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ORIGINAL ARTICLE
Heart Failure

External Validation of the Kumamoto Criteria in Transthyretin Amyloid Cardiomyopathy Screening
— A Retrospective Cohort Study —

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Background: The Kumamoto criteria have been proposed as a non-invasive screen for transthyretin amyloid cardiomyopathy. This study assessed the validity of the Kumamoto criteria externally.

Methods and Results: The study included 138 patients (median age 73 years; 65% male) who underwent ^{99m}Tc-pyrophosphate (PYP) scintigraphy. Patients were divided into 4 groups according to total scores on the Kumamoto criteria (i.e., 0–3) for the following 3 factors: high-sensitivity cardiac troponin T ≥0.0308 ng/mL, wide (≥120 ms) QRS, and left ventricular posterior wall thickness ≥13.6 mm. The diagnostic performance and positive predictive value (PPV) of the Kumamoto criteria for positive ^{99m}Tc-PYP scintigraphy were validated. Eighteen (13%) patients were positive on ^{99m}Tc-PYP scintigraphy. The Kumamoto criteria had a favorable diagnostic performance (area under the curve 0.808). The PPV for groups with scores of 0, 1, 2, and 3 was 0% (n=0/42), 11% (n=6/57), 21% (n=7/33), and 83% (n=5/6), respectively, which is lower, particularly for those with a score of 2, than in the original Kumamoto cohort. However, the PPV increased after combining the Kumamoto criteria with a history of orthopedic diseases (spinal canal stenosis and/or carpal tunnel syndrome).

Conclusions: This study suggests that the Kumamoto criteria have a favorable diagnostic performance; however, the PPV may decrease depending on the study population. Combining the Kumamoto criteria with the presence of orthopedic disease may improve the PPV.

Key Words: Kumamoto criteria; ^{99m}Tc-pyrophosphate scintigraphy; Transthyretin cardiac amyloidosis

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive fatal disorder leading to heart failure (HF).[1] The hereditary subtype of ATTR-CM with transthyretin (*TTR*) gene variants (hATTR-CM) is extremely rare, but ATTR-CM with the wild-type allele of the *TTR* gene (ATTRwt-CM) has been increasing due to the aging population.[2] A recent study reported that ATTRwt-CM accounted for 13% of older patients who had both HF with preserved ejection fraction (HFpEF) and left ventricular hypertrophy (LVH).[3] In fact, recent advances in diagnostic imaging methods revealed that ATTR-CM is more prevalent than previously thought.[4] Cardiac scintigraphy using bone radiotracers, such as ^{99m}Tc-pyrophosphate (PYP), is a remarkably sensitive and specific examination for the detection of myocardial uptake and to confirm TTR amyloid deposition. Although ^{99m}Tc-PYP scintigraphy has been established as a diagnostic modality for ATTR-CM,[5–7] it can only be performed in a limited number of specialized institutions. Therefore, a simple screening method is needed to identify patients, among an increasing number of older patients with HFpEF, who are suitable for ^{99m}Tc-PYP scintigraphy.

Recently, Kumamoto University in Japan proposed the 'Kumamoto criteria' to predict positivity on ^{99m}Tc-PYP

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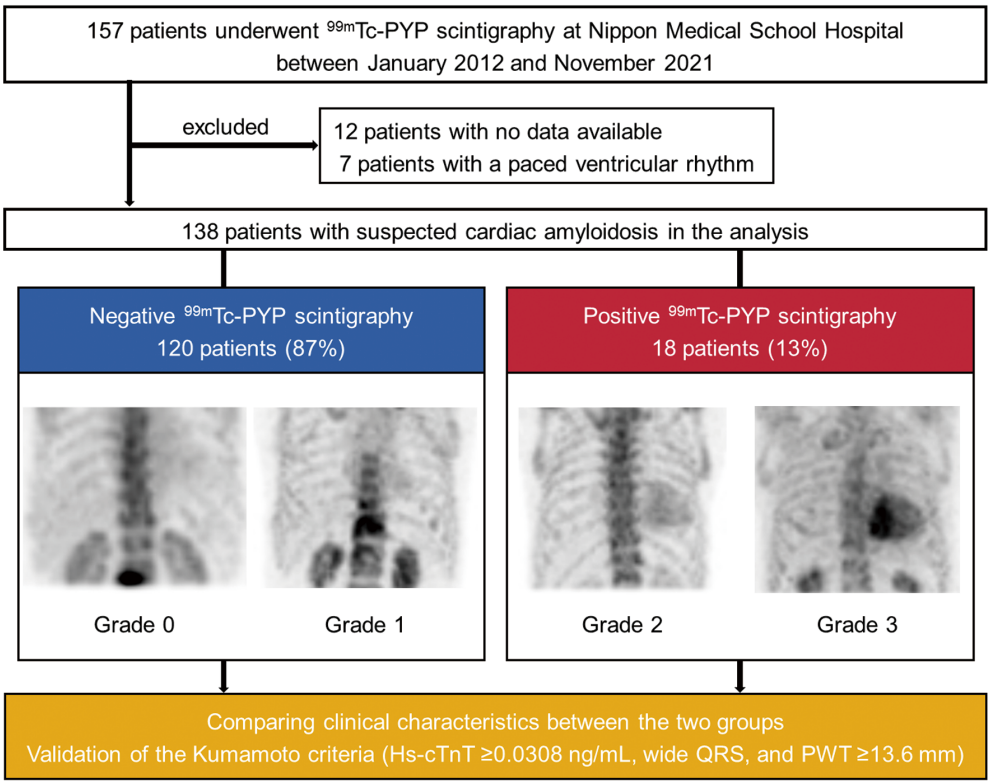

