



Wild-Type Transthyretin Amyloidosis in Female Patients — Consideration of Sex Differences —

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Background: With recent advances in non-invasive diagnostic tools, some studies indicate that wild-type transthyretin amyloidosis (ATTRwt) may be more common in females than previously reported. However, the clinical characteristics of female ATTRwt patients have not been determined.

Methods and Results: Of the 78 consecutive patients with ATTRwt in our cohort, 14 (17.9 %) were female. Compared with male patients, female ATTRwt patients had smaller left ventricular (LV) wall thicknesses (ventricular septum thickness 12.9 vs. 14.2 mm [$P=0.081$]; posterior wall thickness 12.7 vs. 13.6 mm [$P=0.035$]) and a higher LV ejection fraction (EF; mean [\pm SD] 58.4 \pm 8.9% vs. 48.9 \pm 11.8%; $P=0.006$). However, the severity of heart failure (HF), as assessed by HF stage, New York Heart Association functional class and B-type natriuretic peptide concentrations, did not differ between female and male patients. Moreover, LV mass index and relative wall thickness were increased and the stroke volume index was reduced in both female and male patients. In organ biopsies, female patients had a higher sensitivity to transthyretin deposition from abdominal fat than male patients (positive abdominal fat biopsy 80.0 % vs. 26.5%; $P=0.016$).

Conclusions: This study suggests that a relatively large proportion of elderly females have ATTRwt. Female ATTRwt patients had HF symptoms even at the stage of mild LV hypertrophy and preserved EF. Abdominal fat biopsy may be useful to diagnose ATTRwt, especially in female patients with HF.

Key Words: Cardiac amyloidosis; Female patient; Sex differences; Wild-type transthyretin amyloidosis

Wild-type transthyretin amyloidosis (ATTRwt), which has been referred to as senile or age-related amyloidosis, is an underappreciated cause of heart failure (HF) resulting from the deposition of wild-type transthyretin (TTR) that forms amyloid fibrils. Although it has been traditionally perceived as a rare disease and is often underdiagnosed,^{1,2} recent evidence suggests that ATTRwt is probably more common than has been thought, especially in elderly patients with HF.^{3,4} Oral tafamidis has been approved in Japan for the treatment of patients with ATTRwt since 2019.^{5–7} In this new era for patients with ATTRwt, accurate diagnosis is essential for appropriate management.

Previous studies have indicated that ATTRwt has a very strong male predominance;^{2,8–10} therefore, it has been thought that ATTRwt is very rare in female patients. However, these data were based on studies in patients with ATTRwt diagnosed using a conventional diagnostic procedure with biopsy-proven transthyretin amyloid deposi-

tion. Recently, with the development of new diagnostic strategies using non-invasive tools, some studies have indicated that ATTRwt may be more common in females than previously reported.^{11,12} Nevertheless, there have been very few reports about the clinical characteristics of female ATTRwt patients,^{11,13,14} and there has been no report on sex differences in Japanese patients with ATTRwt. Here, we discuss sex differences in patients with ATTRwt in a cohort of Japanese patients.

Methods

Patient Population and Clinical Definitions

Seventy-eight consecutive patients with ATTRwt who were diagnosed as having cardiac amyloidosis (CA) at Kochi Medical School Hospital between April 2012 and October 2020 were included in this study.

In this study, all patients underwent technetium-99m pyrophosphate (^{99m}Tc-PYP) scintigraphy. The diagnosis of

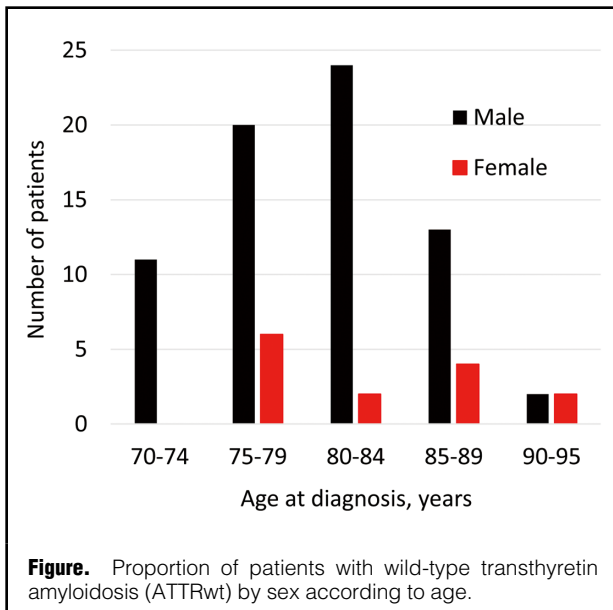
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transthyretin amyloidosis (ATTR) was established by biopsy-proven TTR in at least one involved organ and/or positive uptake on ^{99m}Tc -PYP scintigraphy with a normal free light chain ratio and serum immunofixation according to the Japanese Circulation Society 2020 guidelines.⁷ The subtype of ATTRwt was established by the absence of identifiable mutations following genetic testing and/or apparent signs and a family history indicative of variant ATTR (ATTRv). All patients had CA based on the following criteria: (1) endomyocardial biopsy (EMB)-proven TTR amyloid deposition; and (2) in the absence of an EMB, biopsy-proven TTR amyloid deposits in ≥ 1 extra-cardiac organ with echocardiographically defined evidence of amyloid cardiomyopathy¹⁵ and/or positive uptake on ^{99m}Tc -PYP scintigraphy.^{16,17}

