PREVENTION   WILEY   CLINICAL CARDIOLOGY

CLINICAL INVESTIGATIONS

Stroke or left atrial thrombus prediction using antithrombin III and mean platelet volume in patients with nonvalvular atrial fibrillation

Seo-Won Choi[1] | Bo-Bae Kim[2] | Dong-Hyun Choi[2] | Geon Park[3,4] | Byung Chul Shin[2] | Heesang Song[5] | DongHun Kim[6] | Dong-Min Kim[2]

[1]Department of Cardiology, Gwangju Veterans Hospital, Gwangju, Republic of Korea

[2]Department of Internal Medicine, Chosun University School of Medicine, Gwangju, Republic of Korea

[3]Department of Laboratory Medicine, Chosun University School of Medicine, Gwangju, Republic of Korea

[4]Research Center for Resistant Cells, Chosun University School of Medicine, Gwangju, Republic of Korea

[5]Department of Biochemistry and Molecular Biology, Chosun University School of Medicine, Gwangju, Republic of Korea

[6]Department of Radiology, Chosun University School of Medicine, Gwangju, Republic of Korea

Correspondence
Dong-Hyun Choi, MD, College of Medicine, Chosun University, 375 Seo-suk dong, Dong-Gu, Gwangju 501-759, Republic of Korea
Email: dhchoi@chosun.ac.kr

Background: CHADS$_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke) and CHA$_2$DS$_2$-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age 65 to 74 years, sex category) scores showed just moderate discrimination ability in predicting thromboembolic complications in patients with nonvalvular atrial fibrillation (AF).

Hypothesis: To determine the association of antithrombin III (AT-III) deficiency and mean platelet volume (MPV) with the development of stroke or left atrial (LA) thrombus in patients with AF.

Methods: AT-III and MPV were analyzed in 352 patients with AF. The primary endpoint was a composite of ischemic stroke event and incidental LA thrombus.

Results: There were 50 events (14.2%) during a mean 35.4 months of follow-up. A significantly higher stroke or LA thrombus rate was observed in the low–AT-III group (<70%) than that in the high–AT-III group (≥70%). A significantly higher stroke or LA thrombus rate was observed in the high-MPV group (≥7.0 fL) than that in the low-MPV group (<7.0 fL). AF patients with an MPV ≥7.0 fL and AT-III deficiency had higher stroke or LA thrombus risk than those without an MPV ≥7.0 fL and AT-III deficiency. In the Cox proportional hazard analysis, high MPV was found to be an independent predictor of stroke or LA thrombus risk (hazard ratio: 6.408; 95% confidence interval: 2.874-14.286). Although AT-III deficiency was not an independent predictor of stroke or LA thrombus risk, a trend was observed.

Conclusions: High MPV and AT-III deficiency were predictive markers for stroke or LA thrombus. Their predictive power for stroke was independent of antiplatelet treatment, anticoagulation therapy, and a high CHA$_2$DS$_2$-VASc score in patients with AF.

KEYWORDS

Antithrombin III, Atrial Fibrillation, Left Atrial Thrombus, Mean Platelet Volume, Stroke

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common type of arrhythmia observed in clinical practice. It is associated with substantial morbidity and mortality from stroke events.[1,2] Currently, the risk for stroke and the indication for anticoagulant therapy in AF can be estimated using the CHADS$_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke) and CHA$_2$DS$_2$-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age 65 to 74 years, sex category) scores.[3] Left atrial (LA) thrombus is a risk factor for stroke in patients with AF. It has been estimated that at least two-thirds of the stroke events in patients with nonvalvular AF occur due to LA thrombus drop-off.[4]

Mean platelet volume (MPV), the most frequently used measure of platelet size, is a surrogate marker of platelet function and a potential link between thrombosis and inflammation.[5] It can be measured in an

inpatient or outpatient situation and is a low-cost examination. Bigger platelets are metabolically and enzymatically more active and have greater prothrombotic potential. In addition, evidence demonstrates that MPV is an independent predictor of the risk of stroke among individuals with a history of stroke or transient ischemic attacks and AF.[6–8]