Figure 1. Study flowchart. In all, 138 patients with suspected cardiac amyloidosis were included in the analysis. Eighteen patients (13%) were diagnosed with positive uptake on ^{99m}Tc-pyrophosphate (PYP) scintigraphy based on a visual score of 2–3 using the grading system of Perugini et al.[13] We compared the clinical characteristics of patients with positive and negative ^{99m}Tc-PYP scintigraphy results. Furthermore, we validated the Kumamoto criteria in our cohort. Kumamoto University reported predictive models for positive ^{99m}Tc-PYP scintigraphy including 3 factors (high-sensitivity cardiac troponin T [hs-cTnT] ≥0.0308 ng/mL, QRS duration ≥120 ms, and posterior wall thickness [PWT] ≥13.6 mm).

scintigraphy.[8] This Kumamoto criteria consist of 3 factors: biochemical (high-sensitivity cardiac troponin T [hs-cTnT] ≥0.0308 ng/mL), physiological (QRS duration ≥120 ms), and structural (left ventricular posterior wall thickness [PWT] ≥13.6 mm). The number of variables present (i.e., scores ranging from 0 to 3) correspond to positive predictive values (PPVs) of 13%, 21%, 63%, and 96%, respectively, for positivity on ^{99m}Tc-PYP scintigraphy. Based on these results, ^{99m}Tc-PYP scintigraphy has been recommended for patients with a Kumamoto criteria score ≥2. However, that study had a small sample size and was performed at a single center in a localized population. A small number of Japanese facilities have examined the validity of the Kumamoto criteria externally. Although Kochi University reported favorable performance of the Kumamoto criteria,[9] a facility in Fukuoka reported that half the patients who were positive on ^{99m}Tc-PYP scintigraphy belonged to groups with scores of 0–1, suggesting that many patients with ATTR-CM may be overlooked in the Kumamoto criteria recommendations.[10,11] Thus, the accuracy and completeness of the Kumamoto criteria remain controversial.

The aim of the present study was to assess the validity of the Kumamoto criteria in screening patients with ATTR-CM in a tertiary care center in Tokyo, Japan.

Methods

Study Design, Population, and Data Collection

This was a retrospective observational cohort study that included consecutive suspected ATTR-CM patients who underwent ^{99m}Tc-PYP scintigraphy at Nippon Medical School (NMS) Hospital between January 1, 2012, and November 30, 2021. ^{99m}Tc-PYP scintigraphy was performed at the discretion of cardiologists. The following data were collected from the medical records: demographics, medical history, New York Heart Association (NYHA) functional class, laboratory data, electrocardiogram (ECG), echocardiography results, and pathological findings at the time ^{99m}Tc-PYP scintigraphy was performed. Laboratory data, ECG, and echocardiography findings were obtained when the patient was stable and in a compensated state of HF. Patients with missing data or ventricular pacing were excluded from the study. Clinical characteristics were compared between patients with positive and negative ^{99m}Tc-PYP scintigraphy results and the Kumamoto criteria were validated in our cohort.

This study was approved by the Institutional Review Board of NMS Hospital (Reference no. B-2021-477) and was conducted in accordance with the revised Declaration of Helsinki. The requirement for written informed consent

Table 1. Clinical Characteristics of the NMS Cohort

	All patients (n=138)	^{99m}Tc-PYP uptake		P value
		Negative (n=120)	Positive (n=18)	
Age (years)	73 [63–82]	71 [63–80]	84 [77–87]	<0.001
Male sex	89 (65)	75 (63)	14 (78)	0.207
NYHA functional class				0.099
I	36 (26)	35 (29)	1 (5.6)	
II	86 (62)	73 (61)	13 (72)	
III	15 (11)	11 (9.2)	4 (22)	
IV	1 (0.7)	1 (0.8)	0	
Hypertension	98 (71)	85 (71)	13 (72)	0.904
Atrial fibrillation	61 (44)	49 (41)	12 (67)	0.040
Spinal canal stenosis	20 (15)	8 (6.7)	12 (67)	<0.001
Carpal tunnel syndrome	8 (5.8)	3 (2.5)	5 (28)	0.001
Pacemaker implantation	20 (15)	17 (14)	3 (17)	0.726
Laboratory examinations				
Albumin (g/dL)	3.8 [3.4–4.1]	3.8 [3.4–4.1]	4.0 [3.6–4.3]	0.132
Creatinine (mg/dL)	1.1 [0.8–1.5]	1.0 [0.8–1.6]	1.1 [1.0–1.5]	0.695
hs-cTnT (ng/mL)	0.035 [0.021–0.054]	0.031 [0.020–0.052]	0.053 [0.038–0.077]	0.001
NT-proBNP (pg/mL)	1,325 [395–3,524]	1,193 [291–3,725]	2,254 [1,243–3,054]	0.100
ECG parameters				
Heart rate (beats/min)	71 [61–83]	71 [62–83]	60 [55–77]	0.025
Prolonged PR interval	39 (28)	30 (25)	9 (50)	0.028
Wide QRS	41 (30)	32 (27)	9 (50)	0.043
RBBB	22 (16)	19 (16)	3 (17)	1.000
LBBB	13 (9.4)	8 (6.7)	5 (28)	0.014
Low voltage	14 (10)	10 (8.3)	4 (22)	0.088
Poor R progression	27 (20)	20 (17)	7 (39)	0.050
Echocardiographic parameters				
LVEF (%)	56 [44–69]	56 [43–69]	54 [44–68]	0.892
LVEDD (mm)	48±8	48±8	43±8	0.014
LVESD (mm)	32 [27–41]	33 [27–42]	29 [26–37]	0.227
IVS thickness (mm)	12 [9–13]	12 [9–13]	13 [12–14]	0.009
PWT (mm)	11 [9–13]	11 [9–12]	14 [12–17]	<0.001
Left atrium diameter (mm)	42±8	41±8	43±7	0.389
E/A ratio	0.9 [0.6–1.4]	0.9 [0.6–1.3]	1.6 [1.0–2.9]	0.003
E-wave deceleration time (ms)	194 [154–254]	193 [154–253]	204 [148–313]	0.354
E/e' ratio	16 [12–23]	15 [11–22]	22 [15–31]	0.016
Aortic stenosis	18 (13)	16 (13)	2 (11)	1.000
Pericardial effusion	32 (23)	27 (23)	5 (28)	0.566

