



Tenosynovial and Cardiac Transthyretin Amyloidosis in Japanese Patients Undergoing Carpal Tunnel Release

Kenta Sugiura, MD; Hiroki Kozuki, MD; Hiroaki Ueba, MD; Toru Kubo, MD; Yuri Ochi, MD; Yuichi Baba, MD; Kazuya Miyagawa, MD; Tatsuya Noguchi, MD; Takayoshi Hirota, MD; Naohito Yamasaki, MD; Noriko Wada, MD; Junko Nakashima, MD; Ichiro Murakami, MD; Masahiko Ikeuchi, MD; Hiroaki Kitaoka, MD

Background: Wild-type transthyretin cardiac amyloidosis (ATTRwt-CA) is a life-threatening progressive disease. Recent studies have shown that the detection of transthyretin (TTR) amyloid in tenosynovial tissue may play an important role in the diagnosis of cardiac amyloidosis. The aim of this study was to determine the prevalence of TTR amyloid deposits in surgical tissue of patients undergoing carpal tunnel surgery and to clarify the clinical significance of concomitant cardiac examination with ^{99m}Tc-labeled pyrophosphate (^{99m}Tc-PYP) scintigraphy in those patients with TTR deposition.

Methods and Results: We evaluated 79 consecutive patients undergoing carpal tunnel release surgery and biopsy of tenosynovial tissue. The mean (\pm SD) age of the patients at surgery was 71.6 \pm 12.5 years (range 30–95 years); 32 patients (41%) were male. TTR amyloid deposition in tenosynovial tissue was observed in 27 patients (34%). Sixteen of those 27 patients underwent ^{99m}Tc-PYP scintigraphy. Of those 16 patients, 3 (19%) had Grade 2 uptake on ^{99m}Tc-PYP scintigraphy. None of the 3 patients with a diagnosis of ATTRwt-CA had apparent cardiac symptoms and left ventricular wall thickness >13 mm.

Conclusions: Concomitant cardiac examination with ^{99m}Tc-PYP scintigraphy in patients who had TTR amyloid deposition in tenosynovial tissue resulted in the identification of 19% of patients with a diagnosis of ATTRwt-CA. This diagnostic approach seems to be useful for the early diagnosis of the disease.

Key Words: Cardiac amyloidosis; Carpal tunnel surgery; Transthyretin

Wild-type transthyretin cardiac amyloidosis (ATTRwt-CA) is a life-threatening progressive disease characterized by infiltrative cardiomyopathy caused by deposition of transthyretin (TTR) amyloid in the myocardium.^{1–3} It has been perceived as a rare disease and is often undiagnosed in clinical practice, especially in elderly patients with heart failure. Diagnosis of ATTRwt-CA often takes more than 1 year from the appearance of cardiac symptoms.^{3,4} However, with the introduction of the therapeutic agent tafamidis, early diagnosis of ATTRwt-CA has become increasingly important.⁵

Carpal tunnel syndrome is one of the symptoms of systemic amyloidosis. The reported prevalence of TTR deposition in tenosynovial tissue in Japanese patients with idiopathic carpal tunnel syndrome was 34.0%.⁶ Recent studies have revealed that a history of carpal tunnel syn-

drome was associated with a diagnosis of amyloidosis and heart failure.^{7,8} In addition, it has been shown that carpal tunnel syndrome precedes the diagnosis of ATTRwt-CA by 5–10 years.⁹ Therefore, carpal tunnel syndrome is an important red flag in the diagnosis of ATTRwt-CA.

However, there are very few reports of systematic efforts to detect ATTRwt-CA in collaboration with orthopedic surgeons and cardiologists. Recently, we have built a cooperative system including cardiac evaluations by technetium-99m pyrophosphate (^{99m}Tc-PYP) scintigraphy examination for patients undergoing carpal tunnel release surgery with detection of amyloid deposits in the tenosynovial tissue. To the best of our knowledge, there have been no reports of the prevalence of cardiac involvement at the time of carpal tunnel surgery in Japanese patients with evidence of TTR deposition in tenosynovial tissue.

