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The Guangzhou atrial fibrillation project

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Multiple biomarkers and arrhythmia outcome following catheter ablation of atrial fibrillation: The Guangzhou Atrial Fibrillation Project

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Abstract

Background: Biomarkers have been related to the arrhythmia recurrence following catheter ablation (CA) of atrial fibrillation (AF). We hypothesized that concurrent measurement of several biomarkers would additively improve their predictive value.

Methods: One thousand four hundred and ten consecutive AF patients (68% male; 57.2 ± 11.6 years) undergoing CA were enrolled. Baseline characteristics, serum B type brain natriuretic peptide (BNP) and high sensitivity C reactive protein (hsCRP), estimated glomerular filtration rate (eGFR), ablation parameters, arrhythmia data at discharge, 1, 3, 6, and then every 6 months post CA were collected. Follow-up ended when arrhythmia recurred or until 31st December 2016.

Results: Three hundred and sixty-five (25.9%) patients had arrhythmia recurrence post-CA during a mean follow-up of 20.7 ± 8.8 months. BNP, hsCRP, and eGFR levels and their cut-off values of 237.45 pg/mL, 1.6 mg/dL, and 82.5 mL/min/1.73 m^2 were good predictors for AF recurrence (all $P < 0.01$). On multivariate analysis, increasing BNP and hsCRP, decreasing eGFR, gender, and early recurrence (ER) were independent predictors of AF recurrence (all $P < 0.01$). Compared to BNP alone, BNP plus eGFR or both eGFR and CRP showed incrementally better predictive values (ROC comparisons, all $P < 0.01$). Similar findings were evident in the subgroups of patients with paroxysmal or nonparoxysmal AF.

Conclusion: Measurement of BNP, CRP, and eGFR were incrementally additive to clinical risk factors in a cumulative manner to improve prediction of arrhythmia recurrence post-CA of AF. The implications of poor arrhythmia outcome in AF patients with multiple abnormal biomarkers pre-CA procedure may help with patient selection and inform the likelihood of success or the need of more complicated CA procedure(s).

Yumei Xue and Gregory Y H Lip are joint senior authors.

KEYWORDS
atrial fibrillation, biomarkers, catheter ablation, recurrence

1 | INTRODUCTION

Catheter ablation (CA) of atrial fibrillation (AF) has been performed for more than 20 years and is superior to antiarrhythmic drugs for the prevention of AF recurrences.[1] Relapses of AF post CA remain common, and many factors have been associated with AF progression and recurrence.[2] Based on clinical factors associated with arrhythmia recurrence post-CA, many clinical scoring systems have been proposed.[3] However, there is no general agreement of which score or risk factor is best.

Biomarkers such as NT-proBNP[4,5] and CRP[6] have been involved in the development and recurrence of AF by inducing structural and electrical remodeling.[7] Chronic kidney disease (CKD) as defined by the eGFR is also reported as a predictor of AF recurrence post-CA.[8] Previous reports on these biomarkers generally evaluated their impact as a single predictor but no prior studies have investigated their cumulative impact for predicting arrhythmia recurrent post-CA when used in a cumulative manner.

In this study, we tested the hypothesis that concurrent measurement of several biomarkers reflecting different pathophysiological processes would improve the predictive value of arrhythmia recurrence post-CA.

2 | METHODS

This retrospective study enrolled 1410 consecutive symptomatic adult patients with nonvalvular AF who underwent single CA procedures from June 2011 to August 2015 in Guangdong General Hospital. Patients were refractory to at least one kind of anti-arrhythmic drugs (AADs). Baseline clinical data and ablation parameters were extracted from hospital patient database. The study protocol was approved by the Clinical Research Ethics Committee of Guangdong General Hospital.

2.1 | Definitions

Paroxysmal AF (PAF) was defined as AF that spontaneously terminated or with intervention within 7 days, persistent AF (PeAF) as AF that lasted ≥7 days, and longstanding PeAF (LSPeAF) as AF lasted >1 year.[2] The term "nonparoxysmal" AF (NPAF) included PeAF and LSPeAF. AF types in this study were divided into PAF and NPAF. All patients had at least one symptomatic AF episode recorded before the ablation procedure. Arrhythmia relapse was defined as any symptomatic or asymptomatic atrial tachyarrhythmia (AF, atrial tachycardia[AT] and/or atrial flutter[AFL]) lasting >30 seconds. Arrhythmia relapse recorded within the 3-month "blanking period" after the ablation was defined as early recurrence (ER). Arrhythmia relapse recorded 3 months post procedure without use of AADs was defined as AF recurrence.

The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula ($186 \times Scr^{-1.154} \times Age^{-0.203} \times [1.210 \text{ if Black}] \times [0.742 \text{ if female}]$).[9] A cut-off value of each biomarker for predicting recurrence post-CA was tested using ROC analysis and was used to distinguish patients with "normal" or "abnormal" biomarker serum level. "Abnormal biomarker levels" were defined as BNP and CRP levels higher than the determined cut-off value from ROC analysis, or eGFR levels below the cut-off value.

For the categorical analyses, we scored patients as having 0, 1, 2, and 3 points for those with none, 1, 2, or 3 abnormal biomarker levels. Patients were divided into four groups according the different points and the baseline clinical characteristics and AF relapses post-CA were compared.

