


# An echo score raises the suspicion of cardiac amyloidosis in Chinese with heart failure with preserved ejection fraction

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## Abstract

**Aims** Transthyretin cardiac amyloidosis (ATTR-CA) has been realized as an important cause of heart failure with preserved ejection fraction (HFpEF). We aim to provide insights into its prevalence in Chinese HFpEF patients, which is not known to date, using increased wall thickness (IWT) score by echocardiography.

**Methods** Consecutive patients with HFpEF (EF  $\geq$  40%) and IWT ( $\geq$ 12 mm) were prospectively screened. Echocardiography was performed, and the IWT score incorporated relative wall thickness, E/e' ratio, longitudinal strains, and tricuspid annular plane systolic excursion, and septal apical-to-base ratio was calculated. ATTR-CA was defined as score  $\geq$ 8 in the absence of serum and urine free light chain.

**Results** Six hundred twenty-four HFpEF patients from January 2019 to December 2021 were enrolled, of which 65.2% were males and the median (interquartile range [IQR]) age was 66 (IQR 57, 73) years. Thirty-three patients (5.3%, 95% CI 3.5–7.0%) were with score  $\geq$ 8, and 33.3% were females. They were younger (58 vs. 69 years,  $P < 0.001$ ), had higher NT-proBNP (6525.0 vs. 1741.5 pg/mL,  $P < 0.001$ ) and troponin I (105.2 vs. 27.7 pg/mL,  $P = 0.001$ ) level, and lower LVEF (47% vs. 57%,  $P < 0.001$ ) compared with the patients with score  $<$ 5. In the internal cohort (82 patients) who had undergone scintigraphy, the IWT score  $\geq$ 8 was shown to have a sensitivity of 85.7% (95% CI 56.2–97.5%) and a specificity of 92.6% (95% CI 83.0–97.3%) for diagnosing CA, and the IWT score  $<$ 5 had great accuracy in excluding CA with the negative predictive value of 100%, supporting the clinical usefulness of the IWT score to guide further dedicated testing for ATTR-CA.

**Conclusions** The IWT score by echocardiography was an excellent tool for screening ATTR-CA in HFpEF. In Chinese HFpEF patients associated with a hypertrophic phenotype, the proportion of highly suspected ATTR-CA as detected by IWT score  $\geq$ 8 was 5.3%, lower than the reported prevalence of ATTR-CA in non-Asian patients with the disease.

**Keywords** Heart failure with preserved ejection fraction; Transthyretin amyloid cardiomyopathy; Multi-parametric echocardiography score; <sup>99m</sup>Tc-pyrophosphate scintigraphy

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## Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for up to 50% of all HF patients with mortality as severe as HF with reduced ejection fraction (HFrEF) but generally lacks effective therapeutic agents.<sup>1,2</sup> Transthyretin cardiac amyloidosis (ATTR-CA) is now recog-

nized as a specific but clinically under-diagnosed cause of HFpEF. Its prevalence was ranging from 10 to 19% in HFpEF as reported recently.<sup>3–5</sup> Of two types of ATTR, wild-type (ATTRwt) and mutated ATTR (ATTRm), ATTRwt is the most common one in HFpEF patients older than 60 years.<sup>3</sup> However, all these reports did not include Chinese patients. Other than case reports, by far, there is no

population-based data regarding the prevalence of ATTR-CA in Chinese patients with HFpEF.

With the availability of disease modifying agents such as tafamidis,<sup>6</sup> ATTR-CA has been an increasingly treatable disease, which further underscores the key role of early diagnosis. Nuclear scintigraphy in the absence of serum or urine monoclonal light chains has been validated as a reliable tool for diagnosing ATTR-CA<sup>7</sup> and recommended by 2019 Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis and 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure.<sup>8,9</sup> However, its availability is limited in many areas and unlikely to be used as a screening tool in clinical practice. Similarly, endomyocardial biopsy (EMB), which is the traditional gold standard for cardiac amyloidosis (CA), is also curtailed by its invasive nature and sampling error.<sup>10,11</sup> In addition, initial studies showed that targeted imaging using amyloid binding positron emission tomography (PET) tracers may be able to detect early stage of CA but has not currently been used in clinical practice.<sup>12</sup> In comparison, echocardiography is widely accessible and remains the first-line imaging tool for investigating HF, and some echocardiographic features have been shown to be “red flags” of CA, although the individual echocardiographic variables are inadequately accurate for diagnosing CA.<sup>8,12,13</sup> Recently, Boldrinini *et al.* developed a multi-parametric echocardiography score called increased wall thickness (IWT) score by integrating multiple echocardiographic variables to guide the diagnostic algorithm of ATTR-CA, and its diagnostic accuracy had been verified in patients with left ventricular (LV) hypertrophy.<sup>14</sup> In accordance with this report, a recent Italian multicentric study investigating the prevalence of CA also proved the usefulness and accuracy of a combination of “CA suggestive” echocardiographic features for detecting CA.<sup>15</sup>

We conducted a prospective, observational, and unicentric study. The primary aim of the study was to provide insights into the prevalence of ATTR-CA in Chinese patients with HFpEF admitted to the hospital. Due to the limited access of scintigraphy, the IWT score was used as the diagnosing tool in the study. The score has not been widely accepted as a tool for diagnosing ATTR-CA, and it was established in suspected amyloid patients with a hypertrophic phenotype who were non-Chinese.<sup>14</sup> Therefore, the study evaluated its diagnostic performance for ATTR-CA in a small internal cohort with HFpEF who underwent nuclear scintigraphy. In addition, the main clinical characteristics associated with ATTR-CA diagnosed by IWT score in this large cohort of Chinese patients with HFpEF were described.

## Methods

### Study patients

3486 consecutive patients with suspected HF admitted to the Cardiology Department of Tongji Hospital that is a tertiary

teaching hospital affiliated with Tongji Medical College, Wuhan, China, from January 2019 to December 2021 were prospectively screened (Figure 1).

