ORIGINAL ARTICLE

A new risk model for the evaluation of the thromboembolic milieu in patients with atrial fibrillation: the PALSE score

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ABSTRACT

BACKGROUND   The evaluation of thromboembolic risk is the cornerstone of atrial fibrillation (AF) management. Thromboembolic risk is associated with the presence of left atrial (LA) thrombus and spontaneous echo contrast (SEC), namely the thromboembolic milieu.

AIMS   We aimed to assess the predictors of the thromboembolic milieu in terms of LA thrombus and / or SEC in patients with paroxysmal AF undergoing electrical cardioversion or catheter ablation, and to develop an effective risk model for detecting the thromboembolic milieu.

METHODS   We included a total of 434 patients with nonvalvular paroxysmal AF who underwent transesophageal echocardiography prior to cardioversion or catheter ablation.

RESULTS   In patients with the thromboembolic milieu, total protein and C-reactive protein levels, LA diameter, and systolic pulmonary artery pressure (SPAP) were higher, while left ventricular ejection fraction (LVEF) was lower than in patients without the thromboembolic milieu. In a multivariate logistic regression analysis, age, total protein levels, LVEF, LA diameter, and SPAP were independent predictors of LA thrombus and / or SEC. In a receiver operating characteristic curve analysis, the optimal cutoff values for the discrimination of patients with the thromboembolic milieu were as follows: 60 years for age; 7.3 mg/dl for total protein; 40% for LVEF; 40 mm for LA diameter; and 35 mm Hg for SPAP. Based on these cutoff values, we developed a novel risk model, namely, the PALSE score. The area under the curve for the PALSE score was 0.833. Patients with a PALSE score lower than 1 did not show thrombus or spontaneous echo contrast.

CONCLUSIONS   The PALSE score, which includes total protein levels, age, LA diameter, SPAP, and LVEF, seemed to accurately predict the presence of the thromboembolic milieu in patients with paroxysmal AF.

INTRODUCTION   Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, and its thromboembolic complications can cause significant morbidity and mortality.[1-3] Therefore, the evaluation of thromboembolic risk and the administration of anticoagulant therapy based on this risk are crucial.[4]

In AF patients, left atrial (LA) thrombus and spontaneous echo contrast (SEC), a swirling echo density in the LA and its appendage, constitute the primary cause of thromboembolism.[5,6] Together with LA thrombus, moderate or severe SEC forms the thromboembolic milieu.[7,8] Routine identification of LA thrombus and / or SEC is generally difficult, as it requires semi-invasive procedures, such as transesophageal echocardiography (TEE). The current guidelines on the management of AF recommend the CHA$_2$DS$_2$VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes, history of stroke

WHAT'S NEW?

In our study, we found that age, left atrial diameter, systolic pulmonary artery pressure, left ventricular ejection fraction, and total protein levels were independent predictors of left atrial (LA) thrombus and / or spontaneous echo contrast (SEC) in patients with paroxysmal atrial fibrillation undergoing transesophageal echocardiography prior to cardioversion or catheter ablation. We determined the optimal cutoff values for these parameters and developed a novel risk score (PALSE), which was shown to accurately predict the presence of the thromboembolic milieu. In patients with a PALSE score lower than 1, neither thrombus nor spontaneous echo contrast were found. The PALSE score may facilitate a more comprehensive management of patients with atrial fibrillation.

or thromboembolism, vascular disease, age of 65 to 74 years, female sex) in stroke prevention. However, this score provides inadequate information in the setting of thromboembolic milieu evaluation.[4,9-11]

In this study, we aimed to assess the predictors of the thromboembolic milieu in patients diagnosed with paroxysmal AF who underwent TEE prior to electrical cardioversion or catheter ablation, and to develop an effective risk model for detecting the thromboembolic milieu.

METHODS   Patient selection and study design

We examined the records of 698 consecutive patients with nonvalvular paroxysmal AF who underwent TEE prior to cardioversion or catheter ablation between January 2012 and January 2019. Patients with valvular AF (moderate-to-severe mitral valve stenosis and prosthetic heart valves), congenital heart diseases, malignancy, inflammatory and autoimmune diseases, or renal insufficiency requiring dialysis were excluded from the study.

Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive drugs. Diabetes was defined as fasting blood glucose levels higher than 126 mg/dl or the use of antidiabetic drugs. Hyperlipidemia was defined as total cholesterol levels higher than 200 mg/dl, low-density lipoprotein levels higher than 130 mg/dl, triglyceride levels higher than 150 mg/dl, or the use of lipid-lowering drugs. Coronary artery disease (CAD) was defined as a history of percutaneous or surgical coronary interventions or the presence of a minimum of 50% stenosis in at least 1 of the main coronary arteries. In each patient, a history of ischemic stroke and transient ischemic attack was recorded and the CHA_2DS_2VASc score was calculated. The study protocol was approved by the institutional review board and written informed consent was obtained from all participants.

Echocardiographic data   All participants underwent transthoracic echocardiography and TEE using Vivid 7 Pro (GE Vingmed Ultrasound,

Horten, Norway). All echocardiographic examinations were performed according to the recommendations of the American Society of Echocardiography.[12-15] Left ventricular ejection fraction (LVEF) was measured with the modified Simpson technique. Left ventricular end-diastolic diameter (LVEDD), LA diameter, and systolic pulmonary artery pressure (SPAP) were recorded. All TEE examinations were performed by experienced echocardiographers (OT and ÖÖ) in our echocardiography laboratory. The LA appendage (LAA) was assessed in the midesophageal 4-chamber view at 0° and then by rotating the multiplane angle to 30°, 60°, 90°, and 180°, so as not to overlook thrombus or SEC. The diagnosis of LA thrombus was confirmed by the presence of an echodense mass in the LA or LAA. Mild SEC was identified as minimal echogenicity in the LAA or sparely distributed in the LA, which is detected transiently during the cardiac cycle but not distinguished at operating gain settings for 2-dimensional echocardiographic analysis. Moderate SEC was defined as a dense swirling pattern in the LA or LAA (or both), which is usually associated with slightly lower intensity in the main cavity and which may fluctuate in intensity but is detectable constantly throughout the cardiac cycle. Severe SEC was defined as intense echo density and a very slow swirling pattern in the LA or LAA (or both), with a similar density as in the main cavity.[16] Patients with LA thrombus or moderate or severe SEC (or both) were classified as the group with the thromboembolic milieu.

Blood sampling   Peripheral venous blood was taken from the antecubital vein after a 12-hour overnight fast and collected into yellow tubes without an anticoagulant for biochemical tests and into EDTA tubes for hematologic tests. The red blood cell count, hemoglobin levels, and white blood cell count were measured using an automated hematology analyzer XE-1200 (Sysmex, Kobe, Japan). Other biochemical parameters were measured using a molecular analyzer (Roche Diagnostics, Manheim, Germany).

Statistical analysis   Continuous data were reported as the median (interquartile range) or mean (SD). The Kolmogorov–Smirnov test was used to assess the distribution pattern. Categorical variables were reported as the number and percentage. Comparisons between the 2 groups were performed with the t test for normally distributed variables and the χ^2 test or Fisher exact test for categorical variables. A univariate analysis was used to assess the effects of different variables on the occurrence of the thromboembolic milieu and determine the variables with an unadjusted P value of less than 0.1 as potential risk markers. We developed the final model

by using backward elimination for a multivariate logistic regression analysis. After the multivariate analysis, we created the receiver operating characteristic (ROC) curve models to determine the individual optimal cutoff values. Then, we graded the independent variables in a binary fashion according to the cutoff values (1 point meant above the cutoff, otherwise 0). To evaluate the presence of the thromboembolic milieu, we generated a novel risk score with these cutoff values. The overall discriminative performance of this novel risk score was also assessed in the ROC curve analysis. In all analyses, a P value of less than 0.05 was considered significant. The SPSS 20.0 software (SPSS, Inc., Chicago, Illinois, United States) was used for statistical analysis.

