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ORIGINAL ARTICLE

Prognostic Value of ^{99m}Tc-HMDP Scintigraphy in Elderly Patients With Chronic Heart Failure

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Background This study evaluated the prevalence and prognostic significance of cardiac transthyretin amyloidosis (ATTR) diagnosed using ^{99m}Tc- hydroxymethylene-diphosphonate (^{99m}Tc-HMDP) scintigraphy in an elderly heart failure population.

Methods This retrospective study included 335 patients aged >70 years with heart failure and who underwent ^{99m}Tc-HMDP scintigraphy due to non-cardiac reasons in three imaging centres in Finland (Kymenlaakso Central Hospital, Jorvi Central Hospital, and Meilahti University Hospital). A Perugini grade $\geq$2 and heart-to-contralateral ratio (H/CL) of $\geq$1.30 were considered positive for cardiac ATTR. The overall and cardiovascular mortality were obtained from the national statistical service (Statistics Finland).

Results There were 234 deaths, of which 70 were classified as being due to cardiovascular causes during a median follow-up of 1 (1–3) year. Transthyretin amyloidosis was diagnosed in 22 patients (6.6%) using visual analysis and 17 patients using the H/CL ratio (5.1%). Patients with ATTR were older (85$\pm$5 vs 80$\pm$5 yrs; p=0.002) and had higher N-terminal pro-brain natriuretic peptide (NT-ProBNP) levels (1,451 [813–3,799] vs 6,192 [2,030–8,833] ng/L; p=0.02). Age, bone metastases, and glomerular filtration rate were independent predictors of overall mortality in multivariable analysis. Age, glomerular filtration rate, $\geq$grade 2 visual cardiac uptake, and H/CL ratio were independent predictors of cardiovascular mortality.

Conclusions Cardiac uptake suggestive of ATTR was found in 5% of elderly patients with chronic heart failure. The presence of cardiac uptake on bone scintigraphy did not convey independent prognostic value on overall mortality but was independently associated with cardiovascular mortality.

Keywords Amyloidosis • Transthyretin • Heart failure • Bone scintigraphy • ^{99m}Tc-HMDP

Introduction

Cardiac amyloidosis is an infiltrative myocardial disease resulting in progressive heart failure (HF). The majority of cardiac amyloidoses are caused by either transthyretin amyloidosis (ATTR) or light chain disease [1]. Recent developments in the treatment of ATTR have raised an interest in its early detection [1,2]. Previous imaging studies have indicated that ATTR can be found in 5–14% of individuals with HF with preserved ejection fraction (HEpEF), which constitutes approximately half of all HF cases [3–6]. In contrast, a previous autopsy study found myocardial transthyretin accumulation in 25% of individuals aged >85 years [7]. Unfortunately, there is often a long delay in achieving a correct diagnosis of ATTR cardiomyopathy [8].

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Scintigraphy using bone-avid radiotracers enables early diagnosis of cardiac ATTR, even in its subclinical phase [9,10]. The detection of cardiac uptake has shown prognostic value both in patients with suspected ATTR and as an incidental finding [9,11,12], although the severity of cardiac uptake did not offer additional information on survival in some studies [13]. The clinical value of bone scintigraphy in screening for ATTR in an HF population is currently unclear. Adding bone scintigraphy to the standard assessment of HF could improve prognosis through early detection of individuals who might benefit from anti-amyloid therapies. A previous study showed the efficacy of transthyretin stabilising medication as being greatest in patients with early ATTR and having a poor response in patients with more advanced cardiomyopathy [14].

This study retrospectively evaluated the prognostic value of ^{99m}Tc- hydroxymethylene- diphosphonate (^{99m}Tc-HMDP) scintigraphy in elderly patients with HF. It hypothesised that the cardiac uptake suggestive of ATTR is associated with poor overall survival. An association between cardiac uptake and overall mortality would demonstrate the possible clinical usefulness of screening ATTR in an elderly HF population in which multimorbidity is also common.