Categorical data are presented as n (%). Continuous data are presented as the median [interquartile range] or as the mean±SD, as appropriate. ECG, electrocardiogram; hs-cTnT, high-sensitivity cardiac troponin T; IVS, interventricular septum; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NMS, Nippon Medical School; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PWT, posterior wall thickness; PYP, pyrophosphate; RBBB, right bundle branch block.

was waived because of the observational nature of the study, and an opt-out method was used for participant recruitment. The first and the second authors take complete responsibility for the integrity and accuracy of the data analysis.

Validation of the Kumamoto Criteria

Patients were divided into 4 groups according scores on the Kumamoto criteria (i.e., 0–3). To calculate scores, 1 point was allocated for the presence of each of the following 3 factors: hs-cTnT ≥0.0308 ng/mL, QRS duration ≥120 ms, and left ventricular PWT ≥13.6 mm.[8] Hs-cTnT concentrations were measured using the Elecsys/EcLusys Troponin T-high sensitive (Roche Diagnostics, Indianapolis, IN, USA) assay. A standard 12-lead ECG was performed with patients in the supine position and quietly respiring, and QRS intervals were automatically analyzed (Cardiofax G; Nihon Kohden, Tokyo, Japan). The PWT was measured in accordance with the American Society of Echocardiography recommendations.[12]

Comparison of Patients in the NMS and Other Cohorts

We compared the clinical characteristics of patients in the present study (NMS cohort) and the PPV of the Kumamoto criteria with results from previously studies (i.e., the Kumamoto, Kochi, and Fukuoka cohorts).[8–11]

Table 2. Clinical Characteristics of ^{99m}Tc-PYP Scintigraphy Positive Patients in Each Cohort

	NMS cohort (Tokyo)	Fukuoka cohort[10,11]	Kochi cohort[9]	Kumamoto cohort[8]
% Positive uptake on ^{99m}Tc-PYP scintigraphy	13 (18/138)	18 (18/98)	47 (70/150)	39 (70/181)
Age (years)	84 [77–87]	82±12	81 [77–85]	80±6
Male sex	14 (78)	12 (67)	61 (87)	58 (83)
Hypertension	13 (72)	NA	37 (53)	36 (51)
Atrial fibrillation	12 (67)	9 (50)	38 (54)	24 (34)
Spinal canal stenosis	12 (67)	NA	16 (23)	NA
Carpal tunnel syndrome	5 (28)	NA	32 (46)	NA
Laboratory examinations				
hs-cTnT (ng/mL)	0.053 [0.038–0.077]	NA	0.065 [0.055–0.095]	0.049 [0.035–0.071]
BNP (pg/mL)	NA	NA	304 [216–525]	245 [133–415]
NT-proBNP (pg/mL)	2,254 [1,243–3,054]	4,658 [126–31,096]	NA	NA
ECG parameters				
Wide QRS	9 (50)	NA	30 (43)	31 (44)
Prolonged PR interval	9 (50)	NA	15 (21)	28 (40)
Low voltage	4 (22)	1 (5.6)	29 (48)	15 (21)
Poor R progression	7 (39)	9 (50)	25 (36)	15 (21)
Echocardiographic parameters				
LVEF (%)	54 [44–68]	54±13	52 [43–59]	53±10
LVEDD (mm)	43±8	46±9	46 [42–50]	43±6
LVESD (mm)	29 [26–37]	33±9	34 [30–38]	31±7
IVS thickness (mm)	13 [12–14]	13±4	14 [13–15]	15±2
PWT (mm)	14 [12–17]	13±3	13 [12–15]	15±3

Categorical data are presented as n (%). Continuous data are presented as the median [interquartile range] or as the mean±SD, as appropriate. Abbrevitions as in Table 1.

