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Transthyretin amyloidosis prevalence and characteristics in Korean patients with heart failure with preserved or mildly reduced ejection fractions

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The diagnosis and awareness of transthyretin amyloidosis cardiomyopathy (ATTR-CM) in heart failure with left ventricular ejection fraction (LVEF) > 40% remains under-recognized. This study aimed to investigate the prevalence and characteristics of ATTR-CM in patients with heart failure with LVEF > 40%. Patients with LVEF > 40% and maximal left ventricular wall thickness (MWT) > 10 mm who underwent bone scintigraphy were retrospectively investigated. Patients with a definite cause of heart failure were excluded. ATTR-CM was diagnosed when grade 2 or 3 myocardial uptake was observed on scintigraphy. Among 97 patients (male, 62.5%; median age, 69 years), 13 (13.4%) were diagnosed with ATTR-CM (wild type, 69.2%; hereditary type, 30.8%). Age or biomarker levels did not differ significantly; however, all patients with ATTR-CM were male. The ATTR-CM group had a significantly higher prevalence of polyneuropathy or carpal tunnel syndrome than the non-ATTR-CM group, accompanied by a longer PR interval, thicker MWT, larger left atrial volume index, and higher E/e′. Accordingly, ATTR was present in a substantial number, particularly among men. Clinicians should suspect ATTR when a male patient exhibits neurologic symptoms, diastolic dysfunction, and a long PR interval.

Heart failure with preserved ejection fraction (HFpEF) and heart failure with mildly reduced ejection fraction (HFmrEF) account for > 50% of all heart failure (HF) cases, associated with high mortality and morbidity rates with a gradually increasing prevalence[1,2]. As HFpEF and HFmrEF exhibit multiple cardiac and extra-cardiac pathophysiology and heterogeneous and complex characteristics, standardised diagnosis and treatment approaches may be inadequate[3–6]. Recently, patients with HFpEF and HFmrEF have been shown to benefit from sodium–glucose cotransporter-2 inhibitors; however, identification of HFpEF and HFmrEF aetiology and targeted therapeutic strategies for its subtypes are lacking[6–10]. Transthyretin amyloid cardiomyopathy (ATTR-CM), in which amyloid fibrils infiltrate the myocardium, is one of the etiologies of HFpEF and HFmrEF, especially among older adults[11–14]. Endomyocardial biopsy (EMB) is the gold standard method for ATTR-CM diagnosis. However, in recent studies, scintigraphy revealed an almost 100% positive predictive value, allowing the non-invasive diagnosis of ATTR-CM[14–16]. Patients with ATTR-CM can progress to advanced heart failure and often have arrhythmias or conduction disturbances[17,18]. Tafamidis, a novel drug that inhibits amyloid deposition, was found to improve clinical outcomes in these patients and is known to be more effective when treatment is initiated at an early stage of ATTR-CM[19]. Therefore, early diagnosis and treatment of ATTR-CM in patients with HFpEF or HFmrEF is essential; however, the significance of awareness and ATTR-CM diagnosis remains poorly recognised among physicians. Recently, several studies have reported ATTR-CM prevalence and characteristics in patients with HF with left ventricular hypertrophy (LVH)[20,21]; however, studies among Asians are lacking. In the current study, we aimed to determine the prevalence and characteristics of ATTR-CM in Korean patients with HFpEF or HFmrEF.

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Results

During the study period, 153 patients met the inclusion criteria (Fig. 1). Of these, 56 patients with HF attributed to a definite cause were excluded (6 DCMP, 24 HCMP, 1 myocarditis, 7 AL amyloidosis, 4 MM, etc.). Finally, 97 patients (mean age, 72 years; 60 [62.5%] male; median H_2FPEF score, 3) were analyzed. Among the study participants, 13 (13.4%) were diagnosed with ATTR-CM based on grade 2 or 3 myocardial uptake on bone scintigraphy, whereas 84 (86.6%) had grade 0 or 1 myocardial uptakes on bone scintigraphy. Of the patients diagnosed with ATTR-CM, 11 (84.6%) were confirmed using EMB and genetic testing; 7 were treated with tafamidis, 3 with double-stranded small interfering RNA, and 3 were untreated. The representative case of ATTR-CM patient was shown in Fig. 2.