Inclusion criteria were as follows: (i) diagnosed as HF<sup>16</sup> with New York Heart Association II–IV symptoms; (ii) elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) > 300 pg/mL; (iii) left ventricular ejection fraction (LVEF)  $\geq$  40%; and (iv) presence of LV hypertrophy (LVH) defined as end-diastolic wall thickness  $\geq$ 12 mm (mid-interventricular septum or mid-posterior wall) on transthoracic echocardiography (TTE). Patients with known CA were also included as long as they met all aforementioned criteria.

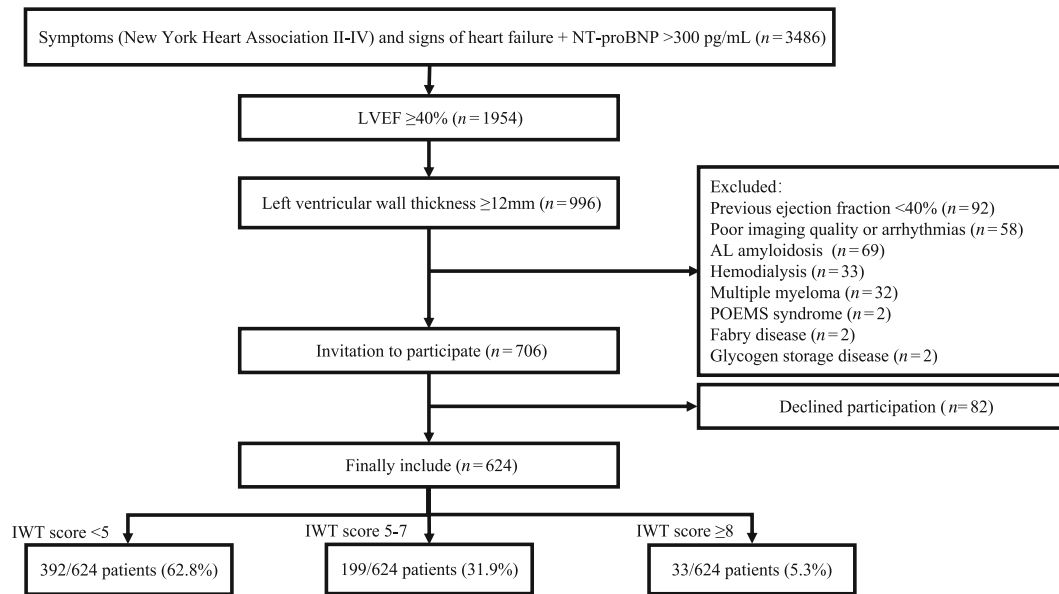
Exclusion criteria were as follows: (i) systemic light chain (AL) amyloidosis, multiple myeloma, or monoclonal gammopathy of undetermined significance; (ii) a history of reduced LVEF (<40%); (iii) a systemic or endocrine disease involving the myocardium; (iv) end-stage kidney disease having been on haemodialysis before the index hospitalization; and (v) poor echocardiographic imaging quality or the presence of arrhythmia that interfered the strain analysis.

The study was approved by the Institutional Review Board of the Ethics Committee of Tongji Hospital and was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consents.

### Study design

Demographic and clinical characteristics of all enrolled patients were collected. Coronary artery disease was defined as a history of myocardial infarction, previous coronary vascularization, or the presence of coronary stenosis >50%. The laboratory variables consisted of troponin I (cTnI), NT-proBNP, serum, and urine biochemistry. Estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI formula. The first electrocardiogram (ECG) at admission was used for analysis. A low voltage pattern was considered present if no QRS amplitude exceeded 0.5 mV in any limb lead or 1 mV in any precordial lead.<sup>17,18</sup> The pseudo-infarct pattern was defined as QS wave in two consecutive leads.

Standard TTE was completed during admission for all enrolled patients, and a multi-parametric echocardiography score, IWT score, was calculated according to the echocardiography protocol described below and previously reported.<sup>14</sup> Some of the patients underwent scintigraphy, and the choice of scintigraphy was decided by the patients' principal physician. Moreover, all patients who had either a positive scintigraphy result or an IWT score  $\geq$ 8 should complete serum and urine protein electrophoresis by immunofixation electrophoresis plus serum-free light chain assay.

**Figure 1** Flow chart for study design, patient inclusion, and group classification by the IWT score.

### Diagnosis and exclusion of ATTR-CA by the IWT score and its clinical usefulness for detecting ATTR-CA

ATTR-CA was defined in the present study as the IWT score  $\geq 8$  plus the absence of serum and urine free light chain. Moreover, CA was excluded if the score was  $< 5$ .

The IWT score was originally developed in suspected amyloid patients with increased heart wall thickness.<sup>14</sup> Its diagnostic performance for CA in HFpEF patients was not known. Therefore, an internal cohort from the study population was comprised, which included a subgroup of patients undergoing scintigraphy. The diagnostic performance of the score for ATTR-CA in HFpEF was assessed in comparison with the results of scintigraphy in this cohort (Figure 2).

### Echocardiography protocol and the IWT score calculation

Standard TTE were performed at rest on a single echocardiographic system (Vivid E9; GE Vingmed; Horten, Norway). All scans were completed during admission in the core echocardiographic laboratory in the Cardiology Department of Tongji Hospital.