RESULTS The study included 434 patients. Patients with the thromboembolic milieu more often had CAD and a CHA_2DS_2VASc of 2 or higher that those without the thromboembolic milieu (TABLE 1). They were also older and had higher urea, creatinine, total protein, and C-reactive protein levels. Moreover, they had greater LVEDD and LA diameters, higher SPAP levels, and lower LVEF than the group without the thromboembolic milieu (TABLE 2).

In a univariate regression analysis, age, CAD, CHA_2DS_2VASc score, glucose, urea, creatinine, total protein, and C-reactive protein levels, LVEF, LVEDD, LA diameter, and SPAP were associated with the presence of the thromboembolic milieu. After adjustment for other parameters, age, total protein, LVEF, LA diameter, and SPAP were determined to be independent predictors of the thromboembolic milieu (TABLE 3).

In the ROC curve analysis, the optimal cutoff values for the discrimination of cases with the thromboembolic milieu were as follows: 60 years for age; 7.3 mg/dl for total protein levels; 40% for LVEF; 40 mm for LA diameter; and 35 mm Hg for SPAP. Detailed data are presented in FIGURE 1. Based on these cutoff values, we developed a risk model, namely, the PALSE score. The ROC curve demonstrating the discriminatory value of the PALSE score for the thromboembolic milieu is presented in FIGURE 2. Additionally, the PALSE score predicted LA thrombus (FIGURE 3A) and moderate or severe SEC (FIGURE 3B).

Of the 259 patients with a CHA_2DS_2VASc score lower than 2, 24 patients (9.3%) had the thromboembolic milieu (thrombus in 12 patients [4.6%] and moderate or severe SEC in 17 patients [6.6%]). Patients with a PALSE score lower than 1 showed neither thrombus nor SEC.

TABLE 1 Baseline clinical characteristics of the study groups

Parameter		Total	Patients without thromboembolic milieu	Patients with thromboembolic milieu	P value
Age, y, mean (SD)		55.5 (12)	54.7 (12.2)	61.2 (8.8)	<0.001
Male sex		242 (55.8)	212 (55.5)	30 (57.7)	0.77
Hypertension		162 (37.3)	138 (36.1)	24 (46.2)	0.16
Diabetes		46 (10.6)	37 (9.7)	9 (17.3)	0.09
CAD		60 (13.8)	48 (12.6)	12 (23.1)	0.04
Stroke / TIA		7 (1.6)	5 (1.3)	2 (3.8)	0.17
History of MI		19 (4.4)	3 (5.8)	16 (4.2)	0.53
$CHA_2DS_2VASc \geq 2$		259 (59.7)	235 (61.5)	24 (46.2)	0.03
ASA		62 (14.3)	49 (12.8)	13 (25)	0.02
Clopidogrel		17 (3.9)	15 (3.9)	2 (3.8)	0.98
Anticoagulant therapy		175 (40.3)	147 (38.5)	28 (53.8)	0.03
NOAC	All	80 (18.4)	67 (17.5)	13 (25)	0.19
	Dabigatran	16 (3.7)	14 (3.7)	2 (3.8)	0.95
	Rivaroxaban	25 (5.8)	21 (5.5)	4 (7.7)	0.52
	Apixaban	33 (7.6)	27 (7.1)	6 (11.5)	0.25
	Edoxaban	6 (1.4)	5 (1.3)	1 (1.9)	0.72
Warfarin		95 (21.9)	80 (20.9)	15 (28.8)	0.2

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: ASA, acetylsalicylic acid; CAD, coronary artery disease; CHA_2DS_2VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, history of stroke or thromboembolism, vascular disease, age of 65 to 74 years, female sex; LA, left atrial; MI, myocardial infarction; NOAC, non–vitamin K antagonist oral anticoagulant; TIA, transient ischemic attack