The baseline clinical characteristics of the study population are shown in Table 1. Of the ATTR-CM patients, nine were diagnosed with wild type (69.2%), and four were diagnosed with a hereditary type (30.8%). The ATTR-CM and non-ATTR-CM groups did not differ significantly in terms of age, the prevalence of hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, H_2FPEF score, and serum biomarker levels (N-terminal pro-B-type natriuretic peptide or high sensitive troponin) between. However, all patients in the ATTR-CM group were male. The prevalence of red flag signs, such as polyneuropathy (61.5% vs. 11.9%, $P<0.001$) or carpal tunnel syndrome (53.8% vs. 1.2%, $P<0.001$), and estimated glomerular filtration rates (71.5 ± 16.3 vs. 53.6 ± 30.3 mL/min/1.73 m^2, $P=0.004$) were significantly higher in the ATTR-CM group; however, the mean body mass index (22.6 ± 3.7 vs. 25.8 ± 5.2 kg/m^2, $P=0.036$) of the ATTR-CM group was significantly lower than that in the non-ATTR-CM group. There was no significant difference in medication history except calcium channel blocker prescription rates.

Table 2 presents the ECG and echocardiographic characteristics of patients with ATTR-CM. Based on the ECG, the ATTR-CM group showed a higher prevalence of low-voltage QRS (41.7% vs 6.0%, $P=0.001$) and longer PR interval (218 vs. 168 ms, $P=0.031$) than the non-ATTR-CM group. Regarding TTE parameters, the mean LVEF of patients with ATTR-CM was lower (57.4% vs. 64.2%, $P=0.021$) than that of non-ATTR-CM patients. Additionally, patients in the ATTR-CM group had greater interventricular septal wall thickness (15 vs. 12 mm, $P<0.001$), posterior wall thickness (14 vs. 11 mm, $P<0.001$), and MWT (15 vs. 12 mm, $P<0.001$) than patients in the non-ATTR-CM groups. In addition, LV mass index (LVMI, 164.8 vs. 122.8 g/m^2, $P<0.001$) and relative wall thickness (0.63 vs. 0.48, $P<0.001$) values were also greater in patients with ATTR-CM. Patients with ATTR-CM had higher values of E/e' ratio (19.5 vs. 14.3, $P<0.001$), E' velocity (4 vs. 5 m/s, $P=0.001$), and

