Comparison of 1-h with 3-h planar $^{99m}$Tc-pyrophosphate scintigraphy in patients with suspected transthyretin cardiac amyloidosis using SPECT as a reference standard

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Abstract

Objectives The purpose of this study was to examine the diagnostic value of planar $^{99m}$Tc-pyrophosphate (PYP) imaging at 1 and 3 h after tracer administration in patients with suspected transthyretin cardiac amyloidosis (ATTR-CA) using SPECT as a reference standard. We also tested whether blood pool activity of PYP is associated with renal dysfunction.

Methods PYP images of 109 consecutive patients with suspected ATTR-CA were retrospectively reviewed. The myocardial PYP uptake was visually graded on a scale of 0 to 3 and quantified with the heart-to-contralateral (H/CL) ratio in accordance with the current expert consensus recommendations. The diagnostic value of planar images for identifying positive PYP SPECT was assessed by a receiver-operating characteristic curve analysis with the area under the curve (AUC). The uptake ratios of the ascending and descending aorta, left atrium, and trapezius muscle divided by the liver uptake were measured on SPECT images and compared to the renal function.

Results A total of 41 patients (38%) had myocardial PYP uptake on SPECT images. In comparison with the visual scores on 1-h anterior planar images, those on 3-h anterior planar images had lower sensitivity (80.5% vs. 97.6%) and higher specificity (86.8% vs. 55.9%) for identifying positive PYP SPECT. The ROC analysis showed that the combination of visual scores on both 1-h and 3-h anterior planar images had significantly higher AUC values in comparison with 1-h anterior planar images alone (0.90 [95% CI 0.83–0.94] vs. 0.83 [95% CI 0.75–0.88]; $P<0.001$), which was comparable to the AUC values on 3-h anterior planar images alone (0.88 [95% CI 0.80–0.92]; $P=0.071$). In comparison with visual scores on 1-h or 3-h anterior planar images alone, the combination of visual scores and H/CL ratio did not significantly improve the diagnostic value for identifying positive PYP SPECT ($P=0.73$ and $P=0.50$, respectively). The uptake ratios of ascending aorta/liver, descending aorta/liver, left atrium/liver, and trapezius muscle/liver were not significantly associated with the serum creatinine level or estimated glomerular filtration rate ($P>0.05$ for all).

Conclusions In the assessment of ATTR-CA using PYP imaging, visual scores on 3-h anterior planar images for identifying positive PYP SPECT had lower sensitivity and higher specificity in comparison with those on 1-h anterior planar images. The diagnostic value of the visual scores on 1-h and 3-h anterior planar images was not improved by adding the H/CL ratio. Blood pool activity of PYP was not significantly associated with renal dysfunction.

Keywords $^{99m}$Tc-pyrophosphate scintigraphy · Transthyretin cardiac amyloidosis · Single-photon emission computed tomography

Introduction

Technetium-$^{99m}$ pyrophosphate (PYP) imaging has been increasingly used for the non-invasive diagnosis of transthyretin cardiac amyloidosis (ATTR-CA) [1, 2]. The recent expert consensus recommendations for multimodal imaging in cardiac amyloidosis uniformly describes various acquisition times (i.e., at 1 and 3 h after tracer administration) and evaluation methods (i.e., visual grading...
on planar images, semi-quantitative evaluation by heart/contralateral lung uptake [H/CL] ratio, and myocardial accumulation by single-photon emission computed tomography (SPECT) [3]. A previous multicenter study reported that 1-h planar PYP images showed high sensitivity, while 3-h planar PYP images showed high specificity for the diagnosis of ATTR-CA [4]. Another study suggested that the addition of SPECT imaging can reduce the rate of misdiagnosis [5]. However, few reports have comprehensively examined the diagnostic value of these image acquisition and analytic methods. Especially in planar images, it is necessary to differentiate the myocardial uptake from blood pool radioactivity, which could lead to false-positive results. Since technetium-99m-labeled bone-avid radiotracers including PYP are excreted in the urine after intravenous injection, renal dysfunction may affect the evaluation of myocardial uptake by causing increased blood pool activity or physiological PYP uptake in the skeletal muscle [3, 6]. Understanding these problems can contribute to improving the diagnostic ability of PYP imaging for ATTR-CA. This study was conducted to examine the diagnostic value of planar PYP imaging at 1 and 3 h after tracer administration in patients with suspected ATTR-CA using SPECT as a reference standard. We also tested whether blood pool activity of PYP was associated with renal dysfunction.