End-diastolic interventricular septum thickness (IVSd) and LV posterior wall thickness (LVPWd), and LV end-diastolic dimensions (LVEDD) were measured from the parasternal long-axis view. LVEF was calculated by the modified biplane Simpson method.<sup>19</sup> In the four-chamber view, tricuspid annular plane systolic excursion (TAPSE) was assessed with

M-mode in the lateral tricuspid annulus; the ratio of LV early (E-wave) to late (A-wave) diastolic filling (E/A) were evaluated with pulsed Doppler; and septal mitral annulus velocity ( $e'$ ) was assessed with tissue Doppler and  $E/e'$  was calculated.<sup>20</sup> Relative wall thickness (RWT) was calculated as previously reported.<sup>21</sup>

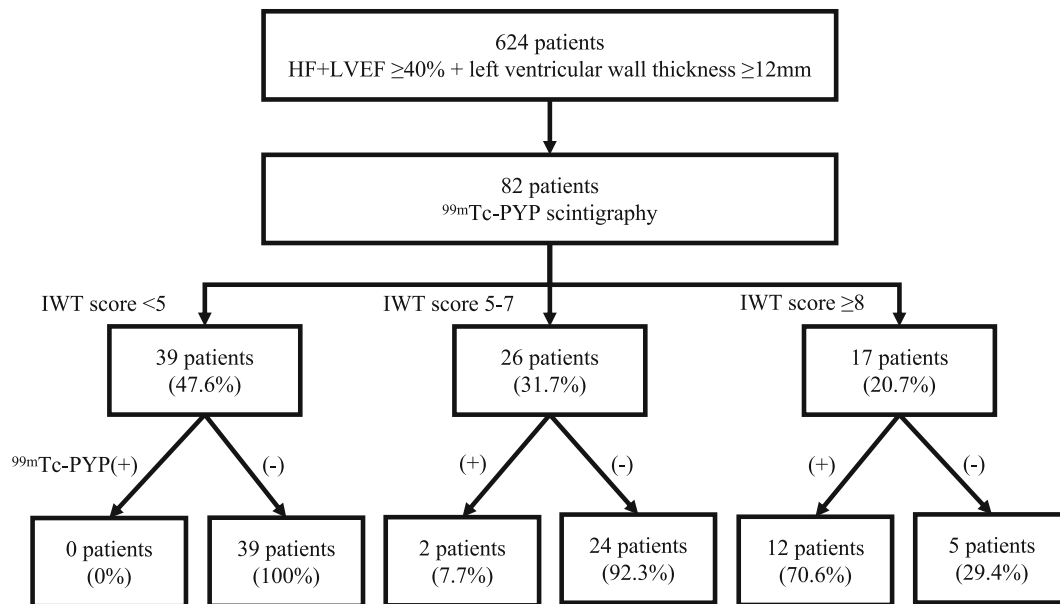
Peak systolic segmental longitudinal strains were obtained by two-dimensional speckle tracking echocardiography (2-D STE). Three consecutive cardiac cycles of 2-D images from apical four-chamber, three-chamber, and two-chamber views with an optimized focus on LV were saved in digital format. Data processing was conducted off-line by using Echo Pac (version: 113, 2017; GE Vingmed, Horten, Norway). Strain was quantified by automated function imaging analysis as previously described<sup>22</sup> and expressed as an absolute value. According to previous study,<sup>14</sup> longitudinal strains (LSs) in the study were the mean value of six segmental longitudinal strains (basal, mid, and apical interventricular septum and basal, mid, and apical lateral wall). The apex-to-base ratio (SAB) was the ratio of systolic longitudinal strains of apical septum to that of basal septum.

As previously described,<sup>14</sup> the IWT score was calculated simply as following: RWT  $> 0.6$  (3 points),  $E/e' > 11$  (1 point), TAPSE  $< 19$  mm (2 points), LSs  $< 13\%$  (1 point), and SAB  $> 2.9$  (3 points).

### Nuclear scintigraphy protocol

Planar imaging with <sup>99m</sup>Tc-pyrophosphate (<sup>99m</sup>Tc-PYP) scintigraphy was performed with a GE Medical Systems

**Figure 2** The validation cohort that was consisted of 82 patients who underwent scintigraphy and the patients' classification by the IWT score and the result of scintigraphy.



single-photon emission computed tomography (SPECT) (Discovery NM/CT 670). The scintigraphy protocol has been described previously.<sup>23</sup> Scans were graded by two experienced, board-certified nuclear cardiologists blinded to patient data and independently analysed the resulting grey-scale images. Discrepancies were resolved by consensus with a third physician. Cardiac  $^{99m}\text{Tc}$ -PYP retention was graded according to a previously reported visual scale ranging from 0 to 3 points; the quantitative heart to contralateral chest ratio (H: CL) was calculated for each scan by calculating counts in equal-sized regions of interest over the heart and contralateral chest. Either a visual score of 2 or 3 or an H: CL of  $> 1.5$  was considered positive and suggestive of ATTR-CA.<sup>24</sup>

### Statistical analysis

Categorical variables are expressed as numbers (percentages), normally distributed continuous data as the mean with standard deviation (SD), and non-normally distributed continuous data as the median with interquartile range (IQR). Differences between groups were analysed with Student's *t*-test or Mann-Whitney *U* test for continuous variables, depending on the normality of the variables, and  $\chi^2$  test or Fisher's exact test for categorical variables. All analyses were performed using SPSS version 25.0 software (SPSS, Inc., Chicago, IL, USA). Statistical tests were two-

tailed, and a *P*-value of  $< 0.05$  was considered statistically significant.

## Results

### Study population

Among total 3486 screened patients, 996 patients meeting the inclusion criteria were identified. Among them, 290 (29.1%) were excluded, including 92 with previous LVEF  $< 40\%$ , 58 with poor imaging quality or arrhythmias, 69 with AL amyloidosis, 32 with multiple myeloma, and 33 on haemodialysis. Of the remaining 706 patients, 82 patients (11.6%) declined to participate in the study. Finally, the study population consisted of 624 of 996 patients (63%) with HFpEF (LVEF  $\geq 40\%$ ) and increased LV wall thickness  $\geq 12\text{mm}$  (Figure 1).