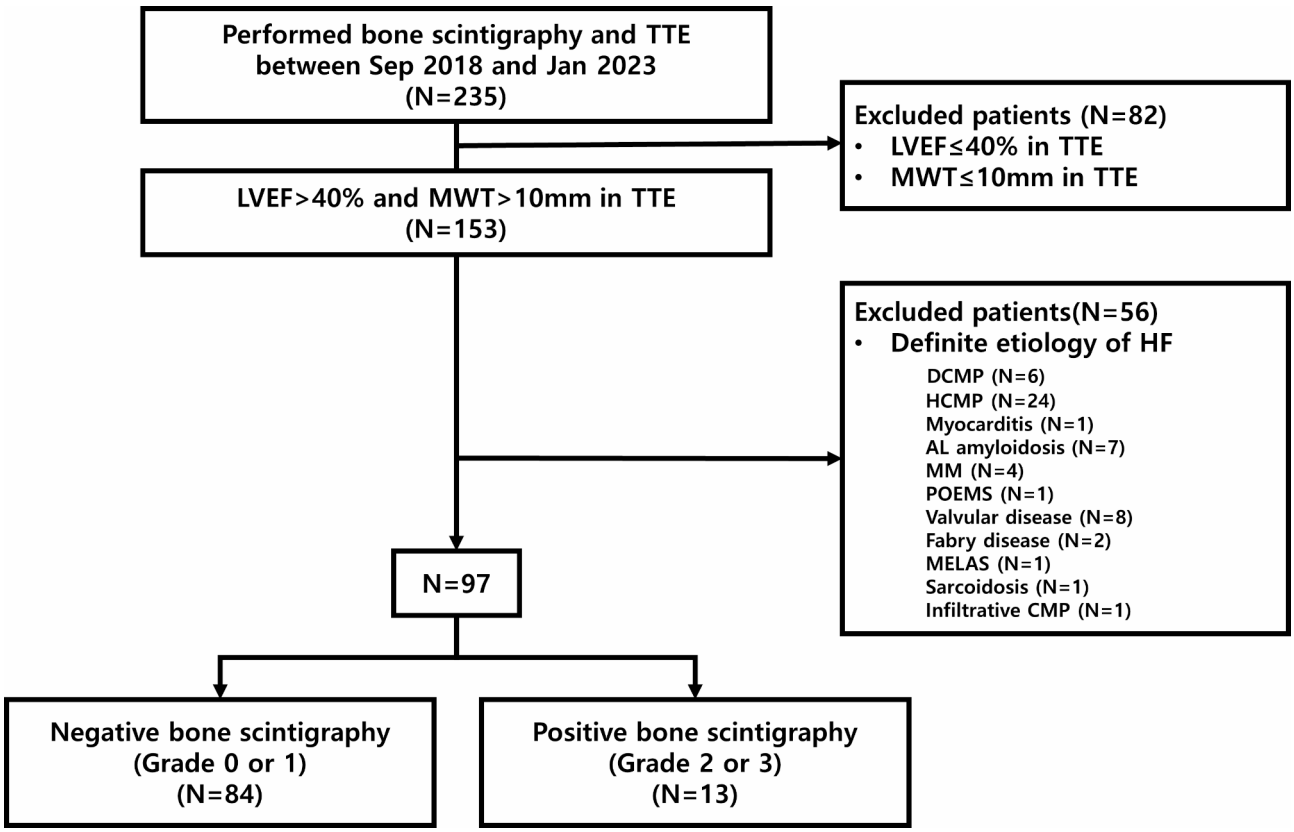

Fig. 1. Flow chart of the study population. *CMP* cardiomyopathy, *DCMP* dilated cardiomyopathy, *HCMP* hypertrophic cardiomyopathy, *HF* heart failure, *LVEF* left ventricular ejection fraction, *MELAS* Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes, *MM* multiple myeloma, *MWT* maximal LV wall thickness, *POEMS* polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes, *TTE* transthoracic echocardiography.

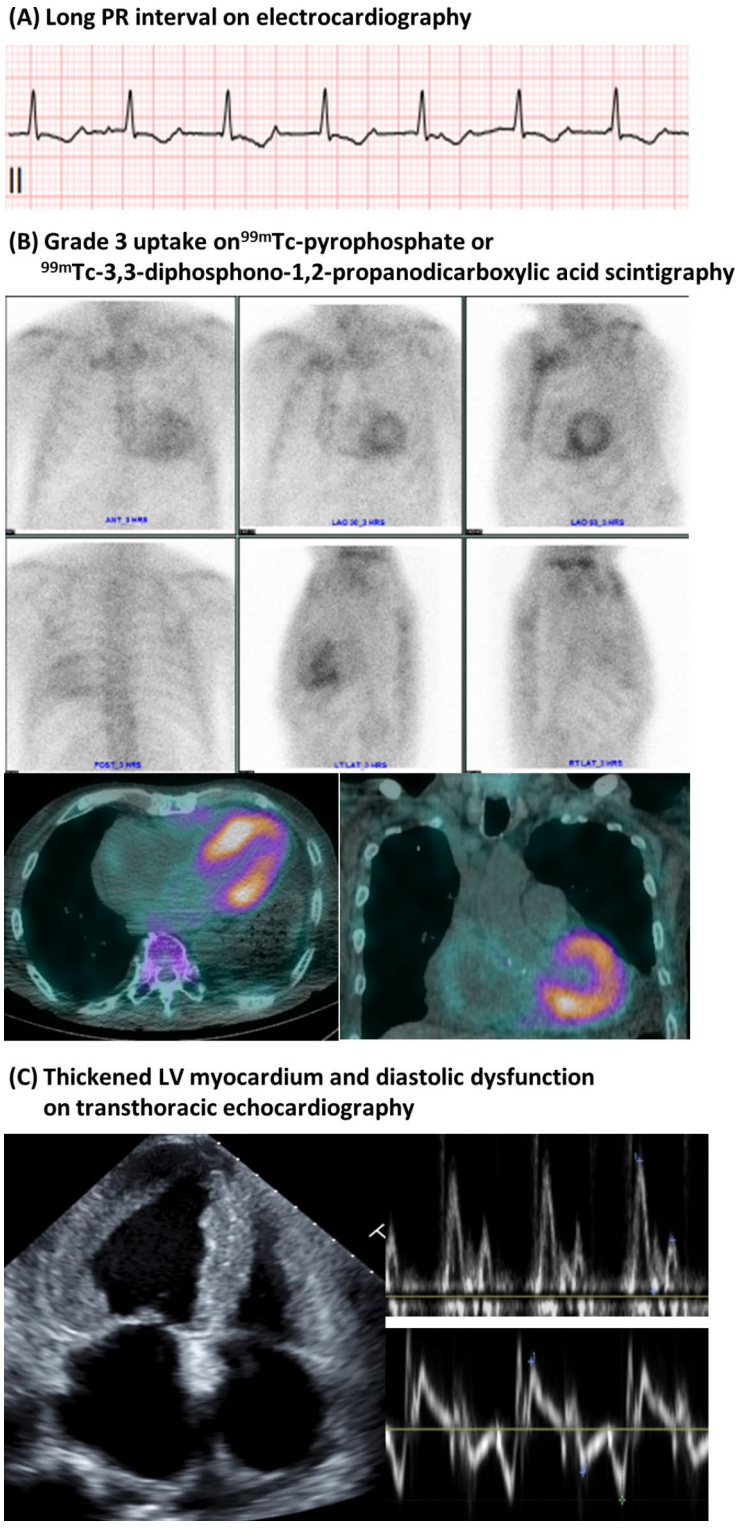

Fig. 2. The representative case of ATTR-CM patient. A 67-year-old male patient was diagnosed with ATTR-CM. (**A**) PR interval was prolonged to 280 ms on electrocardiography. (**B**) Grade 3 uptake in the left ventricular myocardium was showed in bone scintigraphy. (**C**) Transthoracic echocardiography showed advanced diastolic dysfunction with left and right ventricular myocardial wall thickening.