Materials and methods

Study population

This study was a retrospective review of patients who underwent PYP imaging at Hokkaido Cardiovascular Hospital, Japan from May 2020 to October 2020. The main purpose of performing PYP imaging in this population was to evaluate ATTR-CA in patients who had heart failure with a preserved left ventricular ejection fraction and/or increased left ventricular mass index on transthoracic echocardiography [7, 8]. Although the physicians were encouraged to screen for ATTR-CA in elderly patients with heart failure of unknown etiology, PYP imaging was performed at the physician’s discretion. The study protocol was approved by the ethics committee (IRB No. 2021-2). The requirement of written informed consent was waived.

In total, 110 consecutive patients were referred for PYP imaging during the study period. Among these patients, one patient who did not undergo PYP image acquisition at 1 h after tracer injection was excluded. Therefore, 109 patients were included in the present study. Patient background and characteristics were extracted from electronic medical records.

PYP image acquisition and analysis

All patients underwent PYP imaging using a dual-headed gamma camera equipped with low-energy, high-resolution collimators (Infinia, GE Healthcare), after the intravenous administration of 370–740 MBq of PYP (FUJIFILM Toyama Chemical Co., Ltd.). Planar images in the anterior view were acquired at 1 and 3 h after tracer administration; planar images in the 15° left anterior oblique view (LAO) were acquired at 3 h; and SPECT images were acquired at 3 h. PYP imaging acquisition was performed in accordance with the American Society of Nuclear Cardiology (ASNC) expert consensus recommendation [3]. Planar images were obtained with 300 s per view on a 256 × 256 matrix. The SPECT acquisition parameters consisted of a 360° circular orbit, in step and shoot mode, with 30 s per view, on a 64 × 64 matrix. SPECT data were reconstructed using filtered back-projection. The myocardial PYP uptake on planar and SPECT images were visually graded on a scale of 0 to 3 and quantified with the H/CL ratio in accordance with the ASNC recommendation [3]. Circular regions of interest were placed over the heart and contralateral chest with the sternum and ribs avoided. All images were assessed by an experienced radiological technologist (T.S) who was blinded to clinical information. Another experienced radiological technologist (A.N) independently reanalyzed both 1-h and 3-h images in 40 random cases (20 with positive SPECT scans and 20 with negative scans) in a blinded fashion to assess interobserver agreement. The first reader (T.S) also reanalyzed both 1-h and 3-h images in the same 40 cases in a blinded fashion at an interval of 18 months to assess intraobserver agreement.

In 71 patients who underwent clinically indicated computed tomography (CT) using a 256-row detector CT system (Revolution™ CT, GE Healthcare), the fusion of SPECT and CT images was generated using a dedicated workstation (Xeleris, GE Healthcare) and software (Volumetrix MI, GE Healthcare). This software semiautomatically provided optimal alignment for fusion images. Among these 71 patients, 41 underwent CT the day before PYP imaging, 4 underwent CT and PYP imaging on the same day, and the remaining 26 underwent CT the day after PYP imaging. The median interval from the CT scan and PYP imaging was 6 days (IQR −54 to 326 days). To evaluate the association between the renal function and PYP blood pool activity or physiological PYP uptake in the skeletal muscle on SPECT images, we measured the uptake ratios between the inferior right lobe of the liver and (i) ascending aorta, (ii) descending aorta, (iii) left atrium, and (iv) trapezius muscle with circular regions of interest of 3 cm in diameter [9].
**Statistical analysis**

Continuous variables are reported as the median with interquartile range (IQR) and were compared using Wilcoxon’s rank-sum test. Categorical variables are presented as the number and percentage and were compared using Fisher’s exact test. Comparisons between paired data were performed using Wilcoxon’s signed-rank test or the Bowker test, as appropriate. Correlations between continuous variables were assessed by Spearman’s rank correlation coefficient ($\rho$). Agreement regarding visual scores between SPECT and planar images was evaluated by Cohen’s $\kappa$-statistic and the Bowker test. $\kappa$ values were defined as follows: $>0.80$, excellent agreement; $0.61–0.80$, good agreement; $0.41–0.60$, moderate agreement; $0.21–0.40$, fair agreement; $<0.20$, poor agreement. The diagnostic value of planar images for identifying SPECT-positive findings (defined as Grade 2 or 3) was expressed as sensitivity, specificity, positive and negative predictive values with the 95% confidence interval (CI). A receiver-operating characteristic (ROC) curve analysis using the area under the curve (AUC) was also conducted to estimate the diagnostic value of PYP planar images for identifying SPECT-positive findings. The optimal cut-off value for differentiating PYP SPECT positivity was identified using the Youden index. Comparisons between ROC curves were performed using the chi-squared test. In all tests, $P$ values of $<0.05$ were considered to indicate statistical significance. All statistical analyses were performed using JMP Pro 16.1.0 (SAS Institute Inc., Cary, NC, USA).