This investigation was performed in accordance with the tenets of the Declaration of Helsinki. This retrospective study was approved by the Ethics Committee on Medical Research of Kochi Medical School.

Clinical Evaluation

A retrospective review was conducted of the medical records of all patients at the time of ATTRwt diagnosis. We determined the proportion of patients with newly diagnosed ATTRwt in the Kochi Medical School Hospital and assessed differences between male and female patients in terms of clinical manifestations, imaging parameters, and tissue biopsies.

Clinical Characteristics

HF was categorized into subtypes A, B, C, and D according to the American College of Cardiology Foundation/American Heart Association guidelines,¹⁸ and the severity of HF symptoms was assessed by New York Heart Association (NYHA) functional class. Plasma B-type natriuretic peptide (BNP) was measured using an enzyme immunoassay (TOSOH, Tokyo, Japan). Serum high-sensitivity cardiac troponin T (hs-cTnT) was measured using the Elecsys troponin T high sensitivity immunoassay (Roche Diagnostics, Rotkreuz, Switzerland). The results of ^{99m}Tc -PYP scintig-

raphy were analyzed according to a previously reported grading system for planar images: scans were defined as positive when Grade 2 or 3 ^{99m}Tc -PYP uptake was evident in the left ventricle.^{16,17}

Electrocardiography and Echocardiography

Electrocardiograms (ECG) were reviewed for rhythm abnormalities, QRS duration, the presence of low-voltage and poor precordial R wave progression,¹⁹ and arrhythmia.

Data for echocardiographic standard 2-dimensional measurements were obtained as recommended by the current guidelines.²⁰ Left ventricular (LV) ejection fraction (EF) was calculated using the Teichholz method or modified Simpson's method. Stroke volume (SV) was calculated from Doppler measurements of LV outflow tract (LVOT) diameter and the flow time-velocity integral (VTI) as $\text{LVOT area} \times \text{LVOT VTI}$ and was indexed to body surface area (BSA) to obtain the SV index (SVI). LV mass index (LVMI) was calculated by Devereux's formula using diastolic measurements of LV end-diastolic diameter (LVEDD) and interventricular septal (IVS) and posterior wall (PW) thicknesses. Relative wall thickness (RWT) was calculated as $(2 \times \text{PW thickness at end diastole}) / \text{LVEDD}$. Left atrium (LA) volume was measured using the biplane method of disks. The LA volume index (LAVI) was calculated by dividing LA volume by BSA. Mitral peak velocity of early filling (E) was measured using the pulse wave Doppler method. Early diastolic mitral annular velocity (e') was measured using the tissue Doppler method.

Organ Biopsies

The site and yield of tissue sampling for histologic confirmation of TTR-related amyloid protein deposition were assessed. Biopsy specimens were stained with hematoxylin-eosin and Congo red. Immunostaining was performed using monoclonal antibodies directed against amyloid A (AA) protein and TTR amyloid protein.

Statistical Analysis

All variables were compared between male and female patients with ATTRwt. Normality of data distribution was assessed using the Shapiro-Wilk test. Categorical variables are expressed as numbers (percentages) and continuous variables are presented as the mean \pm SD in the case of normally distributed variables) or as the median with interquartile range (IQR) for non-normally distributed variables. To determine the significance of differences between 2 groups, unpaired t-tests or the Mann-Whitney test were used for continuous variables and the Chi-squared test was used for categorical variables.

