Original Article

Factors associated with left atrial appendage filling defects on early-phase cardiac computed tomography in patients with nonvalvular atrial fibrillation: a case-control study

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Background: The significance of left atrial appendage (LAA) filling defects on early-phase cardiac computed tomography (CCT) remains uncertain. This study retrospectively investigated predictive factors of LAA filling defects on early-phase CCT.

Methods: A total of 68 patients with nonvalvular atrial fibrillation (AF) and early filling defect on CCT who underwent transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) were enrolled [48 males, 20 females; mean ± standard deviation (SD) age 62.72±8.13 years]. Additionally 68 sex- and age-matched patients with normal LAA filling were included as the control group. CCT, ultrasound, clinical and laboratory data were analyzed. Baseline data between groups were analyzed using *t*-, Mann-Whitney, and chi-squared tests. Multivariable logistic regression analysis was used to adjust for confounders. Pearson correlation analysis was used to confirm correlations between variables.

Results: Decreased LAA flow velocity [LAAFV; odds ratio (OR) =0.918; 95% confidence interval (CI): 0.883–0.954; P<0.001] and increased left atrial volume index (LAVI; OR =1.055; 95% CI: 1.012–1.099; P=0.011) were significantly associated with early-phase CCT LAA filling defects. The LAAFV threshold for predicting early LAA filling defects was 40.5 cm/s, with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.905 (sensitivity 82.4%, specificity 91.2%); the LAVI predictive threshold was 58.77 mL/m^2 (AUC =0.840, sensitivity 85.3%, specificity 72.1%). A significant positive correlation was detected between LAAFV and the Hounsfield unit (HU) ratio of the LAA to ascending aorta on early-phase CCT (r=0.614; P<0.001), as well as the HU difference in LAA between early and delayed phase CCT (r=0.591; P<0.001). There were significant (P<0.05) differences in LAAFV between different filling defects.

Conclusions: Decreased LAAFV and increased LAVI are independent factors associated with LAA filling defects only on early-phase CCT. Early-phase CCT LAA filling defect is associated with LAA emptying dysfunction. These findings contribute to thrombosis risk stratification in patients with AF.

Keywords: Atrial fibrillation (AF); cardiac computed tomography (CCT); filling defect; left atrial appendage (LAA); left atrial appendage flow velocity (LAAFV)

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Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias, with an incidence of approximately 1–1.5% in the general population and up to 10% in older adults (1). Patients with AF have a higher risk of thromboembolic diseases, and approximately one-third of ischemic strokes are attributed to thromboembolism caused by AF (2). More than 90% of AF thrombi are found in the left atrial appendage (LAA) (3). Catheter ablation and LAA closure have become alternative treatment options for patients with AF, with cardiac computed tomography (CCT) and transesophageal echocardiography (TEE) correspondingly becoming routine preoperative examinations. CCT images can provide high-resolution anatomical definition of the left atrium (LA), including the LAA and pulmonary veins, whereas TEE can be used to evaluate LAA stasis and thrombus. A filling defect of contrast medium in the non-thrombotic LAA only on early-phase CCT in patients with AF occurs from time to time, but the factors affecting the formation of these filling defects are not clear. In this study, we compared the CCT, TEE, transthoracic echocardiography (TTE), and clinical data between nonvalvular AF patients with and without early CCT filling defects. We further analyzed the differences in LAA flow velocity (LAAFV) according to filling degree so as to explore the factors influencing this computed tomography sign and its clinical significance. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-146/rc).

Methods

Participants

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective single-center case–control study was performed in the Department of Cardiology, The Second Hospital of Hebei Medical University, between December 2019 and January 2021. The study was approved by the Ethics Committee of The Second Hospital of Hebei Medical University. All patients provided written informed consent.

Patients with nonvalvular AF who were to be treated by catheter ablation and/or LAA closure were enrolled in the study. The inclusion criteria were patients with LAA filling defect only on early-phase CCT and normal filling on the delayed phase; recent TTE, and TEE examinations (0–26 days; mean 2.82 days); and consistent heart rhythm during CCT, TEE, and TTE. Patients with congenital heart disease, rheumatic heart disease, cardiomyopathy, a history of cardiac surgery, radiofrequency ablation, and LAA closure, pacemaker implantation, moderate to severe mitral stenosis, severe liver and kidney dysfunction, or malignant tumors were excluded from the study. Patients with nonvalvular AF who had an LAA filling defect only on early-phase CCT were enrolled as the early filling defect group, and sex- and age-matched patients with nonvalvular AF and no early LAA filling defect were enrolled as the control group. TEE was used to confirm the absence of thrombus in the LAA in both groups. The flowchart for patient enrollment is shown in *Figure 1*.

Data collection

The following data were collected: baseline clinical data, results of laboratory examinations (routine blood tests, serum lipid, liver function), and CCT parameters [left atrial (LA) volume; LAA morphology, location, volume, depth, ridge width, orifice area, and orifice long and short diameter; and left superior pulmonary vein (LSPV) orifice area]. TEE and TTE parameters were also collected, including spontaneous echo contrast (SEC), LAAFV, mitral annular velocity (e'), left ventricular ejection fraction (LVEF), and mitral regurgitation.

CCT examinations

CCT examinations were performed in patients in the supine position using a Philips 256-slice Ict scanner (Brilliance Ict; Philips Healthcare, Amsterdam, The Netherlands). The early scanning range was from the upper edge of the aortic arch to the diaphragmatic surface of the heart. The nonionic contrast agent iohexol (350 mg I/mL, 0.8 mL/kg) was injected through the antecubital vein at a flow rate of 4–5 mL/s and was followed by injection of 30 mL of normal saline at the same flow rate. CCT was performed with retrospective electrocardiogram (ECG) gating, and the start of the image acquisition was determined using the bolus-triggering technique. A region of interest (ROI) was placed on the ascending aorta, and image acquisition was started when the density in the ROI reached 130 Hounsfield units (HU; approximately 10–15 s after contrast injection). The scanning parameters were as follows: tube voltage 120 Kv, tube current 280–350 mAs/rev, collimation 128×0.625 mm,