Received April 14, 2021; accepted April 14, 2021; J-STAGE Advance Publication released online May 27, 2021 Time for primary review: 1 day

Department of Cardiology and Geriatrics (K.S., T.K., Y.O., Y.B., K.M., T.N., T.H., N.Y., H. Kitaoka), Department of Orthopedic Surgery (H. Kozuki, H.U., M.I.), Department of Pathology (N.W., J.N., I.M.), Kochi Medical School, Kochi University, Nankoku, Japan

H. Kitaoka is a member of *Circulation Reports*' Editorial Team.

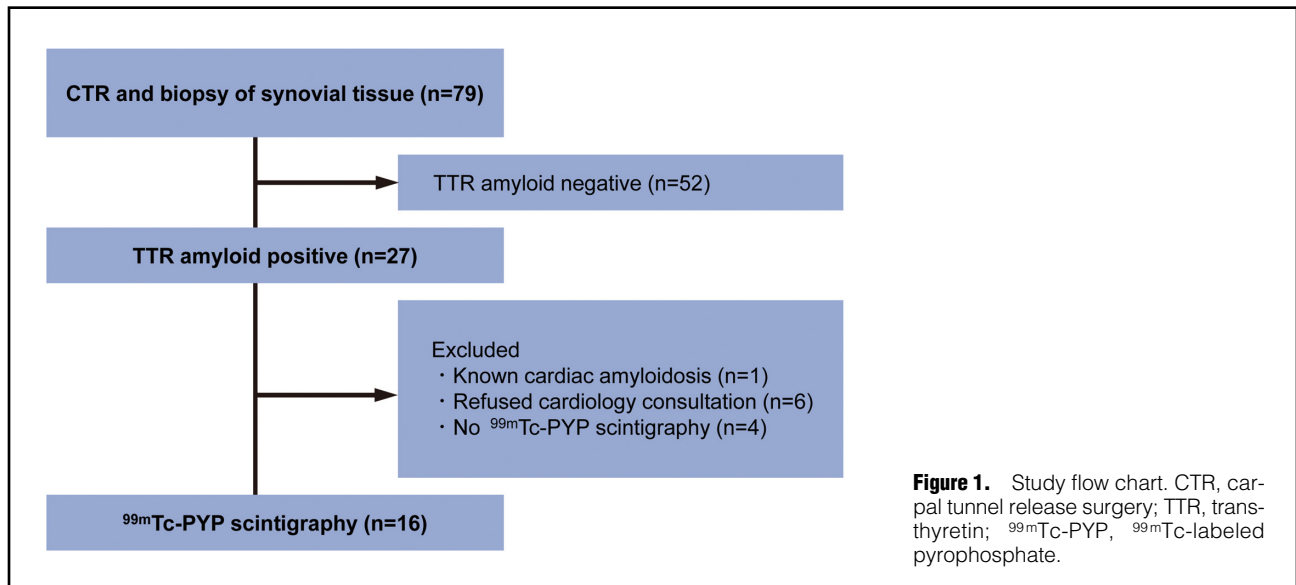
The first two authors contributed equally to this work (K.S., H. Kozuki).

Mailing address: Toru Kubo, MD, FJCS, Department of Cardiology and Geriatrics, Kochi Medical School, Kochi University, Oko-cho, Nankoku 783-8505, Japan. E-mail: jm-kubotoru@kochi-u.ac.jp

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cr@j-circ.or.jp

ISSN-2434-0790





	Total cohort (n=79)	TTR amyloid positive (n=27)	TTR amyloid negative (n=52)	P value
Age (years)	71.6±12.5	79.4±6.1	67.5±13.0	<0.001
BMI (kg/m ²)	24.2±4.3	23.7±3.0	24.6±4.9	0.368
Male sex	32 (41)	16 (59)	16 (31)	0.017
Bilateral CTS	43 (54)	18 (67)	25 (48)	0.239
Hypertension	43 (54)	20 (74)	23 (44)	0.017
Dyslipidemia	29 (37)	15 (56)	14 (27)	0.015
Diabetes	19 (15)	4 (15)	11 (21)	0.561
Coronary artery disease	7 (9)	2 (7)	5 (10)	1.000
Atrial fibrillation	9 (11)	3 (11)	6 (11)	1.000
Dialysis	15 (19)	3 (11)	12 (23)	0.241
Sodium (mmol/L)	140.5±2.6	140.2±3.0	140.7±2.3	0.407
Potassium (mmol/L)	4.2±0.4	4.2±0.4	4.2±0.4	0.490
Creatinine (mg/dL)	1.9±2.5	1.6±1.9	2.0±2.7	0.406
eGFR (mL/min/1.73m ²)	56.7±30.2	51.8±25.1	59.3±32.4	0.294
Albumin (g/dL)	4.1±0.4	4.1±0.5	4.1±0.4	0.811

Unless indicated otherwise, data are given as the mean±SD or n (%). BMI, body mass index; CTS, carpal tunnel syndrome; eGFR, estimated glomerular filtration rate, determined using the Modification of Diet in Renal Disease study equation; TTR, transthyretin.