Two-sided $P < 0.05$ was considered significant. Statistical analyses were performed using IBM SPSS statistics version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Prevalence and Clinical Characteristics of ATTRwt According to Sex

The proportion of patients with newly diagnosed ATTRwt in Kochi Medical School Hospital according to age is shown in the **Figure**. The proportion of females among our ATTRwt patient cohort was 17.9% (14 females among 78 ATTRwt patients). The age at diagnosis did not differ between female and male patients (**Table 1; Figure**).

Table 1 shows the main clinical characteristics of the

	All patients (n=78)	Females (n=14)	Males (n=64)	P value
Age (years)				
At diagnosis	81.3±5.2	82.5±6.0	80.9±4.9	0.292
At onset of cardiac symptoms	79.5±5.4	82.0±6.6	78.4±5.0	0.072
Stage C or D heart failure at diagnosis	60 (76.9)	10 (71.4)	50 (78.1)	0.328
NYHA functional class ≥III at diagnosis	44 (56.4)	8 (57.1)	36 (56.2)	0.807
Body surface area (m ²)	1.56±0.16	1.36±0.09	1.61±0.13	<0.001
Comorbidities				
Hypertension or history of hypertension	42 (53.8)	8 (57.1)	34 (53.1)	0.785
Coronary artery disease	17 (21.8)	4 (28.5)	13 (20.3)	0.498
Aortic valve stenosis	2 (2.6)	0	2 (3.1)	NA
Carpal tunnel syndrome	34 (43.4)	7 (50.0)	27 (42.2)	0.593
Lumbar spinal canal stenosis	22 (28.2)	3 (21.5)	19 (29.7)	0.786
Laboratory data				
BNP (pg/mL)	288 [217–509]	253 [166–528]	296 [221–495]	0.263
hs-cTnT (ng/mL)	0.065 [0.051–0.091]	0.064 [0.036–0.075]	0.065 [0.053–0.094]	0.225
eGFR (mL/min/1.73m ²)	48.9±19.7	51.5±18.5	48.3±20.1	0.589
Hemoglobin (g/dL)	12.7±1.9	11.7±1.2	12.9±1.9	0.030
Serum albumin (g/dL)	3.87±0.48	3.94±0.42	3.86±0.50	0.842
Positive ^{99m} Tc-PYP scintigraphy	74 (94.9)	13 (92.9)	61 (94.9)	0.821

Unless indicated otherwise, data are shown as mean±SD, the median [interquartile range], or as n (%). ATTRwt, wild-type transthyretin amyloidosis; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; NA, not available; NYHA, New York Heart Association; ^{99m}Tc-PYP, technetium-99m pyrophosphate.

	All patients (n=78)	Females (n=14)	Males (n=64)	P value
ECG findings				
Atrial fibrillation	43 (55.1)	7 (50.0)	36 (56.3)	0.670
QRS duration (ms)	116 [99–148]	115 [89–147]	116 [101–147]	0.450
Low voltage	24 (30.8)	6 (42.8)	18 (28.1)	0.516
Poor precordial R wave progression	30 (38.5)	5 (35.7)	25 (39.0)	0.868
Low-voltage and poor precordial R wave progression	13 (16.7)	2 (14.3)	11 (17.2)	0.774
Sick sinus syndrome	2 (2.6)	0	2 (3.1)	NA
High-degree or complete AV block	4 (5.1)	2 (14.3)	2 (3.1)	0.086
Right bundle branch block	17 (21.8)	2 (14.3)	15 (23.4)	0.452
Left bundle branch block	8 (10.3)	1 (7.6)	7 (10.9)	0.672
Echocardiographic findings				
LVEDD (mm)	46.0±6.1	42.0±3.3	46.8±6.2	0.006
LVESD (mm)	34.4±7.1	28.8±3.3	35.6±7.2	<0.001
IVS thickness (mm)	14.0 [12.9–15.0]	12.9 [12.0–14.4]	14.2 [13.4–15.2]	0.081
PW thickness (mm)	13.3 [12.6–14.8]	12.7 [11.8–14.2]	13.6 [13.0–15.1]	0.035
IVS thickness <12 mm	8 (10.3)	4 (28.5)	4 (6.3)	0.013
LVEF (%)	50.6±11.9	58.4±8.9	48.9±11.8	0.006
LVEF ≥50%	51 (65.3)	12 (85.7)	39 (61.0)	0.025
Stroke volume index (mL/m ²)	33.3±9.4	36.6±6.5	32.5±9.7	0.144
LV mass index (g/m ²)	158.1±36.8	146.5±30.8	160.8±37.8	0.193
Relative wall thickness	0.60±0.11	0.62±0.09	0.59±0.12	0.294
Left atrium diameter (mm)	47.4±6.9	44.5±5.2	48.0±7.1	0.087
Left atrium volume index (mL/m ²)	65.1±40.0	56.9±21.3	67.2±43.1	0.355
E/A ratio	1.85 [0.98–2.73]	1.24 [1.07–1.79]	2.24 [0.96–2.77]	0.407
E/e' ratio				
Septal	23.2±8.2	24.4±7.6	22.9±8.4	0.545
Lateral	15.8±5.5	16.8±4.8	15.6±5.7	0.495