^{99m}Tc-PYP Scintigraphy Protocol

^{99m}Tc-PYP scintigraphy was performed using dual-head single-photon emission computed tomography (SPECT)/computed tomography (CT) scanner (Symbia T2; Siemens, Erlangen, Germany). Patients were injected intravenously with 740 MBq ^{99m}Tc-PYP (Fuji Film Toyama Kagaku, Tokyo, Japan), and planar images were obtained for 3 min, with the heart centered in the field of view, 3 h after the injection. Scans were performed with a 256×256 matrix without zoom, and the energy window set at 140 keV (±7.5%). A single reader (T.K.), who was blinded to patient information, scored planar images of ^{99m}Tc-PYP scintigraphy using the following grading system: Grade 0, absence of cardiac uptake; Grade 1, mild uptake (less than bone); Grade 2, moderate uptake (equal to bone); and Grade 3, high uptake (greater than bone).[13] Scans were considered positive if they were Grade 2 or 3.[6] SPECT/CT imaging was used to assess myocardial uptake or the cardiac blood pool.[14]

Statistical Analysis

Categorical variables are presented as numbers and percentages and were compared using the Chi-squared or Fisher's exact test. Normally and non-normally distributed continuous values are presented as the mean±SD and median with interquartile ranges (IQR), respectively, and were compared using Student's t-test and the Mann-Whitney U test, accordingly.

Patients were divided into 4 groups according to the Kumamoto criteria, and the PPV was calculated for each group. The sensitivity, specificity, PPV and negative predictive value (NPV), positive and negative likelihood ratios, and the area under the curve (AUC) of each factor of the Kumamoto criteria were calculated for the study cohort.

Two-sided $P<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 26 (IBM, Armonk, NY, USA).

Results

Clinical Characteristics of Patients in the NMS Cohort

Figure 1 shows the study flowchart. In all, 157 consecutive patients underwent ^{99m}Tc-PYP scintigraphy at NMS Hospital between January 2012 and November 2021. Of these patients, 138 were included in our analysis after excluding 12 patients with missing data and 7 patients with a paced ventricular rhythm. Eighteen patients (13%) were positive on ^{99m}Tc-PYP scintigraphy. All patients with positive ^{99m}Tc-PYP scintigraphy results were confirmed to have myocardial uptake on SPECT/CT. There were 102, 18, 3, and 15 patients with visual ^{99m}Tc-PYP scores of 0, 1, 2, and 3, respectively. ^{99m}Tc-PYP scintigraphy was performed at the discretion of clinicians in the presence of the following symptoms: LVH on echocardiography, low voltage and/or poor R progression or conduction disturbance on the ECG, a previous history of spinal canal stenosis (SCS) and/or carpal tunnel syndrome (CTS), persistent high serum concentrations of hs-cTnT, arrhythmia, non-ischemic HF, and relative apical sparing of longitudinal strain.

Table 1 summarizes the clinical characteristics of patients

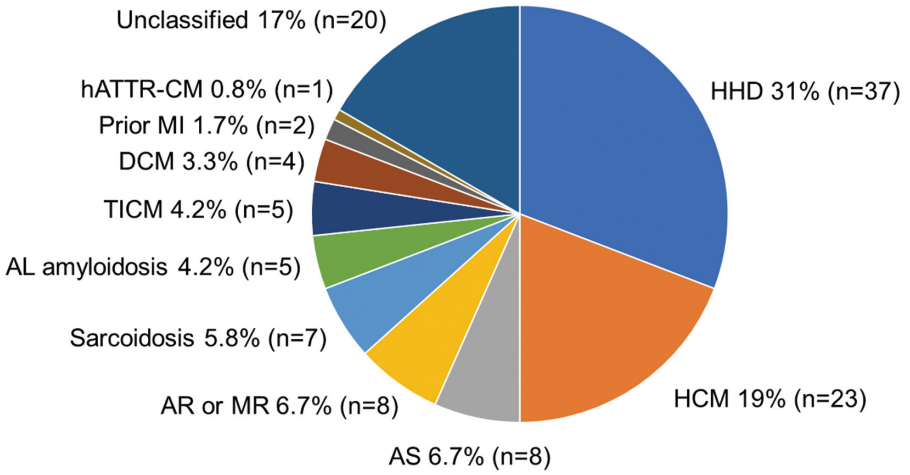

Figure 2. Definitive diagnoses of patients with negative ^{99m}Tc-PYP scintigraphy results in the study cohort (n=120). AL, amyloid monoclonal immunoglobulin light chain; AR, aortic valve regurgitation; AS, aortic valve stenosis; DCM, dilated cardiomyopathy; hATTR-CM, hereditary transthyretin amyloid cardiomyopathy; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; MI, myocardial infarction; MR, mitral valve regurgitation; PYP, pyrophosphate; TICM, tachycardia-induced cardiomyopathy.