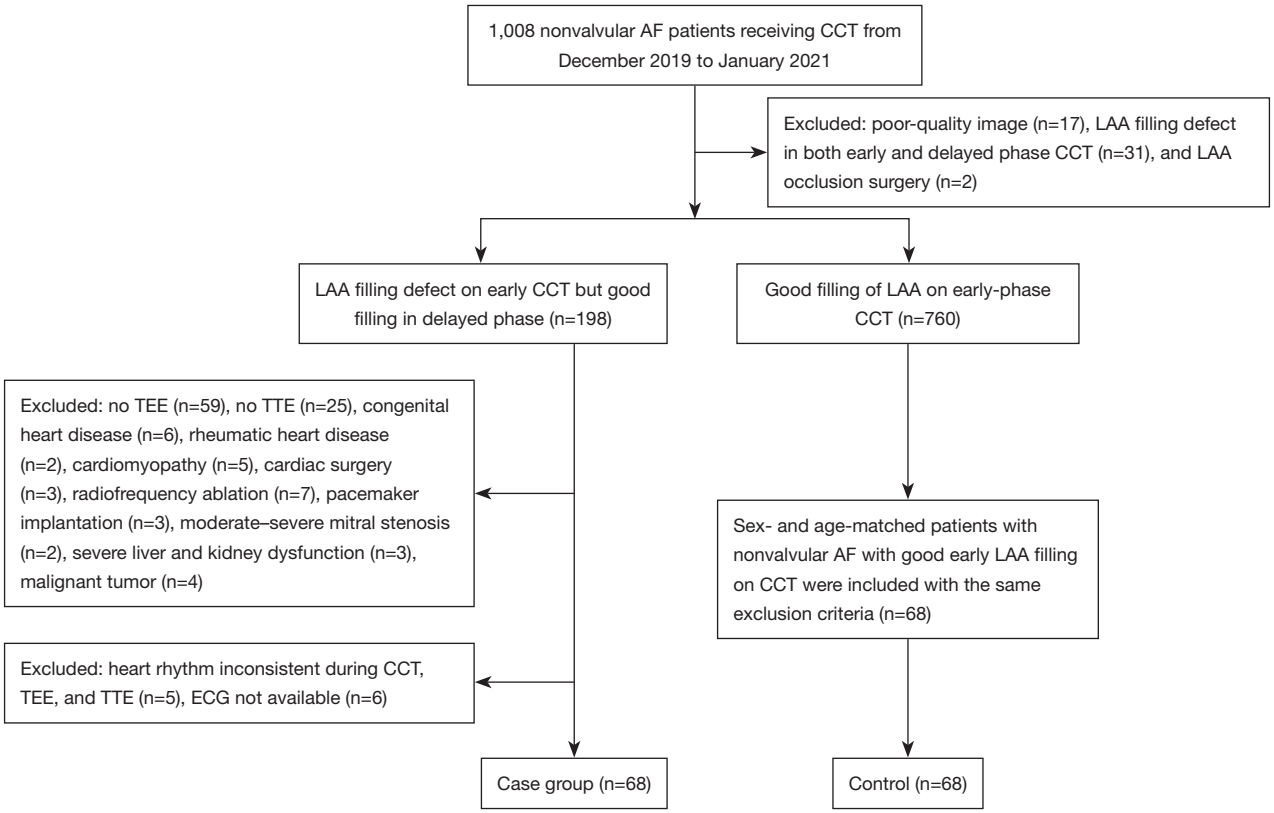

Figure 1 Flowchart of patient enrollment. AF, atrial fibrillation; CCT, cardiac computed tomography; LAA, left atrial appendage; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; ECG, electrocardiogram.

pitch 0.18, rotation time 330 ms, and matrix 512×512. The delayed scan was automatically triggered 50 s after injection of contrast agent mainly for the LAA area. At this time, the tube voltage was 100 kV to reduce the scanning dose. At 45% and 75% of the RR interval, the early and delayed images were reconstructed with a layer thickness of 0.9 mm and a layer spacing of 0.45 mm.

TEE examinations

TEE examinations were conducted in accordance with standard inspection procedures using a Philips Ie33 color Doppler ultrasound diagnostic instrument. LAAFV was measured by placing the pulsed-wave Doppler sample volume at the orifice of the LAA, and the peak emptying velocity signals were averaged over a minimum of 3 cardiac cycles (4) (*Figure 2A,2B*). SEC was regarded as a dynamic "smoke-like" mode (5). The interval between CCT and TEE in the early filling defect group was 0–10 days (mean 2.43 days) and was 0–7 days (mean 2.15 days) in the control group.

TTE examinations

TTE examinations were performed using standard procedures and a Philips Ie33 color Doppler ultrasound diagnostic instrument. LVEF was measured using the improved Simpson method, and e' was measured with tissue Doppler imaging. The interval between CCT and TTE in the early filling defect group was 0–26 days (mean 3.22 days) and was 0–12 days (mean 2.91 days) in the control group.

Measurement of CCT parameters

All images were processed and reviewed using a Philips EBW4.5 workstation. An early LAA filling defect was defined as an obvious area of low attenuation, representing