Unless indicated otherwise, data are shown as mean±SD, the median [interquartile range], or as n (%). ATTRwt, wild-type transthyretin amyloidosis; AV, atrioventricular; ECG, electrocardiogram; IVS, interventricular septum; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; NA, not available; PW, posterior wall.

	All patients (n=78)	Females (n=14)	Males (n=64)	P value
Skin	5/61 (8.2)	1/10 (10.0)	4/51 (7.9)	0.890
Abdominal subcutaneous fatty tissue	21/59 (35.6)	8/10 (80.0)	13/49 (26.5)	0.016
Stomach or jejunal mucosa	5/19 (26.3)	1/2 (50.0)	4/17 (23.5)	0.421
Heart	35/35 (100)	3/3 (100)	32/32 (100)	1

Data show the number of positive biopsies/the number of total biopsies, with percentages in parentheses.

Study (year of publication)	Institution, location	ATTRwt patients	Age at diagnosis (years)	ATTRwt prevalence by sex
Case series study for patients diagnosed with ATTRwt				
Present study	Kochi Medical School Hospital, Kochi, Japan	78 patients with biopsy-confirmed ATTRwt and/or positive uptake on ^{99m} Tc-PYP scintigraphy	81.3±5.2	82% male
Pinney et al ⁸ (2013)	UK National Amyloidosis Centre, London, UK	99 patients with biopsy-confirmed ATTRwt	73.0	89% male
Grogan et al ⁹ (2016)	Mayo Clinic, Rochester, MN, USA	360 patients with biopsy-confirmed ATTRwt	75.5	91% male
Connors et al ² (2016)	Boston University Amyloidosis center, Boston, MA, USA	121 patients with biopsy-confirmed ATTRwt	75.1	98% male
González-López et al ¹¹ (2017)	Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain, and University of Bologna, Bologna, Italy	108 patients with biopsy-confirmed ATTRwt or positive uptake on ^{99m} Tc-DPD scintigraphy	78.6±8.0	81% male
Siepen et al ¹⁰ (2018)	University of Heidelberg, Heidelberg, Germany	191 patients with biopsy-confirmed ATTRwt	73.8±0.5	92% male
Screening studies for subjects without a prior diagnosis of ATTRwt				
Tanskanen et al ²⁴ (2008)	University of Helsinki, Helsinki, Finland	64 patients with post-mortem diagnosis of ATTRwt among 256 patients in a population-based autopsy study	93.8±4.3	Males, 34%; females, 23%
Mohammed et al ²⁵ (2014)	Mayo Clinic, Rochester, MN, USA	18 patients with post-mortem diagnosis of ATTRwt among 109 patients with antemortem diagnosis of HF with an LVEF >40%	89.0±8.0	Males, 19%; females, 15%
González-López et al ⁴ (2015)	Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain	16 patients with positive uptake on ^{99m} Tc-DPD scintigraphy among 120 patients admitted due to HFpEF with LV hypertrophy (≥12 mm)	86.0±6.0	Males, 16%; females, 11%
Scully et al ²⁶ (2018)	Queen Mary University, London, UK	14 patients with positive uptake on ^{99m} Tc-DPD scintigraphy among 101 patients referred for TAVR for aortic valve stenosis	88.0±6.0	Males, 16%; females, 12%
Tsutsui et al ²⁷ (2019)	Saiseikai Fukuoka General Hospital, Fukuoka, Japan	18 patients with positive uptake of ^{99m} Tc-PYP scintigraphy among 98 patients with heart failure screened for ATTR	82.3±11.7	Males, 21%; females, 14%

Data are shown as mean±SD, median or n (%). ATTRwt, wild-type transthyretin amyloidosis; ATTR, transthyretin amyloidosis; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; HF, heart failure; HFpEF, HF with preserved ejection fraction; LV, left ventricle; LVEF, LV ejection fraction; PYP, pyrophosphate; TAVR, transcatheter aortic valve replacement; ^{99m}Tc, technetium-99m.

