrials.gov/ct2/show/ NCT02414035) provides information about inclusion/exclusion criteria, treatment assignment, and outcome measures. The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies (19). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Medical Research Ethics Committee of the Second Affiliated Hospital of Nanchang University (No. 2015001). All 12 participating sub-center hospitals (Fuwai Hospital and Cardiovascular Institute, Guangdong Cardiovascular Institute, the First Affiliated Hospital of Sun Yat-sen University, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Changzheng Hospital Affiliated to the Second Military Medical University, Wuhan ASIA Heart Hospital, Hubei Provincial People's Hospital, Jiangsu Provincial People's Hospital, Wuhan Tongji Hospital, Beijing Anzhen Hospital, Capital Medical University, and China-Japan Friendship Hospital) have informed and agreed with the study. Informed consent was obtained from all individual participants.

During the three months after the outpatient review, 929 participants completed the follow-up. This analysis included 834 participants after exclusion of patients with missing values on GGT (n=94) and albumin (n=1) (*Figure 1*).

Outcome and exposure variables

GGT and albumin detection

We calculated GAR at baseline and following a bleeding event for the exposure and outcome variables. Serum GGT and albumin were measured using "Beckman Synchron LX20" equipment for automated biochemical analysis from Beckman Coulter Inc. (Indianapolis, IN, USA) according to standard methods. The laboratory staff

was unaware of the research objectives and procedures. The primary outcome variable (bleeding) was identified after the clinician's judgment. The term "major bleeding" describes any reduction in haemoglobin concentration of at least 20 grams per liter, the transfusion of at least two units of blood, or symptoms of bleeding in a vital organ or area. Life-threatening bleeding, a category of major hemorrhages, encompassed fatal bleeding, symptomatic brain hemorrhages, and bleeding that resulted in a haemoglobin drop of 50 g/L or more; or bleeding that required at least four units of blood transfusion, inotropic agents, or a surgery. Except for these bleeding events, all others were considered minor (18).

Covariates

Baseline information was collected. Patient demographics, cardiovascular risk factors, medication use, diagnosis, and laboratory tests are also taken into account. There were several cardiovascular risk factors, including hypertension, coronary heart disease (CHD), diabetes, history of stroke, current or previous smoking, and current or previous alcohol consumption. An individual with hypertension is defined as having a systolic blood pressure (SBP) over 140 mmHg or a diastolic blood pressure (DBP) over 90 mmHg, or the use of antihypertensive medications (20). Fasting glucose levels of 7.0 mmol/L and random blood glucose concentrations of 11.1 mmol/L are diagnostic of diabetes, as well as using glucose-lowering drugs or having a self-reported diabetes history. Calculating body mass index (BMI) involves dividing weight in kilograms by height in meters squared. The estimated glomerular filtration rate (eGFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (21).

Statistical analyses

For statistical analysis, R, version 4.2.0 (http://www.r-project.org, The R Foundation) was used. The data are presented as proportions, mean ± standard deviation (SD), geometric mean (SD range), or median and interquartile range for variables not following a normal or log-normal distribution. Two-way proportional comparisons in independent samples were carried out using Fisher's exact test, while Student's *t*-test and Mann-Whitney *U* test were used for normally and non-normally distributed variables, respectively. Multiple comparisons for proportions were conducted using Fisher's exact test or Chi-squared test, analysis of variance (ANOVA) for normally distributed variables, and Kruskal-Wallis test for non-normally distributed variables. Pairwise comparisons for statistically significant trends were adjusted for multiple comparisons using the Bonferroni correction.

We first identified the variables influencing GAR or events that lead to bleeding based on previous research and our clinical experience to analyze the relationship between GAR and bleeding in selected participants. Moreover, univariate and multivariate Cox proportional hazards models were used to investigate associations between GAR and bleeding. The proportional hazards assumption was evaluated using Schoenfeld residual tests, which showed no violations (P>0.05), indicating that the assumption of proportionality was satisfied. Third, we performed a sensitivity analysis, which involved converting GAR into a categorical variable and calculating the trend P value. The fourth step of data analysis is that we performed a smooth curve fit (restricted cubic spline method) and discovered GAR nonlinearities and NVAF patients' bleeding outcome. Moreover, models of stratified linear regression were used for subgroup analyses. Using interaction terms between subgroup indicators, likelihood-ratio tests were used to assess subgroup effect modification. Statistical significance was defined as a P value of less than 0.05 on a two-sided basis.