Antithrombin-III (AT-III) is a naturally occurring anticoagulant protein that plays a key role in controlling thrombus development and spread.[9] AT-III is produced by the endothelium of blood vessels and in the liver, which have linking sites for heparin and thrombin. Once thrombin is produced, it links with AT-III and forms thrombin-AT III complex, which impedes thrombosis.[10] AT-III deficiency is associated with hypercoagulability, causing deep vein thrombosis and pulmonary embolism.[11] However, the association of AT-III deficiency and MPV with the development of an ischemic stroke event and incidental LA thrombus in patients with AF has not been investigated.

The aim of this study was to determine the association of AT-III deficiency and MPV with the development of ischemic stroke event and incidental LA thrombus in patients with AF.

2 | METHODS

2.1 | Study population

A total of 352 consecutive patients with AF who underwent measurements of AT-III activity and MPV between September 2009 and October 2014 were included in this study. This study was approved by the Chosun University Hospital Research Ethics Committee (CHOSUN 2014-09-011). The primary endpoint was a composite of ischemic stroke event and incidental LA thrombus.

2.2 | Blood collection and biomarker measurements

Venous blood samples were collected in K2-EDTA tubes (Becton Dickinson, Franklin Lakes, NJ). MPV was analyzed using an Advia 2120 hematology analyzer (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany) within 2 hours of sample collection. AT-III activity was measured using a HemosIL Liquid Antithrombin kit (Instrumen tation Laboratory, Bedford, MA). According to the manufacturer's recommendations, the normal range of AT-III activity is 83% to 128%. Because the risk of certain hypercoagulability disorders, such as venous thromboembolism, is generally documented in patients with an AT-III level of <70%,[12] we stratified our study population as follows: low–AT-III group (<70%) and high–AT-III group (≥70%).

2.3 | Calculation of CHA$_2$DS$_2$-VASc score

We calculated the CHA$_2$DS$_2$-VASc score as follows: 2 points were assigned for a history of stroke or transient ischemic attack, or age ≥ 75 years; 1 point was assigned for age 65 to 74 years, history of hypertension, diabetes mellitus, recent cardiac failure, vascular disease, and female sex.[3] A patient was considered to have diabetes if it was reported by a physician, or the fasting blood glucose level was ≥126 mg/dL, or the patient was on antidiabetic medication. Hypertension was confirmed if the systolic blood pressure was ≥140 mm Hg, diastolic blood pressure was ≥90 mm Hg, or the patient was on

antihypertensive medication. The presence of heart failure and history of stroke/transient ischemic attack was determined from the patients' medical records.

2.4 | Detection of LA thrombus

Incidental LA thrombus was defined as a circumscribed homogeneous mass with a nonmyocardial texture, which was detected by transesophageal echocardiography (TEE) or multidetector computed tomography (MDCT). TEE was performed using an iE33 system with a multiplane 5 MHz probe (Philips Medical Systems, Bothell, WA) or a VIVID E9 echocardiography system (GE Medical Systems, Horten, Norway). In computed tomography (CT), LA thrombus appears as a nonenhanced, well-circumscribed nodule with irregular margins. For detecting LA thrombus, 16- (Sensation 16, Siemens Medical Systems, Erlangen, Germany), 128- (Ingenuity CT; Philips Healthcare, Best, the Netherlands), and 640-slice CT (Aquilion One; Toshiba Medical Systems Corporation, Otawara, Japan) scanners were used. Figure 1 demonstrates a representative TEE 2-dimensional image and an MDCT image of an LA thrombus.

2.5 | Outcomes

Clinical follow-up data were obtained from outpatient medical records or telephone interviews. The primary endpoint analyzed was a composite of ischemic stroke event and incidental LA thrombus.