### Demographic and clinical characteristics of the entire cohort and the subgroups stratified by the IWT score

For the overall cohort, the median hospital stay was 7 (IQR 5, 11) days, the median age was 66 (IQR 57, 73) years, 65.2% were males, and 48.1% patients were with eGFR lower than  $60\text{ mL/min/1.73m}^2$ . Other detailed characteristics were shown in Table 1.

For the patients with score  $\geq 8$ , 33.3% were female, not different from those with score  $< 5$  (34.4%,  $P = 0.898$ ). Renal function was also not different in patients with score  $\geq 8$  from those with score  $< 5$  (creatinine: 96 vs. 100  $\mu\text{mol/L}$ ,  $P = 0.527$ ; eGFR: 68.2 vs. 61.1  $\text{mL/min/1.73 m}^2$ ,  $P = 0.222$ , respectively). However, in comparison those with score  $< 5$ , the patients with score  $\geq 8$  were younger (58, IQR 53, 69 vs. 69, IQR 59, 75 years,  $P < 0.001$ ) and had lower BMI (23.6, IQR 20.5, 24.6 vs. 24.8, IQR 22.3, 27.4  $\text{kg/m}^2$ ,  $P = 0.008$ ) and lower blood pressure (SBP: 120, IQR 106, 139 vs. 136, IQR 123, 154 mmHg,  $P < 0.001$ ; DBP: 76, IQR 65, 81 vs. 80, IQR 73, 90 mmHg,  $P = 0.007$ , respectively) and longer hospital stay (10, IQR 8, 14 vs. 7, IQR 5, 10 days,  $P < 0.001$ ). They were less likely to have hypertension (27.3% vs. 76.5%,  $P < 0.001$ ) and diabetes (15.2% vs. 34.9%,  $P = 0.021$ ) and more likely to have a permanent pacemaker (21.1% vs. 6.9%,  $P = 0.01$ ). They presented with higher NT-proBNP (6525.0, IQR 2499.0, 10759.8 vs. 1741.5, IQR 846.0, 3937.3  $\text{pg/mL}$ ,  $P < 0.001$ ) and cTnI (105.2, IQR 25.6, 247.1 vs. 27.7, IQR 9.9, 94.2  $\text{pg/mL}$ ,  $P = 0.001$ ) level. In regard to ECG features, they were more with low voltage (12.1% vs. 0%,  $P < 0.001$ ) and pseudo-infarct pattern (24.2% vs. 7.1%,  $P = 0.002$ ) (Table 1). The characteristics in the group of patients with score 5–7 were mostly somewhere between the other two groups (Table 1).

### Echocardiographic characteristics of the entire cohort and the subgroups stratified by the IWT score

For the entire cohort, the median LVEDD was 47.0 (IQR 43.0, 51.0) mm, LVEF was 57% (IQR 48, 63%), IVS was 15.0 (IQR 13.0, 18.0) mm, longitudinal strains were 10.3% (IQR 7.9, 13.4%), and 27.7% of patients were with LVEF  $< 50\%$ .

Compared with the group with score  $< 5$ , the patients with score  $\geq 8$  had lower LVEDD (43.0, IQR 39.0, 47.0 vs. 48.0, IQR 45.0, 51.0 mm,  $P < 0.001$ ) and LVEF (47%, IQR 40, 60% vs. 57%, IQR 50, 63%,  $P < 0.001$ ) and thicker wall thickness (IVS: 18.0, IQR 14.5, 20.5 vs. 14.0, IQR 12.0, 16.0 mm,  $P < 0.001$ ) and being more with LVEF  $< 50\%$  (63.6% vs. 24.2%,  $P < 0.001$ ) and apical sparing (45.5% vs. 0.5%,  $P < 0.001$ ). For the variables included in the IWT score, they had higher RWT (0.7, IQR 0.6, 0.9 vs. 0.5, IQR 0.4, 0.5,  $P < 0.001$ ), higher  $E/e'$  (29.0, IQR 19.0, 39.5 vs. 17.0, IQR 12.8, 24.3,  $P < 0.001$ ), higher SAB (3.9, IQR 3.4, 6.9 vs. 1.1, IQR 0.5, 1.8,  $P < 0.001$ ), and lower longitudinal strains (9.1%, IQR 6.5, 12.2% vs. 11.4%, IQR 8.6, 13.9%,  $P = 0.024$ ). However, TAPSE was not different between the two groups (11.0 vs. 10.0 mm,  $P = 0.600$ ). Whether TAPSE was not good for detecting CA in HFpEF should be further studied. In the group of patients with score 5–7, the features were mostly between the other two groups (Table 2).

### The clinical usefulness of the IWT score for detecting ATTR-CA

Of total 624 patients, 82 patients underwent scintigraphy and comprised an internal validation cohort (Figure 2). Among them, 14 patients (17.1%, 95% CI 8.8–25.4%) were diagnosed as ATTR-CA by positive scintigraphy and absence of free light chain. The major clinical and echocardiographic features of this cohort as compared with the entire cohort were presented in Table S1. Overall, the two cohorts were comparable. But the patients in the validation cohort had longer hospital stay, lower SBP, lower LVEF, and longitudinal strains. They were more likely to have apical sparing and RV wall thickening.

Based on the IWT score, 17 of 82 patients (20.7%, 95% CI 11.8–29.7%) were with score  $\geq 8$ , 26 of 82 patients (31.7%, 95% CI 21.4–42.0%) were with score 5–7, and 39 of 82 patients (47.6%, 95% CI 36.5–58.6%) were with score  $< 5$  (Figure 2). In regard to scintigraphy, total 14 of 82 (17.1%, 95% CI 8.8–25.4%) patients were positive. In detail, 12 of 17 patients with score  $\geq 8$  (70.6%, 95% CI: 46.4%–94.7%), and two of 26 patients with score 5–7 (7.7%, 95% CI 3.3–18.7%) were scintigraphy positive. Of note, no positive scintigraphy was found in 39 patients with score  $< 5$  (Figure 2). Figure 3 showed the images of scintigraphy, TTE, and ECG in a patient with the score = 9.