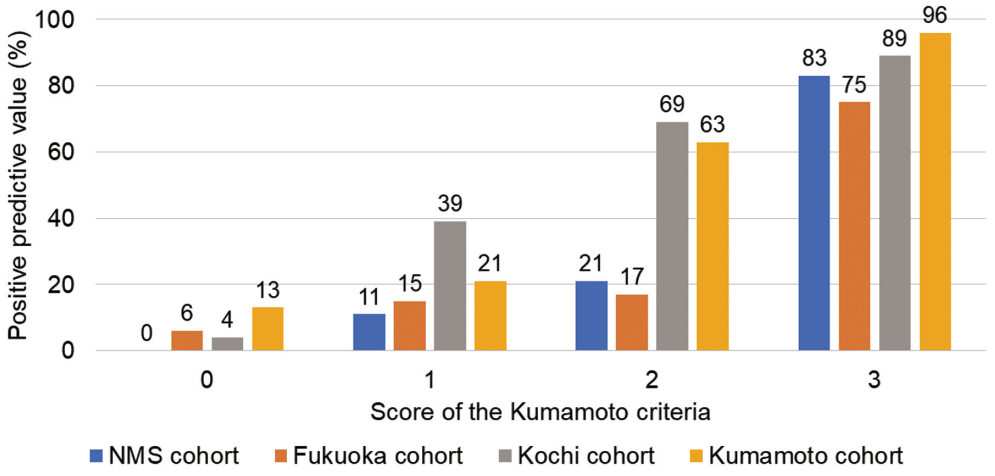

Figure 3. Positive predictive value (PPV) of the Kumamoto criteria in the Nippon Medical School (NMS) and other cohorts.[8–11] The PPV in the NMS group with a score of 3 was high (83%; n=5/6), similar to that in other cohorts. However, the PPV in the NMS group with a score of 2 was lower (21%; n=7/33) than in the Kumamoto[8] (63%; n=29/46) and Kochi[9] (69%; n=27/39) cohorts.

with positive and negative ^{99m}Tc-PYP scintigraphy results in the NMS cohort. Patients with positive ^{99m}Tc-PYP scintigraphy results were older (median [IQR] 84 [77–87] vs. 71 [63–80] years; P<0.001), had a higher prevalence of SCS (67% vs. 6.7%; P<0.001) and CTS (28% vs. 2.5%; P=0.001), and had higher hs-cTnT concentrations (median [IQR] 0.053 [0.038–0.077] vs. 0.031 [0.020–0.052] ng/mL; P=0.001) than those with negative ^{99m}Tc-PYP scintigraphy results. In addition, patients with positive ^{99m}Tc-PYP scintigraphy results had a lower heart rate, a higher prevalence of prolonged PR interval (≥200 ms), and a wide QRS (≥120 ms) more often (50% vs. 27%; P=0.043) than those with negative ^{99m}Tc-PYP scintigraphy results. Echocardiography revealed that patients with positive ^{99m}Tc-PYP scintigraphy results had a smaller left ventricular end-diastolic diameter, a larger interventricular septum (IVS), higher PWT (median [IQR] 14 [12–17] vs. 11 [9–12] mm; P<0.001), and a higher E/A and E/e′ ratio than those negative on ^{99m}Tc-PYP scintigraphy.

Table 2 summarizes the clinical characteristics of patients with positive ^{99m}Tc-PYP scintigraphy results in the NMS cohort and previous cohorts.[8–11] The rate of positivity on ^{99m}Tc-PYP scintigraphy was lower in the NMS and Fukuoka cohorts (13% and 18%, respectively) than in the Kochi and Kumamoto cohorts (47% and 39%, respectively). The prevalence of SCS was higher in the NMS cohort than in the Kochi cohort (SCS data not available for the Fukuoka and Kumamoto cohorts).

Table 3. Factors Associated With Positive Uptake on ^{99m}Tc-PYP Scintigraphy in the NMS and Kumamoto[8] Cohorts

	Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)		Positive LR		Negative LR		AUC	
	NMS	Kumamoto	NMS	Kumamoto	NMS	Kumamoto	NMS	Kumamoto	NMS	Kumamoto	NMS	Kumamoto	NMS	Kumamoto
Kumamoto criteria score ≥2	67	73	78	84	31	74	94	83	3.0	4.6	0.4	0.3	0.808	0.822
hs-cTnT (≥0.0308ng/mL)	89	80	49	59	21	NA	97	NA	1.8	2.0	0.2	0.3	0.739	0.730
Wide QRS (≥120 ms)	50	44	73	80	22	59	91	70	1.8	2.2	0.7	0.7	NA	NA
PWT (≥13.6 mm)	56	70	89	87	44	NA	93	NA	5.1	5.4	0.5	0.3	0.814	0.859
Other factors														
SCS	67	NA	93	NA	60	NA	95	NA	9.6	NA	0.4	NA	NA	NA
CTS	28	NA	98	NA	63	NA	90	NA	14.0	NA	0.7	NA	NA	NA
SCS and/or CTS	78	NA	92	NA	58	NA	97	NA	9.8	NA	0.2	NA	NA	NA

AUC, area under the curve; CTS, carpal tunnel syndrome; hs-cTnT, high-sensitivity cardiac troponin T; LR, likelihood ratio; NMS, Nippon Medical School; NPV, negative predictive value; PPV, positive predictive value; PWT, posterior wall thickness; PYP, pyrophosphate; SCS, spinal canal stenosis.