TABLE 2 Baseline laboratory and echocardiographic findings in the study groups

Parameter	Total	Patients without thromboembolic milieu	Patients with thromboembolic milieu	P value
Glucose, mg/dl	101.2 (27.2)	100.4 (25.8)	107.2 (35.4)	0.09
Urea, mg/dl	31.0 (8.5)	30.5 (7.7)	34.8 (12.8)	<0.001
Creatinine, mg/dl	0.9 (0.2)	0.9 (0.2)	1 (0.3)	0.03
Uric acid, mg/dl	6.2 (4.2)	6.3 (4.3)	6.3 (3.3)	0.11
AST, U/l, median (IQR)	20 (15–26)	20 (15–26)	19.5 (15–26.3)	0.85
ALT, U/l, median (IQR)	21.3 (14–32)	21.6 (14–32)	20.1 (13.3–29.3)	0.45
Albumin, mg/dl	4.2 (0.3)	4.2 (0.3)	4.3 (0.3)	0.19
Total protein, mg/dl	7.1 (0.5)	7.1 (0.5)	7.4 (0.5)	<0.001
LDL cholesterol, mg/dl	100.3 (31.1)	100.3 (30.2)	100.2 (37.6)	0.99
Hemoglobin, mg/dl	14.1 (1.6)	14.1 (1.6)	14.2 (1.5)	0.78
Hematocrit, %	43.2 (4.1)	43.1 (4.1)	43.7 (4.1)	0.35
WBC, × 10³/µl	7.4 (3.3)	7.4 (3.5)	7.6 (1.8)	0.69
Neutrophils, × 10³/µl	4.5 (1.4)	4.5 (1.4)	4.6 (1.5)	0.59
Lymphocytes, × 10³/µl	2.4 (0.9)	2.4 (0.9)	2.2 (0.8)	0.55
CRP, mg/l, median (IQR)	1.3 (0.9–3.4)	1.2 (0.9–3.2)	3.1 (1.1–4.9)	<0.001
LVEF, %	58.4 (7.2)	59.2 (6)	52.8 (11.5)	<0.001
LVEDD, mm	46.6 (3.7)	46.4 (3.4)	48.4 (4.9)	0.001
LA diameter, mm	38.6 (5.2)	38.1 (4.9)	42.6 (5.1)	<0.001
SPAP, mm Hg	30.3 (7)	29.4 (6.1)	37.3 (9.1)	<0.001

Data are presented as mean (SD) unless otherwise indicated.

SI conversion factors: to convert C-reactive protein to nmol/l, multiply by 9.524; glucose to mmol/l, by 0.0555, LDL cholesterol to mmol/l, multiply by 0.0259.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; HDL, high-density lipoprotein; IQR, interquartile range; LA, left atrium; LDL, low-density lipoprotein; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; SPAP, systolic pulmonary artery pressure; WBC, white blood cell; others, see TABLE 1

TABLE 3 Predictors of the thromboembolic milieu in univariate and multivariate regression analyses (continued on the next page)

Parameter	Univariate analysis, OR (95% CI)	P value	Multivariate analysis, OR (95% CI)	P value
Age, y	1.055 (1.024–1.086)	<0.001	1.044 (1.010–1.079)	0.01
Female sex	1.093 (0.609–1.965)	0.77	–	–
Hypertension	1.516 (0.845–2.717)	0.16	–	–
Diabetes	1.952 (0.882–4.319)	0.1	–	–
Stroke / TIA	3.016 (0.570–15.960)	0.19	–	–
CAD	2.087 (1.024–4.257)	0.04	–	–
CHA_2DS_2VASc	1.865 (1.041–3.341)	0.04	–	–
Glucose	1.007 (0.999–1.016)	0.1	–	–
Urea	1.050 (1.018–1.083)	0.002	–	–
Creatinine	3.750 (1.101–12.771)	0.04	–	–
Uric acid	0.940 (0.872–1.014)	0.11	–	–
AST	1.012 (0.990 –1.034)	0.3	–	–

TABLE 3 Predictors of the thromboembolic milieu in univariate and multivariate regression analyses (continued from the previous page)