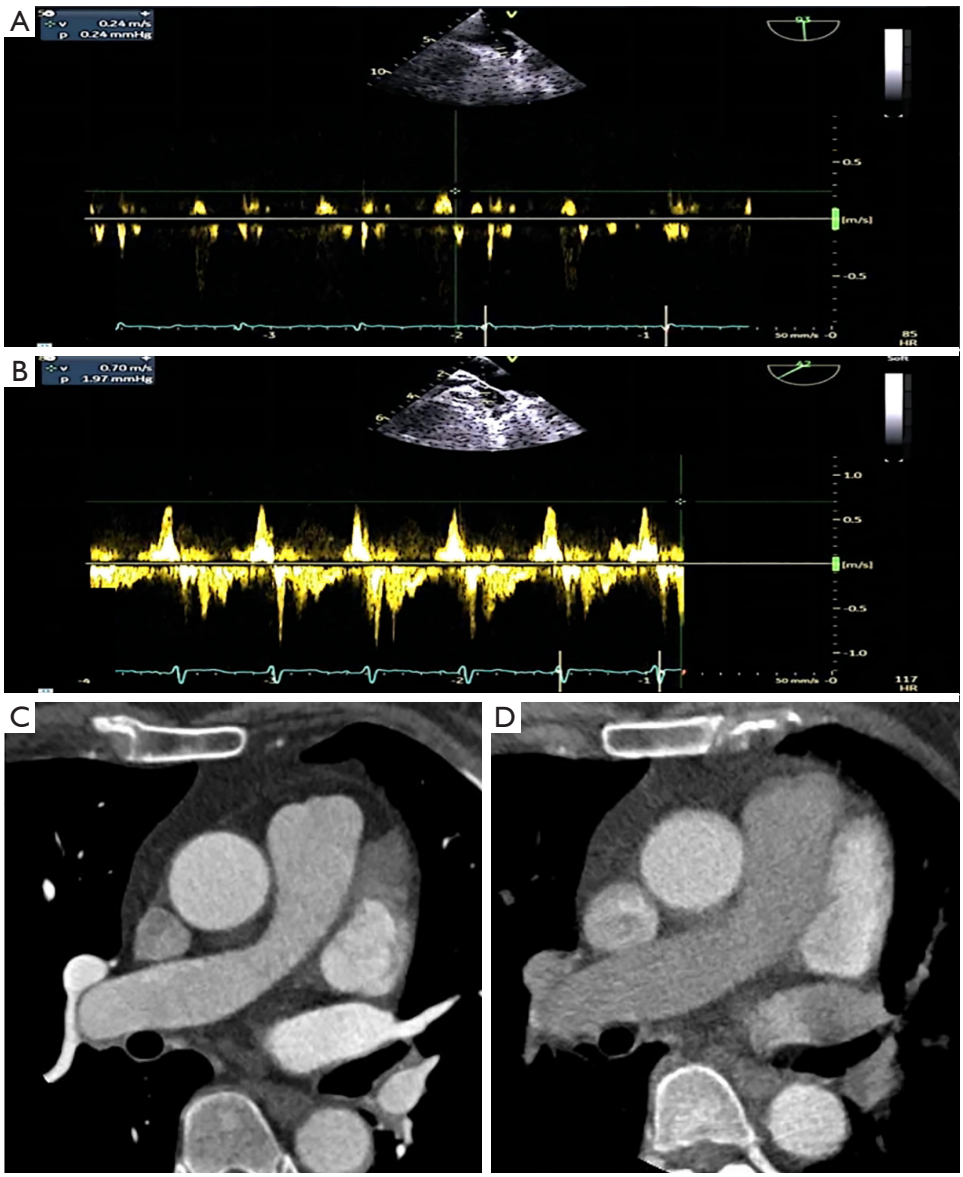

Figure 2 Measurement of LAAFV by TEE and definition of the LAA filling defects on early-phase CCT. (A,B) During TEE, LAAFV was measured by pulse Doppler ultrasound. Representative images are shown for a patient in the early filling defect group (LAAFV 24 cm/s; A) and another patient in the control group (LAAFV 70 cm/s; B). (C,D) CCT of another patient showed an LAA filling defect in the early phase (C) and no filling defect in the corresponding position in the delayed phase (D). LAAFV, left atrial appendage flow velocity; TEE, transesophageal echocardiography; LAA, left atrial appendage; CCT, cardiac computed tomography.

incomplete mixing of contrast medium and blood, that appeared only on early-phase images (*Figure 2C,2D*). All patients enrolled in the study (n=136) were divided into 3 groups according to the degree of the early filling defect (6) (*Figure 3A-3C*): (I) no filling defect, in which the LAA cavity showed contrast enhancement equal to or more than that of the LA cavity; (II) a mild to moderate filling defect, in which the LAA cavity showed contrast enhancement less than that of the LA cavity with preserved contrast between the pectinate muscles and the LAA cavity; and (III) a severe filling defect, in which the LAA cavity showed contrast enhancement less than that of the LA

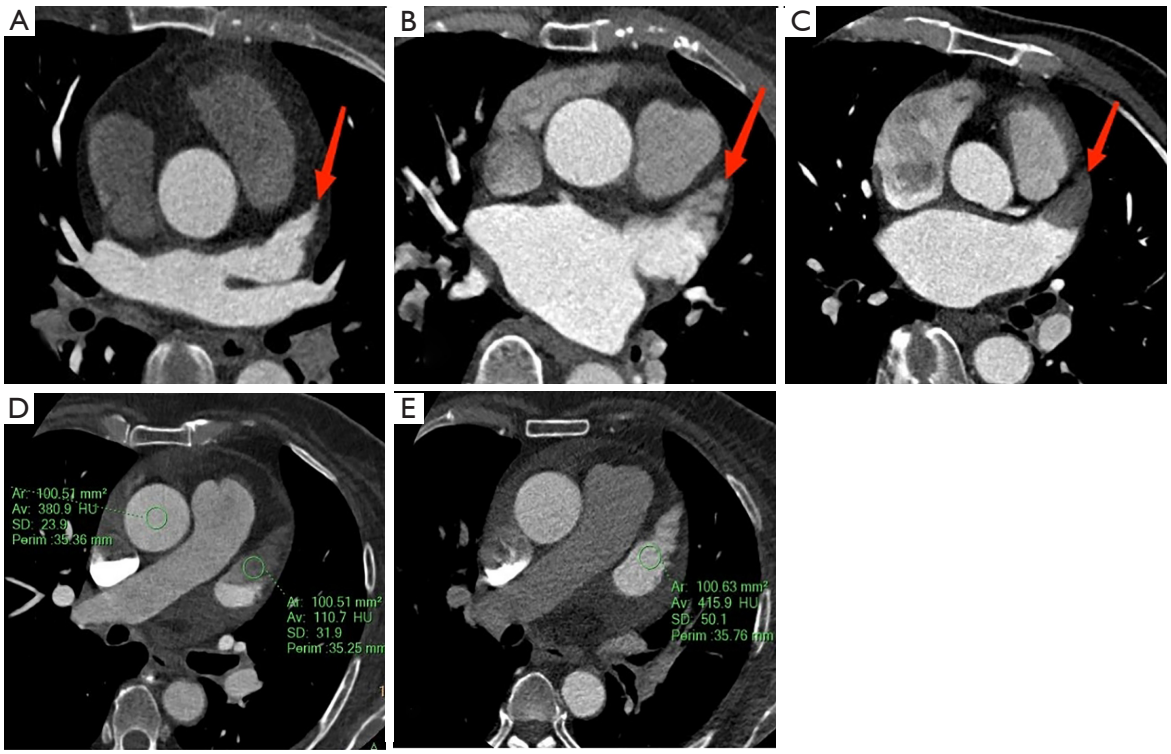

Figure 3 (A-C) Classification of the severity of the early filling defect in the LAA and (D,E) measurement, in HU, of the LAA and AA. (A) Normal filling: contrast enhancement of the LAA cavity (arrow) is equal to or higher than that of LA cavity. (B) Mild to moderate filling defect: contrast enhancement of the LAA cavity (arrow) is lower than that of the LA cavity, but the contrast between the pectinate muscle and LAA cavity is good. (C) Severe filling defect: contrast enhancement of the LAA cavity (arrow) is lower than that of the LA cavity, with no contrast between the pectinate muscle and LAA cavity (arrow). (D) Regions of interest (~10 mm^2) were placed inside the filling defect in the LAA seen on early CCT images and the AA on the same slice to generate an LAA/AA HU ratio. (E) LAA HU on delayed CCT images was measured in the same way to generate the LAAe–LAAd. LAA, left atrial appendage; HU, Hounsfield units; AA, ascending aorta; LA, left atrium; LAAe–LAAd, HU difference between early and delayed CCT of the LAA. CCT, cardiac computed tomography.