**Results**

Table 1 shows the clinical characteristics of the patients. The median age of the patients was 78 (IQR 72–85) years, 38 patients (35%) were women, and the median left ventricular ejection fraction was 57% (IQR 48–63%). A total of 41 patients (38%) had myocardial PYP uptake on SPECT images. Eight of the 41 patients with positive PYP SPECT underwent endomyocardial biopsy, and cardiac ATTR amyloid deposition was histologically confirmed in 5 patients. All of them also underwent sequencing of the transthyretin gene and were diagnosed with wild-type ATTR-CA. Two patients received tafamidis (80 mg, daily); the remaining 3 patients did not because of advanced age. Patients with positive PYP SPECT were older and had a higher prevalence of low voltage on electrocardiography in comparison with those with negative PYP SPECT. Representative images are shown in Figs. 1, 2.

Regarding the visual scores and H/CL ratio on 1-h and 3-h images, patients with positive PYP SPECT had higher visual scores and H/CL ratios on both 1-h and 3-h images in comparison with those with negative PYP SPECT ($P<0.001$ for all). Visual scores on 1-h anterior planar images were significantly higher than those on 3-h planar images ($P<0.001$ for both of anterior and LAO images). There was a significant correlation between the 1-h and 3-h H/CL ratios ($\rho=0.80$, $P<0.001$; mean difference, 0.096 [95% CI 0.077–0.115]).

Among 41 patients with positive PYP SPECT, 40 patients (98%) had a visual grade of $\geq 2$ on 1-h anterior planar images, 33 of these patients also had a visual grade of $\geq 2$ on 3-h anterior planar images, both indicating true-positive test results (Fig. 3). Furthermore, 21 patients (51%) had an
H/CL ratio > 1.5 on the 1-h anterior planar image, and 28 patients (68%) had an H/CL ratio > 1.3 on the 3-h anterior planar image.

Among 68 patients with negative PYP SPECT, 30 patients (44%) had a visual grade of ≥ 2 on 1-h anterior planar images, 9 of whom also had a visual grade of ≥ 2 on 3-h anterior planar images, both indicating false-positive test results (Fig. 3). The estimated glomerular filtration rate was not significantly correlated with the 1-h (\(\rho = 0.15, P = 0.22\)) or 3-h H/CL ratios (\(\rho = 0.12, P = 0.32\)) in patients with negative PYP SPECT.

### Diagnostic value of visual scores on 1-h and 3-h planar images for identifying positive PYP SPECT

Comparisons of visual findings between PYP SPECT and planar images are shown in Table 2. The diagnostic value of the visual scores on 1-h anterior planar images for identifying positive PYP SPECT was as follows: sensitivity, 97.6% (95% CI 87.4–99.6%); specificity, 55.9% (95% CI 44.1–67.1%); positive predictive value (PPV), 57.1% (95% CI 45.5–68.1%); and negative predictive value (NPV), 97.4% (95% CI 86.8–99.5%). In comparison with the visual scores on 1-h anterior planar images, the visual scores on 3-h anterior planar images had lower sensitivity and higher specificity: sensitivity, 80.5% (95% CI 66.0–89.8%); specificity, 86.8% (95% CI 76.7–92.9%); PPV, 78.6% (95% CI 64.1–88.3%); and NPV, 88.1% (95% CI 78.2–93.8%). In comparison with the visual scores on 3-h anterior planar images, 3-h LAO planar images had lower diagnostic value: sensitivity, 78.0% (95% CI 63.3–88.0%); specificity, 76.5% (95% CI 65.1–85.0%); PPV, 66.6% (95% CI 52.5–78.3%); and NPV, 85.2% (95% CI 74.3–92.0%).