Overall, the IWT score  $\geq 8$  had a sensitivity of 85.7% (95% CI 56.2–97.5%) and a specificity of 92.6% (95% CI 83.0–97.3%) for diagnosing CA, and the positive predictive value was 70.6% (95% CI 44.0–88.6%). Of interest, the clinical and echocardiographic characteristics between the patients with IWT score  $\geq 8$  and those with positive scintigraphy were not different (Table S2), which also proved the diagnostic usefulness of the IWT score from another perspective. In addition, the IWT score  $< 5$  had great accuracy in excluding CA with the negative predictive value of 100% (Table 3).

### Proportion of patients with IWT score $\geq 8$ in HFpEF

Of the 624 total HFpEF patients, 33 patients (5.3%, 95% CI 3.5–7.0%) were with IWT score  $\geq 8$  and thus were ATTR-CA based on the definition of the present study. Three hundred ninety-two patients (62.8%, 95% CI 59.0–66.6%) were non-CA with IWT score  $< 5$ , and 199 patients (31.9%, 95% CI 28.2–35.6%) were undetermined with IWT score 5–7 (Figure 1).

Subgroup analysis was performed in 296 patients with age  $\geq 60$  years and LVEF  $\geq 50\%$ , and their clinical and echocardiographic characteristics were presented in Table S3. Among them, only five patients (1.7%, 95% CI 0.2–3.2%) were with IWT score  $\geq 8$ . In addition, subgroup analysis in other clinical settings, including valvular heart disease, suspected hypertrophic cardiomyopathy, LVH with hypertension, LVH with un-

**Table 1** Demographic, clinical, and echocardiographic characteristics of total patients and patients stratified by the IWT score

Variables	Total (n = 624)	<5 (n = 392)	5-7 (n = 199)	≥8 (n = 33)	P value*
<b>Demographic</b>					
Age (years)	66.0 (57.0, 73.0)	69.0 (59.0, 75.0)	62.0 (54.0, 69.0)	58.0 (53.0, 69.0)	<0.001
Male, n (%)	407 (65.2)	257 (65.6)	128 (64.3)	22 (66.7)	0.898
BMI, (kg/m <sup>2</sup> )	24.4 (21.8, 26.8)	24.8 (22.3, 27.4)	23.9 (21.2, 26.4)	23.6 (20.5, 24.6)	0.008
<b>Clinical features</b>					
SBP (mmHg)	135.0 (120.0, 155.0)	136.0 (123.0, 154.0)	136.0 (118.0, 162.0)	120.0 (105.5, 139.0)	<0.001
DBP (mmHg)	80.0 (71.0, 91.0)	80.0 (73.0, 90.0)	81.0 (68.0, 93.0)	76.0 (64.5, 80.5)	0.007
HR (bpm)	76.0 (67.0, 88.0)	76.0 (66.0, 88.0)	76.0 (68.0, 88.0)	76.0 (60.5, 90.0)	0.281
Hospital length (days)	7.0 (5.0, 10.5)	7.0 (5.0, 10.0)	7.0 (5.0, 11.0)	10.0 (7.5, 14.0)	<0.001
<b>Co-morbidities</b>					
Hypertension, n (%)	446 (71.5)	300 (76.5)	137 (68.8)	9 (27.3)	<0.001
Diabetes, n (%)	202 (32.4)	137 (34.9)	60 (30.2)	5 (15.2)	0.021
CAD/PCI, n (%)	186/59 (29.8/9.5)	133/35 (33.9/8.9)	43/21 (21.6/10.6)	10/3 (30.3/9.1)	-
PPM, n (%)	47 (7.5)	27 (6.9)	13 (6.5)	7 (21.1)	0.01
<b>Serum markers</b>					
NT-proBNP (pg/mL)	2211.0 (898.0, 5934.5)	1741.5 (846.0, 3937.3)	3562.0 (967.0, 8136.0)	6525.0 (2499.0, 10759.8)	<0.001
cTnl (pg/mL)	36.5 (12.6, 136.0)	27.7 (9.9, 94.2)	51.1 (23.6, 184.9)	105.2 (25.6, 247.1)	0.001
Creatinine (umol/L)	99.0 (80.0, 149.0)	100.0 (83.0, 131.5)	100.0 (76.0, 171.0)	96.0 (73.0, 145.0)	0.527
eGFR (mL/min/1.73m <sup>2</sup> )	61.2 (37.8, 79.8)	61.1 (41.4, 77.6)	60.0 (34.6, 85.0)	68.2 (34.4, 90.9)	0.222
eGFR <60 mL/min/1.73m <sup>2</sup> , n (%)	300 (48.1)	188 (48.0)	99 (49.7)	13 (39.4)	0.344
<b>Electrocardiographic</b>					
Conduction disorders, n (%)	127 (20.4)	78 (19.9)	40 (20.1)	9 (27.3)	0.313
Af/AF, n (%)	158 (25.3)	129 (32.9)	25 (12.6)	4 (12.1)	0.013
Low voltage, n (%)	11 (1.8)	0 (0)	7 (3.5)	4 (12.1)	<0.001
Pseudo-infarct pattern, n (%)	64 (10.3)	28 (7.1)	28 (14.1)	8 (24.2)	0.002

Af/AF, Atrial flutter/fibrillation. BMI, body mass index; CAD, coronary artery disease; cTnl, cardiac troponin I; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; SBP, systolic blood pressure. Conduction disorders (left/right bundle branch/atrioventricular block).

Data are median (IQR) for continuous variables or number (%) for categorized variables.