2.2 | Laboratory tests

Peripheral blood samples were collected from each patient who were fasting at the second morning after being hospitalized. All samples were sent to the central laboratory of the hospital within 1 hour after collecting. Serum creatinine levels were determined by Jeffe rate method (Synchron LX20, Beckman Coulter Inc, United State, California; Sensitivity 8.84 μmol/L). Plasma BNP levels were determined by ELISA (EE/Cobas 601, Roche, Switzerland, Basel; NT-proBNP, Detection range, 5-35 000 pg/mL; Reference value <125 pg/mL). Serum CRP was determined by Immunoturibidimetry (Immage 800, Beckman Coulter Inc, United State, California; Sensitivity ≤0.011 mg/dL; Reference value <0.744 mg/dL).

2.3 | Ablation procedure

Anticoagulation therapy, AAD therapy, and exclusion of thrombosis procedure were performed following guideline recommendations.[10] Radiofrequency ablation procedures were described detailed as previously which in briefly following a stepwise protocol. The cryoballoon ablation procedure was consecutively performed as previously described.[11] The endpoint of CPVI or cryoballoon catheter ablation was bidirectional conduction block. A cavotricuspid isthmus (CTI) bidirectional block, super vena cava isolation (SVCI), linear ablation of LA roof or mitral isthmus, and complex fractionated atrial electrograms (CFAE) were selected performed as additional ablation. Pharmacological (ibutilide or aminodarone) or electrical cardioversion (ECT) was performed during the procedure when it was necessary.

2.4 | Follow up

Follow up visits were performed at discharge, and at 1, 3, 6 months and every 6 months thereafter. Data on symptoms, ECG and/or 24 hour ECG were collected in each visit. Patients complained to symptoms related to arrhythmia recurrence within the visit interval accepted additional ECG or 24-hour Holter tests. Oral anticoagulants and AAD (amiodarone or propafenone) were administrated to all patients in the first 3 month post the ablation (blanking period). Thereafter, oral anticoagulants were continued in patients with a CHA_2DS_2-VASc score of ≥2, while AAD use was at the discretion of physicians.

Arrhythmia recurrence was defined as the principal study endpoint. Follow-up period of patients with confirmed recurrence was defined as the time of AF/AFL relapse. Patients without evidence of recurrence were followed up for a minimum of 12 months.

TABLE 1 Characteristics and the difference between patients with AF recurrence or not

Characteristics	Total (n = 1410)	Patients with recurrence (n = 365)	Patients without recurrence (n = 1045)	*P* value*
Age (y)	57.18 ± 11.6	58.58 ± 11.3	56.69 ± 11.7	<0.01
Male	960 (68)	251 (68.8)	709 (67.8)	0.79
NPAF	321 (22.8)	162 (44.3)	159 (15.2)	<0.01
AF history	2.70 ± 3.6	3.10 ± 3.8	2.56 ± 3.6	0.22
Cryoballoon	74 (5.2)	22 (6)	52 (5)	0.50
PVI	1394 (98.9)	362 (99.2)	1032 (98.8)	1.0
SCVI	87 (6.2)	19 (5.2)	68 (7.1)	0.45
CTI	337 (23.9)	120 (33)	217 (20.8)	<0.01
CFAE	35 (2.5)	20 (5.5)	15 (1.4)	<0.01
Linear	266 (18.9)	119 (32.6)	147 (14.1)	<0.01
ST	247 (17.5)	71 (19.5)	176 (16.8)	0.27
Pharm CV	221 (15.7)	89 (24.4)	132 (12.6)	<0.01
ECV	157 (11.1)	92 (25.2)	65 (6.2)	<0.01
ER	317 (22.5)	196 (53.7)	121 (11.6)	<0.01
FU (mo)	20.69 ± 8.8	10.05 ± 7.3	24.40 ± 5.6	<0.01
CHF	72 (5.1)	29 (7.9)	42 (4)	<0.01
Hypertension	508 (36)	151 (41.2)	357 (34.2)	0.02
DM	143 (10.1)	40 (11)	103 (9.9)	0.55
Stroke/TIA	84 (6)	31 (8.5)	53 (5.1)	0.02
Vascular disease	49 (3.5)	13 (3.6)	36 (3.4)	0.75
AADs failed	0.97 ± 0.40	1.01 ± 0.42	0.96 ± 0.39	0.03
CAD	105 (7.4)	38 (10.4)	67 (6.4)	0.02
COPD	9 (0.6)	4 (1.1)	5 (0.5)	0.25
BBB	94 (6.7)	29 (7.9)	65 (6.2)	0.27
Smoking	244 (17.3)	62 (16.9)	182 (17.6)	0.87
Alcohol	75 (5.3)	20 (5.5)	55 (5.3)	0.89
LAD (mm)	36.9 ± 5.3	39.5 ± 5.9	36.0 ± 4.8	<0.01
EF	64.7 ± 6.1	63.0 ± 7.4	65.3 ± 5.5	<0.01
eGFR (mL/min/1.73 m^2)	83.8 ± 6.1	73.3 ± 24.0	87.4 ± 25.6	<0.01
BNP (pg/mL)	319.5 ± 465.0	783.5 ± 637.3	158.4 ± 223.1	<0.01
hsCRP (mg/dL)	2.3 ± 3.7	4.5 ± 4.9	1.5 ± 2.9	<0.01
BMI (kg/m^2)	25.5 ± 3.3	24.8 ± 3.6	24.4 ± 3.1	0.05