left atrial volume index (53.7 vs. 39.2 ml/m^2, $P=0.044$) than non-ATTR-CM patients; however, right ventricular systolic pressure and LV end-diastolic dimension did not differ between two groups.

The prevalence of ATTR-CM differed according to MWT, PR interval, E/e', and LVMI. A significantly larger proportion of ATTR-CM was detected among patients with an MWT > 12 mm (84.6% vs. 33.6%, $P=0.002$)

	Total ($n=97$)	ATTR-CM ($n=13$)	Non-ATTR-CM ($n=84$)	*P*-value
Demographics and characteristics				
Age, years	72 (62–79)	78 (73–82)	69 (60–78)	0.052
Male gender, n (%)	60 (62.5%)	13 (100.0%)	47 (56.0%)	0.006
Height, cm	162.5 ± 9.6	163.4 ± 5.8	162.3 ± 10.0	0.581
Weight, kg	66.7 ± 15.1	60.1 ± 10.1	67.7 ± 15.4	0.090
BMI, kg/m^2	25.3 ± 5.2	22.6 ± 3.7	25.8 ± 5.2	0.036
Hypertension, n(%)	65 (67.7%)	6 (46.2%)	60 (71.4%)	0.134
Diabetes mellitus, n(%)	41 (42.7%)	2 (15.4%)	39 (46.4%)	0.071
Atrial fibrillation, n (%)	22 (22.9%)	4 (30.8%)	18 (21.4%)	0.695
Coronary artery disease, n (%)	19 (19.8%)	2 (15.4%)	17 (20.2%)	0.972
H_2FPEF score	3 (2–5)	3 (2–5)	3 (2–5)	0.802
Red flag signs				
Polyneuropathy, n (%)	18 (18.8%)	8 (61.5%)	10 (11.9%)	< 0.001
Carpal tunnel syndrome, n (%)	8 (8.3%)	7 (53.8%)	1 (1.2%)	< 0.001
Lumbar spinal stenosis, n (%)	16 (16.7%)	3 (23.1%)	13 (15.5%)	0.775
Autonomic dysfunction, n (%)	18 (18.8%)	8 (61.5%)	10 (11.9%)	< 0.001
Laboratory test				
Hb, g/dL	12.3 ± 2.3	12.9 ± 2.3	12.2 ± 2.3	0.356
eGFR, ml/min/1.73 m^2	56.1 ± 29.4	71.5 ± 16.3	53.6 ± 30.3	0.004
Albumin, g/dL	4.2 (3.8–4.5)	4.2 (3.7–4.2)	4.3 (3.8–4.5)	0.186
Troponin T, pg/mL	38.0 (20.5–57.5)	55.0 (46.0–57.3)	35.0 (15.8–60.5)	0.112
NT-proBNP, pg/mL	1102 (272–4163)	1534 (865–2340)	1036 (244–4175)	0.447
Medication				
ACEI/ARB	47 (49.0%)	4 (30.8%)	43 (51.2%)	0.283
Beta-blocker	40 (41.7%)	5 (38.5%)	35 (41.7%)	1.000
CCB	37 (38.5%)	1 (7.7%)	36 (42.9%)	0.034
MRA	11 (11.5%)	2 (15.4%)	9 (10.7%)	0.981
Diuretics	45 (46.9%)	7 (53.8%)	38 (45.2%)	0.779
SGLT2 inhibitor	8 (8.3%)	0 (0.0%)	8 (9.5%)	0.535
Statin	58 (60.4%)	6 (46.2%)	52 (61.9%)	0.439

Table 1. Baseline characteristics. Values are mean (standard deviation), n (%, percentage), median (interquartile range). *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ATTR-CM* transthyretin amyloid cardiomyopathy, *BMI* body mass index, *CCB* calcium channel blocker, *eGFR* estimated glomerular filtration rate, *Hb* hemoglobin, *MRA* mineralocorticoid receptor antagonist, *NT-proBNP* N-terminal pro–B-type natriuretic peptide, *SGLT2* sodium-glucose-cotransporter 2.