study cohort at the time of diagnosis stratified by sex. Female patients tended to be older than male patients at the onset of cardiac symptoms and had a smaller BSA than male patients. There were no significant differences between female and male patients in HF stage, NYHA functional class, the prevalence of cardiovascular comorbidities, carpal tunnel syndrome, and lumbar canal stenosis, values of cardiac biomarkers and the prevalence of positive cardiac uptake on ^{99m}Tc-PYP scintigraphy. Most patients had Subtype C or D HF at the time of diagnosis. Plasma BNP and serum hs-cTnT concentrations were significantly elevated in both female and male patients. All patients had hs-cTnT concentrations >0.014 ng/mL (where

0.014 ng/mL is considered normal in healthy adults²¹), with concentrations ranging from 0.018 to 0.232 ng/mL.

ECG and Echocardiographic Parameters According to Sex

Table 2 shows ECG and echocardiographic characteristics. Atrial fibrillation was the most frequent abnormal ECG finding (in >50% of patients) in both female and male patients. LV size was smaller and LVEF was higher (58.4±8.9% vs. 48.9±11.8%; P=0.006) in female than male patients, and the frequency of HF with preserved LVEF (HFpEF; EF >50%) at the time of diagnosis was higher among female than male patients (85.7% vs. 61.0%, respectively; P=0.025). Female patients had a smaller LV wall

thickness (IVS thickness: 12.9 vs. 14.2 mm [$P=0.081$]; PW thickness: 12.7 vs. 13.6 mm [$P=0.035$]) than male patients. The lack of significant LVH (IVS thickness <12 mm) at the time of diagnosis was more frequent in female than patients (28.5% vs. 6.3%, respectively; $P=0.013$). Conversely, there were no significant differences between female and male patients in SVI, LVMI, RWT, and LAVI. SVI was almost equal to the proposed SVI threshold of 35 mL/m^2 as a low-flow state or normal-flow state^{22,23} in both female and male patients.

LVMI and RWT were increased and LAVI was above the normal range in both female and male patients.

Results of Organ Biopsies According to Sex

The results of organ biopsies are presented in **Table 3**. Skin, abdominal subcutaneous fatty tissue, and the upper gastrointestinal tract were common sites for non-cardiac tissue sampling. The rate of TTR detection in abdominal fat tissue was significantly higher in female than male patients. Conversely, all patients, both female and male, in whom EMB was performed were positive for amyloid.

Discussion

In this study, although the number of patients was relatively small, 18% of patients diagnosed with ATTRwt were female, and the male preponderance was lower than in previous studies.^{2,8–10} Female ATTRwt patients had a higher sensitivity for TTR detection in abdominal fat tissue, smaller LV cavity, milder LVH, and a higher frequency of preserved LVEF than male ATTRwt patients.

There have been few studies in which sex differences in ATTRwt have been investigated,^{11,13,14} and information on Japanese female patients with ATTRwt remains insufficient. Below, we discuss the clinical features of ATTRwt in female patients.

Frequency of ATTRwt in Females

The actual overall prevalence and sex-specific characteristics of ATTRwt are unknown because population-based surveillance has never been performed. The proportion of males among patients with ATTRwt in our study and in previous published series is presented in **Table 4**. Some large series reported a strong male predominance in ATTRwt^{2,8–10} (**Table 4**). Conversely, a higher age at diagnosis and a relatively lower predominance of male patients were found in the present study and in a Spanish and Italian cohort study by González-López et al¹¹ compared with other series. These differences in clinical features may have resulted from a bias in patient cohorts from referral tertiary centers or community-based medical facilities. Furthermore, non-invasive diagnostic modalities, including ^{99m}Tc-labelled scintigraphy, were used for some patients in the present study and in the Spanish and Italian cohort study.¹¹ This approach may have increased the rate of diagnosis of female ATTRwt patients, particularly among elderly female patients with mild LVH.

Even more interestingly, several screening studies for subjects without a prior diagnosis of ATTRwt (**Table 4**) found a higher age at diagnosis and no strong male predominance.^{4,24–27} These results suggest that ATTRwt may be more common in females and in the elderly population and that it may have been largely underdiagnosed in daily clinical practice.

