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Original Article

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Clinical Significance of Skin Autofluorescence in Elderly Patients With Long-Standing Persistent Atrial Fibrillation

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Abstract

Background: Recent clinical studies have demonstrated the importance of skin autofluorescence as a cardiovascular risk factor. However, data regarding the relationship between skin autofluorescence and atrial fibrillation are limited. The aim of this study was to clarify the clinical significance of skin autofluorescence in elderly patients with long-standing persistent atrial fibrillation.

Methods: This cross-sectional study enrolled 112 elderly patients with long-standing persistent atrial fibrillation who were treated medically (46 men and 66 women; mean age, 81 ± 9 years). The association between skin autofluorescence and various clinical parameters was examined.

Results: Significant relationships were observed between skin autofluorescence and $CHADS_2$ score ($r = 0.53$, $P < 0.001$), high-sensitivity cardiac troponin T level ($r = 0.43$, $P < 0.001$), reactive oxygen metabolite levels ($r = 0.52$, $P < 0.001$), and whole blood passage time ($r = 0.45$, $P < 0.001$). Furthermore, multiple regression analyses showed that these clinical parameters were independent variables when skin autofluorescence was used as a subordinate factor. Receiver-operating characteristic curve analysis indicated that the risk values of skin autofluorescence for high $CHADS_2$ scores (≥ 2) or elevated high-sensitivity cardiac troponin T levels (> 0.014ng/mL) were 2.6 arbitrary units (AU) and 2.7 AU, respectively.

Conclusions: The findings of this study indicated that skin autofluorescence may be a prognostic factor in elderly patients with long-standing persistent atrial fibrillation. The risk value of skin autofluorescence was considered as 2.6 AU or 2.7 AU.

Keywords: Skin autofluorescence; Long-standing persistent atrial fibrillation; $CHADS_2$ score; Blood rheology; High-sensitivity cardiac troponin T; Oxidative stress; Elderly

Introduction

Atrial fibrillation is a common cardiovascular disease and is associated with other diseases such as ischemic stroke and heart failure [1]. In recent years, the prevalence of atrial fibrillation has increased because of a concomitant increase in life expectancy [2]. Treatment via an electrophysiologic catheter ablation procedure can be performed for selected patients with atrial fibrillation [3], which may achieve a complete cure in some. Catheter ablation is particularly useful in patients with paroxysmal atrial fibrillation, but less so in those with persistent atrial fibrillation [4, 5]. In addition, elderly patients with persistent atrial fibrillation are less likely to receive the procedure for various reasons such as duration of atrial fibrillation, symptoms, activities of daily practice, patient refusal, and limited procedural benefit.

Advanced glycation end products (AGEs) and receptors of AGEs play an important role in the pathophysiology of cardiovascular disease [6, 7]. Among the methods used to evaluate AGEs, skin autofluorescence is known to be a simple and reliable marker of AGEs *in vivo*, and recent clinical studies have indicated that skin autofluorescence is significantly associated with cardiovascular disease [8-10]. However, data regarding the relationship between skin autofluorescence and atrial fibrillation are limited. This cross-sectional study attempted to clarify the clinical significance of skin autofluorescence in elderly patients with long-standing persistent atrial fibrillation.

Materials and Methods

Patients

In this study, 112 elderly outpatients (age ≥ 65 years) with long-standing persistent atrial fibrillation who were being treated medically at the Hitsumoto Medical Clinic, Yamaguchi, Japan were enrolled between January 2017 and December 2018. Long-standing persistent atrial fibrillation (presence of atrial fibrillation for ≥ 1 year after initiation of rhythm control treatment) is defined by the 2010 Guidelines for the Management of Atrial Fibrillation of the European Society of Cardiology [11]. The patients included 46 (41%) men and 66 (59%) women. The mean patient age was 81 ± 9 years. The study was approved by the Institutional Review Board of the Hitsumoto Medical Clinic (approval number 2017-01) and was conducted in compliance with the Declaration of Helsinki. All patients provided informed consent.

Measurement of skin autofluorescence

Skin autofluorescence was measured using a commercial de-

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vice (AGE Reader™; DiagnOptics, Groningen, the Netherlands), as previously described [12, 13]. Autofluorescence was defined as the average light intensity per nanometer between 300 and 420 nm. Skin autofluorescence levels were expressed in arbitrary units (AU). All measurements were performed on the volar side of the forearm approximately 10 - 15 cm below the elbow while the patients were in the sitting position. The value of pentosidine, a major component of AGEs, has been previously measured using skin biopsy on the volar side of the forearm and seemed to correlate with skin autofluorescence [14]. Previous reports have established the validity and reliability of skin autofluorescence level measurements using this method in the Japanese population [13].