than among those with an MWT ≤ 12 mm group. However, two patients with ATTR-CM (15.4%) were in the MWT ≤ 12 mm group, and they were all wild-type ATTR-CMs (Supplementary Fig. S1). Furthermore, PR interval > 200 ms (55.6% vs. 19.0%, $P=0.046$), E/e' > 14 (92.3% vs. 49.4%, $P=0.010$), and LVMI > 115 g/m^2 (100% vs 67.5%, $P=0.036$) were also clinical features of patients with ATTR-CM (Supplementary Fig. S2). Figure 3 shows the distribution of MWT, LVMI, PR interval, and E/e' in ATTR-CM and non-ATTR-CM groups.

Discussion

In this cohort study, the number of patients with scintigraphy-diagnosed ATTR-CM accounted for 13.4% of patients with HFpEF or HFmrEF. Patients with ATTR-CM were all male, often presenting red flag signs such as carpal tunnel syndrome, and showed abnormal findings on ECG and TTE.

ATTR-CM is induced by the deposition of misfolded and transthyretin (TTR) protein aggregates in tissues, particularly in the heart, eventually leading to organ dysfunction[17,22]. It is divided into two subtypes, i.e., hereditary ATTR-CM with TTR gene mutation and wild-type ATTR-CM without mutation, and the proportion of wild-type ATTR-CM is higher among older adults[11,12]. The prevalence of ATTR-CM continues to increase gradually, and the prevalence of ATTR-CM in patients with HFpEF was found to range from 5 to 17%[11,23]. Consistent with previous studies, the current study revealed a prevalence of approximately 13%.

Patients with ATTR-CM are known to have the worst prognosis and substantially lower quality of life than patients with other types of cardiomyopathy[24,25]. ATTR-CM initially appears as HFpEF or HFmrEF; however, as the disease progresses, it eventually presents as heart failure with reduced ejection fraction in the late stage[26]. Accordingly, early identification and diagnosis of ATTR-CM are crucial when patients are in HFpEF or HFmrEF[27]. Early detection of ATTR-CM can be achieved by scintigraphy before ECG, TTE, or biomarker changes[14,16,28]. Therefore, it is reasonable to perform scintigraphy to determine the cause of HFpEF or HFmrEF,

	Total ($n=97$)	ATTR-CM ($n=13$)	Non-ATTR-CM ($n=84$)	*P*-value
Electrocardiography				
PR interval, ms	171 (156–197)	218 (186–236)	168 (156–190)	0.031
QRS voltage, mV	2.0 (1.3–2.6)	1.7 (0.9–2.4)	2.0 (1.4–2.6)	0.215
Left ventricular hypertrophy criteria, n (%)	11 (11.7%)	1 (8.3%)	10 (12.0%)	1.000
Low QRS voltage criteria, n (%)	10 (10.6%)	5 (41.7%)	5 (6.0%)	0.001
QRS duration, ms	95 (83–108)	99 (81–142)	94 (84–108)	0.567
Voltage-to-mass ratio, mV/(cm^2/m^2)	0.15 (0.10–0.21)	0.10 (0.05–0.18)	0.16 (0.11–0.21)	0.049
Any type of AV block, n (%)	21 (21.6%)	5 (38.5%)	16 (20.1%)	0.072
Echocardiography				
LVEF, %	63.4 ± 10.1	57.4 ± 11.1	64.2 ± 9.6	0.021
E/e′ ratio	15.0 (11.9–19.2)	19.5 (17.8–29.0)	14.3 (11.6–18.4)	< 0.001
e′, cm/s	4 (4–6)	4 (3–4)	5 (4–6)	0.001
Deceleration time, ms	206.5 ± 57.3	179.2 ± 44.1	210.6 ± 57.8	0.064
RV systolic pressure, mmHg	28 (22–37)	33 (26–37)	28 (22–37)	0.452
LV end-diastolic dimension, mm	49 (45–52)	48 (44–49)	50 (45–52)	0.204
LA volume index, ml/m^2	39.6 (31.7–53.8)	53.7 (43.4–60.6)	39.2 (31.1–48.5)	0.044
LV mass index, g/m^2	128.8 (112.6-154.8)	164.8 (135.0–220.2)	122.8 (109.3–145.9)	< 0.001
Maximum LV wall thickness, mm	12 (11–13)	15 (14–17)	12 (11–13)	< 0.001
Interventricular septal wall thickness, mm	12 (11–13)	15 (14–17)	12 (11–13)	< 0.001
Posterior wall thickness, mm	12 (11–13)	14 (13–15)	11 (11–12)	< 0.001
Relative LV wall thickness	0.49 (0.44–0.57)	0.63 (0.55–0.67)	0.48 (0.43–0.55)	< 0.001
Pericardial effusion, n (%)	16 (16.7%)	4 (30.8%)	12 (14.3%)	0.276
Bone scintigraphy				
Grade 0	70 (72.9%)	0 (0.0%)	70 (83.3%)	
Grade 1	13 (13.5%)	0 (0.0%)	14 (16.7%)	
Grade 2	1 (1.1%)	1(1.1%)	0 (0.0%)	
Grade 3	12 (12.5%)	12 (12.5%)	0 (0.0%)	