Methods

This study retrospectively screened 2,000 patients who were aged >70 years and underwent bone scintigraphy due to non-cardiac clinical indications during 2012–2018. Patients with a known diagnosis of HF before or within one year of bone scintigraphy were included. The diagnosis of HF was collected from patient records. Exclusion criteria were a known or suspected diagnosis of ATTR at the time of imaging or non-diagnostic image quality of the bone scan. The final study population consisted of 335 patients with HF, and patient selection is shown in Figure 1. Patients were imaged in three nuclear medicine departments in Finland: Kymenlaakso Central Hospital (n=58), Jorvi Central Hospital (n=93), and Meilahti University Central Hospital (n=184). Information on patient mortality was acquired using death certificates from the national statistical service (Statistics Finland). Clinical characteristics and laboratory values were obtained from patient records and the Finnish Institute for Health and Welfare (THL**)**. Patients with information on their ejection fraction (EF) were classified as those with preserved EF (>50%) or reduced EF (<50%). The presence of coronary artery disease was recorded for patients with coronary status verified by either invasive coronary angiography or single-photon emission tomography perfusion imaging. Laboratory values within one year of bone scintigraphy were included into the study. The glomerular filtration rate (GFR) was calculated using the GFR-EPI formula [15]. This study was conducted according to the Declaration of Helsinki. The study protocol was approved by the local ethics committee (decision HUS/1721/2018) and the need for written informed consent was waived.

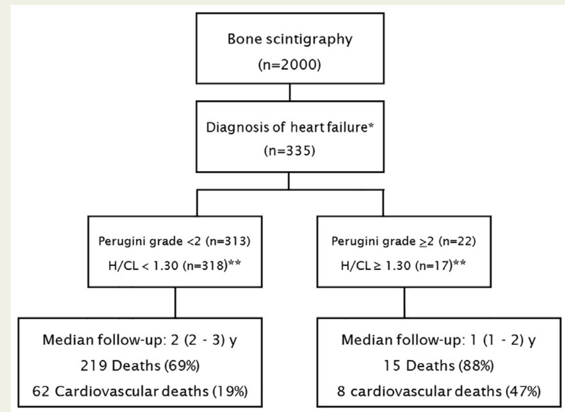

Figure 1 Flow-chart on patient selection. *Diagnosis of heart failure before or within 1 year of bone scintigraphy. **Patients were further stratified based on quantitative heart-to-contralateral ratio (H/CL).

Scintigraphy

All bone scintigrams were imaged using ^{99m}Tc-HMDP with a standard gamma camera at 3 hours after radiotracer injection. Cardiac uptake of all bone scintigraphies were graded using the Perugini grade, as previously described: no uptake (grade 0), less than bone (grade 1), equal to bone (grade 2), and greater than bone (grade 3), as demonstrated in Figure 2 [16–18]. A cardiac uptake ≥Perugini grade 2 (G2) was considered positive for ATTR by visual analysis. Consecutive patients were collected from the hospitals' registries, and patients with any degree of cardiac uptake on the initial screening (OS and VU) were reviewed by a nuclear medicine physician, who then calculated heart-to-contralateral ratio (H/CL). A H/CL ratio of ≥1.30 was considered positive for ATTR and used to define the ATTR group in this study [9,18]. The information on bone metastases was gathered using imaging reports, or by reviewing other available imaging data, when necessary. Images were viewed and analysed using Impax (Agfa Healthcare, Mortsel, Belgium) and Hermes (Hermes Medical Solutions, Stockholm, Sweden) software.

Statistical Analysis

Continuous variables are shown as mean±standard deviation (SD) and categorical values as numbers and percentages. Non-continuous variables are presented as median (interquartile range). Parametric continuous variables were compared using the Student's t-test and non-parametric variables with the Mann-Whitney U test. Categorical variables were compared using the Chi-square test. Intraobserver reproducibility of H/CL measurements was studied in a sample of 30 consecutive patients and the physician was blinded to the initial measurements (17 positive and 23 negative). Cox's proportional hazards models and Kaplan-Meier curves were calculated to study the association between the results of the ^{99m}Tc-HMDP scintigraphy and