without contrast between the pectinate muscles and the LAA cavity. Quantitative measurement of the filling defects was performed (7) (*Figure 3D,3E*). ROIs of approximately 10 mm^2 were placed inside the filling defect of the LAA on early CCT images and the ascending aorta (AA) on the same slice to generate an LAA/AA ratio in HU. The LAA (HU) on delayed CCT images was measured in the same way to generate a difference (in HU) between early and delayed CCT of the LAA (LAAe–LAAd). Multiplanar reconstruction was used to obtain cross-sectional images for measurement of the long and short diameter of the LAA, the area of the LAA opening, and the LSPV orifice area (8) (*Figure 4A-4E*). The internal image of the LA was obtained by using simulation endoscope technology to measure the width of the middle part of the LAA ridge (*Figure 4F*). LA volume, LAA volume, the LA volume index (LAVI; LA volume/body surface area), the LAA volume index (LAA volume/body surface area), the morphology and depth of the LAA, and the positional relationship between the LAA and LSPV were measured using the comprehensive cardiac analysis software built into the Philips EBW4.5 workstation (*Figure 5*). LAA positions were divided into 3 types (9) (*Figure 6*): type I, with LAA higher than the LSPV; type II, with LAA and LSPV at the same level; and type III, with LAA lower than the LSPV. LAA morphology was classified as cactus, chicken wing, windsock, or cauliflower LAA (*Figure 6*) according to Di Biase *et al.* (10).

All measurements were performed by 2 experienced cardiovascular imaging diagnostic physicians [with 8 (XWL) and 2 (GJM) years of experience]. If there was disagreement in the results, another senior physician (XT) was consulted so a consensus could be reached.

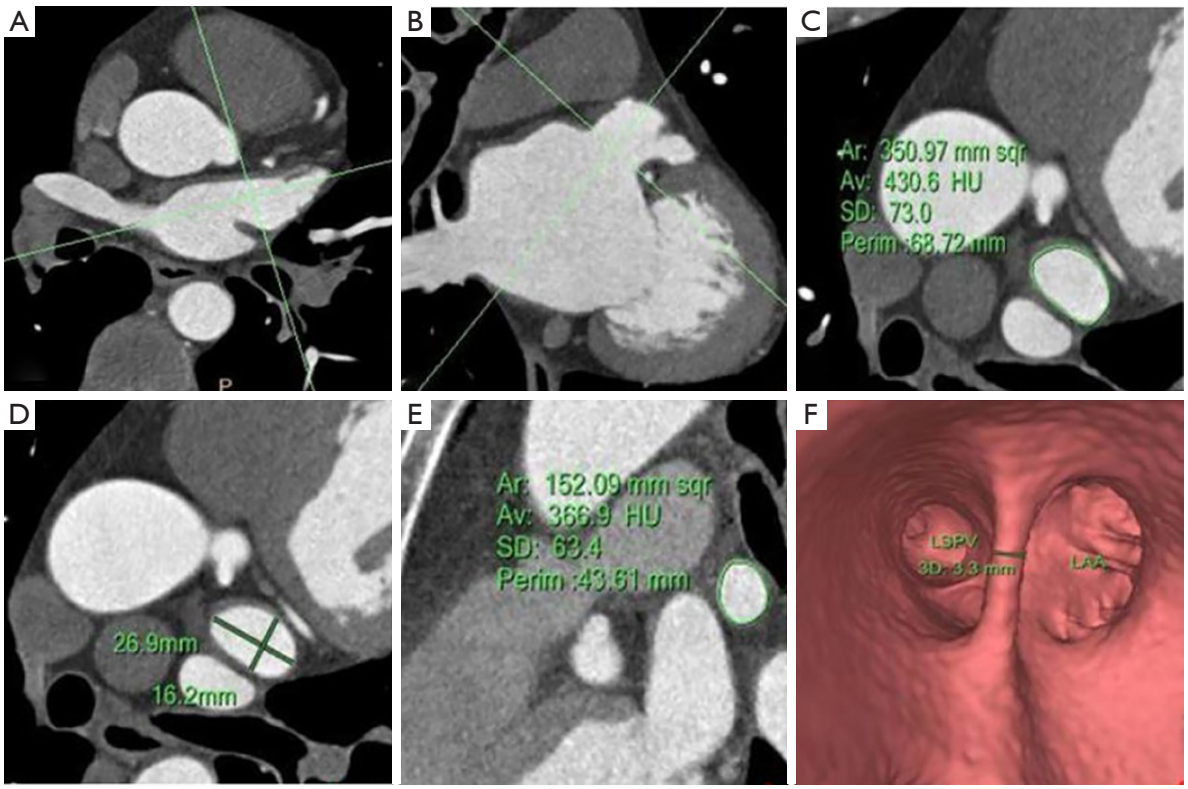

Figure 4 Measurement methods for the LAA orifice, LSPV orifice, and LAA ridge width. (A) The center of the cross-positioning line was placed in the transition area between the LA and LAA, with the 2 positioning lines parallel and vertical to the LAA length. (B-D) On oblique coronal images of the LAA, the cross-positioning line was adjusted at the atrial wall fold in the oblique coronal image transition area, with the 2 positioning lines made parallel and vertical to the LAA (B) to obtain an image of the LAA orifice to measure the orifice area (C) and the long and short diameters (D). (E) The same multiplanar reconstruction method was used to obtain the orifice section of the LSPV for measurement. (F) The width of the middle of the LAA ridge was measured by virtual endoscopy. LAA, left atrial appendage; LSPV, left superior pulmonary vein; LA, left atrium.

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables with a normal distribution are presented as the mean ± standard deviation (SD) and were compared between groups using independent *t*-tests. Data with a skewed distribution are presented as the median with interquartile range (IQR) and were compared between groups using Mann-Whitney tests. Categorical data are presented as numbers and percentages and were compared between groups with the chi-squared test. Binary multivariable logistic analyses were performed to screen independent predictive factors for early LAA filling defect. The area under the curve (AUC) and the optimal threshold of the influencing factors were determined by receiver operating characteristic (ROC) curve analysis. Pearson correlation, Kruskal-Wallis tests, and Bonferroni correction were performed for correlation and comparison of data. A P value <0.05 was considered to be statistically significant.