Parameter	Univariate analysis, OR (95% CI)	P value	Multivariate analysis, OR (95% CI)	P value
ALT	0.987 (0.970–1.005)	0.16	–	–
Albumin	1.972 (0.709–5.487)	0.19	–	–
Total protein	4.326 (2.168–8.633)	<0.001	4.234 (1.91–9.386)	<0.001
LDL cholesterol	1.000 (0.991–1.009)	0.97	–	–
Hemoglobin	1.028 (0.851–1.241)	0.78	–	–
Hematocrit	1,035 (0.962–1.113)	0.35	–	–
WBC	1.015 (0.943–1.092)	0.69	–	–
Neutrophils	1.056 (0.866–1.287)	0.59	–	–
Lymphocytes	0.923 (0.730–1.168)	0.5	–	–
CRP	1.102 (1.017–1.194)	0.02	–	–
LVEF	0.918 (0.888–0.948)	<0.001	0.954 (0.919–0.991)	0.02
LVEDD	1.131 (1.050–1.218)	0.001	–	–
LA diameter	1.148 (1.087–1.212)	<0.001	1.080 (1.013–1.151)	0.02
SPAP	1.139 (1.094–1.186)	<0.001	1.087 (1.036–1.140)	0.001

Abbreviations: OR, odds ratio; others, see TABLES 2 and 3
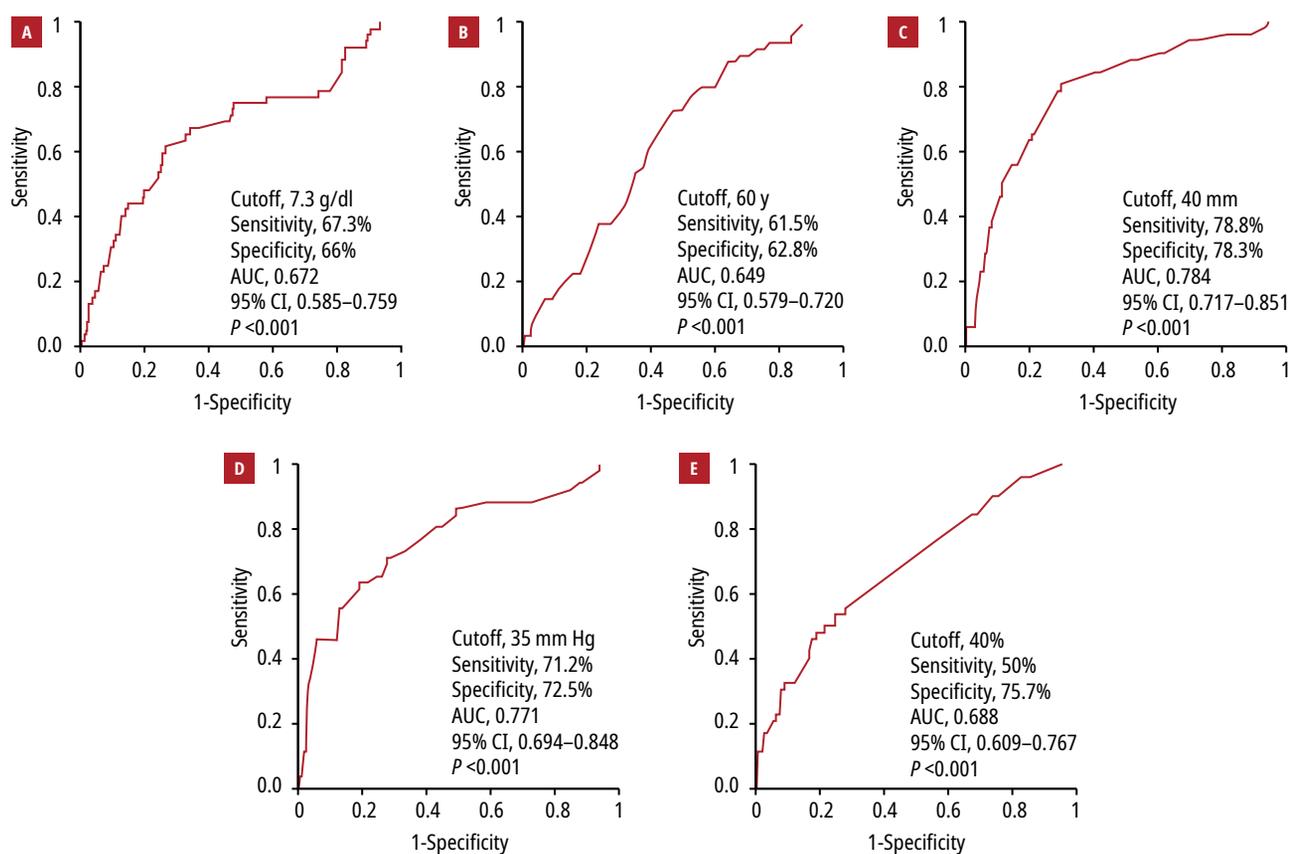