Evaluation of clinical parameters

Various clinical parameters were evaluated, including classic risk factors of cardiovascular disease, such as $CHADS_2$ score [15], echocardiographic findings, kidney function, brain natriuretic peptide level, high-sensitivity cardiac troponin T (hs-cTnT) level, reactive oxygen metabolites (a marker of oxidative stress), and whole blood passage time (a marker of blood rheology). Obesity was identified using body mass index, calculated as the weight (kg) divided by the squared height (m^2). Current smoking was defined as smoking at least one cigarette per day over the previous 28 days. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or the use of antihypertensive medication. Dyslipidemia was defined as low-density lipoprotein cholesterol level ≥ 140 mg/dL, high-density lipoprotein cholesterol level ≤ 40 mg/dL, triglyceride level ≥ 150 mg/dL, or the use of lipid-lowering medication. Diabetes mellitus was defined as fasting blood glucose level ≥ 126 mg/dL, hemoglobin A1c (HbA1c) level ≥ 6.5%, or the use of antidiabetic medication or exogenous insulin. Standard echocardiography was performed using the HI VISION Avius ultrasound system (Hitachi Medical Corporation, Tokyo, Japan). Left ventricular wall thickness, left ventricular end-diastolic diameter, left ventricular ejection fraction, and left atrial dimension were measured by echocardiography. The estimated glomerular filtration rate was calculated using the adjusted Modification of Diet in Renal Disease Study equation, which was proposed by the working group of the Japanese Chronic Kidney Disease Initiative [16]. Brain natriuretic peptide levels were measured using the SHIONOSPOT® Reader (Shionogi & Co., Osaka, Japan), and hs-cTnT levels were measured using an hs-cTnT assay (Roche Diagnostics, Basel, Switzerland) [17]. As an *in vivo* oxidative stress marker [18], the reactive oxygen metabolites (d-ROMs) test was performed (Diacron, Grosseto, Italy). Blood rheology was evaluated by measuring whole blood passage time with an MC-FAN HR300 rheometer (MC Healthcare, Tokyo, Japan), as previously reported [19, 20].

Statistical analysis

In this study, data were expressed as mean ± standard deviation. Comparisons were made using the Student's *t*-test. Simple regression analysis was performed using the Pearson or Spearman rank correlation, and a multivariate analysis was performed using multiple regression. Receiver-operating characteristic curve analysis was performed, and the maximum Youden's index [21] was used to determine the optimal skin autofluorescence cutoff values for high $CHADS_2$ scores and high hs-cTnT levels. $P < 0.05$ was considered to be statistically significant. StatView J5.0 (HULINKS, Tokyo, Japan) and MedCalc for Windows (MedCalc Software, Ostend, Belgium) software were used for analysis.

Results

Table 1 summarizes the patients' characteristics. The overall mean skin autofluorescence was 2.8 ± 0.5 AU (range, 2.0 - 4.6 AU). Eighty-six patients (77%) had a $CHADS_2$ score ≥ 2. Figure 1 shows the significant positive correlation between skin autofluorescence and the $CHADS_2$ score. Figure 2 shows the relationship between skin autofluorescence and the components of the $CHADS_2$ score. Skin autofluorescence had a significant correlation with the following components: congestive heart failure, age, diabetes mellitus, and stroke/transient ischemic attack. Table 2 presents the correlation between skin autofluorescence and various clinical parameters. Smoking status, HbA1c, estimated glomerular filtration rate, brain natriuretic peptide level, hs-cTnT level, d-ROMs test, whole blood passage time, and renin-angiotensin inhibitor use significantly correlated with skin autofluorescence. Table 3 summarizes the results of multiple regression analysis with skin autofluorescence as a subordinate factor. Explanatory factors were selected by examining the multicollinearity among the variables using stepwise regression; four factors ($CHADS_2$ score, whole blood passage time, d-ROMs test, and hs-cTnT level) were identified as independent variables. Figure 3 shows the receiver-operating characteristic curve analysis for the detection of high $CHADS_2$ scores (≥ 2) and elevated hs-cTnT levels (> 0.014 ng/mL), based on previous studies [22, 23]. The maximum Youden's index indicated that the optimal cutoff values of skin autofluorescence to determine high $CHADS_2$ scores and elevated hs-cTnT levels were 2.6 AU and 2.7 AU, respectively.