Results

Clinical data

A total of 68 patients with nonvalvular AF who had an LAA filling defect only on early-phase CCT were enrolled as the early filling defect group (48 males, 20 females; age range 39–79 years, mean age 62.72±8.13 years) and 68 sex- and age-matched patients with nonvalvular AF but no LAA filling defect were enrolled as the control group. All patients with paroxysmal AF in both groups showed sinus rhythm during CCT, TEE, and TTE examinations, and those with persistent AF during imaging showed an AF rhythm. Early

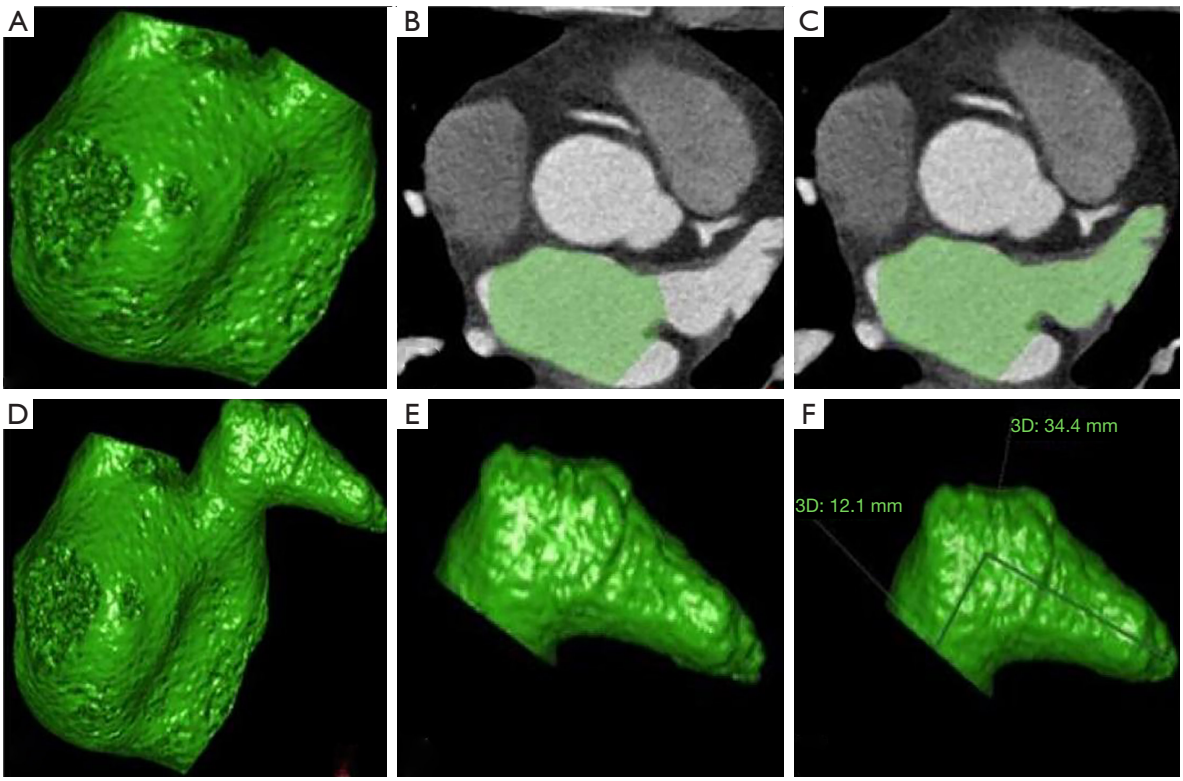

Figure 5 Measurement of the volume and depth of the LAA using cardiac function analysis software. (A) The 3D image and volume of the LA were obtained automatically. (B-D) The filling tool was used to fill in the LAA on the axial image (B,C) to obtain the 3D image (D) of the LA and LAA. (E,F) The cutting tool was used to separate the LA and LAA from the LAA orifice to obtain the LAA volume (E) and to measure the depth of the LAA along its direction (F). LAA, left atrial appendage; 3D, 3-dimensional; LA, left atrium.

LAA filling defects occurred significantly (P<0.05) more frequently in patients with persistent AF during imaging, congestive heart failure, a history of brain infarction, and accelerated heart rate (*Table 1*).

Comparisons of CCT, TEE, and TTE variables between the filling defect and control groups

Among the CCT parameters (*Table 2*), LAVI, LAA volume index, LAA orifice area, LAA long and short diameters, and LAA depth were significantly (P<0.001) increased in the filling defect compared with control group. There was no significant (P>0.05) difference between the 2 groups in LAA shape, LSPV orifice area, left upper and lower pulmonary vein cotrunk, LAA orifice position, or LAA ridge width.

With regard to TEE and TTE parameters (*Table 2*), LAAFV and LVEF decreased significantly (P<0.001), whereas the LAA SEC ratio increased significantly (P<0.001) in the filling defect compared with control group. There was no significant (P>0.05) difference in e' between the 2 groups.

Laboratory test results

The results of laboratory tests are presented in *Table 3*. The erythrocyte count, hemoglobin, aspartate aminotransferase, and serum uric acid were significantly higher in the early filling defect than in the control group (P<0.05).

Multivariable logistic regression analysis

The multiple collinearity test revealed collinearity between cardiac rhythm and AF type at the time of examination. There was also collinearity between the LAA opening area and the long and short diameter of the opening, as well as between the LAA depth and the LAA volume index. Based on clinical experience as well as the results of the univariable analysis and multicollinearity test, cardiac rhythm, heart