Table 2. Electrocardiographic and echocardiographic parameters. Values are mean (standard deviation), n (%, percentage), median (interquartile range). *ATTR-CM* transthyretin amyloid cardiomyopathy, *AV* atrioventricular, *LA* left atrium, *LV* left ventricle, *LVEF* left ventricular ejection fraction, *RV* right ventricle.

even in the absence of changes in the other tests. In addition to grade 2 or 3 uptake on bone scintigraphy, non-invasive features suggestive of ATTR-CM include low-voltage QRS on ECG, and increased LV wall thickness or apical sparing patter of LV strain image on TTE[17,29]. In our study, a low voltage was observed in less than 50% of patients with ATTR-CM only, which is less than that reported previously[30]; however, a PR interval of ≥ 200 ms in electrocardiography was identified as an important clinical feature of ATTR-CM in a Korean population. Thus, we believe that diagnosing ATTR-CM by serial monitoring the PR interval would be helpful. Furthermore, 15.4% of the patients in this study were diagnosed with ATTR-CM by scintigraphy despite having an MWT of ≤ 12 mm. Furthermore, a recent study has revealed that ATTR-CM was confirmed using scintigraphy in 5% of patients even without LVH; these patients all had wild-type ATTR-CM[23]. Similarly, in our study, approximately 3.5% of patients with an MWT of ≤ 12 mm were diagnosed with wild-type ATTR-CM. The fact that ATTR-CM can be diagnosed even in patients with LV wall thickness ≤ 12 mm represents the limitations of the current guidelines for suspecting and testing ATTR-CM in patients with LV wall thickness > 12 mm in HFpEF or HFmrEF[31,32]. In addition, given that female individuals have thinner LV walls than males, certain females may experience ATTR-CM even if the LV wall thickness does not exceed 12 mm[33]. Therefore, in patients with HFpEF or HFmrEF of unknown cause, ATTR-CM should be suspected, and active diagnosis using scintigraphy, a non-invasive test, is needed.

Unlike Western populations, data on Asians with ATTR-CM are limited. In a recently published Japanese multi-centre registry, 14.2% of patients with HFpEF who underwent bone scintigraphy regardless of LV wall thickness were diagnosed with ATTR-CM[34]. Meanwhile, in data from China, the prevalence of ATTR-CM in patients with HFpEF or HFmrEF with an LV wall thickness > 12 mm was approximately 5.3%, which was significantly lower than that reported among Western populations[35]. Among Asian populations, only one multinational study identified the common genetic variation and phenotypic characteristics of hereditary TTR amyloidosis in a Southeast Asian cohort. However, the cohort size was markedly limited, comprising less than 30 patients[36]. Therefore, continued research on ATTR-CM in Asians is necessary, and future large-scale multinational studies are required to further advance our understanding of this disease.

This study had some limitations. First, given that this study was conducted in a single centre with a small study population, it is difficult to generalize the findings, and a larger study is warranted. Second, as this was a retrospective study, scintigraphy was performed at the clinicians' discretion rather than in all patients with