The ROC analysis of visual scores for identifying positive PYP SPECT is shown in Fig. 4a. The AUC values for 1-h and 3-h anterior planar images, and 3-h LAO planar images were 0.83, 0.88 (\(P = 0.10\) vs. 1-h anterior planar images), and 0.81 (\(P = 0.66\) vs. 1-h anterior planar images; \(P = 0.015\) vs. 3-h anterior planar images), respectively. In comparison with the visual scores on 1-h anterior planar images alone, the combination of visual scores on both 1-h and 3-h anterior planar images had a significantly higher AUC for identifying positive PYP SPECT (AUC = 0.90; \(P < 0.001\)). In contrast, the AUC did not differ to a statistically significant extent between 3-h anterior planar images alone and the combination of 1-h and 3-h anterior planar images (\(P = 0.071\)).

### Diagnostic value of 1-h and 3-h H/CL ratios for identifying positive PYP SPECT

The diagnostic value of an H/CL ratio of > 1.5 at 1 h for identifying positive PYP SPECT was as follows: sensitivity, 51.2% (95% CI 40.2–60.3%); specificity, 85.3% (95% CI 78.7–90.8%); PPV, 67.7% (95% CI 53.2–79.7%); and NPV, 74.4% (95% CI 68.6–79.1%). The combination of an H/CL ratio of > 1.5 and a visual grade of ≥ 2 at 1 h had a similar diagnostic value for identifying positive PYP SPECT as follows: sensitivity, 51.2% (95% CI 40.5–59.5%); specificity, 88.2% (95% CI 81.8–93.2%); PPV, 72.4% (95% CI 57.3–84.1%); and NPV, 75.0% (95% CI 69.5–79.2%).

The AUC of the H/CL ratio at 1 h for identifying positive PYP SPECT was 0.74, which was significantly lower than that of the visual scores on 1-h anterior planar images (AUC = 0.83; \(P = 0.040\), Fig. 4b). The H/CL ratio at 1 h distinguished PYP SPECT positivity with 61.0% sensitivity and 76.5% specificity when using the best cutoff value of 1.45. In comparison with the visual scores on
1-h anterior planar images alone, the combination of visual scores and the H/CL ratio at 1 h did not significantly improve the diagnostic value for identifying positive PYP SPECT (AUC = 0.81; \(P = 0.73\), Fig. 4b).

The diagnostic value of an H/CL ratio of > 1.3 at 3 h for identifying positive PYP SPECT was as follows: sensitivity, 68.3% (95% CI 56.4–78.5%); specificity, 67.6% (95% CI 60.5–73.8%); PPV, 56.0% (95% CI 46.2–64.3%); and NPV,
78.0% (95% CI 69.7–85.0%). The combination of an H/CL ratio of > 1.3 and a visual grade of ≥ 2 at 3 h had similar diagnostic value for identifying positive PYP SPECT as follows: sensitivity, 61.0% (95% CI 50.2–69.1%); specificity, 88.2% (95% CI 81.7–93.1%); PPV, 75.8% (95% CI 62.3–85.9%); and NPV, 78.9% (95% CI 73.1–83.3%).

The AUC of the H/CL ratio at 3 h for identifying positive PYP SPECT was 0.80, which was significantly lower than that of the visual scores on 3-h anterior planar images (AUC = 0.88; P = 0.036, Fig. 4c) and was significantly higher than that of the H/CL ratio at 1 h (AUC = 0.74; P = 0.015). The H/CL ratio at 3 h distinguished PYP SPECT positivity with 87.8% sensitivity and 57.3% specificity when using the best cutoff value of 1.25. In comparison with the visual scores on 3-h anterior planar images alone, the combination of visual scores and the H/CL ratio at 3 h did not significantly improve the diagnostic value for identifying positive PYP SPECT (AUC = 0.89; P = 0.50, Fig. 4c).

**Relationship between the renal function and PYP blood pool activity and muscle uptake**

Among 71 patients who underwent both PYP SPECT and CT, none of the patients had visible PYP uptake in the skeletal muscle on SPECT images. The estimated glomerular filtration rate was not significantly correlated with the uptake ratios of the ascending aorta/liver (ρ = 0.06, P = 0.61), descending aorta/liver (ρ = 0.06, P = 0.63), left atrium/liver (ρ = −0.07, P = 0.59), or trapezius muscle/liver (ρ = 0.17, P = 0.15). Furthermore, the serum creatinine level was not significantly correlated with the uptake ratios of the ascending aorta/liver (ρ = −0.04, P = 0.73), descending aorta/liver (ρ = −0.03, P = 0.80), left atrium/liver (ρ = 0.06, P = 0.63), or trapezius muscle/liver (ρ = −0.09, P = 0.45).