The aims of this study were to determine the prevalence of TTR amyloid deposits in surgical tissues of patients undergoing carpal tunnel surgery and to clarify the clinical significance of concomitant examination with ^{99m}Tc-PYP scintigraphy in those patients with evidence of TTR deposition.

Methods

Subjects

We retrospectively evaluated 79 consecutive patients who underwent carpal tunnel release surgery and biopsy of tenosynovial tissue between August 2017 and October 2020 at Kochi Medical School Hospital. Data for these patients were obtained from medical records.

This study was approved by the Ethics Committee on Medical Research of Kochi Medical School and was conducted in accordance with the Declaration of Helsinki and the ethical standards of the responsible committee on human experimentation.

Surgical Procedure and Clinical Evaluation

After transection of the transverse carpal ligament, the median nerve and flexor tendons were protected, and a small sample of synovial tissue was excised. The tenosynovial tissue was then formalin fixed and subsequently evaluated by hematoxylin-eosin and Congo red staining by pathologists. Biopsy specimens with confirmed amyloid deposits by Congo red staining were further analyzed using immunohistochemistry for subtyping.

Table 2. Cardiac Evaluation in the 16 Patients Undergoing ^{99m}Tc-Pyrophosphate Scintigraphy

Patient no.	Age (years)	Sex	Bilateral CTS	^{99m} Tc-PYP scintigraphy		Laboratory findings			
				Grade	Time from surgery (months)	BNP (ng/mL)	hs-cTnT (ng/mL)	eGFR (mL/min/1.73m ²)	Albumin (mg/dL)
1	69	M	+	2	1	62.3	0.040	47.1	3.9
2	85	M	-	2	3	105.2	0.039	35.3	3.9
3	78	F	+	2	1	75.0	0.018	85.8	4.1
4	78	F	+	1	13	59.7	0.015	80.6	4.7
5	80	M	+	1	1	291.0	0.029	57.7	3.8
6	86	F	-	0	2	76.2	0.032	53.1	4.2
7	78	M	+	0	5	37.7	0.012	34.2	3.5
8	84	F	+	0	6	55.3	0.015	49.9	4.3
9	79	F	+	0	5	36.5	0.013	59.7	4.0
10	93	F	-	0	10	57.7	0.020	56.8	4.4
11	82	M	+	0	1	13.4	0.012	72.9	4.3
12	78	M	+	0	2	36.1	0.386	4.7	3.9
13	68	M	-	0	2	76.7	0.013	61.1	3.8
14	89	F	-	0	1	NA	NA	38.8	3.0
15	81	F	-	0	33	41.0	0.031	36.6	4.0
16	68	M	+	0	23	31.0	0.010	85.4	4.5