NPAF: AADs failed, refractory to anti-arrhythmic drug; AF history, refers time that AF has been diagnosed; BBB, bundle branch block; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; Cryoballoon, cryoballoon ablation; CRP, C reactive protein; CTI, cavo-tricuspid isthmus ablation; CFAE, complex fractionated atrial electrogram ablation; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ECV, electrical cardioversion; ER, early recurrence; EF, ejection fraction; FU, follow up period; eGFR, estimated glomerular filtration rate; HF, history of congestive heart failure; LAD, left atrial diameter; Linear, linear ablation; Pharm CV, pharmaceutical cardioversion; PVI, pulmonary vein isolation; TIA, transient ischemic attack; SCVI, superior vena cava ablation; ST, with smart touch ablation catheter.

Chi-square test and independent *t* test. *Statistically significant $P < 0.05$.

Variables are n (%) or mean ± SD.

2.5 | Statistical analysis

All continuous variables were presented as mean ± standard deviation and categorical variables were summarized as percentages. The area under ROC curve (AUC) was used to test the predictive probability of biomarkers or their combination for AF recurrence. Cut-off analyses were also performed with specificity and sensitivity calculated. ANOVA or Chi-square tests were used to test the differences in continuous or categorical variables among four groups with none, 1, 2, or 3 abnormal biomarkers. The association of the clinical variables with AF recurrence was analyzed using univariate and multivariate Cox regression models. Cox proportional-hazards models with time-dependent covariates for changing biomarker combination and AF recurrence was built to evaluate the independent effect of different biomarker combination on outcomes.

Kaplan-Meier analysis was used to test the difference of time-dependent outcome in patients between four groups patients with different biomarker combination. Log rank tendency test was used to compare the Kaplan-Meier curve. A two-sided *P* value of <0.05 was considered statistically significant. All the analyses were performed using the SPSS software version 16.0 (IBM Corporation, Armonk, NY, USA) and statistical software R version 3.0.2 (R Core Team, 2013).

TABLE 2 Multivariate analysis of risk factors for AF recurrence post ablation

Risk factors	Hazard ratio (95% CI)	*P* value*
Age	0.97 (0.96-0.98)	<0.01
NPAF	1.59 (1.26-2.01)	<0.01
ER	3.12 (2.48-3.93)	<0.01
CAD	1.46 (1.03-2.07)	<0.01
LAD (mm)	1.04 (1.02-1.06)	<0.01
eGFR (mL/min/1.73 m^2)	0.96 (0.95-0.97)	<0.01
BNP (pg/mL)	1.00 (1.00-1.001)	<0.01
hsCRP (mg/dL)	1.06 (1.04-1.08)	<0.01

ER, early recurrence; CHF, history of congestive heart failure; LAD, left atrial diameter; eGFR, estimated glomerular filtration rate; BMI, body mass index); CI, confidence interval.
Multivariate Cox Regression analysis; *Statistically significant $P < 0.05$.
Adjusted for gender, alcohol consumption, smoking, presence of COPD, heart failure, hypertension, diabetes mellitus, stroke/transient ischemic attack, and body mass index.

3 | RESULTS

We included 1410 patients (mean age 57.2 ± 11.6 years; 68%) male, of which 1089 (77.2%) had PAF. Radiofrequency CA and cryoballoon ablation were performed in 1336 and 74 patients respectively. Mean follow-up period was 20.7 ± 8.8 months. Recurrence occurred in 365 (27.9%) patients (18.6% PAF and 50.5% NPAF).

Clinical, biochemical, echocardiographic, and procedural characteristics of patients with AF recurrence or not are summarized in Table 1. Patients with AF recurrence were older and had larger left atrial size, much more cardiac diseases or stroke, much more additional ablation, higher serum BNP and CRP, lower eGFR compared to those without recurrence (all $P < 0.05$).

3.1 | Biomarkers and AF recurrence

Based on differences seen on the univariate comparisons in Table 1, multivariate regression analysis using the variables that were