FIGURE 1 Receiver operating characteristic curves demonstrating the discriminatory power of total protein levels (**A**), age (**B**), left atrial diameter (**C**), systolic pulmonary artery pressure (**D**), and left ventricular ejection fraction (**E**) for the thromboembolic milieu
Abbreviations: AUC, area under the curve
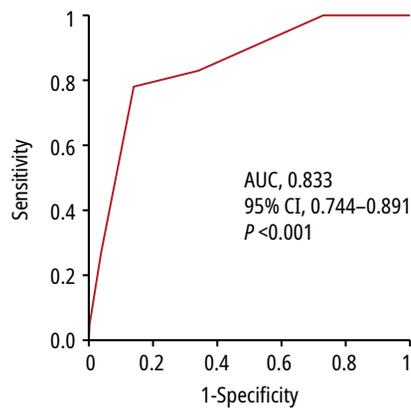
FIGURE 2 Receiver operating characteristic curve demonstrating the predictive value of the PALSE score for the thromboembolic milieu
Abbreviations: see FIGURE 1
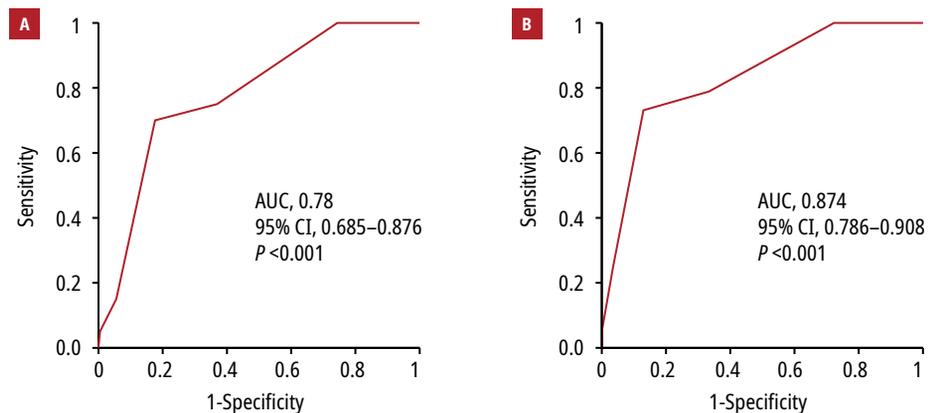
FIGURE 3 Receiver operating characteristic curves demonstrating the predictive value of the PALSE score separately for left atrial thrombus (**A**) and moderate or severe spontaneous echo contrast (**B**)
Abbreviations: see FIGURE 1