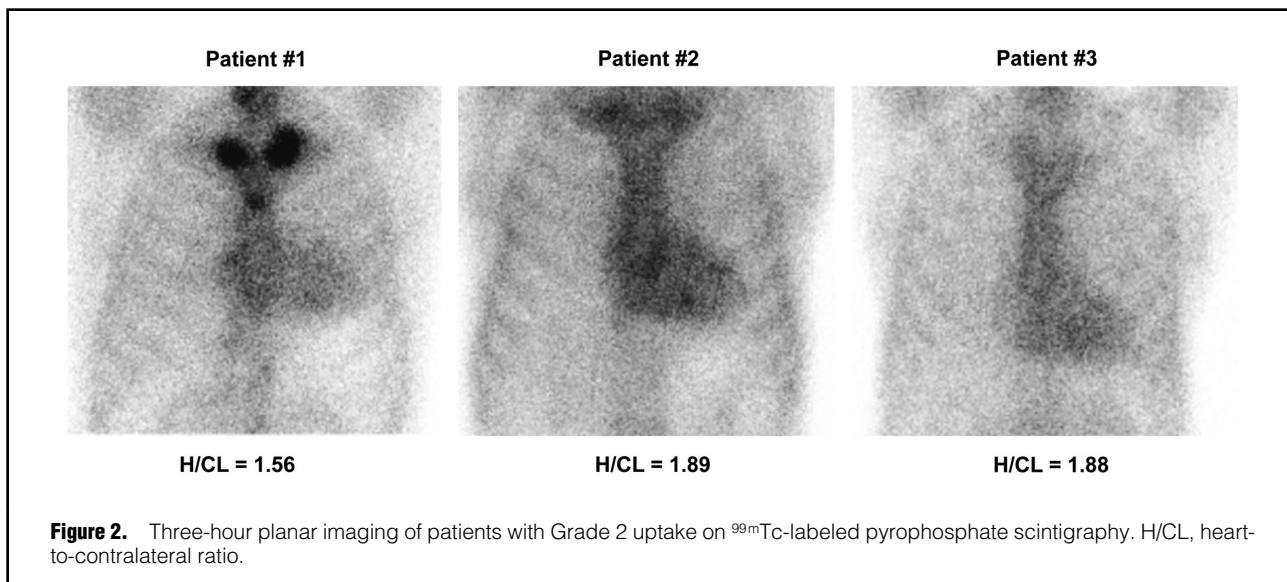
Patient no.	ECG findings			Echocardiographic findings				
	QRS width (ms)	Low voltage in limb leads	Pseudo-infarction pattern	LVEF (%)	IVST (mm)	PWT (mm)	Mean E/e'	Apical sparing
1	112	-	-	59	11	11	9.4	-
2	90	+	+	61	11	11	10.4	-
3	113	-	+	67	12	12	20.9	+
4	110	-	+	58	11	8	23.0	-
5	100	-	+	48	10	11	26.3	+
6	88	-	-	65	10	8	6.0	-
7	97	-	-	66	9	8	13.0	-
8	88	-	-	65	9	9	14.2	-
9	98	-	-	67	9	10	12.1	-
10	95	-	-	67	8	9	17.4	-
11	122	-	-	52	10	9	8.1	-
12	90	-	-	62	9	8	7.9	-
13	89	-	-	66	10	10	8.5	-
14	133	-	-	79	14	12	NA	NA
15	102	-	-	68	10	10	8.7	-
16	107	-	-	82	13	11	14.9	-

^{99m}Tc-PYP, ^{99m}Tc-labeled pyrophosphate; BNP, B-type natriuretic peptide; CTS, carpal tunnel syndrome; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate, determined using the Modification of Diet in Renal Disease study equation; F, female; hs-cTnT, high-sensitivity cardiac troponin T; IVST, interventricular septal thickness; LVEF, left ventricular ejection fraction; M, male; NA, not available; PWT, posterior wall thickness.

In accordance with the Japanese Circulation Society 2020 Guideline on Diagnosis and Treatment of Cardiac Amyloidosis,¹⁰ the diagnosis of ATTRwt-CA was established by tenosynovial tissue biopsy-proven TTR amyloid deposition and Grade 2 or 3 positive uptake on ^{99m}Tc-PYP scintigraphy accompanied by clinical and laboratory findings suggesting cardiac amyloidosis, with normal free light chain ratio and serum immunofixation. The subtype of wild-type TTR amyloid was established on the basis of the absence of TTR mutations.

Evaluation of patients included a medical history, clinical examination, 12-lead electrocardiogram (ECG), labo-

ratory variables, B-type natriuretic peptide (BNP), high-sensitivity cardiac troponin T (hs-cTnT), echocardiography, and ^{99m}Tc-PYP scintigraphy. BNP was measured using an enzyme immunoassay (TOSOH, Tokyo, Japan) and hs-cTnT was measured using an Elecsys troponin T high-sensitivity immunoassay (Roche Diagnostics, Rotkreuz, Switzerland). A standard 12-lead ECG was performed for each patient and was reviewed retrospectively. Low voltage was assessed by limb criteria (QRS amplitude ≤0.5mV in all limb leads). A pseudo-infarction pattern was defined as pathological Q waves or QS waves in at least 2 consecutive leads in the absence of evidence of akinetic/



dyskinetic wall segments. Echocardiographic parameters were measured in a standard manner as recommended by the American Society of Echocardiography guidelines.¹¹ Apical sparing was evaluated by using a systolic longitudinal base-to-apex strain gradient (average apical to average basal longitudinal peak systolic strain ratio >2.1).¹² In the present study, ^{99m}Tc -PYP scintigraphy was defined as significant for a definite diagnosis of cardiac TTR amyloidosis when there was Grade 2 or 3 uptake of ^{99m}Tc -PYP in the left ventricle (LV) according to previously reported grading systems.^{10,13,14} Visual and quantitative assessments were established in the 3-h imaging. In patients undergoing ^{99m}Tc -PYP scintigraphy, we assessed the following 3 factors in the 'Kumamoto criteria': QRS width ≥ 120 ms, LV posterior wall thickness (LVPWT) ≥ 13.6 mm, and hs-cTnT ≥ 0.0308 ng/mL. The Kumamoto criteria were introduced for good performance to predict ^{99m}Tc -PYP scintigraphy positivity.^{15,16}

Statistical Analysis

Categorical variables are expressed as numbers (percentages) and continuous variables are presented as the mean \pm SD. The significance of differences between the 2 groups was assessed using unpaired t-tests for continuous variables and the χ^2 test for categorical variables. All analyses were performed using IBM SPSS version 21.0.0.0 (IBM Corp., Armonk, NY, USA).