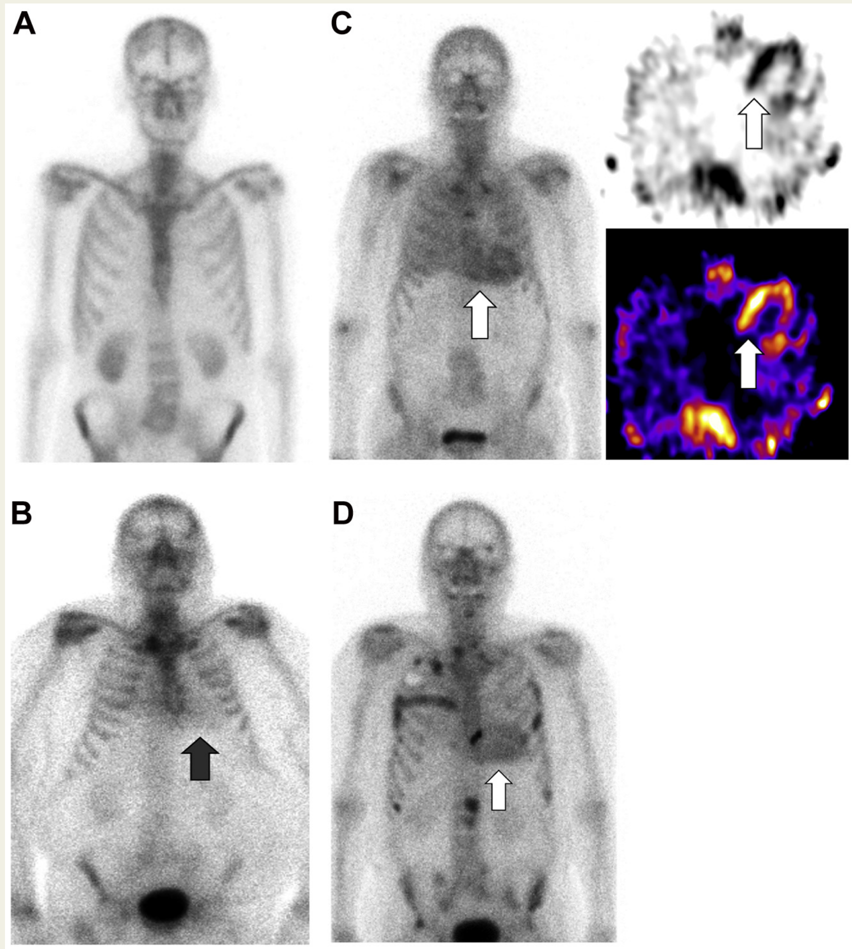

Figure 2 Examples of incidental myocardial uptake on bone scintigraphy in patients with heart failure. (A) Typical normal bone scintigram without cardiac uptake (Perugini grade 0). (B) Mild Perugini grade 1 cardiac uptake in a patient with reduced ejection fraction (EF) due to ischaemic cardiomyopathy (black arrow). (C) A patient with positive cardiac and pulmonary uptake on planar imaging (Perugini grade 3). Single-photon emission tomography (SPECT) performed on the same imaging session confirmed myocardial uptake, which is most intense in the left ventricular septum (white arrows). SPECT image on the right are presented with (up panel right) and without a colour map (down panel right). (D) Positive myocardial uptake (Perugini grade 3) in a patient with metastatic prostate cancer (white arrow). Patients C and D had a hyperthropic left ventricle on echocardiography.

patient survival. Overall mortality due to any cause and cardiovascular mortality were used as outcome variables. The overall mortality figures include cardiovascular deaths. Covariates with p-values $\leq$0.10 in univariate analysis were selected for further multivariate analysis. A p-value of <0.05 was considered to be statistically significant.

Results

Patient Characteristics

The patient characteristics of all included 335 patients with HF are shown in Table 1. The average age was 80±6 years, and the study included 60 women (18%). There were 105 patients (31%) with any degree of cardiac uptake on bone scintigraphy, of which 82 were grade 1 (25%), 11 were grade 2 (3%), and 11 were grade 3 (3%), respectively. Thus, 22 patients (7%) had suspected ATTR based on visual analysis. Of all patients, 17 (5%) had an H/CL $\geq$1.30 and were considered positive for ATTR based on a quantitative threshold. As shown in Table 1, indications for bone scintigraphy were similar in patients with and without significant cardiac uptake.

Transthyretin amyloidosis patients (n=17) were older than those without a significant cardiac uptake (85±5 vs 80±5 yrs; p=0.002). The presence of incidental cardiac uptake was equally prevalent in patients with preserved or reduced EF and in patients with and without verified CAD. Individuals with and without suspected ATTR had similar kidney function as measured by GFR (53±19 vs 62±19; p=0.07). The ATTR patients had higher measured N-terminal pro-brain natriuretic peptide (NT-ProBNP) compared with

Table 1 Patient characteristics in patients with and without cardiac uptake on bone scintigraphy.

Variable	Grade <2 (n=313)	Grade ≥2 (n=22)	P-value
Clinical characteristics			
Age (y)	80±6	83±5	0.01
Female	56 (18%)	3 (14%)	0.59
Reduced EF (<50%)	124/222 (56%)	5/13 (38%)	0.22
Verified CAD[b]	132/171 (77%)	12/14 (86%)	0.46
Bone metastasis	108 (35%)	7 (32%)	0.80
Indication for bone scintigraphy			0.35[a]
Prostate cancer	234 (75%)	18 (82%)	
Breast cancer	44 (14%)	3 (14%)	
Other	35 (11%)	1 (5%)	
Laboratory values			
Glomerular filtration rate (mL/min)	62±19	53±18	0.04
NT-Pro-BNP (ng/L)	1,464 (823–3,856)	5,393 (1,586–7,917)	0.07
Adverse events			
Follow-up (yr)	2 (1–5)	1 (1–3)	0.25
Death	216 (69%)	15 (82%)	0.21
Cardiovascular death	60 (19%)	10 (45%)	<0.01

Data are presented as mean±SD, N (%) or median (interquartile range).