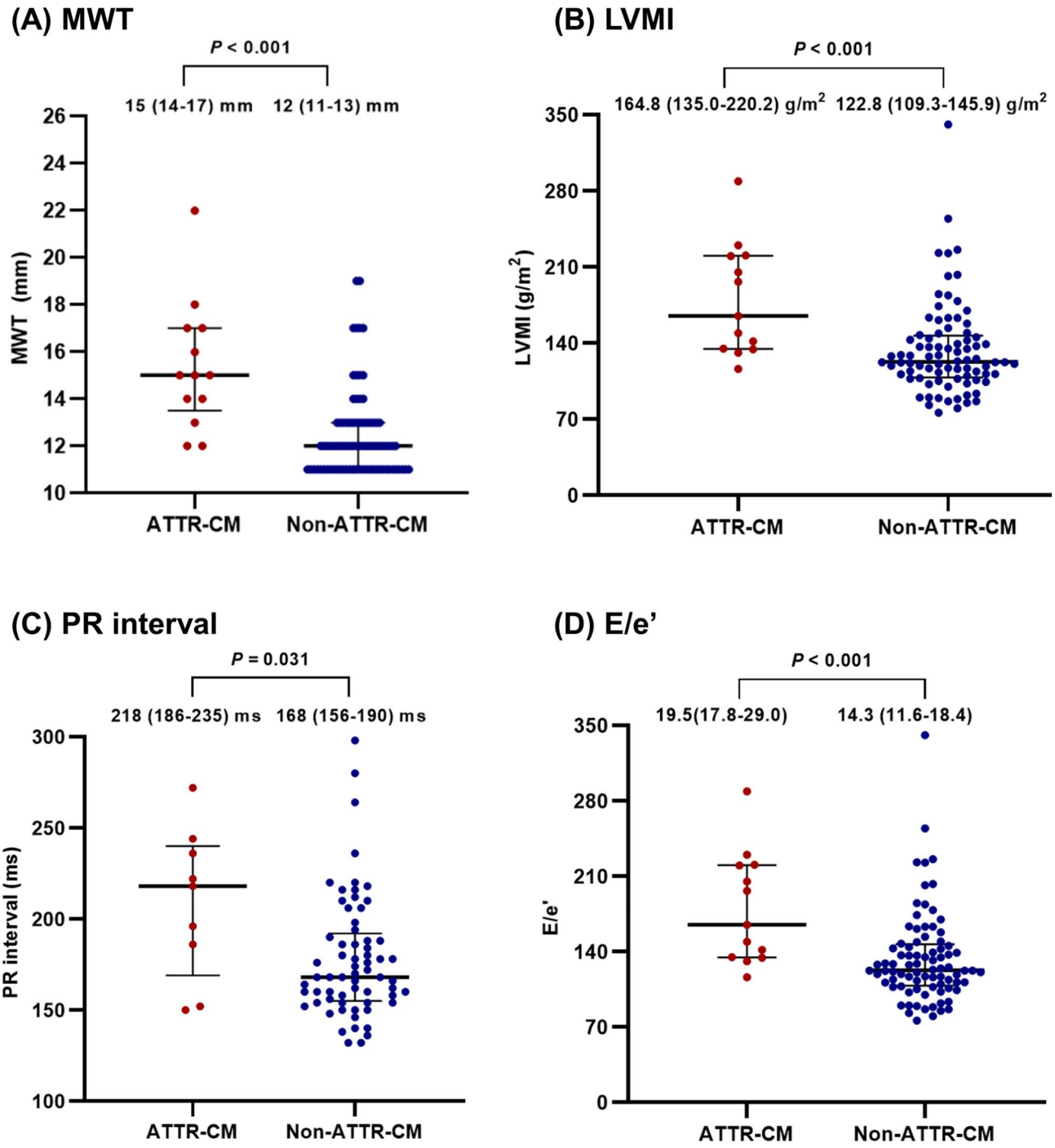

Fig. 3. The distribution of MWT, LVMI, PR interval, and E/e′ in ATTR-CM and non-ATTR-CM. In analysis for PR interval, values from 9 patients in the ATTR-CM group and 64 patients in the non-ATTR-CM group were used in the analysis, excluding patients with no values; in analysis for MWT, LVMI, E/e′, values from all patients were used in the analysis. *MWT* maximal wall thickness, *LVMI* left ventricular mass index.

HFpEF or HFmrEF presenting with LV wall thickness greater than 10 mm, potentially introducing a selection bias in the study population. Nevertheless, to the best of our knowledge, the current study represents the largest investigation of scintigraphy among a Korean population with HFpEF and HFmrEF. Third, data on the prognosis of ATTR-CM are lacking. Because ATTR-CM can progress to advanced heart failure, its diagnosis and treatment remain crucial. Given that the current study focused only on diagnosis, the prognosis of Korean patients with ATTR-CM needs to be examined in future investigations. However, a key strength of this study is that it was conducted on patients with a definitive diagnosis of HFpEF or HFmrEF, where research results related to ATTR-CM in patients with HFpEF or HFmrEF are rare.

In conclusion, to the best of our knowledge, this is the first study to present the prevalence and characteristics of ATTR-CM in Korean patients with HFpEF or HFmrEF diagnosed using scintigraphy. Therefore, the findings of this study suggest that ATTR-CM should be suspected in patients with HFpEF or HFmrEF, particularly in specific subgroups, such as males with neurologic symptoms, diastolic dysfunction, long PR interval, and/or low-voltage QRS, in the Korean population.