Results

Clinical Characteristics in Patients Undergoing Carpal Tunnel Release

Figure 1 shows the study patient flow chart. All patients underwent biopsy of tenosynovial tissue. The clinical characteristics of the 79 patients who underwent carpal tunnel release surgery are summarized in **Table 1**. The mean age of the patients at surgery was 71.6 ± 12.5 years (range 30–95 years), and 32 patients (41%) were male. Forty-three patients (54%) had bilateral carpal tunnel syndrome.

TTR amyloid in the tenosynovial biopsy was found in 27 patients (34%). TTR amyloid-positive patients were

significantly older and there was a significantly larger proportion of male patients in this group. Regarding comorbidities, hypertension and dyslipidemia were more frequent in TTR amyloid-positive patients. No differences were found in other parameters.

Cardiac Involvement

Of the 27 TTR amyloid-positive patients, 1 with a prior diagnosis of ATTRwt-CA, 6 who refused to be referred by cardiologists, and 4 who did not want to have a ^{99m}Tc -PYP scintigraphy examination were excluded (**Figure 1**). This left 16 patients who underwent ^{99m}Tc -PYP scintigraphy after the biopsy for assessment in the present study.

Table 2 presents the findings of cardiac evaluation in the 16 patients undergoing ^{99m}Tc -PYP scintigraphy. Most patients had cardiac evaluation within 1 year after carpal tunnel release surgery. Of these 16 patients, 3 had Grade 2 uptake and 2 had Grade 1 uptake on ^{99m}Tc -PYP scintigraphy. **Figure 2** shows 3-h planar imaging and the heart-to-contralateral ratio of the 3 patients with Grade 2 uptake. These 3 patients (Patients #1, #2, and #3) with Grade 2 uptake on ^{99m}Tc -PYP scintigraphy showed a normal free light chain ratio and serum immunofixation, and TTR mutations were not identified. Patients #1 and #3 had no symptoms (New York Heart Association [NYHA] functional class I). Patient #2 had very mild dyspnea (NYHA functional class II). The ECG showed a pseudo-infarction pattern in Patients #2 and #3. Low voltage in limb leads was observed in Patient #2. Echocardiography showed an interventricular septal thickness (IVST) of 11 mm in Patients #1 and #2 and an IVST of 12 mm in Patient #3. Positive apical sparing was confirmed in 1 patient. BNP concentrations in Patients #1, 2, and 3 ranged from 62 to 105 pg/mL. According to the current Japanese guideline,¹⁰ the 3 patients with Grade 2 uptake on ^{99m}Tc -PYP scintigraphy were finally diagnosed as having ATTRwt-CA; that is, a diagnosis of ATTRwt-CA at the time of carpal tunnel surgery was obtained in 3 (19%) of the 16 patients.

Table 3 presents the 3 factors in the 'Kumamoto criteria' and apical sparing on echocardiography in patients with Grade 2 uptake on ^{99m}Tc -PYP scintigraphy. None of these

Table 3. Kumamoto Criteria and Apical Sparing on Echocardiography in Patients With Grade 2 Uptake on ^{99m}Tc-Pyrophosphate Scintigraphy

Patient no.	^{99m} Tc-PYP scintigraphy grade	Wide QRS ≥120 ms	LVPWT ≥13.6 mm	hs-cTnT ≥0.0308 ng/mL	Apical sparing on echocardiography
1	2	–	–	+	–
2	2	–	–	+	–
3	2	–	–	–	+

^{99m}Tc-PYP, ^{99m}Tc-labeled pyrophosphate; hs-cTnT, high sensitivity cardiac troponin T; LVPWT, left ventricular posterior wall thickness.