Discussion

This study aimed to clarify the clinical significance of skin autofluorescence in elderly patients with long-standing persistent atrial fibrillation. The results showed an independent association between skin autofluorescence and $CHADS_2$ score, whole blood passage time, hs-cTnT level, and d-ROMs test. In addition, the receiver-operating characteristic curve analysis indicated that the skin autofluorescence values associated with high $CHADS_2$ scores and elevated hs-cTnT levels in this study population were > 2.6 AU and > 2.7 AU, respectively.

The $CHADS_2$ score is a well-known predictor of ischemic stroke in patients with atrial fibrillation [15, 22]. Therefore, the

Table 1. Patient Characteristics

n (male/female)	112 (46/66)
Age (years)	81 ± 9
Skin autofluorescence (AU)	2.8 ± 0.5
$CHADS_2$ score	3 ± 2
Body mass index (kg/m^2)	22.6 ± 3.5
Current smoker, n (%)	14 (13)
Hypertension, n (%)	75 (67)
Systolic blood pressure (mm Hg)	131 ± 11
Diastolic blood pressure (mm Hg)	76 ± 9
Dyslipidemia, n (%)	76 (68)
Total cholesterol (mg/dL)	218 ± 41
LDL cholesterol (mg/dL)	137 ± 37
Triglyceride (mg/dL)	127 ± 66
HDL cholesterol (mg/dL)	55 ± 15
Diabetes mellitus, n (%)	30 (27)
Fasting blood glucose (mg/dL)	104 ± 32
Hemoglobin A1c (%)	5.9 ± 0.6
IVSTd (mm)	9.7 ± 2.2
LVDd (mm)	51.5 ± 5.9
LVEF (%)	64.4 ± 12.2
LAD (mm)	46.9 ± 6.8
eGFR (mL/min/1.73m^2)	51.8 ±19.1
Log-BNP (pg/mL)	2.3 ± 0.4
Log-hs-cTnT (ng/mL)	-1.8 ± 0.4
d-ROMs test (U. CARR)	325 ± 82
WBPT (s)	59.5 ± 18.3
Medication	
RAS inhibitor, n (%)	61 (55)
β blocker, n (%)	23 (21)
Diuretics, n (%)	31 (28)
Statin, n (%)	35 (31)
Warfarin/DOAC, n (%)	33 (29)/79 (71)

Continuous values are mean ± SD. AU: arbitrary units; LDL: low-density lipoprotein; HDL: high-density lipoprotein; IVSTd: interventricular septal thickness at end-diastole; LVDd: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LAD: left atrial dimension; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; hs-cTnT: high sensitivity cardiac troponin T; d-ROMs: derivatives of reactive oxygen metabolites; WBPT: whole blood passage time; RAS: renin-angiotensin system; DOAC: direct oral anticoagulant.

independent association between skin autofluorescence and the $CHADS_2$ score in this study suggests that increased skin autofluorescence is closely associated with ischemic stroke incidence. Although several physiologic processes are involved in ischemic stroke, vascular dysfunction is one of the main causes. Basic science studies have reported that AGEs or receptors of AGEs can induce vascular cell dysfunction [24-26].

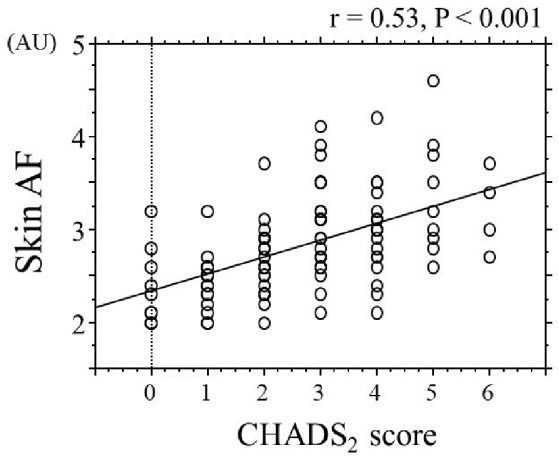

Figure 1. Correlation between skin autofluorescence and $CHADS_2$ score. AF: autofluorescence; AU: arbitrary unit.