\*P value calculated for IWT score ≥8 vs. IWT score <5 patients.

**Table 2** Echocardiographic characteristics of the total patients and patients stratified by the IWT score

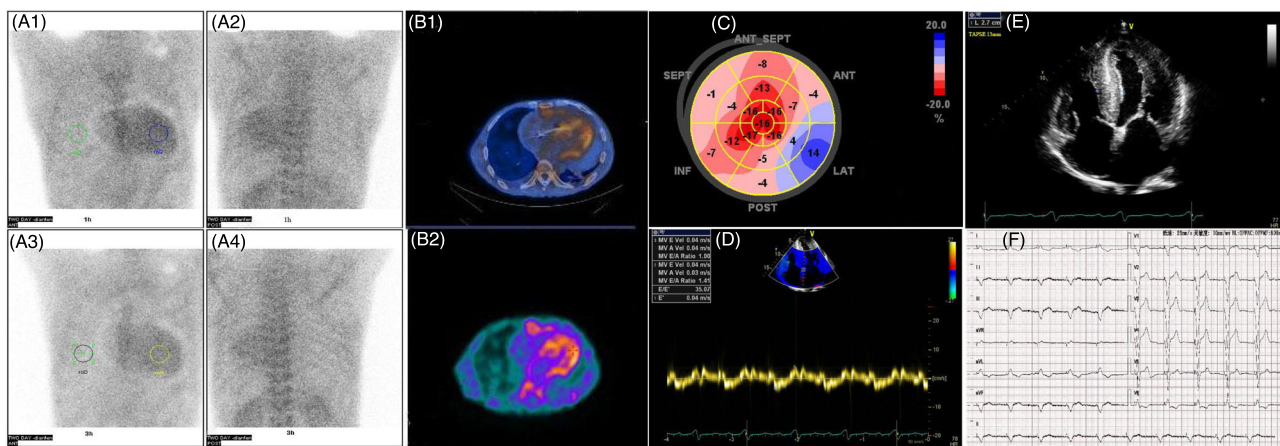
Echocardiography	Total (n = 624)	<5 (n = 392)	5–7 (n = 199)	≥8 (n = 33)	P value*
LVEDD (mm)	47.0 (43.0, 51.0)	48.0 (45.0, 51.0)	44.0 (40.0, 49.0)	43.0 (39.0, 47.0)	<0.001
IVS (mm)	15.0 (13.0, 18.0)	14.0 (12.0, 16.0)	17.0 (15.0, 20.0)	18.0 (14.5, 20.5)	<0.001
LVPW (mm)	12.0 (12.0, 14.0)	12.0 (11.0, 12.0)	15.0 (13.0, 16.0)	16.0 (14.5, 17.5)	<0.001
LVEF (%)	57.0 (48.0, 63.0)	57.0 (50.0, 63.0)	58.0 (48.0, 64.0)	47.0 (40.0, 59.5)	<0.001
LVEF, n (%)					<0.001
≥50%, n (%)	451 (72.3)	297 (75.8)	142 (71.4)	12 (36.4)	
<50%, n (%)	173 (27.7)	95 (24.2)	57 (28.6)	21 (63.6)	
IWT score					
RWT	0.5 (0.5, 0.6)	0.5 (0.4, 0.5)	0.7 (0.6, 0.8)	0.7 (0.6, 0.9)	<0.001
E/e'	20.0 (14.0, 27.0)	17.0 (12.8, 24.3)	24.0 (18.0, 32.0)	29.0 (19.0, 39.5)	<0.001
TAPSE (mm)	12.0 (10.0, 17.0)	10.0 (10.0, 16.0)	14.5 (11.8, 18.0)	11.0 (10.0, 15.5)	0.600
SAB	1.7 (0.9, 3.0)	1.1 (0.5, 1.8)	2.1 (1.2, 3.1)	3.9 (3.4, 6.9)	<0.001
LSs (%)	10.3 (7.9, 13.4)	11.4 (8.6, 13.9)	9.8 (7.9, 13.4)	9.1 (6.5, 12.2)	0.024
Apical sparing (visual), n (%)	49 (7.9)	2 (0.5)	32 (16.1)	15 (45.5)	<0.001
RV wall thickening, n (%)	76 (12.2)	7 (1.8)	51 (25.6)	18 (54.5)	<0.001
PAH, n (%)	81 (13.0)	45 (11.5)	35 (17.6)	1 (3.0)	0.227
Pericardial effusion, n (%)	240 (38.5)	119 (30.4)	99 (49.7)	22 (66.7)	<0.001

E/e', E wave/e' wave; IVS, interventricular septum thickness; LSs, longitudinal strains; LVEDD, left ventricular end-diastolic dimensions; LVEF, left ventricular ejection fraction; LVPW, left ventricular posterior wall thickness; PAH, max pulmonary artery pressure (>45 mmHg). RV, right ventricular; RWT, relative wall thickness; SAB, systolic apex to base ratio; TAPSE, tricuspid annular plane systolic excursion. Apical sparing (visual), annotated by visual assessment of the bullseye peak segmental strain pattern.

Data are median (IQR) for continuous variables or number (%) for categorized variables.

\*P value calculated for IWT score ≥8 vs. IWT score <5 patients.

**Figure 3** A HFpEF patients with the IWT score = 9 and a positive <sup>99m</sup>Tc-PYP scintigraphy. (A) <sup>99m</sup>Tc-PYP SPECT and (B) <sup>99m</sup>Tc-PYP SPECT/CT (grade 3 radiotracer uptake on the Perugini scale at 1 and 3 h and 1-h heart-to-lung ratio of 1.72 and 3 h of 1.77). (C) A “bull’s-eye” presentation of LV longitudinal strains by TTE showing typical apical sparing pattern and low longitudinal strains (3.2%). (D) Doppler was restrictive with the E/e' ratio of 35.07. (E) TTE (four-chamber view) showed left ventricular hypertrophy. (F) ECG presented atrial fibrillation and pacemaker rhythm. CT, computed tomography.