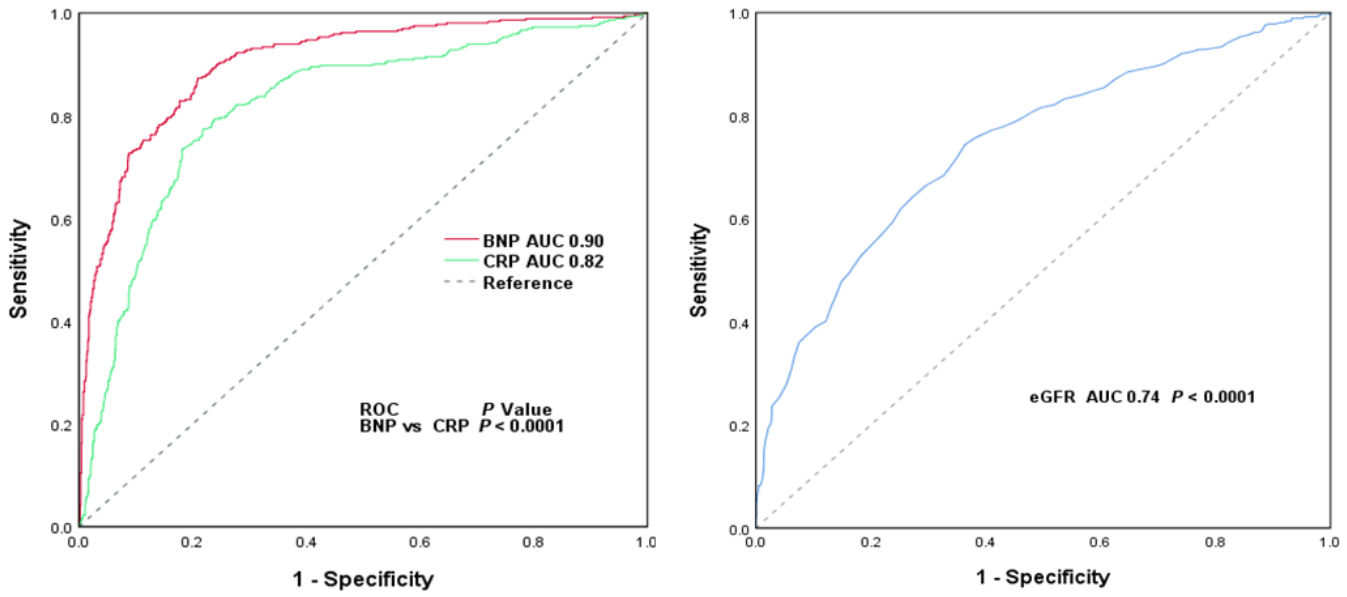

FIGURE 1 Receiver operating curve analysis of serum BNP, CRP, and eGRF. AUC, area under curve; ROC, receiver operating characteristic; eGFR, estimate glomerular filtration rate; BNP, B type brain natriuretic peptide; CRP, C reactive protein

significant found only that age, AF types, prior history of coronary artery disease (CAD), LAD, early recurrence (ER), BNP, and CRP emerged as independent risk factors of AF recurrence, as was low eGFR (see Table 2).

Using ROC analysis for biomarkers as continuous variables, good predictive ability for AF recurrence was evident for eGFR (AUC 0.74, CI 0.71-0.77, $P < 0.001$), CRP (AUC 0.82, CI 0.79-0.85, $P < 0.001$) and BNP (AUC 0.90, CI 0.88-0.92, $P < 0.001$) (Figure 1). Cut-off analyses gave eGFR, CRP, and BNP values of 82.5 mL/min/1.73 m^2 (specificity 64%, sensitivity 74%), 1.6 mg/dL (specificity 76%, sensitivity 79%), and 237.45 pg/mL (specificity 79%, sensitivity 87%), respectively, as biomarker levels that were predictive of AF recurrence.

Using these cut-off values to categorize normal or abnormal values, covariate regression analysis gave hazard ratios for eGFR (HR 2.07, CI 1.63-2.65, $P = 0.001$), CRP (HR 3.04, CI 2.32-3.99, $P = 0.001$), and BNP (HR 7.0, CI 5.05-9.72, $P = 0.001$) as independent predictors for AF recurrence (see Table 3). ROC analysis demonstrated good predictive ability of the categorized "cut-off values" of eGFR, CRP, and BNP, with AUCs of 0.69 (CI 0.66-0.72), 0.78 (CI 0.75-0.81), and 0.83 (CI 0.81-0.86) respectively (all $P < 0.001$; Figure 2).

3.2 | Predictive value for AF recurrence by combining multiple biomarkers

As the biomarker with the largest AUC, the cut-off of BNP was then combined with other biomarkers. The AUCs of BNP alone, BNP plus eGFR, then BNP plus eGFR, and CRP were 0.83 (CI 0.81-0.86), 0.85 (CI 0.83-0.88), and 0.90 (CI 0.88-0.92), respectively, with differences that were significant ($P < 0.001$, Delong's method) (see Figure 3).

We scored patients as having 0, 1, 2, and 3 points for those with none, 1, 2, or 3 abnormal biomarker levels. With increasing points, patients had corresponding increases in AF recurrence events (trend $P < 0.001$), ER events (trend $P < 0.001$) and left atrial size (trend $P < 0.001$) (see Table 4). History of various cardiovascular comorbidities (trend, $P < 0.001$) also increased with increasing points. Increasing points were associated with more pharmacological or electricial cardioversion, as well as linear or complex fractionated atrial electrograms (CFAE) ablation (all $P < 0.001$; see Table 4).

TABLE 3 Cut-off value of biomarkers and their predictive value for AF recurrence under multivariate analysis

Risk factors	Hazard ratio (95% CI)	*P* value*
Gender	0.80 (0.64-1.00)	0.046
ER	2.80 (2.25-3.49)	<0.01
eGFR ≤ 82.5 mL/min/1.73 m^2	2.07 (1.63-2.65)	<0.01
BNP ≥ 237.45 pg/mL	7.00 (5.05-9.72)	<0.01
hsCRP ≥ 1.6 mg/dL	3.04 (2.32-3.99)	<0.01

ER, early recurrence; eGFR, estimated glomerular filtration rate; BNP, B type brain natriuretic peptide; CRP, C reactive protein); CI, confidence interval.
Multivariate Cox Regression analysis; *Statistically significant $P < 0.05$.
Adjusted for age, nonparoxysmal AF, alcohol consumption, smoking, presence of COPD, coronary artery disease, heart failure, hypertension, diabetes mellitus, stroke/transient ischemic attack and body mass index.