In addition, clinical studies have indicated a significant association between skin autofluorescence and pulsatility index at the common carotid artery, which reflects vascular resistance in cerebral vessels [27]. Thus, the relation of ischemic stroke and skin autofluorescence can be partly explained by vascular dysfunction in cerebral vessels caused by AGEs. Another mechanism of ischemic stroke is cerebral embolism, which is closely associated with atrial fibrillation. In this clinical setting, thrombosis is known to be produced mainly in the left atrium or left atrial appendage, where impaired blood rheology has been shown to be an important factor [28, 29]. Basic science investigations have indicated that AGEs cause impaired blood rheology by mechanisms such as leukocyte-endothelial interaction, activation of platelet aggregation, and increased levels of plasminogen activator inhibitor-1 [30-32]. Therefore, the independent association between skin autofluorescence and whole blood passage time in this study can be explained by hypothesizing that AGEs play an important role in impairing blood rheology in elderly patients with long-standing persistent atrial fibrillation; consequently, treatment directed at decreasing AGEs may prevent ischemic stroke by improving blood rheology.

Recent clinical studies have shown the clinical importance of hs-cTnT levels as a prognostic factor in patients with atrial fibrillation [23, 33]. In addition, hs-cTnT is used as a biomarker to clinically evaluate the severity of myocardial injury. Hofmann et al found a significant relationship between AGE-modified cardiac tissue collagen and skin autofluorescence [34]. They also showed that the AGE level found at the volar side of the forearm seemed to reflect the degree of AGE accumulation in cardiomyocytes. In addition, basic science studies have indicated that AGEs or receptors of AGEs could influence myocardial injury via several pathways [35, 36]. Thus, the results of this study and previous ones suggest that AGEs play a crucial role in the progression of myocardial damage in elderly patients with long-standing persistent atrial fibrillation.

Several researchers have emphasized the importance of oxidative stress in the pathogenesis of atrial fibrillation [37, 38], and a number of basic science and clinical studies have