**Table 3** The diagnostic accuracy of the IWT score as compared with <sup>99m</sup>Tc-PYP in the absence of monoclonal protein

	<sup>99m</sup> Tc-PYP (+), n	<sup>99m</sup> Tc-PYP (-), n	Se (CI), %	Sp (CI), %	PPV (CI), %	NPV (CI), %
≥8 points	12	5	85.7 (56.2–97.5)	92.6 (83.0–97.3)	70.6 (44.0–88.6)	96.9 (88.4–99.5)
≥5 points	14	29	100 (73.2–100)	57.4 (44.8–69.1)	32.6 (19.5–48.7)	100 (88.8–100)

<sup>99m</sup>Tc-PYP, <sup>99m</sup>Tc-pyrophosphate; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

known causes, and renal insufficiency with eGFR <60% but not on haemodialysis, were shown in *Figure S1*. It showed that 0.6–13.3% of patients were with IWT score  $\geq 8$ , and the highest proportion of patients with IWT score  $\geq 8$  was seen in the group with LVH with unknown causes.

## Discussion

To the best of our knowledge, this is the first cohort study of ATTR-CA prevalence in Chinese population. It demonstrated that the proportion of highly suspected ATTR-CA in Chinese hospitalized patients with HFpEF ( $\geq 40\%$ ) and LVH ( $\geq 12$  mm) was 5.3%, as revealed by the IWT score derived from echocardiographic measurements. In a small subgroup of patients who underwent scintigraphy, the IWT score was shown to have a sensitivity of 85.7% and a specificity of 92.6% for detecting ATTR-CA, revealing that the IWT score was very useful for screening ATTR-CA in HFpEF patients associated with a hypertrophic phenotype.

Because the role of ATTR-CA in HFpEF was realized in the last decade, a couple of studies had investigated the prevalence of ATTR-CA in HFpEF, all of which were in non-Asian patients.<sup>3–5</sup> González-López *et al.* reported a 13% prevalence of ATTRwt in HFpEF. They included hospitalized HFpEF patients associated with LVH ( $\geq 12$  mm) and age  $\geq 60$  years, and LVEF  $\geq 50\%$  was used to define HFpEF.<sup>3</sup> Lo Presti *et al.* performed the study in acute HFpEF (LVEF  $\geq 50\%$ ) but without age and wall thickness requirements. They found that myocardial ATTRwt was present in 19% of patients.<sup>4</sup> In another similar cohort with HFpEF (LVEF  $\geq 50\%$ ), ATTR-CA including wild-type and hereditary ATTR was found in 10% of patients by EMB.<sup>5</sup> Other than these clinical studies, a study performed histological analysis in LV specimens from patients with antemortem diagnosis of HFpEF without clinically apparent cardiac amyloid deposition. It revealed 17% ATTRwt deposition, of which 5% were moderate or severe interstitial deposition of heart.<sup>25</sup> In comparison, a prevalence of 5.3% that was much lower than those reported in the above studies was revealed by our study. It is noteworthy that our patient cohort was somewhat different from the other cohorts, except for racial disparity. The major difference was the definition of HFpEF, being LVEF  $\geq 40\%$  in our study instead of 50%. Although the current guidelines use LVEF  $\geq 50\%$  to define HFpEF, the optimal LVEF cut-off for HF patients without overtly reduced LVEF is lack of consensus.<sup>9,16</sup> Moreover, it was reported that about 50% of ATTR-CA patients had LVEF <50%.<sup>26,27</sup> In our study, among 33 (5.3%) patients who were diagnosed as ATTR-CA, 21 patients (63.6%) were with LVEF <50%. Therefore, we used LVEF  $\geq 40\%$  as the cut-off for HFpEF in the study. Regarding the age, 17 of 33 patients (51.5%) were aged <60 years in the study. To compare with the study cohort by González-López *et al.*, we also performed subgroup analysis in patients with age  $\geq 60$  and LVEF  $\geq 50\%$ ,

and an even lower prevalence of 1.7% (95% CI 0.2–3.2%) for ATTR-CA was revealed. Thus, our results demonstrated the remarkably lower prevalence of ATTR-CA in Chinese HFpEF patients. However, whether it was solely caused by the racial disparity remained undetermined. Future multicentre study that involves wider areas of China and using scintigraphy as the diagnosing tool is needed to underpin the low prevalence of ATTR-CA in Chinese HFpEF patients and its association with racial disparity.

In addition, the previous studies used either nuclear scintigraphy or histological analysis as the tool for diagnosing ATTR-CA. In contrast, our study used the IWT score derived from echocardiography. Characteristic echocardiographic presentations of CA have long been described, such as wall thickening, bi-atrial enlargement, restrictive pattern of LV filling, reduced longitudinal strains, and relative apical sparing of longitudinal strains.<sup>8,12,13,28,29</sup> These indices are considered as ‘red flags’ of CA and are important for early awareness of the disease.<sup>30</sup> Moreover, with artificial intelligence, the clinical utility of echocardiographic variables may be greatly improved and is of importance in disease screening.<sup>31,32</sup> However, they alone are not adequately accurate in diagnosing CA. In comparison with the individual variable, a combination of echocardiographic CA ‘red flags’ may improve the diagnostic utility of echocardiography for CA.<sup>15</sup> And the IWT score that integrated multiple echocardiographic CA suggestive variables is by far the best predicting model for CA and has been verified in patients with LVH.<sup>14</sup> To further confirm its utility in Chinese HFpEF patients, in the study, we comprised an internal cohort consisted of 82 patients undergoing scintigraphy in which the utility of the IWT score was assessed against scintigraphy. Our results showed that the IWT score  $\geq 8$  in the absence of serum and urine free light chain had good diagnostic performance (sensitivity 85.7% and specificity 92.6%, respectively) for ATTR-CA as compared with scintigraphy in HFpEF. Moreover, the score <5 can exclude CA. Recent studies have suggested that scintigraphy may not be adequately sensitive to detect early stage of CA.<sup>7,12</sup> In the present study, five patients with IWT score  $\geq 8$  were scintigraphy negative, which also queried the sensitivity of scintigraphy. Interestingly, among 26 of 82 patients with the IWT score 5–7, two were scintigraphy positive. Whether this intermediate group represented early stage of CA or had other underlying aetiologies were unclear. Herein, we strongly propose using the IWT score to guide diagnostic algorithm for ATTR-CA in HFpEF patients. However, it should be emphasized that the IWT score may only serve as a screening tool in clinical practice. Cardiac scintigraphy and absence of monoclonal protein in serum and urine are indispensable to confirm the diagnosis of ATTR-CA, according to Gillmore’s algorithm<sup>7</sup> and diagnostic algorithm recommended by 2019 Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis,<sup>8</sup> even in patients with score  $\geq 8$ . In addition,