Results

Patient characteristics

Baseline characteristics of selected participants according to tertiles of GAR are shown in *Table 1*. The analytic cohort included 56.8% male, 15.9% current smokers, and 9.7% current alcohol users. A history of hypertension was observed in 52.9%, heart failure in 24.8%, and stroke in 12.1%. No statistically significant differences were detected in BMI, SBP, CHA_2DS_2-VASc score, HAS-BLED score, history of hypertension, CHD, transient ischemic attack (TIA) or stroke, and peripheral arterial diseases (PAD), taken calcium channel blockers (CCBs), proton pump inhibitors (PPIs), statins, and glucose-lowering drugs, and eGFR among different GAR groups (all P values >0.05). Participants with the highest GAR (T3) were more likely to be males, smokers, and alcohol users and had a higher DBP, blood hemoglobin (HGB), and total bilirubin than those with the lower GAR (T1–T2).

Table 1 Baseline characteristics of participants stratified by tertiles of GAR

Variable	Total	Tertile 1 (≤0.58)	Tertile 2 (0.59–1.03)	Tertile 3 (≥1.04)	P value
N	834	269	286	279	–
Age (years)	65.6±11.1	64.4±10.6	65.8±11.6	66.5±10.9	0.042
Male	474 (56.8)	126 (46.8)	165 (57.7)	183 (65.6)	<0.001
Current smoking	132 (15.9)	22 (8.2)	51 (17.9)	59 (21.1)	0.002
Current drinking	81 (9.7)	11 (4.1)	27 (9.4)	43 (15.4)	0.001
BMI (kg/m^2)	24.3±3.4	24.1±3.2	24.4±3.4	24.5±3.8	0.44
SBP (mmHg)	127.4±16.3	125.5±14.8	128.9±17.4	127.6±16.4	0.13
DBP (mmHg)	76.0±11.3	74.2±9.5	76.5±11.2	77.3±12.8	0.004
CHA_2DS_2-VASc score					0.07
<2	280 (33.6)	102 (37.9)	98 (34.3)	80 (28.7)	
≥2	554 (66.4)	167 (62.1)	188 (65.7)	199 (71.3)	
HAS-BLED score					0.16
<3	800 (95.9)	263 (97.8)	273 (95.5)	264 (94.6)	
≥3	34 (4.1)	6 (2.2)	13 (4.5)	15 (5.4)	
Atrial fibrillation type					<0.001
Paroxysmal	437 (52.5)	184 (68.4)	152 (53.3)	101 (36.2)	
Persistent	396 (47.5)	85 (31.6)	133 (46.7)	178 (63.8)	
Radiofrequency ablation	522 (62.6)	208 (77.3)	176 (61.5)	138 (49.5)	<0.001
Medical history					
Hypertension	441 (52.9)	128 (47.6)	156 (54.5)	157 (56.3)	0.10
CHD	60 (7.2)	17 (6.3)	21 (7.3)	22 (7.9)	0.77
Heart failure	207 (24.8)	35 (13.0)	60 (21.0)	112 (40.1)	<0.001
PAD	19 (2.3)	7 (2.6)	5 (1.7)	7(2.5)	0.76
TIA	8 (1.0)	2 (0.7)	5 (1.7)	1 (0.4)	0.22
Stroke	101 (12.1)	27 (10.0)	37 (12.9)	37 (13.3)	0.45
Medication use					
ACEIs/ARBs	296 (35.5)	75 (27.9)	90 (31.5)	131 (47.0)	<0.001
β-blockers	341 (40.9)	78 (29.0)	111 (38.8)	152 (54.5)	<0.001
CCBs	157 (18.8)	52 (19.3)	64 (22.4)	41 (14.7)	0.06
Diuretic	132 (155.8)	15 (5.6)	30 (10.5)	87 (31.2)	<0.001
Antiplatelet	18 (2.2)	6 (2.2)	5 (1.7)	7 (2.5)	0.82
Amiodarone	337 (40.4)	128 (47.6)	115 (40.2)	94 (33.7)	0.004
Digoxin	47 (5.6)	3 (1.1)	16 (5.6)	28 (10.0)	<0.001
PPIs	368 (44.1)	131 (48.7)	124 (43.4)	113 (40.5)	0.15
Glucose-lowering drugs	71 (8.5)	16 (5.9)	25 (8.7)	30 (10.8)	0.13