Table 4. Four Factors Suggestive of Wild-Type Transthyretin Cardiac Amyloidosis (ATTRwt-CA) in the 16 Patients Undergoing ^{99m}Tc-Pyrophosphate Scintigraphy

Patient no.	^{99m} Tc-PYP scintigraphy grade	hs-cTnT ≥0.0308 ng/mL	Low voltage in limb leads	Pseudo-infarction pattern	Apical sparing	No. positive findings
1	2	+	–	–	–	1
2	2	+	+	+	–	3
3	2	–	–	+	+	2
4	1	–	–	+	–	1
5	1	–	–	+	+	2
6	0	+	–	–	–	1
7	0	–	–	–	–	0
8	0	–	–	–	–	0
9	0	–	–	–	–	0
10	0	–	–	–	–	0
11	0	–	–	–	–	0
12	0	+	–	–	–	1
13	0	–	–	–	–	0
14	0	NA	–	–	NA	0
15	0	+	–	–	–	1
16	0	–	–	–	–	0

^{99m}Tc-PYP, ^{99m}Tc-labeled pyrophosphate; hs-cTnT, high sensitivity cardiac troponin T; NA, not available.

patients fulfilled the criteria of QRS width ≥120ms and LVPWT ≥13.6mm. Regarding hs-cTnT values, 2 of the 3 patients with Grade 2 uptake on ^{99m}Tc-PYP scintigraphy had hs-cTnT ≥0.0308 ng/mL.

Next, we focused on the 16 patients who underwent ^{99m}Tc-PYP scintigraphy in order to identify the clinical markers providing better pretest probability for a positive uptake (Grade 2 uptake) on ^{99m}Tc-PYP scintigraphy. **Table 4** presents the 4 factors suggestive of ATTRwt-CA that can be easily obtained in routine examination: hs-cTnT ≥0.0308 ng/mL, the presence of low voltage in limb leads, the presence of a pseudo-infarction pattern, and the presence of apical sparing. There were 8 patients with 1 or more positive findings for these 4 factors: the sensitivity, specificity, positive predictive value, and negative predictive value for ^{99m}Tc-PYP scintigraphy positivity were 100%, 62%, 38%, and 100%, respectively.

Discussion

In this study we found that 34% of patients who underwent carpal tunnel release surgery for carpal tunnel syndrome had TTR amyloid deposition in tenosynovial tissue. Of the 16 patients with TTR deposition who underwent ^{99m}Tc-PYP scintigraphy for concomitant cardiac examination, 3 patients (19%) were diagnosed with ATTRwt-CA. Notably, none of these 3 patients had obvious heart failure symp-

toms or septal and posterior wall thicknesses of more than 13 mm. ATTRwt-CA could be diagnosed at an early stage in these patients. Our diagnostic approach, conducted by a collaboration between orthopedic surgeons and cardiologists, could lead to an opportunity for the early diagnosis of ATTRwt-CA.

Sperry et al reported the prevalence of amyloid deposition in 98 patients who underwent carpal tunnel surgery.¹⁷ Ten patients (10%) had a positive biopsy for amyloid (8 patients with TTR amyloid and 2 patients with AL amyloid). Of these 10 patients, cardiac involvement was found in 2 (1 patient with AL amyloidosis and 1 patient with ATTRwt-CA).¹⁷ Compared with the results of Sperry et al,¹⁷ the reported prevalence of TTR amyloid deposition in tenosynovial tissue in Japanese patients is relatively high (34.0%),⁶ and is similar to the results in the present cohort. Although the deposition of amyloid fibers has been noted to increase with aging,^{18–20} the mean age of patients in these studies (68.0, 67.3, and 71.6 years old) was equivalent to that in the present study. Racial differences may affect the prevalence of amyloid deposition.

Regarding the diagnostic approach to ATTRwt-CA, concomitant cardiac evaluation with ^{99m}Tc-PYP scintigraphy resulted in the identification of patients with cardiac involvement among patients with TTR deposition in tenosynovial tissue. A definite diagnosis was made in 19% of patients in the present study. According to the Kumamoto

criteria, 3 factors, namely wide QRS (QRS \geq 120ms), LVPWT \geq 13.6mm and hs-cTnT \geq 0.0308ng/mL, are useful predictors of positive ^{99m}Tc -PYP scintigraphy findings in the elderly.^{15,16} However, none of the 3 patients diagnosed with ATTRwt-CA in our study fulfilled the criteria for QRS width on ECG or LVPWT on echocardiography (Table 3). These findings suggest that wide QRS (QRS \geq 120ms) and LVPWT \geq 13.6mm are useful markers for patients with heart failure or arrhythmic symptoms, but are not sufficient to diagnose a very early stage of ATTRwt-CA in patients without cardiac symptoms. With regard to hs-cTnT, 2 of the 3 patients with Grade 2 uptake fulfilled this criterion. Although apical sparing on echocardiography was shown to contribute to the diagnosis of ATTRwt-CA in a previous study,¹² there were 2 patients in the present study in whom apical sparing was not shown. Conversely, ^{99m}Tc -PYP scintigraphy may play an important role even in very early diagnosis of ATTRwt-CA.