2.6 | Statistical analysis

All values are expressed as the mean ± standard deviation/median (interquartile range [IQR]) or as a number (percentage). The baseline characteristics of the groups were compared using the Student t test for continuous variables and the χ^2 statistic for noncontinuous variables.

The primary endpoint-free survival according to AT-III activity and MPV was estimated using the Kaplan–Meier method, and the outcomes were compared using the log-rank test. Cox proportional hazards regression was used for the calculation of independent predictors of the primary endpoint. We entered into a forward stepwise multivariate Cox proportional hazards model aspirin therapy, warfarin therapy, CHA$_2$DS$_2$-VASc score, AT-III, and MPV. Receiver operating characteristic (ROC) analysis was performed for determination of sensitivity and specificity with 95% confidence interval (CI) for the MPV at cutoff values. The Statistical Package for the Social Sciences software version 12.0 (IBM, Armonk, NY) was used to perform all statistical analyses, and $P < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Primary endpoint MPV cutoff value

Median MPV for the overall study population was 7.0 fL (IQR, 6.6–7.6 fL; normal range, 7.2–11.1 fL). The cutoff value for MPV level predictive of the primary endpoint was evaluated using ROC analysis. When the MPV cutoff level was set to 7.0 fL using the ROC curve, the sensitivity was 84.0% (95% CI: 70.9-92.8) and specificity was 59.5%
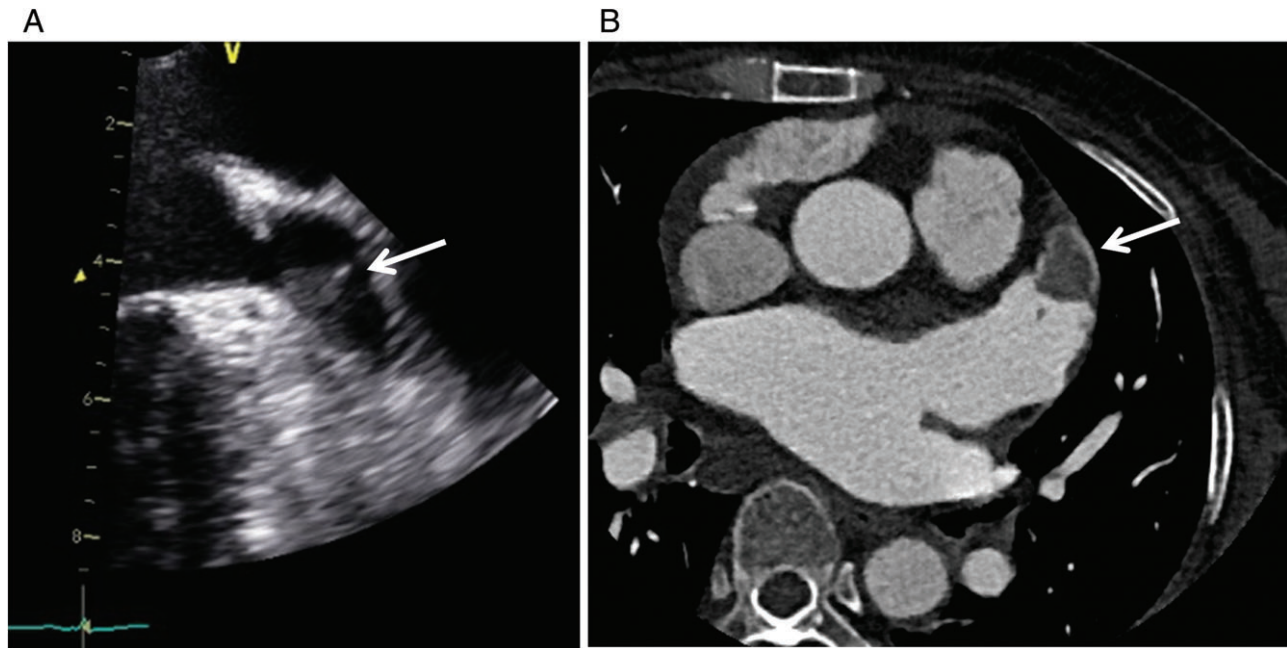
FIGURE 1 (A) A 51-year-old male with an LAA thrombus (arrow) detected by transesophageal echocardiography. (B) A 63-year-old female with an LAA thrombus. A thoracic axial MDCT scan shows a well-demarcated thrombus without enhancement within the tip of the LAA (arrow). Abbreviations: LAA, left atrial appendage; MDCT, multidetector computed tomography