Abbreviations: CAD, coronary artery disease; EF, ejection fraction; H/CL, heart-to-contralateral side ratio; NT-ProBNP, n-terminal pro-brain natriuretic peptide.

[a]Between all groups.

[b]Screened for CAD by either invasive angiography or single-photon emission tomography perfusion.

other patients (1,451 [813–3,799] vs 6,192 [2,030–8,833] ng/L; p=0.02). The prevalence of bone metastases did not differ between the ATTR and non-ATTR groups (35% vs 34%; p=0.93). The intraclass correlation coefficient for absolute agreement for repeated H/CL measurements was 0.85 (95% CI 0.70–0.93; p<0.001) and the coefficient of variation 12%. There was no change in patient classification between negative and positive patients in repeatability analysis (H/CL threshold of 1.30). The associations between the degree of cardiac uptake, NT-ProBNP, and GFR are shown in Figure 3. There were no significant correlations between NT-ProBNP, GFR, and the degree of cardiac uptake in individuals with or without ATTR.

Scintigraphy and Overall Mortality

There were 234 deaths (69%) during a median follow-up of 1 (1–3) year, of which 15 were in individuals with ATTR. Overall mortality was comparable in patients with and without cardiac uptake (88% vs 69%; p=0.09). The ATTR patients had a comparable median follow-up time to patients without ATTR (2 [2–3] vs 1 [1–2] year; p=0.07). Univariate and multivariate associations between patient characteristics, cardiac uptake, and overall mortality are shown in Table 2. Univariate predictors of death were age, bone metastases, NT-ProBNP, GFR, Perugini grade 3 cardiac uptake, and diagnosis of ATTR based on H/CL ratio. Of these, independent predictors of mortality in multivariate analysis were age, the presence of bone metastases, and GFR. Neither, visual nor quantitative diagnosis of ATTR were predictive of overall mortality in multivariate models (p always >0.05). Figure 4 demonstrates the association between diagnosis of ATTR and overall survival in Kaplan-Meier analysis.

Scintigraphy and Cardiovascular Mortality

From the 234 deaths during follow-up, 70 (30%) were classified as being due to a cardiovascular cause based on the death certificates that were obtained. Cardiovascular mortality was higher in patients with incidental cardiac uptake (47% vs 19%; p<0.01). Univariate and multivariate associations between patient characteristics, cardiac uptake, and cardiovascular mortality are shown in Table 3. Univariate predictors of cardiovascular mortality were age, GFR, and a diagnosis of ATTR based on both visual (≥grade 2) and quantitative (H/CL ≥1.30) criteria. Age, GFR, and both visual and H/CL diagnosis of ATTR were independent predictors of cardiovascular mortality in multivariate analysis. Figure 4 shows the association between diagnosis of ATTR and cardiovascular mortality in Kaplan-Meier analysis.

Discussion

This study evaluated the prevalence of cardiac ATTR and the prognostic value of ^{99m}Tc-HMDP scintigraphy in elderly patients with HF. Transthyretin amyloidosis was a rare finding in unselected elderly HF patients, but was associated with poor outcome. Cardiac uptake was not an independent