Based on the findings presented in Table 4, hs-cTnT \geq 0.0308ng/mL, the presence of low voltage in limb leads or a pseudo-infarction pattern on ECG, as well as apical sparing in echocardiographic findings, may be useful determinants to narrow down candidates for ^{99m}Tc -PYP scintigraphy. Patients having at least 1 factor had a negative predictive value of 100% for Grade 2 uptake in ^{99m}Tc -PYP scintigraphy. Based on our results, patients in whom TTR amyloid is detected in tenosynovial tissue and who have at least 1 of the 4 factors should undergo ^{99m}Tc -PYP scintigraphy.

With the introduction of tafamidis as a therapeutic agent for ATTRwt-CA amyloidosis, the importance of early diagnosis of the disease has increased further.^{5,21} A beneficial effect of tafamidis on mortality has been reported to appear after 18 months of treatment. Thus, it is important to start tafamidis treatment as early as possible for those who are expected to survive for a long time. In the present study, we were able to diagnose ATTRwt-CA in 3 patients at the time of carpal tunnel surgery. These patients were considered to have a favorable long-term prognosis according to proposed prognostic factors, including BNP or hs-cTnT values and echocardiographic findings.²²⁻²⁴ Although none of the patients diagnosed with ATTRwt-CA in this study satisfied current patient requirements for treatment with tafamidis for ATTRwt-CA because of the early diagnosis, they could be eligible for timely treatment with tafamidis as soon as they satisfy the patient requirements.

Carpal tunnel syndrome has been reported to precede the diagnosis of ATTRwt-CA by 5–10 years.⁹ For that reason, patients with no evidence of cardiac amyloidosis in the present study could also develop prospective cardiac involvement. Therefore, they need to be followed-up from the viewpoint of having a risk of developing cardiac amyloidosis.

Study Limitations

This study has several limitations that need to be considered. First, this study was a single-center retrospective study. Second, the number of patients in the study was relatively small. Third, ^{99m}Tc -PYP scintigraphy was not performed for all TTR amyloid-positive patients. This was due to the retrospective nature of the investigation. Some patients did not want to be referred by cardiologists and to have a ^{99m}Tc -PYP scintigraphy examination. Fourth, cardiac biopsy was not performed in patients who had Grade

2 uptake on ^{99m}Tc -PYP scintigraphy, although these patients had a definite diagnosis of ATTRwt-CA according to the current guidelines.¹⁰ Fifth, the prognosis of patients with an early diagnosis of ATTRwt-CA is still incompletely understood. We need to investigate the clinical relevance of an early diagnosis with this protocol.

Conclusions

In a cohort of Japanese patients undergoing carpal tunnel release surgery, TTR amyloid deposition in tenosynovial tissue was observed in 34% of patients. Concomitant cardiac examination with ^{99m}Tc -PYP scintigraphy in those patients with evidence of TTR deposition resulted in the identification of a considerable number of patients with a definite diagnosis of ATTRwt-CA. This diagnostic approach seems to be useful for the early diagnosis of this progressive disease.

Sources of Funding

This work was supported, in part, by a research grant from the Japan Society for the Promotion of Science (18k08078) to H. Kitaoka.

Disclosures

T.K. and H. Kitaoka have received remuneration from Pfizer. H. Kitaoka 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-002378).