(95% CI: 53.7-65.1) for differentiating between the groups with and without the primary endpoint (area under the curve = 0.800, $P < 0.001$).

3.2 | Clinical characteristics

The mean MPV and AT-III activity for the overall study population were 7.3 ± 1.1 fL (median, 7.0 fL; IQR 6.6–7.6 fL; normal range, 7.2–11.1 fL) and $88.7\% \pm 17.4\%$ (median, 91.0%; IQR, 78.3–101.0;

normal range > 80%), respectively. The baseline clinical characteristics according to the cutoff value for MPV are shown in Table 1. Overall clinical characteristics, except AT-III activity, were generally comparable between the 2 groups. The CHA_2DS_2-VASc score was also similar between the 2 groups.

Majority of the patients used >1 antithrombotic agent. Aspirin was the most frequently prescribed antithrombotic agent, followed by warfarin and clopidogrel.

TABLE 1 Baseline characteristics and medication data on the basis of treatment strategy of atrial fibrillation

Characteristic	Total (N = 352)	MPV <7 fL (N = 168)	MPV ≥7 fL (N = 184)	P Value
Age, y	68.4 ± 12.1	68.3 ± 12.1	68.5 ± 12.2	0.860
Female sex (%)	42.6	42.3	42.9	0.899
Hypertension (%)	50.9	52.4	49.5	0.584
Diabetes (%)	19.0	17.3	20.7	0.418
Antithrombin III activity (%)	88.7 ± 17.4	90.7 ± 17.0	87.0 ± 17.7	0.045
Antithrombin III <70% (%)	13.1	11.3	14.7	0.350
Mean platelet volume (fL)	7.25 ± 1.00	6.53 ± 0.30	7.92 ± 0.94	<0.001
LVEF (%)	55.4 ± 12.4	56.0 ± 11.6	54.9 ± 13.0	0.391
LVEF <35% (%)	7.7	5.4	9.8	0.119
Previous stroke or TIA (%)	4.5	5.4	3.8	0.485
Vascular disease history (%)	6.5	4.8	8.2	0.199
Any antithrombotic agents (%)	87.2	85.7	88.6	0.420
Aspirin (%)	48.9	47.0	50.5	0.509
$P2Y_{12}$ inhibitor (%)	10.2	9.5	10.9	0.677
Dual antiplatelet therapy (%)	9.7	8.3	10.9	0.421
Warfarin (%)	44.6	44.0	45.1	0.841
CHA_2DS_2-VASc score	2.3 ± 1.6	2.3 ± 1.6	2.4 ± 1.6	0.531
High (score ≥ 2, %)	63.1	60.1	65.8	0.273
Follow-up duration (d)	1063 ± 756	1130 ± 757	1002 ± 752	0.113

Abbreviations: CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age 65 to 74 years, sex category; LVEF, left ventricular ejection fraction; MPV, mean platelet volume; TIA, transient ischemic attack.

3.3 | Correlation between MPV and AT-III activities

There was a weak and negative correlation between MPV and AT-III activity ($r = -0.135$, $P = 0.011$). The mean AT-III activity was lower in participants with a high MPV than in those with a low MPV (87.0 vs 90.7%, $P = 0.045$). The mean MPV tended to be higher in participants with lower AT-III activity than in those with higher AT-III activity (7.52 vs 7.21, $P = 0.055$).