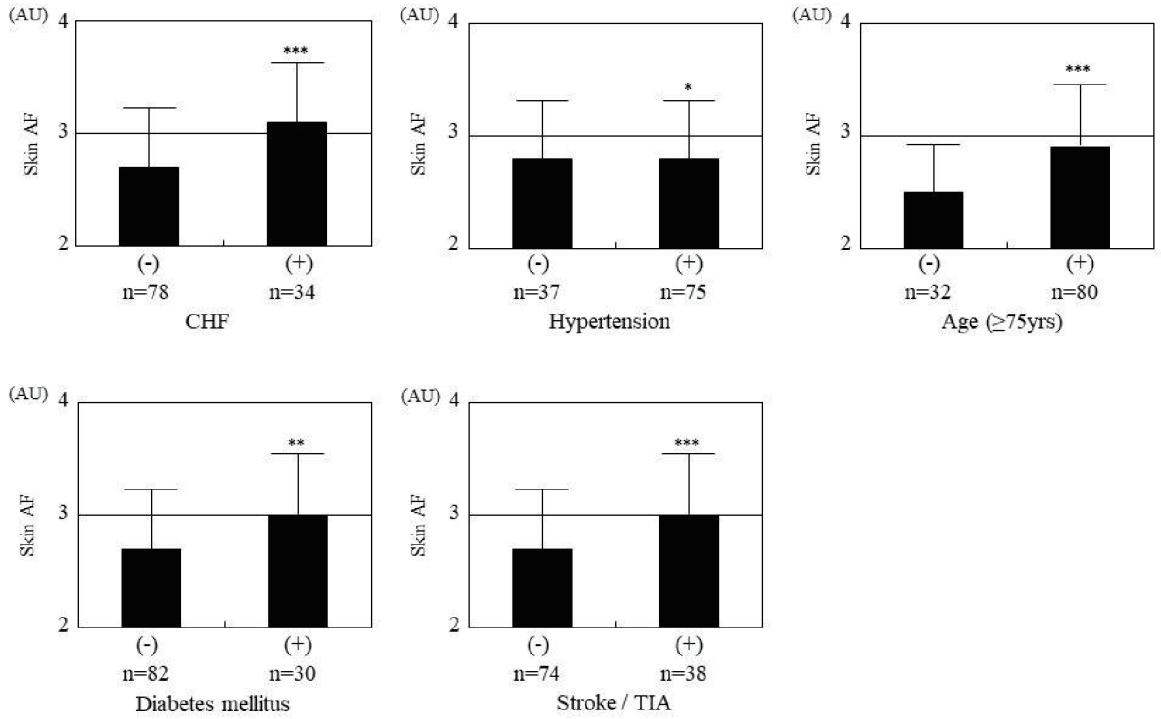

Figure 2. Relationship between skin autofluorescence and components of the $CHADS_2$ score. Comparisons are between those with and without the following factors: CHF (3.1 ± 0.5 AU vs. 2.7 ± 0.5 AU, respectively, P < 0.001), age ≥ 75 years (2.9 ± 0.5 AU vs. 2.5 ± 0.4 AU, respectively, P < 0.001), diabetes mellitus (3.0 ± 0.5 AU vs. 2.7 ± 0.5 AU, respectively, P = 0.019), and stroke/TIA (3.0 ± 0.5 AU vs. 2.7 ± 0.5 AU, respectively, P < 0.001). *P = 0.598, **P = 0.019, ***P < 0.001. AF: autofluorescence; AU: arbitrary units; CHF: congestive heart failure; TIA: transient ischemic attack.

shown a close association between AGEs or receptors of AGEs and oxidative stress in the heart and arterial vessels [24, 39, 40]. The results of this study also indicated that the d-ROMs test as an *in vivo* marker of oxidative stress is an important factor for skin autofluorescence. A previous study reported that increased activity of the renin-angiotensin system caused increased oxidative stress or AGE production, and the use of an angiotensin receptor blocker decreased both oxidative stress and receptors of AGEs [41]. This study showed a significantly negative association between angiotensin receptor blocker use and skin autofluorescence, even though angiotensin receptor blocker use was not selected in the multivariate model. Therefore, we have started to intervene by prescribing an angiotensin receptor blocker for patients with high skin autofluorescence; consequently, we expect a reduction in cardiovascular events, including ischemic stroke or heart failure, in elderly patients with long-standing persistent atrial fibrillation.

This study clarified the clinical usefulness of assessing skin autofluorescence to detect a high $CHADS_2$ score ≥ 2 or an elevated hs-cTnT level > 0.014 ng/mL, which are associated with cardiovascular events such as ischemic stroke, heart failure, and coronary artery disease in patients with atrial fibrillation according to previous reports. The receiver-operating characteristic curve analysis indicated that skin autofluorescence values > 2.6 AU and > 2.7 AU are the optimal cutoff points to identify a high $CHADS_2$ score and an elevated hs-cTnT level, respectively. Therefore, this study indicated that maintaining skin autofluorescence values ≤ 2.6 AU or ≤ 2.7 AU in elderly patients with long-standing persistent atrial fibrillation may decrease cardiovascular events. Genevieve et al performed a study regarding the association between skin autofluorescence and HbA1c levels in patients with diabetes mellitus, and reported that skin autofluorescence was significantly associated with the means of the last five and 10 HbA1c values [42]. In addition, Isami et al reported that lifestyle habits such as physical activity, nonsmoking, adequate sleep, low mental stress level, eating breakfast, and abstaining from sugary foods were independently associated with lower skin autofluorescence [43]. Therefore, it appears that long-term adequate blood glucose control and good lifestyle habits are important to maintain lower skin autofluorescence as early as possible.

Limitations

This study has several limitations. First, the various medical treatments may have affected the study results. Second, skin autofluorescence was measured in only Japanese patients; previous studies have indicated that skin autofluorescence varies according to race [44, 45]. Therefore, the cutoff values for skin autofluorescence found in this study may not apply to non-Japanese populations. Finally, the study design was a single-center cross-sectional study, and the sample size was relatively small. Additional prospective studies, including evaluations

Table 2. Relationship Between Skin Autofluorescence and Various Clinical Parameters

	r	P value
Sex (female = 0, male = 1)	-0.14	0.139
Body mass index	-0.13	0.183
Current smoker (no = 0, yes = 1)	0.24	0.009
Systolic blood pressure	0.02	0.852
Diastolic blood pressure	-0.03	0.732
Dyslipidemia (no = 0, yes = 1)	0.02	0.852
Total cholesterol	0.02	0.837
LDL cholesterol	0.01	0.924
Triglyceride	0.05	0.582
HDL cholesterol	-0.12	0.190
Fasting blood glucose	0.06	0.566
Hemoglobin A1c	0.24	0.012
IVSTd	0.02	0.861
LVDd	0.08	0.319
LVEF	0.11	0.251
LAD	0.19	0.051
eGFR	-0.37	< 0.001
Log-BNP	0.32	< 0.001
Log-hs-cTnT	0.43	< 0.001
d-ROMs test	0.52	< 0.001
WBPT	0.45	< 0.001
RAS inhibitor (no = 0, yes = 1)	-0.16	0.048
β blocker (no = 0, yes = 1)	0.14	0.137
Diuretics (no = 0, yes = 1)	0.18	0.062
Statin (no = 0, yes = 1)	0.09	0.351
Anticoagulant (warfarin = 0, DOAC = 1)	-0.04	0.965