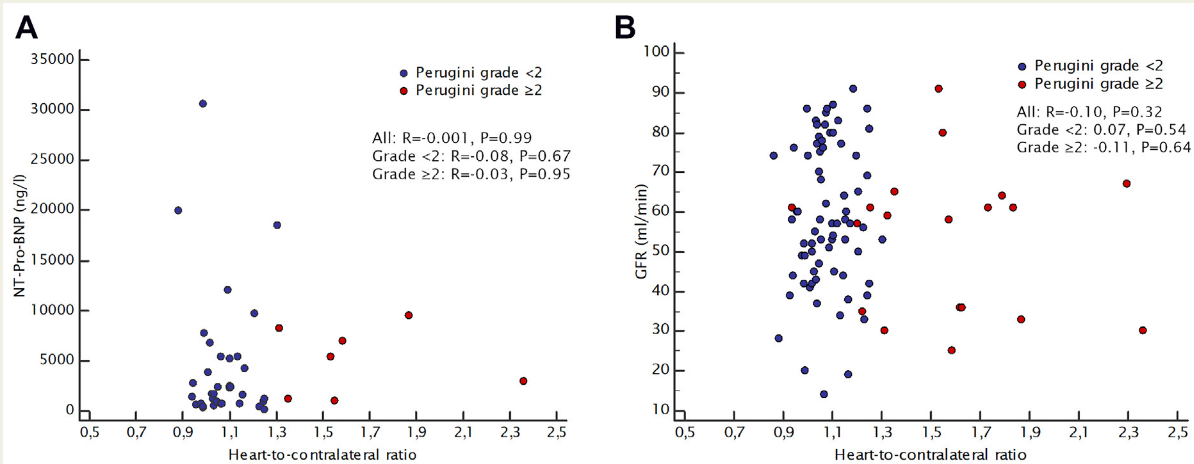

Figure 3 (A) Scatter plot on correlation between N-terminal pro-brain natriuretic peptide (NT-ProBNP) level and heart-to-contralateral ratio (H/CL) on bone scintigraphy. (B) Correlation between H/CL ratio and kidney function as measured by glomerular filtration ratio (GFR).

predictor of overall survival when adjusted for other baseline characteristics, as ATTR patients were older and had higher NT-ProBNP values suggestive of more advanced cardiomyopathy compared with non-ATTR patients. However, cardiac ^{99m}Tc-HMDP uptake was a strong predictor of cardiovascular mortality. In clinical practice, early detection of ATTR in HF patients has an effect on the selection of preferable initial heart failure treatments, clinical risk assessment, and, in some cases, initiation of novel anti-amyloid treatments.

The prevalence of ATTR in this HF population was 7% by visual analysis and 5% using quantitative H/CL threshold. This is in line with previous studies, in which ATTR was found in 5–14% of individuals with HFpEF, which constitutes approximately half of all HF cases [3–6]. The current study did not observe a significant difference in the rate of cardiac uptake in patients with reduced or preserved ejection fraction, which might be explained by the small ATTR population or prevalent advanced amyloid cardiomyopathy. Based on these results, bone scintigraphy should be targeted at patients with a higher pretest probability of ATTR, based on clinical suspicion and initial diagnostic testing. Unfortunately, individual clinical characteristics and echocardiographic findings are inaccurate in the diagnosis of amyloidosis [19]. Speckle tracking echocardiography could be an optimal radiation-free technique for initial screening of ATTR, but is dependent on image quality [18]. Magnetic resonance imaging (MRI) enables accurate confirmation of suspected amyloidosis and further characterisation of other possible causes of HF. However, unlike MRI, bone scintigraphy is not contraindicated in severe kidney failure or in the case of ferromagnetic implants, which both are common in elderly amyloid patients. In addition, both speckle tracking and MRI could pose difficulties in patients with atrial fibrillation or other arrhythmias frequently found in ATTR patients. Furthermore, the detection of early cardiac amyloidosis might be more difficult using echocardiography and MRI compared to scintigraphy, which allows detection of cardiac ATTR already in its subclinical phase [10,20]. Moreover, it is not uncommon that an HF patient undergoes bone scintigraphy due to non-cardiac reasons, which enables opportunistic screening of cardiac ATTR similar to the current study setting. The prognostic value of ^{99m}Tc-HMDP scintigraphy was compared with NT-ProBNP and GFR, which are both associated with mortality in ATTR. A NT-ProBNP level of 3,000 ng/L has previously been used as a prognostic cut-off value [21].

This study used previously accepted visual and quantitative thresholds for the detection of ATTR-positive bone scintigraphy to increase the generalisability of the results. A cardiac uptake ≥Perugini grade 2 cardiac uptake is currently accepted as a visual threshold for diagnosis of ATTR [16–18]. An H/CL ratio of ≥1.30 has previously been validated for diagnosis of ATTR, using a 3-hour bone scintigraphy protocol [9]. The current study population differs from those with clinically suspected amyloidosis; thus, the optimal threshold for screening ATTR in a lower pretest probability population might differ from one used in suspected amyloid cardiomyopathy. Furthermore, the decreased clearance of radiotracers in elderly patients with poor kidney function, dehydration or difficulties in voiding might result in false-positive diagnoses of ATTR, due to left ventricular blood pool activity. Our imaging staff encourage sufficient fluid intake before and after the radiotracer injection to increase image quality by decreasing blood radioactivity. The later imaging of ^{99m}Tc-HMDP at 3 hours post injection also decreases blood pool activity, due to better radiotracer clearance compared to a standard regime of 1-hour imaging used in pyrophosphate scintigraphy. There was no correlation between diminished GFR and cardiac ^{99m}Tc-HMDP uptake

Table 2 Univariable and multivariable analysis of patient characteristics, bone scintigraphy and overall mortality.