3.4 | Primary endpoint-free survival: AT-III activity

During a mean follow-up period of 35.4 months, 50 patients (14.2%) experienced the primary endpoint (32 had ischemic stroke events, 16 had incidental LA thrombus, and 2 had both).

The Kaplan–Meier primary endpoint-free survival curves of the patients according to AT-III activity are shown in Figure 2A (<70% [46 patients] and ≥70% [306 patients]. The primary endpoint rates showed a significant increase in the low–AT-III activity group. Log-rank analysis showed a significant association between low AT-III activity and the primary endpoint (23.9% vs 12.7%, log-rank: $P = 0.0287$).
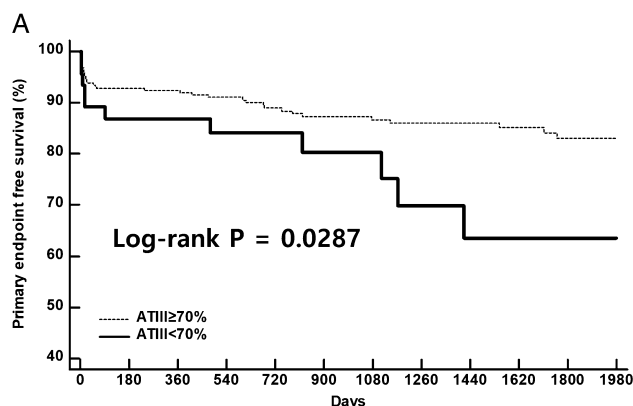
3.5 | Primary endpoint-free survival: MPV

The patients were stratified into 2 groups based on the cutoff values of baseline MPV as <7.0 fL (168 patients) and ≥7.0 fL (184 patients).

The Kaplan–Meier primary endpoint-free survival curves of the patients according to MPV are shown in Figure 2B. The primary endpoint rates showed a significant increase in the high-MPV group. Log-rank analysis showed a significant association between MPV and the primary endpoint (23.4% vs 4.2%, log-rank: $P < 0.0001$). This value was more useful in patients with a high AT-III level (Figure 2C,D).
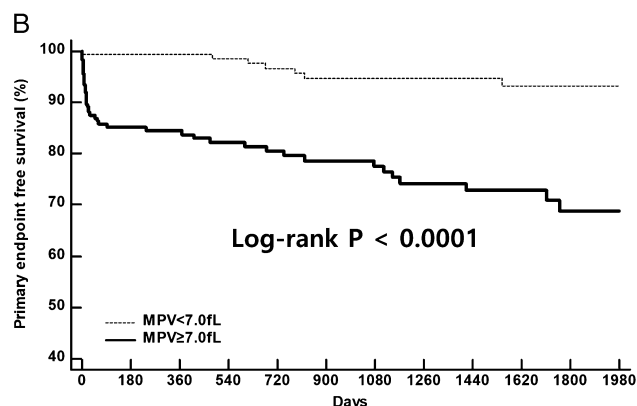
3.6 | Independent predictors of primary endpoint

In multivariable analysis, after adjustment for aspirin therapy, warfarin therapy, CHA_2DS_2-VASc score, AT-III, and MPV, MPV was an independent risk factor of the primary endpoint (hazard ratio: 6.41, 95% CI: 2.87-14.29, $P < 0.0001$) (Table 2). Even though low AT-III activity was not a significant independent risk factor of the primary endpoint, it showed a trend toward an increased risk for the primary endpoint (hazard ratio: 1.84, 95% CI: 0.93-3.65, $P = 0.078$) (Table 2).
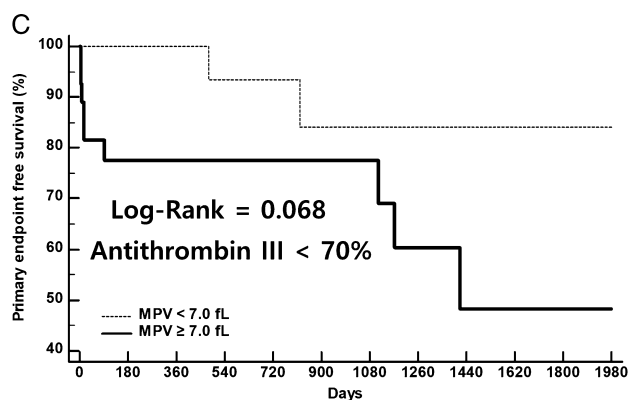