r expressed correlation coefficient. LDL: low-density lipoprotein; HDL: high-density lipoprotein; IVSTd: interventricular septal thickness at end-diastole; LVDd: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LAD: left atrial dimension; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; hs-cTnT: high sensitivity cardiac troponin T; d-ROMs: derivatives of reactive oxygen metabolites; WBPT: whole blood passage time; RAS: renin-angiotensin system; DOAC: direct oral anticoagulant.

of interventional therapies, are required to clarify the clinical significance of skin autofluorescence in elderly patients with long-standing persistent atrial fibrillation.

Conclusions

In conclusion, the findings of this study showed that skin autofluorescence may be a prognostic factor in elderly patients with long-standing persistent atrial fibrillation. The risk value of skin autofluorescence was considered as 2.6 AU or 2.7 AU. Further prospective studies that include the evaluation of therapies are required to validate the results of this study.

Table 3. Multiple Regression Analysis for Skin Autofluorescence

Explanatory factor	β	P value
$CHADS_2$ score	0.33	< 0.001
WBPT	0.25	0.002
d-ROMs test	0.21	0.019
Log-hs-cTnT	0.19	0.020

R^2 = 0.47. WBPT: whole blood passage time; d-ROMs: derivatives of reactive oxygen metabolites; hs-cTnT: high sensitivity cardiac troponin T; β: standardized regression coefficient; R^2: coefficient of determination.

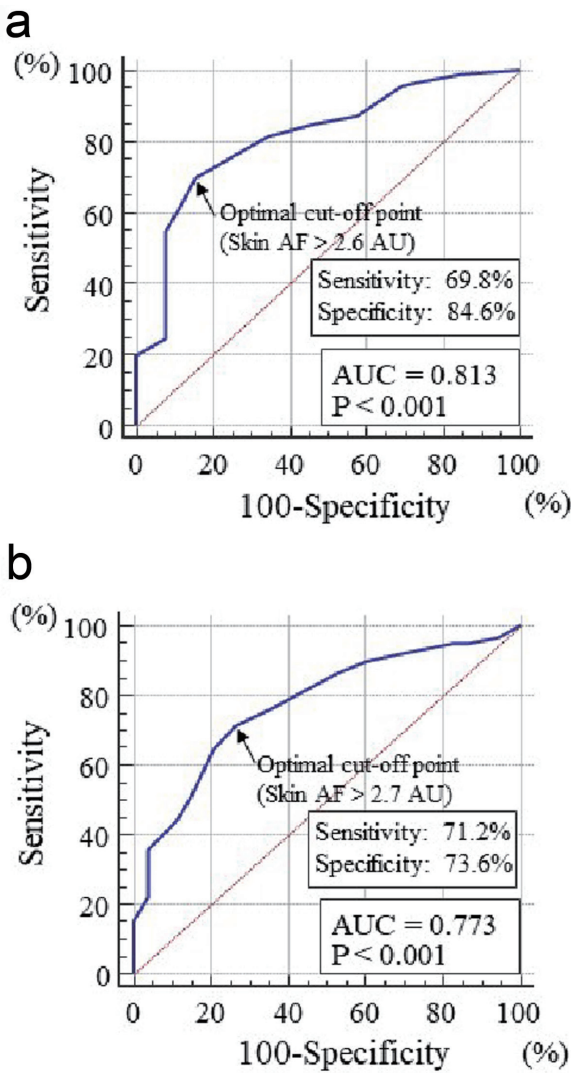

Figure 3. Receiver-operating characteristic curve analysis for the detection of high $CHADS_2$ scores or elevated hs-cTnT levels based on skin autofluorescence. The maximum Youden's index indicated that skin autofluorescence values > 2.6 AU and > 2.7 AU are the optimal cutoff points to identify high $CHADS_2$ scores (≥ 2) or elevated hs-cTnT levels (> 0.014 ng/mL), respectively. (a) $CHADS_2$ score. (b) hs-cTnT levels. AF: autofluorescence; AU: arbitrary unit; hs-cTnT: high-sensitivity cardiac troponin T; AUC: area under the curve.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

All patients provided informed consent.

Author Contributions

The author was involved in preparing the study design as well as in the acquisition, analysis, and interpretation of data.

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