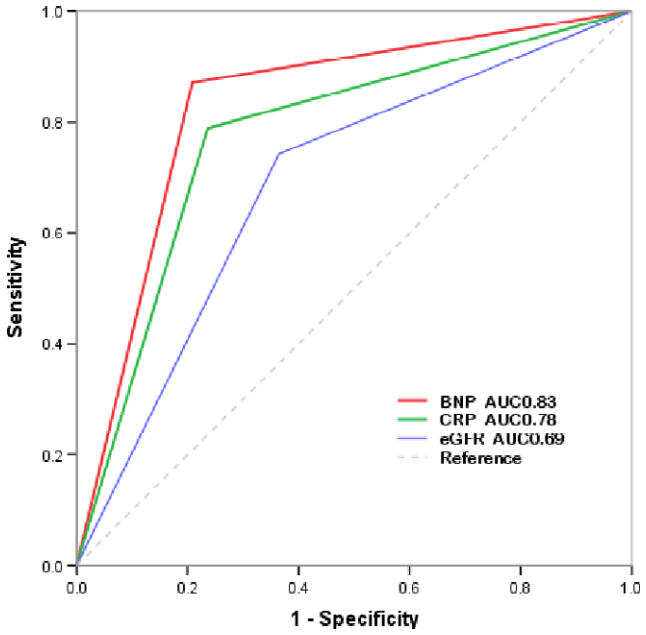

FIGURE 2 Area under curve of BNP, CRP, and eGFR (using cut-off value). AUC, area under curve; ROC, receiver operating characteristic; eGFR, estimate glomerular filtration rate; BNP, B type brain natriuretic peptide; CRP, C reactive protein

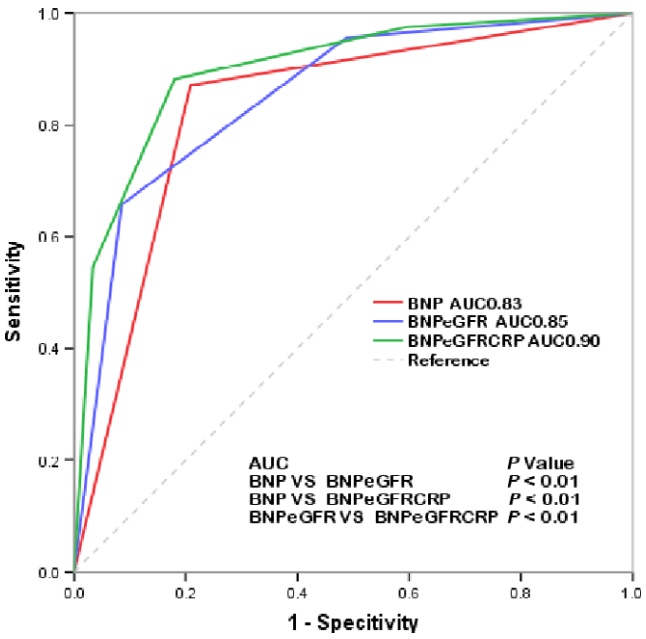

FIGURE 3 Area under curve of combining biomarkers and comparison. AUC, area under curve; ROC, receiver operating characteristic; eGFR, estimate glomerular filtration rate; BNP, B type brain natriuretic peptide; CRP, C reactive protein. BNPeGFR = BNP plus eGFR; BNPeGFRCRP = BNP plus eGFR plus CRP

When adjusted by gender, age, history of prior stroke/TIA, heart failure, coronary artery disease, hypertension, diabetes mellitus, nonparoxysmal AF, early recurrence, left atrial diameter, and body mass index, multivariate Cox regression analysis showed that patients with two or three abnormal biomarkers had rapid increasing risk of AF recurrence (all $P < 0.01$) when compared to those without abnormal biomarkers (see Table 5). Using multivariate analysis, patients without abnormal biomarkers had a lower risk of AF recurrence ($P < 0.01$) with no statistically significant association in those with only one abnormal biomarker ($P > 0.05$). Apart from two or multiple abnormal biomarkers, those patients at younger age, with large left atrial diameter and early recurrence were independent predictors of AF recurrence on multivariate analysis ($P < 0.05$). Nonparoxysmal AF was not an independent predictor using multivariate analysis ($P > 0.05$).

Kaplan-Meier analysis demonstrated that the sinus rhythm maintenance rate decreased sharply with increasing "abnormal biomarker" points while the risk of AF recurrence increased (see Figure 4). Similar findings were evident in the subgroups of patients with paroxysmal or nonparoxysmal AF, where increasing "abnormal biomarker" points were related to more AF recurrence (see Figures 5, 6).