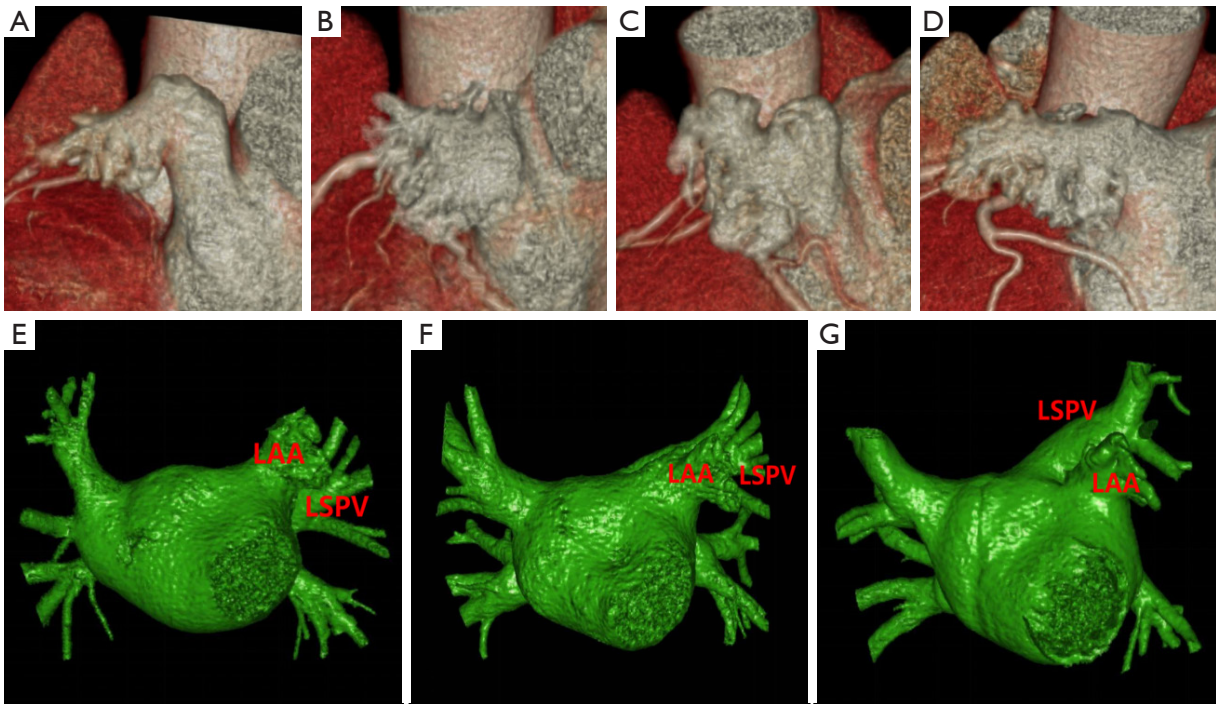

Figure 6 (A-D) Morphology and (E-G) location of the LAA. (A) Chicken wing, (B) cauliflower, (C) cactus, and (D) windsock morphology. (E-G) Classification of LAA location was based on the relationship between the LAA and LSPV. LAA location was classified as either type I (E; the LAA is higher than the LSPV), type II (F; the LAA and LSPV are at the same level), or type III (G; the LAA is lower than the LSPV). LAA, left atrial appendage; LSPV, left superior pulmonary vein.

rate, LAVI, LAA volume index, LAA orifice area, SEC, LAAFV, LVEF, mitral regurgitation, red blood cell count, aspartate aminotransferase, and uric acid were included in the multivariable logistic regression analysis.

Decreased LAAFV [odds ratio (OR) =0.918; 95% confidence interval (CI): 0.883–0.954; P<0.001; *Figure 7A*], and increased LAVI (OR =1.055; 95% CI: 1.012–1.099; P=0.011; *Figure 7B*) were independent factors associated with LAA filling defect on early-phase CCT (*Table 4*). The LAAFV threshold for predicting early filling defects was 40.5 cm/s, with an AUC of the ROC curve of 0.905 (sensitivity 82.4%, specificity 91.2%). The LAVI threshold was 58.77 mL/m^2, with an AUC of 0.840 (sensitivity 85.3%, specificity 72.1%).

Quantitative measurement and grading of LAA filling defects

The LAAFV measured on TEE was significantly (P<0.001) positively correlated with the LAA/AA ratio (r=0.614; *Figure 7C*) and LAAe–LAAd (r=0.591; *Figure 7D*) measured on CCT. The LAAFV was also determined for each of the early filling defect categories. The median LAAFV was 56 cm/s (IQR 44–75 cm/s) in control patients with no filling defect (n=68), 28 cm/s (IQR 23–34 cm/s) in patients with a mild to moderate filling defect (n=45), and 21 cm/s (IQR 19–25 cm/s) in patients with a severe filling defect (n=23); the differences between groups were significant (P<0.05; *Figure 7E*).

Discussion

Principal findings

In the present study, after adjusting for confounders, LAAFV and LAVI were found to be independent factors associated with early LAA filling defects in AF patients, which partially supports the findings reported by Ouchi *et al.* (11). When the LAAFV was <40.5 cm/s and/or the LAVI was >58.77 mL/m^2, the probability of LAA filling defects on early-phase CCT was significantly increased. The LAA/AA ratio and LAAe–LAAd were significantly

Table 1 Clinical data for the control and early LAA filling defects groups

Variables	Early filling defects (n=68)	Control (n=68)	P value
Age (years)	64 [59–67]	65 [58–69]	0.589
Male sex	48 (70.6)	46 (67.6)	0.710
BMI (kg/m^2)	26.33±3.62	26.31±3.67	>0.9
Type of AF			<0.001
Paroxysmal	8 (11.8)	55 (80.9)	
Persistent	60 (88.2)	13 (19.1)	
Time since AF diagnosis (months)	36 [6.5–81]	24 [6.5–60]	0.656
Heart failure	43 (63.2)	25 (36.8)	0.002
Hypertension	42 (61.8)	41 (60.3)	0.860
Diabetes	14 (20.6)	9 (13.2)	0.253
Hyperlipidemia	14 (20.6)	15 (22.1)	0.834
CHD	45 (66.2)	37 (54.4)	0.161
Brain infarction	23 (33.8)	8 (11.8)	0.002
Smoking	20 (29.4)	15 (22.1)	0.327
Anticoagulation or antiplatelet medication	57 (83.8)	57 (83.8)	>0.9
Heart rate (bpm)	81 [74–98]	72 [63–87]	<0.001

Unless indicated otherwise, data are presented as the mean ± SD, median [interquartile range], or n (%). LAA, left atrial appendage; BMI, body mass index; AF, atrial fibrillation; CHD, coronary heart disease; SD, standard deviation.

positively correlated with LAAFV measured on TEE. There was a significant difference in LAAFV between groups with different degrees of filling defect. LAA morphology was independent of filling defects. An early LAA filling defect was associated with LAA emptying dysfunction. These findings contribute to thrombosis risk stratification in patients with AF.

LAAFV and LAA early filling defects

In the present study, LAAFV was an independent factor associated with early LAA filling defects in patients with AF, which is consistent with the outcomes of a previous study (11). This is easy to explain because slow blood flow prevents adequate mixing of blood with contrast agent and contributes to creating an early filling defect. LAAFV is a parameter widely used to evaluate LAA function (3). LAAFV >50 cm/s is considered normal (12). A reduction in LAAFV is a sign of LAA dysfunction that worsens as a continuous process, resulting in a continuous increase in the possibility of SEC and thrombosis (13). LAAFV <35 cm/s was significantly related to embolic risk and SEC (5). Some studies have reported that a decrease in the LAA flow rate is associated with an increase in the clinical severity of stroke and is an independent risk factor for stroke (14). In the present study, the LAAFV threshold for the risk of LAA early filling defect was 40.5 cm/s, which is lower than the normal LAAFV level, indicating that an LAA filling defect reflects a decrease in LAAFV. SEC is also an independent predictor of cardiogenic thrombosis and thromboembolic events in patients with AF (15). In this study, early LAA filling defects were significantly correlated with SEC because slow blood flow is the common basis of these two phenomena. Therefore, early an LAA filling defect primarily reflects a reduction in LAA function and may be associated with embolization and stroke.