Univariable			
Variable	**HR**	**95% CI**	**P-value**
Age (y)	1.05	1.03–1.07	<0.0001
Female	1.02	0.73–1.43	0.90
Bone metastasis	2.72	2.09–3.56	<0.001
Reduced vs preserved EF	0.92	0.67–1.25	0.58
Coronary artery disease	1.13	0.74–1.72	0.59
NT-ProBNP (per 100 ng/L)	1.00	1.00–1.01	<0.001
GFR (mL/min)	0.99	0.98–0.99	<0.001
Any cardiac uptake (≥G1)	0.87	0.66–1.16	0.35
Cardiac uptake (≥G2)	1.47	0.91–2.38	0.12
Cardiac uptake (G3)	2.05	1.05–4.00	0.04
H/CL ratio ≥1.30	1.88	1.11–3.17	0.02
Multivariable (Model 1)			
Variable (n=137)	**HR**	**95% CI**	**P-value**
Age (y)	1.05	1.02–1.09	<0.01
Bone metastasis	2.26	1.45–3.51	<0.001
NT-ProBNP (per 100 ng/L)	1.00	1.00–1.01	0.10
GFR (mL/min)	0.99	0.98–1.00	0.04
H/CL ratio ≥1.30	0.82	0.38–1.81	0.63
Multivariable (Model 2)			
Variable (n=310)	**HR**	**95% CI**	**P-value**
Age (y)	1.04	1.01–1.06	0.001
Bone metastasis	2.72	2.06–3.60	<0.0001
GFR (mL/min)	0.99	0.98–1.00	<0.01
H/CL ratio ≥1.30	1.36	0.76–2.33	0.31

Abbreviations: CI, confidence interval; EF, ejection fraction; G1, Perugini grade 1; G2, Perugini grade 2; G3, Perugini grade 3; GFR, glomerular filtration rate; H/CL, heart-to-contralateral side; HR, hazard ratio; NT-ProBNP, n-terminal pro-brain natriuretic peptide.

in the current study. Unfortunately, single-photon emission tomography (SPECT) data were unavailable for more accurate characterisation of cardiac uptake.

Detected ATTR was associated with poor survival in this study. In a previous study of 229 patients, who underwent pyrophosphate scintigraphy for suspected amyloidosis, both visual and quantitative diagnosis of ATTR was associated with overall mortality [9]. Similarly, Rapezzi et al. found a relationship between myocardial ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) uptake and adverse events including cardiac death or hospitalisation in 63 patients with diagnosed ATTR [11]. Moreover, incidentally detected cardiac ^{99m}Tc-HMDP uptake was associated with both elevated overall and cardiovascular mortality in a recent study by Suomalainen et al. [12]. However, it is unclear whether the degree of cardiac uptake severity itself has a prognostic value. Study of 602 ATTR patients by Hutt et al. found no significant association between Perugini grade severity and total mortality; however, a negative bone scintigraphy predicted a good outcome [13]. The prognostic utility of scintigraphy might be improved by cross-sectional SPECT imaging. Lack of an apical sparing phenomenon on SPECT was a strong independent predictor of survival in a study by Sperry et al. [22]. A quantitative SPECT analysis could both exclude left ventricular blood pool activity and further aid in risk stratification [23]. Interestingly, significant CAD was highly prevalent in the current patients with cardiac uptake, which could mask ATTR in a diagnostic work-up of HF.

Previous findings have suggested that further risk assessment of incidental suspected ATTR on bone scintigraphy should be performed using a multimodality approach. Most importantly, SPECT imaging should be utilised when possible to avoid false-positive findings. Initial cardiological evaluation should establish the patient's functional and symptomatic status, and be supplemented by echocardiography to assess the stage of the amyloid process. Addition of speckle tracking to standard echocardiography might enable more accurate detection of early amyloidosis [1,10]. Cardiac MRI may offer additional value in confirming the diagnosis but a histological verification with endomyocardial or extra-cardiac biopsy is essential when the possibility of light chain disease cannot be excluded by laboratory testing [1]. As cardiac uptake did not predict overall mortality in the current study, the need for any diagnostic testing should be pragmatically evaluated in each patient, depending on the severity of their primary disease. It is to be noted that ATTR is a multisystem disease that might have significant non-cardiac implications, which may also affect overall mortality.