DISCUSSION In our study, we found that total protein levels, LA diameter, SPAP, age, as well as LVEF were independent predictors of the thromboembolic milieu in patients with paroxysmal AF undergoing cardioversion or catheter ablation. We also determined the optimal cutoff values for these parameters and developed a novel risk model, namely, the PALSE score, which was shown to accurately predict the presence of LAT. Besides, the PALSE score was shown to accurately predict the presence of LA thrombus and SEC both in combination or separately. Patients with a PALSE score lower than 1 did not have thrombus or SEC on TEE. In contrast, CHA$_2$DS$_2$VASc did not demonstrate satisfactory results in terms of predicting the thromboembolic milieu.

The evaluation of the thromboembolic risk in AF remains the cornerstone of patient management.[4] In current practice, clinical risk scores such as CHADS$_2$ (congestive heart failure, hypertension, diabetes, age ≥75 years, history of stroke or transient ischemic attack) and its more comprehensive variant, CHA$_2$DS$_2$VASc, predict the 1-year thromboembolic risk and are

routinely used in decision-making concerning anticoagulant therapy.[4] However, in the setting of the thromboembolic milieu, these risk scores seem to provide controversial data, which precludes their routine use.[9-11,17] The prediction of the thromboembolic milieu may provide additional information beyond traditional risk scores in the evaluation of the thromboembolic risk in patients with AF.

Left atrial thrombus and SEC are well-known manifestations of the thromboembolic milieu in AF patients.[8,18] They are caused by different pathological conditions and interrelated anatomical, hemodynamic, and biological factors, such as decreased blood flow velocity as well as increased blood viscosity and coagulopathy.[16,19-21] Therefore, the evaluation of the thromboembolic risk should account for all these conditions in a more comprehensive manner.

In contrast to traditional risk scores depending on the cumulative thromboembolic risk, those depending on the presence of the thromboembolic milieu may provide better identification of high-risk patients. Current literature

suggests that patients with a visible thrombus or SEC in the LA are at higher thromboembolic risk.[6-8] Therefore, assessing the thromboembolic risk on the basis of the thromboembolic milieu may offer a more robust approach to the management of AF.

Although TEE is the gold standard for thrombus and SEC detection, this procedure is semi-invasive and costly and is associated with considerable risks such as trauma, vagal and allergic reactions, hypotension, or anesthetic reactions.[22] Because of these limitations, TEE cannot be performed in some patients. Therefore, the noninvasive identification of the thromboembolic milieu may be beneficial in some cases.

In accordance with previous research, our study demonstrated that the CHA_2DS_2VASc score does not seem to be useful for identification of the thromboembolic milieu in patients with paroxysmal AF.[11,23] Several mechanisms may explain this finding. First, the CHA_2DS_2VASc score includes a wide range of stroke risk factors other than the thromboembolic milieu including atherosclerotic process. This heterogeneity may reduce the usefulness of this score in the identification of the thromboembolic milieu. In contrast, the PALSE score directly takes a picture of the left atrium at the moment of TEE representing the thromboembolic risk. Second, the CHA_2DS_2VASc score includes the general patient risk profiles, which may be inadequate for LA thrombus and / or SEC identification. The inclusion of biochemical and echocardiographic data in addition to general risk profiles in the PALSE score may enhance the discriminatory value of the risk model and provide a more detailed insight. In our study, of the 259 patients with a CHA_2DS_2VASc score lower than 2, 9.3% had LA thrombus and / or SEC. On the other hand, none of the patients with a PALSE score lower than 1 had SEC or thrombus. Therefore, the PALSE score seems to be a better risk model, at least for the identification of patients with LA thrombus and / or SEC.

One of the main components of the PALSE score is the LA diameter. In line with previous studies, the presence of LA dilation with a cutoff value of 40 mm was found to be a significant predictor of the thromboembolic milieu.[24,25] Considering the pathophysiology of the thromboembolic milieu, this result is not surprising. The enlargement of the LA is associated with low velocity, which predisposes to the development of the thromboembolic milieu. Moreover, the LA diameter can be a marker of AF burden.[26] Therefore, the LA size should always be included in the decision-making process in patients with AF.

Another important component of the score is SPAP. We speculated that increased SPAP in patients with AF is a sign of increased LA pressure. In patients with nonvalvular AF, the markers of increased left ventricular filling pressure such as

brain natriuretic peptide and Doppler-derived E/e' ratio were shown to be closely related with the thromboembolic milieu.[27,28] Kishima et al[23] investigated the predictors of the thromboembolic milieu in patients with acute stroke. They demonstrated that left ventricular hypertrophy, which is closely related to pulmonary capillary wedge pressure (PCWP) was significantly associated with left atrial thrombus and SEC.[23,29] Similarly, Tabata et al[30] indicated that elevated PCWP was associated with reduced LAA velocities. The invasive evaluation of loading conditions such as PCWP and direct measurements of pulmonary artery pressures may be difficult and has limited use in comprehensive clinical assessment. On the other hand, SPAP, which reflects a passive increase in LA pressure in patients with AF, is a simple and more feasible marker that can be included in routine clinical evaluation.