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Total	Tertile 1 (≤0.58)	Tertile 2 (0.59–1.03)	Tertile 3 (≥1.04)	P value
Statins	251 (30.1)	67 (24.9)	92 (32.2)	92 (33.0)	0.08
Laboratory tests					
Leukocyte count (10^9/L)	6.3±1.8	6.0±1.7	6.6±1.9	6.4±1.8	<0.001
HGB (g/L)	134.2±17.9	131.4±17.3	134.8±18.2	136.3±17.9	0.004
PLT (10^9/L)	181.8±53.9	183.8 ±56.4	187.5±51.9	173.9±52.7	0.009
Total bilirubin (μmol/L)	13.7 [10.8–18.5]	12.7 [9.8–16.5]	13.3 [10.8–16.8]	15.8 [12.0–22.4]	<0.001
Albumin (g/L)	39.3±3.8	39.8±3.7	39.4±3.8	38.8±3.7	0.01
eGFR (mL/min/1.73 m^2)	81.1±17.5	83.0±17.1	81.6±16.5	78.9±18.6	0.059
Gamma-glutamyl transferase (U/L)	30.0 [21.0–51.0]	17.4 [14.5–20.7]	30.0 [26.3–34.0]	66.1 [50.5–89.8]	<0.001

Data are presented as mean ± standard deviation, median [interquartile range] or n (%). GAR, gamma-glutamyl transferase-to-albumin ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; PAD, peripheral arteriopathy; TIA, transient ischemic attack; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; PPIs, proton pump inhibitors; HGB, blood hemoglobin; PLT, blood platelet; eGFR, estimated glomerular filtration rate.

Table 2 The unadjusted and adjusted association between GAR and bleeding

GAR	N	Events, n (%)	Bleeding								
			Model 1			Model 2			Model 3		
			HR (95% CI)†	P value	P for trend	HR (95% CI)†	P value	P for trend	HR (95% CI)†	P value	P for trend
Continuous (per 1 unit change)	834	82 (9.83)	0.75 (0.54, 1.03)	0.08	–	0.81 (0.57, 1.14)	0.218	0.01	0.74 (0.50, 1.08)	0.12	–
Tertiles					0.004						0.009
Tertile 1 (≤0.58)	269	42 (15.61)	Ref.			Ref.			Ref.		
Tertile 2 (0.59–1.03)	286	19 (6.64)	0.38 (0.22, 0.66)	<0.001		0.28 (0.15, 0.55)	<0.001		0.28 (0.14, 0.55)	<0.001	
Tertile 3 (≥1.04)	279	21 (7.53)	0.50 (0.29, 0.85)	0.01		0.54 (0.30, 0.96)	0.04		0.47 (0.25, 0.89)	0.02	

Model 1: adjusted for age, gender; Model 2: adjusted for age, gender, smoking, drinking, BMI; Model 3: adjusted for age, gender, smoking, drinking, BMI, SBP, DBP, atrial fibrillation type, radiofrequency ablation, hypertension, CHD, heart failure, antiplatelet, β-blockers, diuretic, amiodarone, PPIs, leukocyte counts, HGB, PLT, total bilirubin, eGFR. †, Cox proportional hazards models were used to estimate HR and 95% CI. GAR, gamma-glutamyl transferase-to-albumin ratio; HR, hazard ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; PPIs, proton pump inhibitors; HGB, blood hemoglobin; PLT, blood platelet; eGFR, estimated glomerular filtration rate; Ref., reference.

Association between GAR and the risk of bleeding

The mean (SD) time to first bleeding event was 65.7 (32.5) days. Bleeding occurred in 82 participants, with an incidence rate of 9.83% (82/834). All bleeding events were minor, with 49 hematuria cases, 10 gastrointestinal bleeding cases, 12 gingival bleeding cases, 10 skin ecchymosis cases, and one other. Moreover, the association between GAR and bleeding was evaluated (*Table 2*). Per 1 unit increment in GAR, the HR of the risk of bleeding was 0.74 [95% confidence interval (CI): 0.50, 1.08] in the fully adjusted model (model 3). GAR was also evaluated according to tertile for categorical variables. The multivariate-adjusted HRs (95% CIs) were 0.28 (95% CI: 0.14–0.55; P<0.001) and 0.47 (95% CI: 0.25–0.89; P=0.02), respectively, for bleeding events associated with tertiles 2 and 3 compared to the tertile