There were no significant differences in the estimated glomerular filtration rate (55.6 [IQR 37.6–67.9] vs. 49.5 [IQR 37.1–72.0] mL/min/1.73 m²; P = 0.94) or serum creatinine level (0.98 [IQR 0.75–1.41] vs. 0.94 [IQR 0.76–1.24] mg/dL; P = 0.52) between patients with and without an overestimated visual score on 1-h anterior planar image in comparison with PYP SPECT.

### Table 2 Comparisons of visual findings between PYP SPECT and planar images

| SPECT            | Grade 0 | Grade 1 | Grade 2 | Grade 3 |
|------------------|---------|---------|---------|---------|
| a. SPECT vs. 1-h anterior planar images |         |         |         |         |
| 1-h anterior planar | Grade 0 | 3       | 1       | 0       |
|                  | Grade 1 | 10      | 24      | 1       |
|                  | Grade 2 | 3       | 24      | 25      |
|                  | Grade 3 | 0       | 3       | 7       | 8       |
| κ = 0.34 (95% CI 0.21–0.47) Bowker’s P < 0.001 |
| b. SPECT vs. 3-h anterior planar images |         |         |         |         |
| 3-h anterior planar | Grade 0 | 8       | 11      | 0       |
|                  | Grade 1 | 8       | 32      | 8       |
|                  | Grade 2 | 0       | 9       | 25      |
|                  | Grade 3 | 0       | 0       | 0       | 8       |
| κ = 0.50 (95% CI 0.37–0.64) Bowker’s P = 0.997 |
| c. SPECT vs. 3-h LAO planar images |         |         |         |         |
| 3-h LAO planar | Grade 0 | 8       | 2       | 0       |
|                  | Grade 1 | 8       | 34      | 9       |
|                  | Grade 2 | 0       | 16      | 24      |
|                  | Grade 3 | 0       | 0       | 0       | 8       |
| κ = 0.50 (95% CI 0.36–0.65) Bowker’s P = 0.47 |

CI confidence interval
Intraobserver and interobserver agreement in the assessment of PYP imaging

As shown in Supplemental Table 1, the intraobserver agreement was good for the assessment of PYP planar images ($\kappa = 0.63–0.70$; Bowker’s $P > 0.05$ for all). As shown in Supplemental Table 2, the interobserver agreement was moderate for the assessment of PYP planar images ($\kappa = 0.55–0.58$; Bowker’s $P > 0.05$ for all).

Discussion

In this study, we investigated the diagnostic value of 1-h and 3-h planar PYP imaging in patients with suspected ATTR-CA using SPECT as a reference standard. We showed that: (i) in comparison with the visual scores on 1-h anterior planar images, those on 3-h anterior planar images had lower sensitivity and higher specificity; (ii) the combination of 1-h and 3-h anterior planar images significantly improved the diagnostic value for identifying positive PYP SPECT in comparison with 1-h anterior planar images alone; (iii) in comparison with 1-h or 3-h anterior planar images alone, the combination of visual scores and H/CL ratios did not significantly improve the diagnostic value for identifying positive PYP SPECT; and (iv) there was no significant relationship between renal dysfunction and residual tracer activity in the blood pool or physiological PYP uptake in the skeletal muscle.

The differences in the diagnostic value of visual scores between 1-h and 3-h anterior planar images were in line with previous studies reporting high sensitivity at 1 h and high specificity at 3 h [4]. The ASNC Practice Points describe that imaging procedures for PYP scintigraphy can be modified based on local camera capabilities and expertise. PYP scintigraphy is sensitive and specific for ATTR-CA in cases with either absent cardiac activity or apparent myocardial uptake, but less accurate in equivocal cases with residual activity in the cardiac blood pool. A high blood pool activity was sometimes difficult to distinguish from myocardial PYP uptake and could influence the visual and semi-quantitative interpretation, especially for planar images. Whereas there was a significant correlation between the 1-h and 3-h H/CL ratios, similar to previous reports [10], both the 1-h visual scores and the H/CL ratios were significantly higher than those at 3 h in this study. This could be explained by high blood pool activity at 1 h, resulting in a low specificity for the diagnosis of ATTR-CA.