Methods

Study design and population

Between September 2018 and January 2023, patients who underwent transthoracic echocardiography (TTE) and ^{99m}Tc-pyrophosphate (PYP) or ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic (DPD) acid scintigraphy in Severance hospital were retrospectively investigated. Among them, patients with a left ventricular (LV) ejection fraction (LVEF) > 40% and maximal LV wall thickness (MWT) > 10 mm were included (Fig. 1). Patients with the following definite causes of heart failure were excluded: dilated cardiomyopathy (DCMP), hypertrophic cardiomyopathy (HCMP), myocarditis, AL amyloidosis, multiple myeloma (MM), valvular disease, sarcoidosis, other infiltrative cardiomyopathy (CMP), Fabry disease, 'Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes' (POEMS) disease, or 'Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes' (MELAS). The present study was reviewed and approved by the Institutional Review Board of Yonsei University College of Medicine (Approval number: 4-2022-1550) and adheres to the principles outlined in the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective study design.

Baseline and data collection

Laboratory and clinical data were collected from electronic medical records. Laboratory results within the nearest 3 months of TTE and bone scintigraphy data were collected. The H_2FPEF score was calculated to assess simple clinical features of HFpEF[37]. Polyneuropathy, carpal tunnel syndrome, lumbar spinal stenosis, and autonomic dysfunction were identified as red flag signs that are typical clinical features of patients with ATTR-CM and were defined as diagnosed by nerve conduction velocity, autonomic function, or imaging tests.

Echocardiographic parameters

TTE was performed by an expert using Vivid 7 or Vivid E9 (GE Healthcare, Chicago, IL, USA) and iE33 or Epiq7 (Phillips Healthcare, Best, The Netherlands) with the 2.5-MHz transducer. Standard two-dimensional, Doppler, and tissue Doppler imaging parameters were measured according to the recommendations of the current American Society of Echocardiography[38,39]. Left atrial volume and LVEF were assessed using the Simpson biplane method from the apical 4- and 2-chamber views. LV wall thickness was measured in the parasternal short-axis view. LV mass and relative wall thickness were calculated using the recommended formula. Diastolic function was assessed using mitral inflow pulsed-wave and mitral annular tissue Doppler. Right ventricular systolic pressure was determined using tricuspid velocity and inferior vena cava diameter. All measurements were digitally stored. MWT was defined as the thickest interventricular septal wall thickness and posterior wall thickness.

Electrocardiogram parameters

All (ECGs) were reviewed and measured manually. For the LV hypertrophy criteria, the Sokolow criteria was used[40], and the voltage-to-mass ratio obtained by dividing the Sokolow index by the LV mass index was also evaluated[30]. The low voltage QRS was defined as when the QRS voltage was < 5 mm in the limb leads or < 1 mV in all precordial leads.

^{99m}Tc-pyrophosphate or ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy

PYP or DPD scintigraphy was performed using GE Medical Systems single-photon emission computed tomography/computed tomography (SPECT/CT) (Discovery NM/CT 670) with a standardized protocol[41]. The patients were administrated 740 MBq PYP or DPD intravenously and scanned at 1 h when using PYP and 3 h when using DPD after injection. An additional 3-h scan was obtained in the PYP scan if significant blood pool activity was noted in the 1-h scan. Two experienced nuclear medicine physicians evaluated the results to confirm the presence and degree of myocardial uptake and distribution, rating it from grade 0 to 3 as follows: grade 0, no myocardial uptake; grade 1, less myocardial uptake than ribs; grade 2, myocardial uptake equal to ribs; grade 3, greater myocardial uptake than ribs with weak or absent rib uptake. Cases with grade 2 or 3 myocardial uptake were confirmed positive and diagnosed with ATTR-CM.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median (inter-quartile range [IQR]), and categorical variables as percentages. The differences between the ATTR-CM and non-ATTR CM groups were compared using the Student's t-test, Chi-square test, or Fisher's exact test. Because t-tests was primarily used to test our hypotheses, a t-test-based method was implemented to estimate the sample size. In detail, the "pwrss.t.2means" function in pwrss package was utilized with 0.8 of Cohen's D and 0.13 of disease/sample ratio. With a power of 0.8 and a significance level of 0.05, the sample size to test the hypothesis was estimated to be 124 (Supplementary Fig. S3). Statistical significance was set at a two-sided $P < 0.05$. Statistical analyses were conducted using the R software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

Data availability

The datasets generated and/or analysed during the current study are not publicly available due privacy/ethical restrictions but are available from the corresponding author on reasonable request.

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S.-E.K.: data acquisition, data analysis, data interpretation, and manuscript drafting and review; S.-H.L., C.J.L., S.H.H., W.J.K., S.-M.K.: data acquisition, data interpretation, and manuscript review; J.O.: study concept and design, data analysis, data interpretation, manuscript review, and study supervision.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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