LAVI and LAA early filling defect

The present study found, for the first time, that LAVI was an independent factor associated with early LAA filling defects. This can be explained as follows. The main pattern of LAA blood flow is predominantly determined by passive and active LAA emptying (16,17). The LAA is directly

Table 2 CCT, TEE, and TTE variables in the filling defect and control groups

Variables	Early filling defects (n=68)	Control (n=68)	P value
LAA morphology			0.651
Cauliflower	22 (32.4)	25 (36.8)	
Windsock	7 (10.3)	6 (8.8)	
Chicken wing	17 (25.0)	21 (30.9)	
Cactus	22 (32.4)	16 (23.5)	
LSPV and LIPV common trunk	1 (1.5)	3 (4.4)	0.612
LAA location			0.415
I	3 (4.4)	1 (1.5)	
II	27 (39.7)	23 (33.8)	
III	38 (55.9)	44 (64.7)	
LA volume (mL)	137.96±37.74	96.63±28.58	<0.001
LAA volume (mL)	11.15 [8.23–16.05]	7.30 [5.23–9.18]	<0.001
LAVI (mL/m^2)	69.09±17.67	48.59±13.14	<0.001
LAA volume index (mL/m^2)	5.82 [4.35–8.15]	3.55 [2.58–4.75]	<0.001
LAA depth (mm)	46.76±8.71	41.72±8.55	0.001
LAA ridge width (mm)	4.80 [4.00–7.28]	5.65 [4.42–7.55]	0.300
LAA orifice area (cm^2)	4.13 [3.43–4.98]	2.78 [2.15–4.03]	<0.001
LAA orifice long diameter (mm)	27.43±4.74	24.00±4.42	<0.001
LAA orifice short diameter (mm)	20.39±3.40	16.55±4.58	<0.001
LSPV orifice area (cm^2)	2.24 [1.71–3.18]	1.99 [1.60–2.68]	0.124
SEC	23 (33.8)	2 (2.9)	<0.001
LAAFV (cm/s)	25 [21–32]	56 [44–75]	<0.001
LVEF (%)	58.86±10.18	66.17±6.99	<0.001
e' (cm/s)	6 [6–7]	6 [5–8]	>0.9
Mitral regurgitation	67 (98.5)	59 (86.8)	0.009

Unless indicated otherwise, data are presented as the mean ± SD, median [interquartile range], or n (%). CCT, cardiac computed tomography; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; LAA, left atrial appendage; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; LA, left atrium; LAVI, left atrial volume index; SEC, spontaneous echo contrast; LAAFV, left atrial appendage flow velocity; LVEF, left ventricular ejection fraction; e', mitral annular velocity; SD, standard deviation.

connected to the LA and receives blood flow directly from it as one continuous space. Therefore, LA pressure is also a major determinant of LAA flow (16). The development of AF results in LA dilatation, contractile dysfunction, increased LA pressure, progressive fibrosis, and atrial myopathy (18). The increase in LA pressure can lead to an increase in the afterload of the LAA but a decrease in LAAFV (19), which affects the mixing of the contrast agent with the blood in the LAA. It has been reported that LAVI is independently associated with cardioembolic stroke (20), and LA enlargement is an independent predictor of stroke and systemic embolism in patients with nonvalvular AF (21). Therefore, it is more reasonable to suggest that early filling defects in LAA are also associated with the risk

Table 3 Laboratory test results in the filling defect and control groups

Variables	Early filling defects (n=68)	Control (n=68)	P value
RDW-CV (%)	12.94±0.97	12.94±0.77	0.984
PDW (fL)	14.1 [11.8–16.5]	16.2 [12.3–16.7]	0.160
White blood cell count ($\times10^9$/L)	6.21±1.48	6.06±1.69	0.562
Red blood cell count ($\times10^{12}$/L)	4.65±0.52	4.39±0.52	0.005
Hemoglobin (g/L)	148 [133–157]	140 [129–150]	0.005
Platelet count ($\times10^9$/L)	207.60±51.28	208.00±55.08	0.965
Alanine aminotransferase (U/L)	21.0 [13.6–30.3]	19.8 [13.3–26.8]	0.344
Aspartate aminotransferase (U/L)	20.0 [17.3–27.0]	17.5 [14.3–22.8]	0.033
Creatinine (μmol/L)	74.13±14.51	73.32±12.97	0.732
Uric acid (μmol/L)	354.49±86.10	317.72±76.50	0.009
Total cholesterol (mmol/L)	4.02±0.85	4.02±0.86	0.886
Triglyceride (mmol/L)	1.25 [1.00–1.59]	1.33 [0.94–1.71]	0.571
High-density lipoprotein (mmol/L)	1.16±0.26	1.16±0.23	0.914
Low-density lipoprotein (mmol/L)	2.38±0.72	2.33±0.78	0.693
Fibrinogen (g/L)	2.72±0.71	2.59±0.58	0.362

Unless indicated otherwise, data are presented as the mean ± SD, median [interquartile range], or n (%). RDW-CV, red cell distribution width; PDW, platelet distribution width; SD, standard deviation.

of embolization and stroke.

LAA morphology

Our study did not find LAA morphology to be associated with early LAA filling defects, which differs from the results reported by Ouchi *et al.* in 2020 (22), who found that chicken wing LAA was an independent predictor of LAA filling defects. However, in another recent article, Ouchi *et al.* reported that LAA morphology was not associated with LAA filling defects (11), which is consistent with our study results. These different conclusions may be due to variability among different observers, sampling error, ethnic differences, or differences in the incidence of LAA morphology reported (23,24).

TEE and CCT examinations

There are many imaging modalities available to assess cardiac morphology and function (25,26). TEE is the most widely used and accepted method to evaluate LAA function and the risk of thromboembolism. However, TEE is semi-invasive, requires anesthesia, and may cause some complications (27). CCT can intuitively and reliably provide 3-dimensional high-resolution anatomy of the LA, LAA, and pulmonary vein in different cardiac cycles for evaluation of LA and LAA function, LAA thrombosis, and pulmonary vein stenosis. The present study found that the quantitative measurement index LAA/AA of filling defects on CCT was significantly positively correlated with LAAFV, which is in line with the outcomes of a previous study (7). In addition, the present study found, for the first time, that LAAe–LAAd was also positively correlated with LAAFV. Therefore, hemodynamic information can be partially obtained from still images of CCT when TEE is not feasible. CCT is helpful in predicting the decrease of LAAFV.