4 | DISCUSSION

In this study, of the impact on arrhythmia outcome by using three biomarkers our main findings are as follows: (a) eGFR, CRP, and BNP were independent predictors of AF relapse post CA; and (b) Biomarkers had accumulative predictive effect when used in combination. Thus, measurement of multiple biomarkers, including BNP,

TABLE 4 Characteristics of patients with or without accumulated numbers (given as points) of abnormal biomarkers

Characteristics	Total	Group 1 (0 point)[a]	Group 2 (1 point)[a]	Group 3 (2 points)[a]	Group 4 (3 points)[a]	*P* value*
n (%)	1410 (100)	431 (30.5)	469 (33.3)	276 (19.6)	234 (16.6)	
Recurrence	364 (25.8)	9 (2.1)	34 (7.2)	123 (44.6)	199 (85)[b]	<0.01
Age (y)	57.3 ± 11.5	53.9 ± 12.4	58.1 ± 11.1	57.6 ± 11.6	61.1 ± 9.8	<0.01
LAD (mm)	36.9 ± 5.3	34.9 ± 4.7	36.5 ± 4.8	38 ± 5.5	39.8 ± 5.6[b]	<0.01
BMI (kg/m^2)	24.5 ± 3.3	24.2 ± 3.3	24.7 ± 3.0	24.4 ± 3.1	24.9 ± 3.7	<0.01
EF (%)	64.7 ± 6.1	65.1 ± 6.2	64.6 ± 6.0	63.3 ± 6.5	63.9 ± 6.5	0.031
Fu (mo)	20.7 ± 8.8	23.9 ± 6.2	23.4 ± 7.0	18.1 ± 9.3	12.4 ± 9.1	<0.01
Male	960 (68.1)	300 (69.6)	322 (68.7)	189 (68.5)	149 (63.7)	0.45
NPAF	320 (22.7)	53 (12.3)	80 (17.1)	83 (30.1)	105 (44.9)[b]	<0.01
COPD	9 (0.6)	0	4 (0.9)	2 (0.7)	3 (1.2)	0.20
HF	71 (5)	7 (1.6)	14 (3)	24 (8.7)	26 (11.1)[b]	<0.01
Hyperternsion	508 (36.1)	113 (26.2)	179 (38.2)	105 (38)	111 (47.4)	<0.01
DM	143 (10.1)	30 (7)	67 (14.3)	25 (9.1)	21 (9)	<0.01
Stroke/TIA	84 (6)	19 (4.4)	21 (4.5)	16 (5.8)	28 (12)	<0.01
CAD	105 (7.4)	17 (3.9)	32 (6.8)	29 (10.5)	27 (11.5)[b]	<0.01
Cryoballoon	74 (5.2)	18 (4.2)	31 (6.6)	8 (2.9)	17 (7.3)	0.05
ECV	157 (11.1)	25 (5.8)	33 (7.0)	39 (14.1)	60 (25.6)[b]	<0.01
ER	317 (22.5)	49 (11.4)	69 (14.7)	81 (29.3)	123 (52.6)[b]	<0.01
PVI	1391 (98.7)	426 (98.8)	464 (98.9)	271 (98.2)	233 (99.6)	0.28
Linear	266 (18.9)	54 (12.5)	60 (12.8)	70 (25.4)	82 (35)[b]	<0.01
CFAE	35 (2.5)	4 (0.9)	7 (1.5)	11 (4)	13 (5.6)[b]	<0.01
CTI	337 (23.9)	90 (20.9)	91 (19.4)	76 (27.5)	80 (34.2)[b]	<0.01
SCVI	87 (6.2)	28 (6.5)	31 (6.6)	14 (5.1)	14 (6.0)	0.85
Pharm CV	221 (15.7)	45 (10.4)	59 (12.6)	56 (20.3)	61 (26.1)[b]	<0.01

BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; Cryoballoon, cryoballoon ablation; CRP, C reactive protein; CTI, cavo-tricuspid isthmus ablation; CFAE, complex fractionated atrial electrogram ablation; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ECV, electrical cardioversion; ER, early recurrence; EF, ejection fraction; FU, follow up period; eGFR, estimated glomerular filtration rate; HF, history of congestive heart failure; LAD, left atrial diameter; Linear, linear ablation; NPAF, non-paroxysmal atrial fibrillation; Pharm CV, pharmaceutical cardioversion; PVI, pulmonary vein isolation; Re, recurrence; TIA, transient ischemic attack; SCVI, superior vena cava ablation.

Variables are n (%) or mean ± SD; Chi-square test and ANOVA test; *Statistically significant $P < 0.05$.

[a]Group 1, no abnormal biomarkers (0 point); Group 2, one abnormal biomarker (1 point); Group 3, two abnormal biomarkers (2 points); Group 4, three abnormal biomarkers (3 points). Abnormal biomarker cut-offs, as defined in Table 3.

[b]Compared to other three groups.

TABLE 5 Multivariate analysis of combining biomarkers for AF recurrence

Categories	Adjusted HR (95% CI)	*P* value*
Group 1[a]	0.29 (0.14-0.60)	0.01
Group 3	6.70 (4.57-9.82)	<0.01
Group 4	14.09 (9.63-20.63)	<0.01
Age	0.99 (0.98-1.00)	0.046
LAD	1.02 (1.00-1.04)	0.018
ER	2.90 (2.33-3.61)	<0.01

HR, hazard ratio; Biomarkers (BNP, B type brain natriuretic peptide; CRP, C reactive protein; GFR, glomerular filtration rate); CI, confidence interval.
Multivariate Cox regression analysis; *Statistical significant, $P < 0.05$.
[a]Reference group; Group 1, no abnormal biomarkers (0 point); Group 2, one abnormal biomarker (1 point); Group 3, two abnormal biomarkers (2 points); Group 4, three abnormal biomarkers (3 points). Abnormal biomarker cut-offs, as defined in Table 3.
Adjusted for gender, body mass index, COPD, smoking, alcohol consumption, presence of coronary artery disease, heart failure, hypertension, diabetes mellitus, stroke, transient ischemic attack, and nonparoxysmal AF.