FIGURE 2 Primary endpoint-free survival according to (A) ATIII activity and (B) MPV. (C, D) Primary endpoint-free survival according to MPV based on ATIII activity. Abbreviations: ATIII, antithrombin III; MPV, mean platelet volume

TABLE 2 Multivariate Cox proportional hazard analyses determining the significant and independent predictors for the primary endpoint

Factor	HR (95% CI)	P Value
Aspirin therapy	0.95 (0.46-1.96)	0.880
Warfarin therapy	1.04 (0.50-2.16)	0.910
CHA$_2$DS$_2$-VASc score ≥ 2	1.11 (0.61-2.03)	0.725
Antithrombin III <70%	1.84 (0.93-3.65)	0.078
Mean platelet volume ≥ 7.0 fL	6.41 (2.87-14.29)	<0.001

Abbreviations: CHA$_2$DS$_2$-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age 65 to 74 years, sex category; CI, confidence interval; HR, hazard ratio.

3.7 | Combined effect of AT-III and MPV

A combined analysis of primary endpoint according to both AT-III and MPV using the Kaplan–Meier event-free survival curve is shown in Figure 3. It demonstrated an exaggerated primary endpoint risk in the combined low–AT-III activity and high-MPV group.

4 | DISCUSSION

The main findings of the current observational study showed that high MPV and AT-III deficiency were predictive markers for stroke or LA thrombus in patients with AF, and their predictive power for these events was independent of antiplatelet treatment, anticoagulation therapy, and high CHA$_2$DS$_2$-VASc score. Although AT-III deficiency is a modest predictor of stroke or LA thrombus, it might help to stratify the risk of these events in patients with AF. In our analysis, this relationship between MPV and the primary endpoint appeared to be more obvious in patients of the high–AT-III group. Furthermore, stroke or LA thrombus risk was exaggerated in AF patients with an MPV of ≥7.0 fL and AT-III deficiency compared to those with a low-MPV and high–AT-III level.

Many studies have reported regarding the association between MPV levels and stroke[6,13–15] or LA stasis,[16] especially in patients with AF.[7,17–19] Moreover, some investigations have demonstrated the controversial relationship between AT-III and stroke.[20,21] However, the association of AT-III deficiency and MPV with the development

of ischemic stroke event and incidental LA thrombus in patients with AF has not been investigated. To the best of our knowledge, this is the first study to investigate the long-term (mean follow-up period of 3 years, with a maximum of 5.9 years) impact of AT-III deficiency and MPV level on the occurrence of stroke or LA thrombus in patients with AF.

Although the prevalence of AT-III deficiency is 0.02% to 0.17% in a healthy population and 1.1% in patients with venous thromboembolism,[22,23] AT-III deficiency has been recognized as an important thrombophilic condition and is an established risk factor mainly for venous thromboembolism.[24–27] In fact, there were no precise data about the prevalence of AT-III deficiency in patients with AF. In this cohort, however, the prevalence of AT-III deficiency in patients with AF was estimated to be somewhat high (13.1%). This finding needs to be validated by further studies.