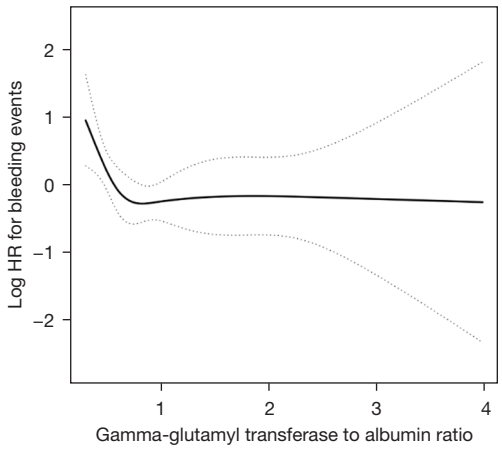

Figure 2 The relations of GAR with bleeding events. The solid line represents the smooth curve ft between variables. The dotted lines represent the 95% CI from the fit. All adjusted for age, gender, smoking, drinking, BMI, SBP, DBP, atrial fibrillation type, radiofrequency ablation, hypertension, CHD, heart failure, antiplatelet, β-blockers, diuretic, amiodarone, PPIs, leukocyte counts, HGB, PLT, total bilirubin, and eGFR. HR, hazard ratio; GAR, gamma-glutamyl transferase-to-albumin ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; PPIs, proton pump inhibitors; HGB, blood hemoglobin; PLT, blood platelet; eGFR, estimated glomerular filtration rate.

1. The risk of bleeding demonstrated a reduction as the tertiles of GAR increased (P for trend =0.009).

Nonlinearity between GAR and the risk of bleeding

A nonlinear relationship between baseline GAR and bleeding was observed (with a L-shaped relationship, P for non-linear =0.003) using a smooth curve fitting method after adjusting for age, gender, smoking, drinking, BMI, SBP, DBP, AF type, radiofrequency ablation, HAS-BLED score, hypertension, CHD, heart failure, antiplatelet, β-blockers, diuretic, amiodarone, PPIs, leukocyte counts, HGB, blood platelet (PLT), total bilirubin, and eGFR (*Figure 2*). Furthermore, the Cox proportional hazard regression and the two-piecewise Cox proportional hazard regression models were used to fit the association between GAR and bleeding events. The P value for the log likelihood ratio test is 0.004. The results suggested that the two-stage Cox proportional hazard regression model was more suitable for evaluating the relationship between GAR and bleeding because it precisely reflected the relationship between GAR and bleeding. The inflection point was determined to be 0.68 using correlation analysis (*Table 3*). The effect size, 95% CI, and P value for GAR <0.68 were 0.05, 0.01–0.31 and 0.002, respectively.

Table 3 Saturation effect analysis of GAR and bleeding

GAR	N	Events, n (%)	Bleeding								
			Model 1			Model 2			Model 3		
			HR (95% CI)†	P value	P‡	HR (95% CI)†	P value	P‡	HR (95% CI)†	P value	P‡
Inflection point			0.68		0.03	0.68		0.002	0.68		0.004
<0.68	340	46 (13.53)	0.11 (0.02, 0.58)	0.009		0.05 (0.01, 0.28)	0.001		0.05 (0.01, 0.31)	0.002	
≥0.68	494	36 (7.29)	0.91 (0.67, 1.22)	0.52		1.02 (0.79, 1.30)	0.91		0.96 (0.70, 1.31)	0.78	

Model 1: adjusted for age, gender; Model 2: adjusted for age, gender, smoking, drinking, BMI; Model 3: adjusted for age, gender, smoking, drinking, BMI, SBP, DBP, atrial fibrillation type, radiofrequency ablation, hypertension, CHD, heart failure, antiplatelet, β-blockers, diuretic, amiodarone, PPIs, leukocyte counts, HGB, PLT, total bilirubin, eGFR. †, Cox proportional hazards models were used to estimate HR and 95% CI; ‡, log likelihood ratio test. GAR, gamma-glutamyl transferase-to-albumin ratio; HR, hazard ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; PPIs, proton pump inhibitors; HGB, blood hemoglobin; PLT, blood platelet; eGFR, estimated glomerular filtration rate.

To investigate whether the relationship between GAR and the risk of bleeding was stable across different populations, we performed subgroup analysis according to age, gender, BMI, non-drinker, therapeutic strategy and hypertension using stratified Cox proportional hazards regression models (Table S1). Further analysis revealed that reduced GAR was independently and consistently associated with the increased risk of bleeding across the subgroups (all P values for interaction >0.05).

Discussion

The incidence of minor bleeding associated with dabigatran was determined to be 9.83% in the current study. Moreover, we have identified the GAR as an independent predictor of bleeding incidents in NVAF patients. To our knowledge, this is the first study to discover an L-shaped correlation between GAR and bleeding events. The results of further stratification analysis are also similar.

Current recommendations (22) state that the need for antithrombotic therapy in NVAF patients should be personalized according to the risk of stroke and bleeding. Therefore, identifying patients at high risk of bleeding and who may benefit from antithrombotic therapy remains a significant challenge for clinicians (23,24). The prognostic role of hematological biomarkers, such as peripheral leukocyte count (11), platelet count (14), red blood cell distribution (25) and total bilirubin (12), has been recognized recently. These biomarkers efficiently predict bleeding events in NVAF patients taking oral dabigatran.