scintigraphy should also be performed in patients with score  $\geq 5$  but may not be necessary in patients with score  $< 5$ . In patients with score  $\geq 8$ , if scintigraphy is negative, EMB or targeted imaging method using amyloid binding PET tracers<sup>12</sup> is suggested.

Based on the previous case series studies, ATTR, particularly ATTRwt, has been considered as a late-onset disease, of which symptoms are usually manifested in patients 60 years of age or older. Moreover, it is a remarkably male-predominant disease with rate of males ranging from 81.5 to 98%.<sup>26,33</sup> Although the most clinical and ECG manifestations were similar between HFpEF-ATTR and general ATTR, as shown by our study and the previous studies,<sup>3–5</sup> ATTR patients with a HFpEF phenotype were more likely to be females, being 33.3% in our study, 40 and 59% in the two previous studies.<sup>3,5</sup> In addition, HFpEF-ATTR patients had higher level of NT-proBNP and troponin I in comparison with other forms of HFpEF, as shown by our and the previous findings.<sup>3,5</sup> Interestingly, in comparison with other forms of HFpEF, the HFpEF patients with ATTR-CA were younger (58 years) in our study, which were different from the findings in non-Asian patients (74–86 years).<sup>3–5</sup> It is likely but needs further study in the future that Chinese patients with ATTR-CA may develop symptoms early and have a more aggressive profile of disease.

## Limitations

The present study had some limitations. First, it was a single-centre study. The population of the study were patients referred to our hospital with decompensated HF who were mostly in advanced stage of HF and selection bias cannot be excluded. Second, we used the echocardiography-based the IWT score to diagnose ATTR-CA, which has not been widely accepted as the diagnostic criterion for CA. Although we comprised a validation cohort with 82 HFpEF patients and confirmed its great diagnostic performance as compared with scintigraphy in detecting CA in Chinese patients with HFpEF, the cohort was an internal validation cohort, included relatively low number of patients, and thus had no adequate power. Therefore, the ATTR-CA patients defined in the study, in fact, were just patients with high risk of ATTR-CA or highly suspected ATTR-CA patients. In a large population study as the present study, the IWT score may be adequate for the purpose of evaluating the prevalence of ATTR-CA. In clinical practice, it can only be used as a screening tool, and the confirmed diagnosis of ATTR-CA still relies on the scintigraphy and search of monoclonal protein in serum and urine. Likewise, because we used IWT score as the diagnosing tool, the characteristics related to ATTR-CA as described in the study maybe inadequately correct. However, no difference was found for the characteristics between the patients with IWT score  $\geq 8$  and those with pos-

itive scintigraphy (Table S2), and we believe that our study provides valuable information regarding the clinical characteristics of ATTR-CA-HFpEF patients. Third, genetic testing was not performed, and specific types of ATTR, ATTRwt or ATTRm, cannot be differentiated in the study. Thus, our results represented the entire entity of ATTR, but not just ATTRwt. Overall, further larger studies are needed to verify the low prevalence of ATTR-CA in Chinese patients with HFpEF as well as their clinical characteristics.

## Conclusions

The study revealed that the proportion of highly suspected ATTR-CA as detected by IWT score  $\geq 8$  in Chinese patients with HFpEF and a hypertrophic phenotype was 5.3%, suggesting likely that the prevalence of ATTR-CA in Chinese HFpEF patients is remarkably lower than that in non-Asian patients with the disease. Due to the difference in patient cohorts as well as different diagnostic tool adopted between our study and other studies, how much racial disparities contributed to the low prevalence of ATTR-CA in Chinese HFpEF patients was uncertain. Moreover, Chinese patients with ATTR-CA were likely having earlier onset of symptoms and disease progression. The IWT score derived from echocardiographic measurements had good diagnostic performance in diagnosing (score  $\geq 8$  and absence of free light chain) and excluding (score  $< 5$ ) ATTR-CA and is an excellent tool for screening and guiding further testing for CA in HFpEF patients.

## Conflict of interest

None declared.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** The proportion of suspicion ATTR-CA based on the IWT score in different clinical settings.

Valvular heart disease were patients with history of valve replacement or presence of significant valvular disease; Suspected hypertrophic cardiomyopathy were patients with LV wall thickness  $\geq 15$  mm; Renal insufficiency with eGFR  $< 60\%$  but not on haemodialysis.

**Table S1.** Demographic, clinical and echocardiographic characteristics of the overall cohort and validation cohort.

**Table S2.** Demographic, clinical and echocardiographic characteristics of the IWT score  $\geq 8$  and positive scintigraphy.

**Table S3.** Demographic, clinical and echocardiographic characteristics in patients with age  $\geq 60$  years and LVEF  $\geq 50\%$ .

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