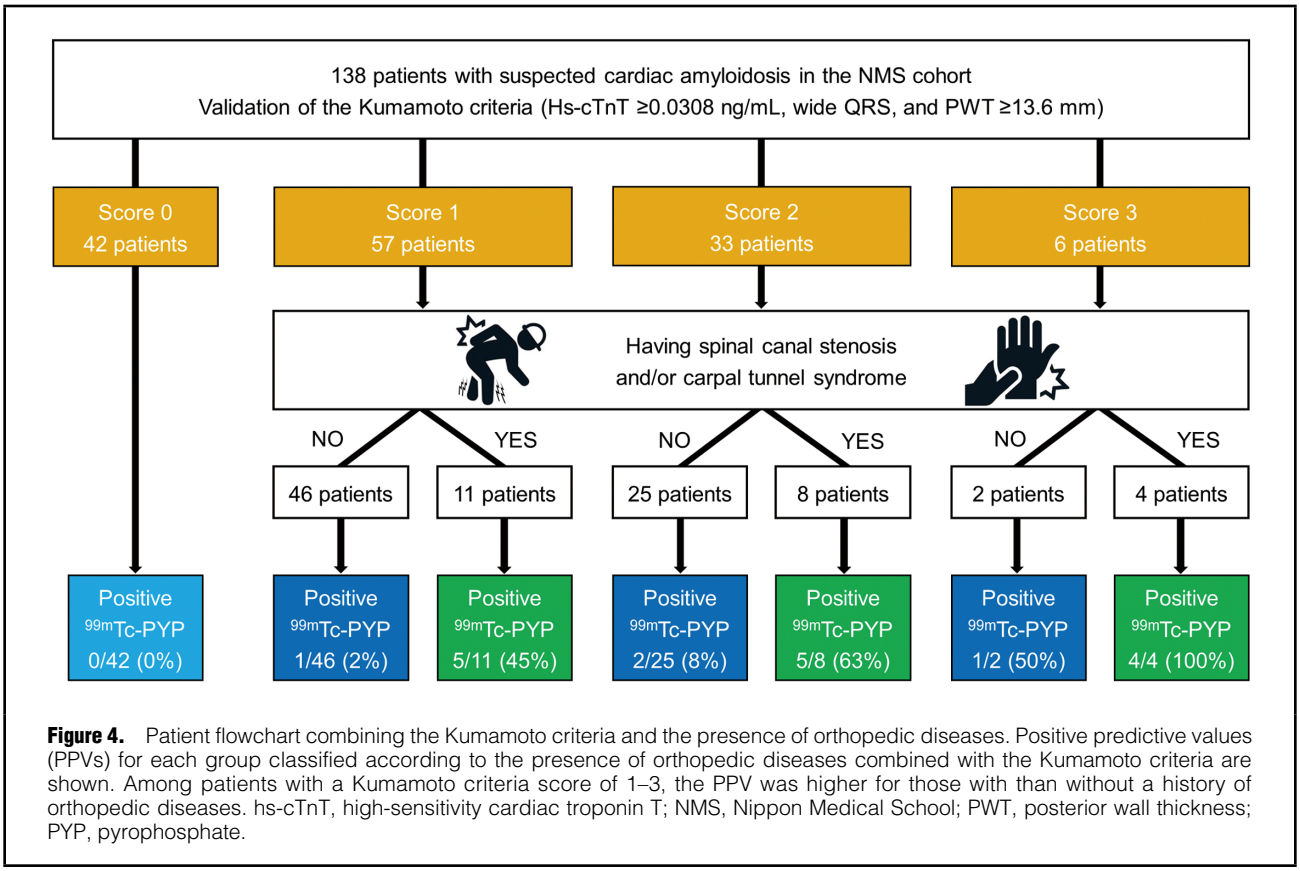

Figure 4. Patient flowchart combining the Kumamoto criteria and the presence of orthopedic diseases. Positive predictive values (PPVs) for each group classified according to the presence of orthopedic diseases combined with the Kumamoto criteria are shown. Among patients with a Kumamoto criteria score of 1–3, the PPV was higher for those with than without a history of orthopedic diseases. hs-cTnT, high-sensitivity cardiac troponin T; NMS, Nippon Medical School; PWT, posterior wall thickness; PYP, pyrophosphate.

The clinical characteristics of the study populations in the NMS and other cohorts[8–11] are presented in **Supplementary Table 1**. The NMS cohort (present study) had a lower median age (73 [IQR 63–82] years) and left ventricular wall thickness (IVS, 12 [IQR 9–13] mm; PWT, 11 [9–13] mm) than the other cohorts.

Clinical Diagnoses of Patients in the NMS Cohort

The clinical characteristics of each patient in the NMS cohort with positive ^{99m}Tc-PYP scintigraphy results are presented in **Supplementary Table 2**. Of the 18 patients with positive ^{99m}Tc-PYP scintigraphy results, 11 were diagnosed with ATTRwt-CM through pathology and genetic testing. One patient (No. 2) underwent only abdominal fat pad biopsy without endomyocardial biopsy; however, no amyloid was identified. In this patient, monoclonal protein was observed, which was considered to be associated with monoclonal gammopathy of undetermined significance. Another patient (No. 11) had TTR amyloid confirmed without genetic testing. The remaining

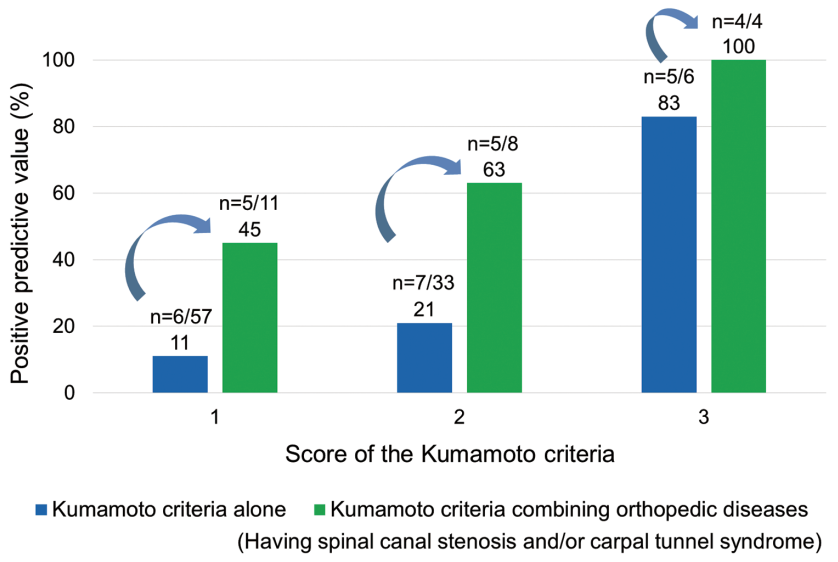

Figure 5. Positive predictive value (PPV) of the Kumamoto criteria alone and in combination with orthopedic diseases. Among patients with a Kumamoto criteria score of 1–3 points, the PPV was higher for those with than without a history of orthopedic diseases.