GAR can predict bleeding events and mortality (9), the severity of coronary artery disease (26), significant fibrosis and cirrhosis (27), the overall survival rate and disease-free survival (28). Zheng *et al.* (9) conducted a retrospective cohort study including 5,638 coronary artery disease patients undergoing percutaneous coronary intervention. The results showed that patients with a ≥0.62 ratio had a lower risk of bleeding events (HR =0.616, 95% CI: 0.446–0.852, P=0.003) compared to patients with GAR <0.62. Consistent with the above results, our study discovered a negative correlation between GAR and bleeding events at a ratio of <0.68. Only minor bleeding events were observed in this study, probably due to the short follow-up duration and small sample size. However, minor bleeding cannot be ignored in clinical practice. The first is that a minor bleeding event could be a sign of a major bleeding event (29). The second is that bleeding risk changes over time, and the change in bleeding risk profile is a more accurate predictor of bleeding events, especially in the first three months (30). Third, both major and minor bleeding events are the most common reasons for reducing or discontinuing oral anticoagulants (31).

The mechanisms underlying the relationship between GAR and bleeding are not yet fully understood. A possible explanation for it is that the GAR is a combination index of GGT and albumin. In general, low serum albumin levels and elevated GGT indicate spoiled liver function and malnutrition status. GGT is instrumental in the metabolism of glutathione. Not only does it defend cells from oxidative injury, but it also assists to oxidative stress, effecting cellular proliferation, programmed cell death, and immunoreaction. Likewise, serum albumin, which reflects nutritional status and liver function, acts as an effective scavenger of free radical, antioxidant, and immunomodulatory as well as its part in carrying substances and stabilizing vascular pressure. It reacts with a variety of substances which includes inflammatory mediators, toxic metabolites, and metal ions, consequently affecting the body's antioxidant and inflammation responses (32-34). Moreover, various sorts of pathological conditions including weakened immune defenses, malnutrition and cell dysfunction are closely related to these factors (35). Therefore, GAR is not only an indicator of nutrition status as well as liver health but also an index of systemic inflammation that indicates antioxidant balance. Kittleson *et al.* (36) have found that increased GGT activity, even in the normal range, was associated with increased oxidative stress. Albumin contains 80% of thiol groups that play a role in scavenging free oxygen radicals from the plasma. Low albumin is associated with increased oxidative stress, PLT aggregation, and activation (37). Moreover, some researchers hold the speculation that hypoalbuminemia might be associated with the vulnerability of the systemic capillary, particularly malnutrition associated with vitamin C and K insufficiency, leading to an increased risk of coagulation disorders and bleeding tendency (38,39). Patients who bled may be predisposed to bleeding because of low serum albumin or lower level of albumin may have given rise to greater exposure to anticoagulation and higher risk of bleeding (19).

Study limitations

The current study is the first to our knowledge to establish a national multicenter, prospective cohort of patients with AF treated with non-vitamin K antagonist oral anticoagulants (NOACs) anticoagulant therapy in China and found that GAR can serve as an early warning indicator of bleeding

risk in dabigatran anticoagulant therapy. However, several limitations of this study also exist. First, the exact biological mechanism underlying the association between GAR and bleeding events is not identified. Second, the possibility of residual confounding by unmeasured variables cannot be eliminated completely despite careful adjustment for potential confounders. Third, all participants in this study were Chinese patients with NVAF taking dabigatran (110 mg) orally, inclusion of other NOACs, such as apixaban or rivaroxaban, was not considered in our study design, which may affect the generalization of results.

Conclusions

GAR is a novel and independent prognostic indicator for bleeding events in NVAF patients treated with anticoagulant dabigatran. Moreover, an L-shaped exposure-response correlation exists between GAR and the risk of bleeding events.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-258/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-258/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Medical Research Ethics Committee of the Second Affiliated Hospital of Nanchang University (No. 2015001). All 12 participating sub-center hospitals (Fuwai Hospital and Cardiovascular Institute, Guangdong Cardiovascular Institute, the First Affiliated Hospital of Sun Yat-sen University, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Changzheng Hospital Affiliated to the Second Military Medical University, Wuhan ASIA Heart Hospital, Hubei Provincial People's Hospital, Jiangsu Provincial People's Hospital, Wuhan Tongji Hospital, Beijing Anzhen Hospital, Capital Medical University, and China-Japan Friendship Hospital) have informed and agreed with the study. Informed consent was obtained from all individual participants.

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