Limitations

Unfortunately, information on clinical diagnoses of ATTR after bone scintigraphy was unavailable. Echocardiography or other multimodality imaging data would have been valuable in classification of the HF population, but was not consistently available in patient records due to the retrospective study setting and non-cardiac imaging indications. As a confounding factor, light chain amyloidosis might also be a rare cause of increased cardiac uptake, but data on laboratory tests of light chains in this population were unavailable. Nevertheless, light chain disease has poor prognosis and its incidental detection by scintigraphy would be valuable. The prevalence of cardiac uptake was rare in this study, which resulted in a small absolute number of adverse events in this group, while the relative mortality was high. The representation of the female sex was uneven in this study due to prostate cancer being the most common indication for bone scintigraphy in the departments. Histological biopsy data would have strengthened the study design. Patients with cardiac uptake were older and had higher NT-ProBNP values than other patients, which might have influenced the mortality analyses. Unfortunately,

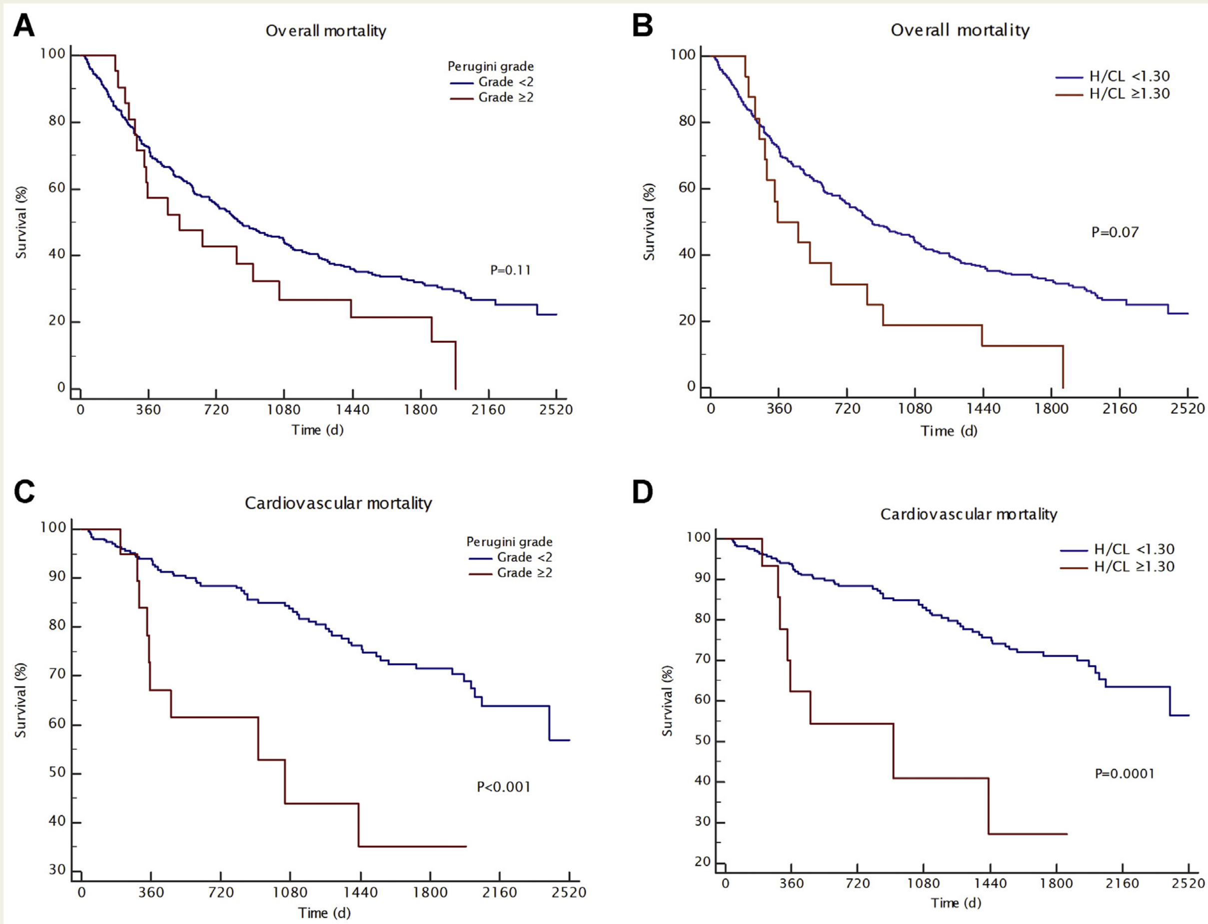

Figure 4 Kaplan-Meier analysis on association between cardiac uptake on bone scintigraphy and patient survival. Overall mortality in patients diagnosed using visual (A) and quantitative heart-to-contralateral side (H/CL) criteria; (B) for suspected cardiac ATTR. Cardiovascular mortality in patients with suspected ATTR based on both visual (C) and quantitative H/CL analysis of cardiac uptake (D).