Clinical significance

Thromboembolic complications seriously affect the health of patients with AF and are the main cause of death and disability. Our study suggests that LAAFV and LAVI are independent factors associated with early LAA filling defects in patients with AF, representing decreases in LAA function and an increase in thrombosis risk. The imaging sign of an early filling defect is easy to obtain, helps with the early

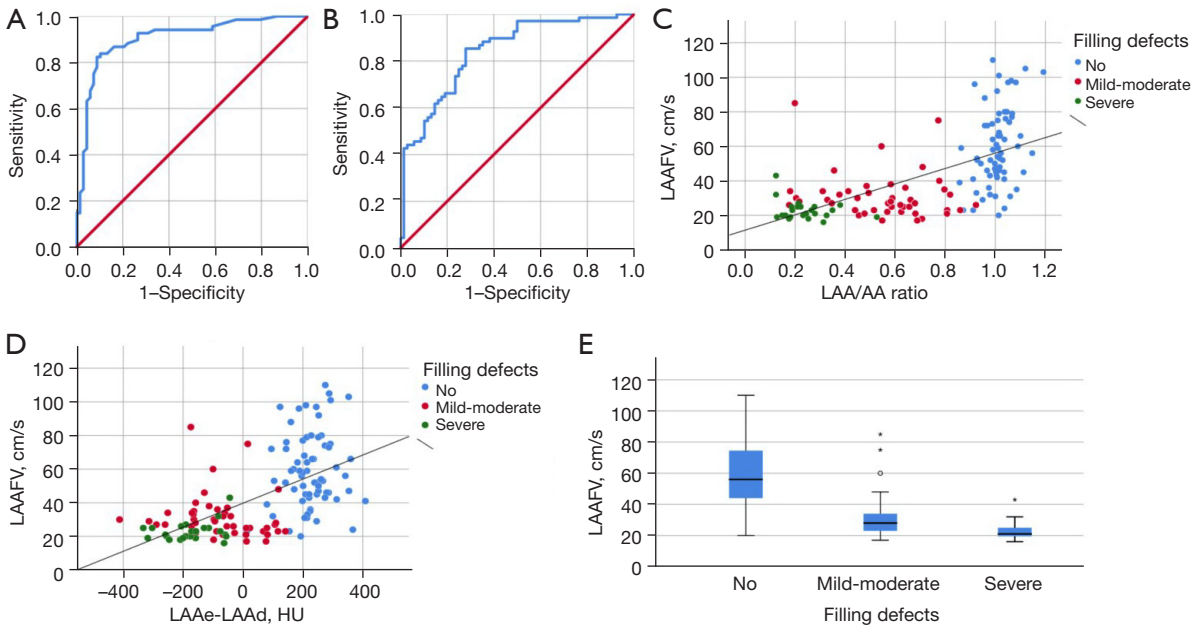

Figure 7 ROC curve analysis of the early filling defect in the LAA, relationships between LAAFV and the LAA/AA HU ratio or the LAAe–LAAd, and box plots of LAAFV according to the severity of the LAA filling defect. (A) Using ROC curve analysis, a cutoff value for LAAFV of 40.5 cm/s was established, which had an AUC of 0.905 (sensitivity 82.4%, specificity 91.2%). (B) Using ROC curve analysis, a cutoff value for the left atrium volume index of 58.77 mL/m^2 was established, which had an AUC of 0.840 (sensitivity 85.3%, specificity 72.1%). (C,D) Significant positive correlations were found between LAAFV and both the LAA/AA HU ratio of early-phase CCT (C; r=0.614; P<0.001) and LAAe–LAAd (D; r=0.591; P<0.001). (E) Significant (P<0.05) differences were detected in LAAFV according to the severity of the LAA filling defect (no defect: median 56 cm/s, IQR 44–75 cm/s; mild to moderate filling defect: median 28 cm/s, IQR 23–34 cm/s; severe filling defect: median 21 cm/s, IQR 19–25 cm/s). The boxes show the IQR, with the median value indicated by the horizontal line; whiskers show the range. ROC, receiver operating characteristic; LAA, left atrial appendage; LAAFV, left atrial appendage flow velocity; AA, ascending aorta; HU, Hounsfield unit; CCT, cardiac computed tomography; LAAe–LAAd, HU difference between early and delayed CCT of the LAA; AUC, area under the curve; IQR, interquartile range.

identification of high-risk factors for LAA thrombosis, and is a valuable index of thrombosis risk stratification. For LAA early filling defects in patients with AF, timely initiation of anticoagulant therapy may be of considerable help in preventing thromboembolic events. However, further studies on anticoagulation therapy are necessary to prevent the risk of hemorrhage.

Strengths and limitations

Compared with previous studies (11,22), our study had the following advantages. First, the cardiac rhythm of each patient included in this study was consistent during CCT, TTE, and TEE examinations, which ensured the accuracy of the study results; previous studies did not exclude this confounding factor. Second, many new relevant factors were been considered in this study, including LAVI, LAA structure, adjacent structural parameters of the LAA, and laboratory indicators. Third, LA- and LAA-related parameters were measured in the same phase of the cardiac cycle. In the study of Ouchi *et al.*, persistent AF, decreased LAAFV, increased LAA volume, and low LVEF were independent predictors of early LAA filling defects (11), which is not completely in line with the findings of our study. These differences may be explained by the reasons given above.

This study also has some limitations, including its retrospective, single-center design, the small cohort of patients, with the possibility of selection bias, and the enrollment only of patients with nonvalvular AF who were to have radiofrequency ablation or LAA closure. Patients did not undergo CCT, TEE and TTE on the same day, which might have affected the outcomes of the study. The enhancement of LAA is related to the concentration

Table 4 Logistic regression analysis of factors associated with early LAA filling defects

Variables	OR	95% CI	P value
AF during imaging	3.462	0.592–20.238	0.168
LAVI	1.055	1.012–1.099	0.011
LAA volume index	1.426	0.814–2.499	0.215
LAA orifice area	0.613	0.273–1.379	0.237
Heart rate	0.979	0.946–1.014	0.229
LAAFV	0.918	0.883–0.954	<0.001
SEC	2.185	0.352–13.557	0.401
LVEF	0.959	0.89–1.033	0.270
Mitral regurgitation	3.455	0.269–44.46	0.341
Red blood cell count	0.803	0.232–2.777	0.729
Aspartate aminotransferase	1.007	0.944–1.074	0.841
Uric acid	1.006	0.999–1.013	0.099

LAA, left atrial appendage; OR, odds ratio; CI, confidence interval; AF, atrial fibrillation; LAVI, left atrial volume index; LAAFV, left atrial appendage flow velocity; SEC, spontaneous echo contrast; LVEF, left ventricular ejection fraction.

of iodine in the contrast medium, the injection rate, the trigger time for early-phase scanning, and the amount of the contrast medium used. Therefore, differences in scanning protocols and device performance may affect the reproducibility of this study. These data must be interpreted with caution. Future studies will have to resolve these issues for improved outcomes.

Conclusions

Decreased LAAFV and increased LAVI are independent factors associated with LAA filling defects only on early-phase CCT. These factors are also high-risk factors for LAA thrombosis and stroke. Early filling defects reflect a reduction in LAA function and the degree of LAA dysfunction. CCT can easily and noninvasively evaluate LAA and identify high-risk factors for LAA thrombosis, providing valuable imaging information for the risk stratification of thromboembolism in patients with AF.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-146/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-146/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The Second Hospital of Hebei Medical University. Written informed consent was obtained from all patients.

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