Our data have some significant clinical implications in several important aspects. Systemic thromboembolism is a serious problem in patients with AF.[28] In the preceding years, numerous forms of risk stratification methods, such as the CHADS$_2$ and CHA$_2$DS$_2$-VASc scores, have been used for predicting the risk of embolic events in AF patients.[3,29] However, in several studies, the CHADS$_2$ and CHA$_2$DS$_2$-VASc scores showed just moderate discrimination ability in predicting thromboembolic complications.[2,30,31] In this study, the CHA$_2$DS$_2$-VASc score was not an independent risk predictor of ischemic stroke or LA thrombus. In addition, 16 patients with low CHA$_2$DS$_2$-VASc scores had ischemic stroke or incidental LA thrombus during follow-up in this study. The risk of ischemic stroke and LA thrombus in patients with low CHA$_2$DS$_2$-VASc scores should not be underestimated. In our study, MPV and AT-III activity were independently predictive of the development of ischemic stroke or incidental LA thrombus in multivariate analysis after adjusting for the CHA$_2$DS$_2$-VASc scores. It seemed that high-MPV level and AT-III deficiency could potentially improve the CHA$_2$DS$_2$-VASc scores in predicting ischemic stroke or LA thrombus.

The gold and conventional standard for ruling out an LA thrombus is TEE; however, this is a somewhat invasive study, and there are several contraindications for this technique, such as esophageal bleeding or recent surgery.[32] Hence, an alternative examination procedure for detecting LA thrombus is required. MDCT is a potential alternative for the assessment of LA thrombus because appropriate temporal and spatial resolution can be attained with this method.[33–37] In addition, MDCT is a noninvasive modality, and can be applied to the head area for diagnosing stroke with an extended scan range. In most studies evaluating LA thrombus, TEE has been used for detecting LA thrombus.[16,38–40] In this cohort, however, MDCT was used for detecting LA thrombus in around 60% of the patients. This was another unique aspect of our investigation.

4.1 | Study limitations

The current investigation has some limitations, commonly stemming from its relatively small sample size. In addition, this study was not a prospective study, and the results and conclusions are subject to the limitations inherent in these forms of investigations. Due to our original inclusion criteria, which only included patients with AF who were
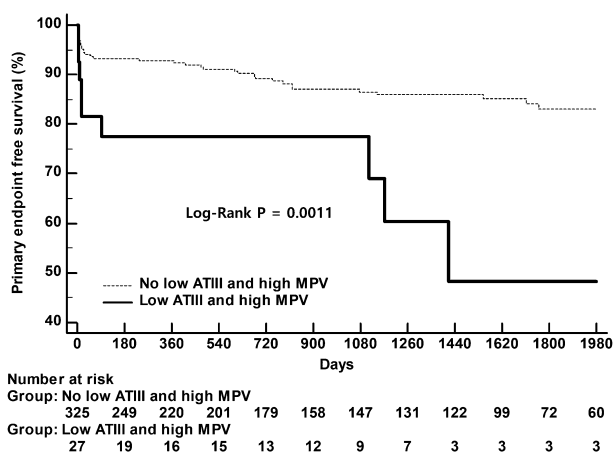
FIGURE 3 Primary endpoint-free survival according to a combination of ATIII activity and MPV. Abbreviations: ATIII, antithrombin III; MPV, mean platelet volume

evaluated for MPV and AT-III activity, selection bias was possible. This cohort had a small number of patients with AT-III deficiency. However, the prevalence of AT-III deficiency is very low. Thus, a relatively high proportion of patients with AT-III deficiency have been included in this study population.

5 | CONCLUSION

The results of this study demonstrated that high MPV and AT-III deficiency were predictive markers for stroke or LA thrombus. Their predictive power for stroke was independent of antiplatelet treatment, anticoagulation therapy, and high CHA_2DS_2-VASc score in patients with AF. It seemed that high MPV level and AT-III deficiency could potentially improve the ability of CHA_2DS_2-VASc scores in predicting ischemic stroke or LA thrombus.

Author contributions

Seo-Won Choi, MD, and Bo-Bae Kim, MD, contributed equally to the study. All authors had access to the data and played a role in writing this article.

Conflicts of interest

The authors declare no potential conflicts of interest.

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