5 patients did not undergo either tissue biopsy or genetic testing.

Figure 2 shows the definitive diagnoses of 120 patients with negative ^{99m}Tc-PYP scintigraphy results. The most common diagnosis was hypertensive heart disease (37 patients; 31%) followed by hypertrophic cardiomyopathy (23 patients; 19%). Among the patients with negative ^{99m}Tc-PYP scintigraphy results, 29 underwent tissue biopsies; 4 patients underwent both endomyocardial and abdominal fat pad biopsy, 11 patients underwent endomyocardial biopsy, and 14 patients underwent abdominal fat pad biopsy. One patient had been diagnosed with hATTR-CM by confirmation of TTR amyloid deposition and *TTR* gene mutation (Tyr114His).

Validation of the Kumamoto Criteria in the NMS Cohort

Figure 3 shows the comparison of the PPV of the Kumamoto criteria between the NMS and other cohorts.[8–11] In the NMS cohort, the PPV in the group with a score of 3 was as high (83%; n=5/6) as that in other cohorts. However, in the group with a score of 2, the PPV was noticeably lower (21%, n=7/33) than in the Kumamoto and Kochi cohorts. The PPV in the groups with scores of 0 and 1 was 0 (n=0/42) and 11% (n=6/57), respectively.

The sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios, and the AUC for each factor for positive ^{99m}Tc-PYP scintigraphy results in the NMS and Kumamoto cohorts are presented in **Table 3**. The Kumamoto criteria showed favorable diagnostic performance in our (NMS) cohort, with an AUC of 0.808, which was as high as in the Kumamoto cohort (0.822). The sensitivity and specificity of hs-cTnT and wide QRS were similar; however, the sensitivity of PWT seemed to be lower in the NMS than Kumamoto cohort. Regarding factors outside the Kumamoto criteria, a medical history of SCS and/or CTS was a strong predictor of positive ^{99m}Tc-PYP scintigraphy findings.

We focused on orthopedic disease (SCS and/or CTS) as a strong predictor of positive ^{99m}Tc-PYP scintigraphy results. In addition, we sought to establish a more accurate screening method for ATTR-CM by combining the Kumamoto criteria with a history of orthopedic disease. **Figure 4** shows the PPVs for each group classified according to the presence of orthopedic diseases combined with the Kumamoto criteria. Among patients with Kumamoto criteria scores of 1–3, the PPV was higher for those with than without a history of orthopedic diseases (**Figure 5**).

Discussion

This study assessed the accuracy and completeness of the Kumamoto criteria to screen for patients with ATTR-CM and identified factors associated with positive ^{99m}Tc-PYP scintigraphy results in our cohort. The major findings of this study are that: (1) the rate of positive ^{99m}Tc-PYP scintigraphy results in our cohort was relatively low (13%); (2) the Kumamoto criteria showed favorable diagnostic performance for positive ^{99m}Tc-PYP scintigraphy results with an AUC of 0.808; (3) the PPV in the group with a Kumamoto criteria score of 2 was unexpectedly low (21%), although the PPV of the group with a score of 3 was high (83%); and (4) a medical history of orthopedic disease (SCS and/or CTS) was useful as an additional predictor of positive ^{99m}Tc-PYP scintigraphy results.

The rate of positive ^{99m}Tc-PYP scintigraphy results was low in the NMS cohort, but high in the Kumamoto[8] and Kochi[9] cohorts; this may be attributed to differences in the study populations. The NMS cohort included patients who were younger and/or had unremarkable LVH compared with the other cohorts, suggesting that ^{99m}Tc-PYP scintigraphy was performed even in patients with low pretest probability of ATTR-CM. Reports on the rate of positive ^{99m}Tc-PYP scintigraphy results in clinical practice are limited. Unlike the high rate of positive ^{99m}Tc-PYP scintigraphy results in Kumamoto and Kochi University, leading specialized institutions for amyloidosis in Japan, the low positivity rate in the NMS and Fukuoka[10,11] cohorts may reflect the facts in daily practice. Performing scintigraphy indiscriminately in an increasing number of patients with HFpEF leads to higher healthcare costs. Therefore, a

screening method to identify patients suitable for ^{99m}Tc-PYP scintigraphy, like the Kumamoto criteria, is desired.