References

1. Yamamoto H, Yokochi T. Transthyretin cardiac amyloidosis: An update on diagnosis and treatment. *ESC Heart Fail* 2019; **6**: 1128–1139.
2. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. *Circulation* 2012; **126**: 1286–1300.
3. Connors LH, Sam F, Skinner M, Salinaro F, Sun F, Ruberg FL, et al. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: A prospective, observational cohort study. *Circulation* 2016; **133**: 282–290.
4. Pinney JH, Whelan CJ, Petrie A, Dungu J, Banyersad SM, Sattianayagam P, et al. Senile systemic amyloidosis: Clinical features at presentation and outcome. *J Am Heart Assoc* 2013; **2**: e000098.
5. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *New Engl J Med* 2018; **379**: 1007–1016.
6. Sekijima Y, Uchiyama S, Tojo K, Sano K, Shimizu Y, Imaeda T, et al. High prevalence of wild-type transthyretin deposition in patients with idiopathic carpal tunnel syndrome: A common cause of carpal tunnel syndrome in the elderly. *Hum Pathol* 2011; **42**: 1785–1791.
7. Fosbøl EL, Rørth R, Leicht BP, Schou M, Maurer MS, Kristensen SL, et al. Association of carpal tunnel syndrome with amyloidosis, heart failure, and adverse cardiovascular outcomes. *J Am Coll Cardiol* 2019; **74**: 15–23.
8. Zegri-Reiriz I, de Haro-Del Moral FJ, Dominguez F, Salas C, de la Cuadra P, Plaza A, et al. Prevalence of cardiac amyloidosis in patients with carpal tunnel syndrome. *J Cardiovasc Transl Res* 2019; **12**: 507–513.
9. Nakagawa M, Sekijima Y, Yazaki M, Tojo K, Yoshinaga T, Doden T, et al. Carpal tunnel syndrome: A common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. *Amyloid* 2016; **23**: 58–63.
10. Kitaoka H, Izumi C, Izumiya Y, Inomata T, Ueda M, Kubo T, et al. JCS 2020 guideline on diagnosis and treatment of cardiac amyloidosis. *Circ J* 2020; **84**: 1610–1671.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quan-

- tification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; **28**: 1–39.e14.
12. Liu D, Hu K, Niemann M, Herrmann S, Cikes M, Störk S, et al. Effect of combined systolic and diastolic functional parameter assessment for differentiation of cardiac amyloidosis from other causes of concentric left ventricular hypertrophy. *Circ Cardiovasc Imaging* 2013; **6**: 1066–1072.
 13. Castano A, Haq M, Narotsky DL, Goldsmith J, Weinberg RL, Morgenstern R, et al. Multicenter study of planar technetium 99m pyrophosphate cardiac imaging: Predicting survival for patients with ATTR cardiac amyloidosis. *JAMA Cardiol* 2016; **1**: 880–889.
 14. Perugini E, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. *J Am Coll Cardiol* 2005; **46**: 1076–1084.
 15. Marume K, Takashio S, Nishi M, Hirakawa K, Yamamoto M, Hanatani S, et al. Combination of commonly examined parameters is a useful predictor of positive ^{99m}Tc-labeled pyrophosphate scintigraphy findings in elderly patients with suspected transthyretin cardiac amyloidosis. *Circ J* 2019; **83**: 1698–1708.
 16. Ochi Y, Kubo T, Baba Y, Ueda M, Miyagawa K, Noguchi T, et al. Validation of the Kumamoto criteria for prediction of ^{99m}technetium pyrophosphate scintigraphy positivity as a strategy for diagnosis of transthyretin cardiac amyloidosis: A retrospective cohort study in Kochi. *J Cardiol* 2021; **77**: 124–130.
 17. Sperry BW, Reyes BA, Ikram A, Donnelly JP, Phelan D, Jaber WA, et al. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. *J Am Coll Cardiol* 2018; **72**: 2040–2050.
 18. Cornwell GG 3rd, Murdoch WL, Kyle RA, Westermark P, Pitkänen P. Frequency and distribution of senile cardiovascular amyloid. A clinicopathologic correlation. *Am J Med* 1983; **75**: 618–623.
 19. Tanskanen M, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: A population-based autopsy study. *Ann Med* 2008; **40**: 232–239.
 20. Ueda M, Horibata Y, Shono M, Misumi Y, Oshima T, Su Y, et al. Clinicopathological features of senile systemic amyloidosis: An ante- and post-mortem study. *Mod Pathol* 2011; **24**: 1533–1544.
 21. Endo J, Sano M, Izumiya Y, Tsujita K, Nakamura K, Tahara N, et al. A statement on the appropriate administration of tafamidis in patients with transthyretin cardiac amyloidosis. *Circ J* 2020; **84**: 15–17.
 22. Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. *J Am Coll Cardiol* 2016; **68**: 1014–1020.
 23. Gillmore J, Damy T, Fontana M, Hutchinson M, Lachmann H, Martinez-Naharro A, et al. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J* 2018; **39**: 2799–2806.
 24. Ochi Y, Kubo T, Baba Y, Nakashima Y, Ueda M, Takahashi A, et al. Prediction of medium-term mortality in Japanese patients with wild-type transthyretin amyloidosis. *Circ Rep* 2020; **2**: 314–321.