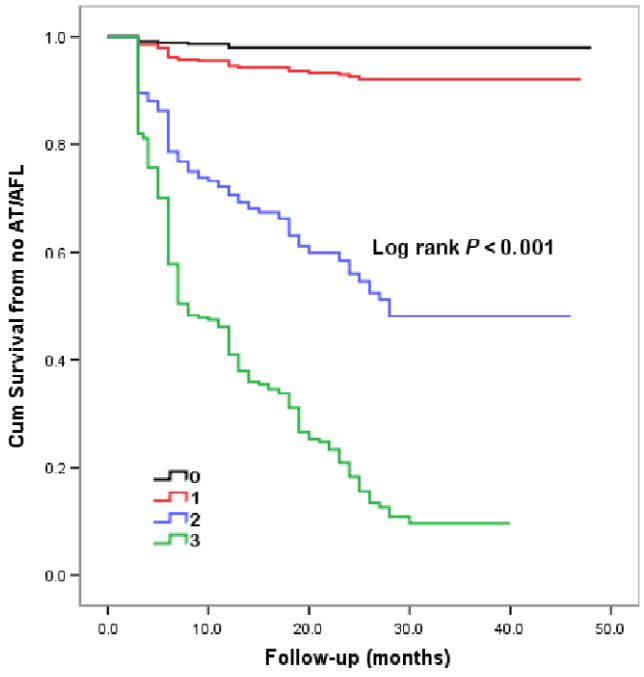

FIGURE 4 Kaplan-Meier curves of freedom from atrial tachyarrhythmias. Biomarker abnormal, serum BNP/CRP ≥ the cut-off value or eGFR ≤ the cut-off value; 0, Patients without biomarker abnormal; 1, Patients with any one biomarker abnormal; 2, Patients with any two biomarkers abnormal; 3, Patients with three biomarkers abnormal

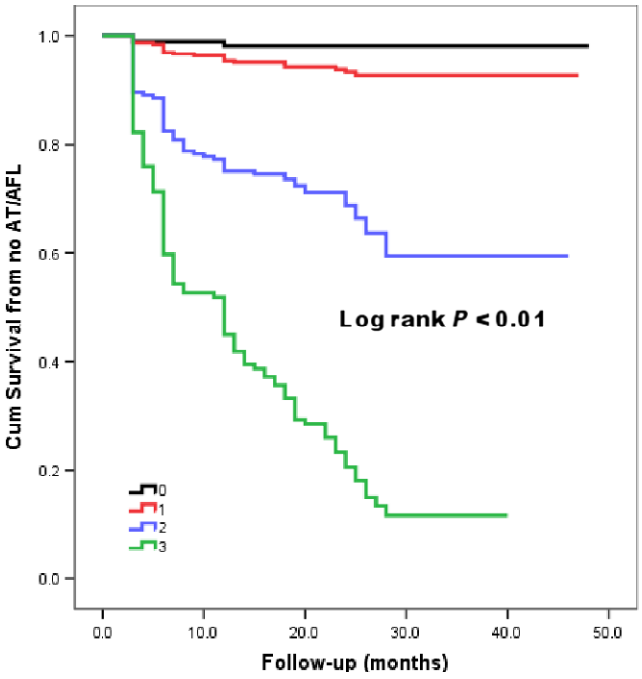

FIGURE 5 Kaplan-Meier curves of different sums of abnormal biomarkers in the PAF subgroup. (Footnote as Figure 4)

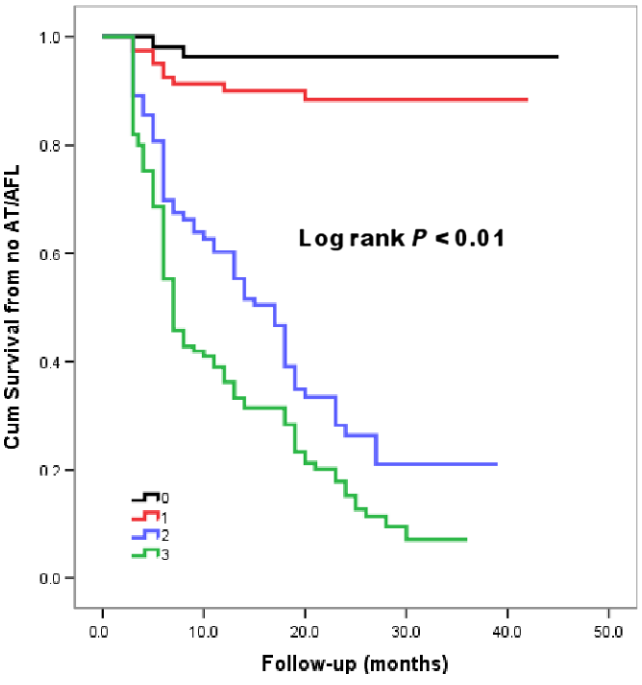

FIGURE 6 Kaplan-Meier curves of different sums of abnormal biomarkers in the NPAF subgroup. (Footnote as Figure 4)

CRP, and eGFR were incrementally additive to clinical risk factors in a cumulative manner to improve prediction of arrhythmia recurrence post-CA of AF. Similar findings were evident in the subgroups of patients with paroxysmal or nonparoxysmal AF, where increasing "abnormal biomarker" points were related to more AF recurrence.