We performed ^{99m}Tc-PYP scintigraphy even in younger patients (median age 73 years [IQR 63–82 years]) than in the other cohorts.[8–11] The age cut-off for suspecting ATTR-CM is controversial and has ranged from 60 to 70 years in previous studies.[15–17] Note that although the Kumamoto criteria do not contain an age cut-off, patients aged <70 years were excluded from the study population in the Kumamoto cohort. When we excluded patients aged <70 years, as in the Kumamoto cohort, the rate of positive ^{99m}Tc-PYP scintigraphy results increased from 13% (n=18/138) to 20% (n=17/83; **Supplementary Table 3**), but in this case 1 patient aged 68 years (No. 13; **Supplementary Table 2**) would have been overlooked. A recent report from the Swedish national population-based registers showed that 18% of patients with ATTR-CM had been diagnosed in their 60s.[18] Thus, we suggest that the appropriate age to suspect ATTR-CM would be ≥60 years.[15]

Although the present study population is different from that of the Kumamoto cohort, the Kumamoto criteria for our cohort had good diagnostic performance, with an AUC of 0.808, which is as high as in the Kumamoto cohort. In particular, the sensitivity and specificity of hs-cTnT and wide QRS were similar; however, the sensitivity of PWT seemed to be lower in the present than Kumamoto cohort.[8] This may be due to differences in the degree of cardiac hypertrophy in patients with ATTR-CM between the NMS and Kumamoto cohorts. The degree of LVH seemed to be greater for patients with ATTR-CM in the Kumamoto than NMS cohort. This difference can be attributed to errors due to sample size and/or the possibility that many patients with advanced amyloidosis are clustered at Kumamoto University, which is a specialized facility for amyloidosis.

In our cohort, the PPV in the group with a score of 3 was high (83%). This result is consistent with the findings of previous studies, which reported PPVs of 96%, 89%, and 75% in the Kumamoto, Kochi, and Fukuoka cohorts, respectively.[8–11] A score of 3 on the Kumamoto criteria was a robust predictor of positive uptake on ^{99m}Tc-PYP scintigraphy in all cohorts. Clinicians should confidently perform ^{99m}Tc-PYP scintigraphy in patients with a Kumamoto criteria score of 3. However, the PPV in the group with a score of 2 was lower in the present than Kumamoto[8] and Kochi[9] cohorts (21% vs. 63% and 69%, respectively). The Fukuoka[10,11] cohort showed a PPV of 17%, similar to the findings in the present study. This may have been caused by differences in the pretest probability of ATTR-CM in each cohort, because this affects PPV. Thus, the PPV in the group with a score of 2 may decrease depending on study population.

Regarding factors outside the Kumamoto criteria, SCS and/or CTS were significantly associated with positive uptake on ^{99m}Tc-PYP scintigraphy in our cohort. A medical history of CTS and SCS is known as "red flag" for ATTR-CM.[15–17] The most common orthopedic manifestation is CTS, which is present in 45–60% of patients with ATTR-CM.[19–21] The prevalence of SCS in patients with ATTR-CM was reported to be 12–23%.[9,19,20] In our cohort, combining the Kumamoto criteria with the presence of orthopedic disease improved the PPVs among patients with scores of 1–3; therefore, confirmation of a medical history of orthopedic diseases may raise the pretest probability of positive ^{99m}Tc-PYP results. However, SCS may be overestimated as a predictor of ATTR-CM because the prevalence of SCS in patients with ATTR-CM in our cohort was higher than in previous reports.[9,19,20] This difference may be attributed to errors due to sample size. Otherwise, it may have accurately reflected the prevalence of SCS in patients with ATTR-CM because this was a small-scale, single-center study that allowed the collection of a detailed medical history.

The Kumamoto criteria may have overlooked patients with ATTR-CM at an early stage. The 3 factors included in the Kumamoto criteria depend on disease progression and can be negative in the early stages of amyloidosis.[22–24] In our cohort, most patients with a score of 1 on the Kumamoto criteria were in the early stage of NYHA Class II, whereas most patients with a score of 3 were in NYHA Class III (**Supplementary Table 2**). Given that tafamidis shows prognostic benefit only in patients with NYHA Classes I–II,[25] screening using the 3 factors in the Kumamoto criteria may not contribute to an improvement in clinical outcomes. However, orthopedic conditions, such as SCS and CTS, appear earlier than HF signs. CTS is the most common initial symptom in patients with ATTR-CM,[26] and precedes the diagnosis of ATTR-CM by 5–9 years.[27] Thus, screening focused on orthopedic conditions can detect patients with ATTR-CM at an early stage and improve clinical outcomes.

Study Limitations

This study had several limitations. First, it was conducted at a single center in Tokyo and had a small sample size. Second, this was a retrospective study, and data accuracy was limited. Specifically, the prevalence of CTS may be underestimated. In our cohort, the prevalence of CTS among patients with ATTR-CM was lower (28%) than reported previously (45–60%).[19–21] Third, tissue biopsies were not performed in all patients, and we may have over- or underdiagnosed patients with ATTR-CM. Finally, ^{99m}Tc-PYP scintigraphy was performed at the discretion of clinicians, and selection bias may have existed. Moreover, the decisions of clinicians were based on the Kumamoto criteria, which may have affected the results. Future large-scale multicenter studies are needed to establish an accurate screening method to identify patients with ATTR-CM.

Conclusions

In our cohort, the diagnostic performance of the Kumamoto criteria for positive ^{99m}Tc-PYP scintigraphy results was acceptable. However, the PPV, especially for those with a score of 2, in our cohort was lower than that in the original Kumamoto cohort. Among patients with a Kumamoto criteria score of 1–3, the PPV was higher for those with than without a history of orthopedic diseases such as SCS and/or CTS, highlighting that a medical history of orthopedic diseases may be helpful in screening for ATTR-CM.

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Disclosures

W.S. is a member of *Circulation Journal*'s Editorial Team. E.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 Institutional Review Board of Nippon Medical School Hospital (Reference no. B-2021-477) and was conducted in accordance with the revised Declaration of Helsinki.

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Supplementary Files

Please find supplementary file(s);
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