Clinical Characteristics of Female ATTRwt Patients

We focused on cardiac structure or function according to sex, and identified some trends in our cohort as also reported in a previous review of ATTR-CA,¹⁴ specifically lower LV wall thickness, smaller LV size, and higher LVEF in female than male patients. Furthermore, the severity of HF (HF stage, NYHA functional class, and plasma BNP concentration) did not differ between female and male patients in our cohort. LVMI and RWT were increased, LAVI was greater, and the SVI tended to be reduced in both female and male patients. According to LVMI and RWT values, almost all our patients, both female and male, were categorized as having concentric LV hypertrophy with geometric patterns.

A previous study showed that despite EF often being initially normal in CA, the actual physiologic performance of the LV is not intact because of amyloid-associated changes in ventricular remodeling, reduced chamber capacitance, and decreased chamber contractility.²⁸ In addition, in patients with HFpEF, so-called diastolic HF, some studies have suggested that a low-flow phenotype (SVI $<35 \text{ mL/m}^2$) in HFpEF was independently associated with low exercise capacity, poor quality of life, and a high risk of HF hospitalization.^{29,30} Our Japanese female elderly patients had a small BSA, and so concentric LV hypertrophy and a low-flow state may easily appear. Consequently, Japanese female ATTRwt patients may be more symptomatic under conditions of HFpEF even before the advanced phase of ATTRwt, with reduced LVEF and moderately increased LV wall thickness.

Thus, clinicians should be aware of the possibility of ATTRwt in female patients with a low threshold even if they are at the stage of preserved EF and mild LV hypertrophy. The use of lower cut-off values or cardiac dimensions indexed by BSA to diagnose ATTR-CA in females has been discussed¹⁴ because females are less likely to meet the diagnostic wall thickness threshold.

The mechanism responsible for the disparities in the prevalence and onset of cardiomyopathy between male and female ATTRwt patients remains to be clarified and the reasons for sex differences in ATTR fibril formation are also unknown. A few reports suggest that the cardioprotective effects of estrogen may be related to the low frequency and late onset of ATTRwt in females.^{31,32} Additional studies into the detailed clinical characteristics of ATTRwt in females and the mechanism underlying the sex differences are needed.

Abdominal Fat Pad Biopsy: Potential Diagnostic Utility in Female ATTRwt Patients

Regarding the biopsy site, a recent study on ATTRv-CA showed that female patients had a higher sensitivity to TTR deposition from abdominal fat than male patients.³³ Based on results of previous studies showing that male patients were more prone to cardiac ATTR deposition than female patients,^{32,34,35} it was speculated that females may develop cardiomyopathy at later stages of the disease, thus allowing for more amyloid accumulation in non-cardiac tissues. It has not been determined whether this rule applies to patients with ATTRwt. However, 80% of female patients in our cohort in whom an abdominal fat pad biopsy was performed were positive for amyloid. Abdominal fat biopsy is clearly less invasive than EMB, and we therefore suggest that abdominal fat biopsy should be performed particularly in elderly female patients with sus-

pected ATTRwt.

Study Limitations

One limitation of the present study is its single-center design and relatively small number of patients. A center-specific bias and limited data may have affected some of the statistical analyses. More data from larger groups are needed to validate our results. Second, there was a lack of information about prognosis because the number of mortality events was limited in female ATTRwt patients. During the follow-up period (median 1.54 years; IQR 1.04–2.88 years), 4 (28.6%) of the 14 female ATTRwt patients died. Further studies on sex-related differences in the clinical course in patients with ATTRwt are needed to provide important information for management and decisions regarding treatment strategies.

As a further limitation of this retrospective study, in the diagnostic work-up of patients with HF, each physician decided whether to perform ^{99m}Tc-PYP scintigraphy in patients with HF. This may have affected some of the results.

Conclusions

There was a considerably large number of females with ATTRwt in our Japanese cohort. Female ATTRwt patients had HF symptoms at the stage of preserved EF and mild LV hypertrophy accompanied by low cardiac output. We should be aware of the possibility of ATTRwt in elderly female patients with HF, particularly in patients with HFpEF. For elderly female patients with mild LV hypertrophy, abdominal fat pad biopsy may have a high potential to identify ATTRwt.

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Disclosures

T.K. and H.K. have received consulting fees or honoraria and remuneration for lectures from Pfizer Japan Inc.

H.K. is a member of *Circulation Reports*' Editorial Team. The remaining authors have no conflicts of interest to declare.

IRB Information

This study was approved by the Ethics Committee on Medical Research of Kochi Medical School (Reference no. ERB-002080).

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