Reduced LVEF and older age are well-known risk factors for the thromboembolic milieu in patients with AF.[31-33] However, the reported cutoff values for age were slightly higher than the cutoff of 60 years in our study. In our research, we found an association between plasma protein levels and LA thrombus and / or SEC. Considering its pathomechanism, SEC is thought to be a manifestation of red blood cell aggregation, arising from the interaction between red blood cell and plasma proteins, mainly fibrinogen, at low shear rates.[5,34] In patients with stroke, Briley et al[35] found that elevated plasma proteins reflecting increased blood viscosity, such as fibrinogen and gamma globulin, were associated with SEC formation unlike the previously reported blood markers such as hematocrit, white blood cell count, and platelet levels. In accordance with their results, we did not observe any associations between the thromboembolic milieu and hematocrit, white blood cell and platelet counts, or albumin levels.

Plasma D-dimer levels and von Willebrand factor were also reported to be associated with SEC.[36,37] To our knowledge, our study is the first to investigate the relationship between total protein levels and the thromboembolic milieu. We hypothesized that increased plasma levels of total protein might be a simple biomarker of increased blood viscosity and thus of a procoagulant state. Blood viscosity is the primary component of the Virchow triad; however, it is usually neglected because of the difficulties in measurement that requires specific equipment and provides variable results. The determination of the total protein level may be more feasible and may provide valuable information about the presence of the thromboembolic milieu.

The incidence of LA thrombus and / or SEC in our study was slightly higher (11.1%) than in previous research.[11] The main reason for this discrepancy is that all our patients underwent TEE. Some previous studies included low-risk patients

in whom TEE was not performed, which might have resulted in a selection bias.[11] Moreover, patients classified as low risk with traditional risk scores, in fact, had LA thrombus and/or SEC, which may predispose them to thromboembolic events if they do not receive anticoagulant therapy. Patients with AF require a more proactive and thorough approach.[38] The PALSE score may provide additional risk classification in this specific population and may facilitate a more comprehensive patient management.

The aim of developing a novel risk model was to enable identification of patients who are categorized as low risk with classic risk models and therefore do not receive anticoagulant therapy, but who may actually have LA thrombus and/or SEC. In other words, "low-risk" patients may in fact not be at low risk. In view of this aim, the strength of our study is that all patients with nonvalvular AF had undergone TEE irrespective of their thromboembolic risk.

Another important aspect of our study is that the parameters included in the PALSE score (LA size, LV systolic dysfunction, age, and SPAP) are predictors of AF recurrence after catheter ablation.[39] In addition to thrombogenicity, these parameters also seem to reflect the progression of AF in atrial tissue.[40] However, prospective trials are needed to assess the usefulness of the PALSE score for predicting AF recurrence.

Limitations As our study had a cross-sectional design, follow-up data on thromboembolic events were unavailable. A follow-up of at least 1 year would strengthen our results. Moreover, all our patients had paroxysmal AF, so the PALSE score should be validated in other AF types such as persistent or paroxysmal AF. As a single-center study, it was limited to our institution (a high--volume tertiary electrophysiology center) and thus represented only the patient profile of our country. Therefore, although the score has been validated internally, an external validation would be valuable. Another limitation is the lack of sufficient data on the flow velocity of the LAA in our patients. Previous echocardiographic studies revealed its importance in predicting the thrombogenic milieu and thus thromboembolic events.[41] The inclusion of LAA velocity in the PALSE score might reveal some important mechanisms that could enhance our clinical knowledge. On the other hand, our aim in this study was to identify patients at high risk prior to TEE. Therefore, the addition of LAA velocity, which is measured by TEE, might reduce the usefulness of this risk score in a general patient population.

Conclusions In conclusion, in patients with paroxysmal AF, total protein level, LA diameter, SPAP, age, and LVEF were identified as independent predictors of the thromboembolic milieu.

Our new risk model, the PALSE score, which is composed of these parameters, seemed to accurately predict the presence of the thromboembolic milieu. Further prospective studies are warranted to confirm our findings.

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