The diagnostic value of the H/CL ratio at 3 h was higher than that at 1 h. However, adding the H/CL ratio to the visual assessment did not improve the diagnostic ability of PYP planar images, which was consistent with previous studies reporting that the H/CL ratio approach may decrease the diagnostic accuracy of planar imaging [5, 11].
together, while the H/CL ratio was introduced as a quantitative parameter to describe myocardial PYP uptake and has been reported as a prognostic factor for poor survival in ATTR-CA [4], we could not rely solely on the H/CL ratio to diagnose ATTR-CA.

Optional delayed PYP images are suggested at 3 h when the blood pool activity is persistent on 1-h images due to renal failure in the ASNC Practice Points. The clearance of injected PYP from the blood pool is partially dependent on the renal function; thus, the possible overestimation of PYP visual scores and H/CL ratios in patients with chronic kidney disease is a concern. In the current study, the PYP blood pool activity and muscle uptake were not significantly associated with renal dysfunction. None of the patients had visible uptake of PYP in the skeletal muscle, which was similar to the previous report [12]. Furthermore, there were no significant differences in renal dysfunction between patients with and without an overestimated visual score on the 1-h planar PYP image, suggesting that renal failure is not an important contributing factor to the overestimation of PYP imaging.

For the diagnosis of ATTR-CA, given the high sensitivity of 1-h planar images and the high specificity of 3-h planar images, it is desirable to evaluate the images at 1 h first. When there is accumulation in the cardiac blood pool at 1 h, it is recommended that the images be assessed at 3 h, when there is less blood pool activity. However, optimizing gamma camera occupation while preserving diagnostic accuracy is mandatory in a busy nuclear medicine department [13]. Given the fact that the combination of 1-h and 3-h anterior planar images did not significantly improve the diagnostic value for identifying positive PYP SPECT in comparison with 3-h anterior planar images alone in this study, a single acquisition protocol at 3 h after tracer administration may be an acceptable option for improving patient throughput, depending on the circumstances. In contrast, planar images and SPECT at 3 h may be omitted for patients with a visual grade 0 or 1 on 1-h planar images, as shown in Fig. 3. To reduce the total examination time, it is better to decide the necessity of mono-acquisition or sequential acquisition on an individual basis. The diagnostic ability of LAO planar images was lower than that of 3-h anterior planar images in this study, suggesting that the additional value of LAO planar images is very limited.

The present study has some methodological limitations. First, this was a retrospective study and included a relatively small number of patients. The rate of positive PYP SPECT (38%) in the present study was somewhat higher in comparison with other studies (25–30%) [5, 10–12], which may reflect differences in patient characteristics or screening protocols for ATTR-CA. In addition, the intraobserver and interobserver agreement in the assessment of PYP planar images ranged from moderate to good in this study, which is in line with a previous report [10]. Second, the PYP uptake was not compared with pathological findings. Nearly half of the patients with positive PYP SPECT in this cohort were ≥80 years of age and had atrial fibrillation requiring anticoagulation, which precluded an aggressive diagnostic approach, including endomyocardial biopsy. Furthermore, the rapid spread of the COVID-19 pandemic throughout the study period limited the traditional diagnostic approach requiring hospitalization. Although endomyocardial biopsy is not routinely performed for the diagnosis of cardiac amyloidosis in contemporary clinical practice because of concerns about safety [3], further studies are needed to validate the diagnostic accuracy of PYP imaging in comparison with endomyocardial biopsy.

Conclusions

In the assessment of ATTR-CA using PYP imaging, visual scores on 3-h anterior planar images for identifying positive PYP SPECT had lower sensitivity and higher specificity in comparison with those on 1-h anterior planar images. The diagnostic value of the visual scores on 1-h and 3-h anterior planar images was not improved by adding the H/CL ratio. Blood pool activity of PYP was not significantly associated with renal dysfunction.

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Author contributions TS and TA contributed to the study conception and design. Material preparation, data collection and analysis were performed by TS, TA and AN. The first draft of the manuscript was written by TS, TA and OM. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Dr. Noriko Oyama-Manabe acts as a consultant to Canon Medical Systems and received payment for lectures from Philips Medical Systems, Eisai, Bayer Healthcare, GE Healthcare Pharma, and Canon Medical Systems. The other authors declare no financial conflicts of interest.

Ethical approval The study protocol was approved by the ethics committee of Hokkaido Cardiovascular Hospital (IRB No. 2021-2). The requirement of written informed consent was waived.
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