NT-ProBNP was only available in a subset of the patients. Follow-up time of the study was short, but 69% of the elderly population met an end-point. Only elderly HF patients were included in this study, as hereditary ATTR is rare in Finland. Thus, the results should not be directly applied to younger HF populations or populations with a higher possibility of mutant ATTR. Bone metastases, arthrosis, costochondral calcification, scoliosis, renal failure, and surgical breast scars are all prevalent in an elderly oncological population and might influence image analysis.

It was chosen to emphasise the semiquantitative H/CL ratio in the definition of the ATTR population, which resulted in fewer positive patients than only visual grading. Therefore, visual scoring might be more sensitive for ATTR screening, but might also include false-positive diagnoses due to mild borderline radiotracer uptake in the cardiac region. A mild grade 1 uptake was prevalent in this study; however, considering the low pretest probability for ATTR in a HF population with non-cardiac imaging indications, true positive amyloid findings with a grade 1 uptake would be unlikely. Cardiac HMDP imaging and its quantitation is less validated than other similar radiotracers used, which was a limitation in this study. Both overall and cardiovascular mortality were used as outcome variables, since oncological disease was a common indication for bone scintigraphy in this study. Therefore, this study might better reflect the opportunistic screening of ATTR in a real-world HF population who undergo bone scintigraphy due to non-cardiac indications than the prospective screening of a general HF population. Nevertheless, based on the results, the presence of cardiac uptake on bone scintigraphy is associated with high cardiovascular mortality in elderly HF patients. Thus, further clinical assessment of the incidentally detected cardiac uptake is warranted.

Conclusions

Cardiac uptake suggestive of ATTR was found in 5% of elderly patients with chronic heart failure. The presence of cardiac uptake on bone scintigraphy did not convey an independent prognostic value on overall mortality but was independently associated with cardiovascular mortality.

Table 3 **Univariable and multivariable analysis of patient characteristics, bone scintigraphy, and cardiovascular mortality.**

Variable	HR	95% CI	P-value
Univariable			
Age (y)	1.09	1.05–1.13	<0.0001
Female	1.01	0.55–1.86	0.97
Bone metastasis	1.65	0.98–2.80	0.06
Reduced vs preserved EF	0.67	0.38–1.16	0.15
Coronary artery disease	0.99	0.49–2.00	0.97
NT-ProBNP (per 100 ng/L)	1.00	1.00–1.01	0.32
GFR (mL/min)	0.98	0.96–0.99	0.0001
Any cardiac uptake (≥G1)	1.17	0.72–1.91	0.53
Cardiac uptake (≥G2)	3.29	1.67–6.47	<0.001
Cardiac uptake (G3)	4.41	1.75–11.09	<0.01
H/CL ratio ≥1.30	4.05	1.92–8.54	<0.001
Multivariable (Model 1)			
Variable	**HR**	**95% CI**	**P-value**
Age (y)	1.08	1.04–1.13	<0.001
GFR (mL/min)	0.98	0.97–0.99	<0.01
Cardiac uptake (≥G2)	2.84	1.42–5.69	<0.01
Multivariable (Model 2)			
Variable	**HR**	**95% CI**	**P-value**
Age (y)	1.08	1.04–1.12	<0.001
GFR (mL/min)	0.98	0.97–0.99	<0.01
Cardiac uptake (G3)	3.12	1.20–8.09	0.02
Multivariable (Model 3)			
Variable	**HR**	**95% CI**	**P-value**
Age (y)	1.08	1.04–1.13	<0.001
GFR (mL/min)	0.98	0.97–0.99	<0.01
H/CL ratio ≥1.30	3.09	1.43–6.66	<0.01

Abbreviations: CI, confidence interval; EF, ejection fraction; G1, Perugini grade 1; G2, Perugini grade 2; G3, Perugini grade 3; GFR, glomerular filtration rate; H/CL, heart-to-contralateral side; HR, hazard ratio; NT-ProBNP, NT-terminal pro-brain natriuretic peptide.

ATTR patients were older and had more advanced heart failure compared with non-ATTR patients.

Declarations

Funding: Not applicable.

Conflicts of Interest

Dr Valtteri Uusitalo: Compensation for lecture from GE healthcare and Pfizer. Dr Tiina Heliö: Compensation for scientific advisory board activity from Alnylam and Sanofi.

Availability of Data and Material

The dataset of the current study are available from the corresponding author on reasonable request.

Compliance With Ethical Standards

The study was approved by the ethical board of Helsinki University Hospital and the need for informed consent was waived (decision HUS/1721/2018).

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