4.1 | Biomarkers and catheter ablation outcome

Biomarkers especially inflammatory indices have been related to the AF relapse post CA. Many inflammatory factors, including CRP,[12,13] TNF-α, ET-1,[14] CD 36,[7] and heat shock protein,[15] as well as other

biomarkers of cardiac hemodynamic stress such as BNP[16] and oxidative stress markers[17] had been associated with AF recurrence.[18,19] A previous meta-analysis has shown that CRP was associated with higher risk of AF recurrence in patients underwent catheter ablation.[20]

BNP is elevated in AF patients with increased atrial pressure,[4] and has been related to AF recurrence post CA.[19,21] Serum BNP was found to be elevated preablation and declined postablation in patients with persistent AF, and BNP was reported as independent predictor of AF recurrence in the study.[22] Similarly, CKD as diagnosed by decreased eGFR has been related to AF recurrence post CA.[8,23] In our analysis, we found that serum BNP and CRP significantly elevated and eGFR decreased in patients with AF recurrence. Meanwhile, using multivariate analysis with a Cox hazard model, high cut-off values of BNP (≥237.45 pg/mL), CRP (≥1.6 mg/dL), and eGFR (≤82.5 mL/min/1.73 m^2) were all independent predictors for AF recurrence of our cohort. Although all three biomarkers were individual predictors, the present study also shows how these biomarkers are additive *in combination*, for predicting AF recurrence post-CA.

To evaluate the additive predictive ability in combination of BNP, CRP, and eGFR, we also scored patients when they had one or more "abnormal" biomarkers. Patients with different points presented numbers of "abnormal" biomarkers and the association of the points and the AF recurrence illustrates the additive predictive ability of biomarkers in combination. The cut-off value of biomarker was used to divide serum level as "normal" or "abnormal" in our study population, and we recognize that a local laboratory "abnormal cut-off value" could be different based on different cohorts. For example, in our cohort, BNP ≥ 237.45 pg/mL was defined as "abnormal", while in another study cohort, "abnormal" BNP was defined as ≥ 423.20 pg/mL.[4]

4.2 | Cumulative predictive impact of combing biomarkers

Several clinical scores are combination of several risk factors used to predict arrhythmia outcome of patients with AF post CA.[3] Many clinical risk factors were included in these scores but only the ALARMEc[24] and APPLE[9] score, which included eGFR as one of the risk factors. Indeed, Shaikh et al included BNP ≥ 100 pg/mL as an additional biomarker predictor added to the $CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2 and HATCH scores and reported significantly improved the predictive probability of these clinical scores for arrhythmia recurrence post CA in patients with AF.[25]

In this study, patients undergoing CA had increasing risk of AF recurrence when quantity of abnormal biomarkers was increased. Patients with more abnormal biomarkers required more additional ablation or cardioversion during the procedure which perhaps implies the presence of a more complicated AF substrate.

Our findings show that baseline biomarkers levels measured before an ablation procedure have good predictive value for AF recurrence postablation. Most clinical scores derived for predicting AF recurrence include important risk factor(s) for early recurrence, allows predict only following the ablation procedure; nevertheless, baseline biomarkers levels may be used as an alternative tool for estimation of the likelihood of AF recurrence, and help with patients selection.

4.3 | Limitations

This was a single centre, retrospective, and observational study. While patient follow-up was based on symptoms, 12 lead ECG and 24 hour Holter ECG examinations during follow-up visits, asymptomatic AF might still be missed. The follow-up period was limited, and patients undergoing multiple ablation procedures were not included. About 1% patients of this cohort had accepted ablation elsewhere before the enrolment which might also have implications for ablation outcomes, but our objective was to study a complete "real world" cohort of patients undergoing CA our centre—not to focus on selected subgroups which may be small and underpowered. We do recognize that recurrent risk factors of PAF and NPAF may be different as well as the impact of each biomarker(s) in combination in these separate subgroups. Nevertheless, we are clearly underpowered for detailed analyses of the PAF and NPAF subgroups separately, and our subgroup analyses in relation to recurrences with increasing "abnormal biomarker" points (Figures 5 and 6) should only be regarded as exploratory.

In conclusion, multiple biomarkers, including BNP, CRP, and eGFR are incrementally additive to clinical risk factors in a cumulative manner to improve prediction of arrhythmia recurrence post-CA of AF. The implications of poor arrhythmia outcome in AF patients with multiple abnormal biomarkers pre-CA procedure may help with patient selection and inform the likelihood of success or the need of more complicated CA procedure (s).

CONFLICTS OF INTEREST

GYHL has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, BoehringerIngelheim, Microlife, Roche, and Daiichi-Sankyo. Other authors: None declared.

AUTHOR CONTRIBUTION

HD performed the analysis and wrote the paper. AS and PG helped to perform the analysis. GYHL and YMX contributed to the idea and instruction of the paper. All authors gave comments of the paper and approved the final version.

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