

Supplemental Table 1. Baseline characteristics according to referral indication.

	All patients n=11,527 (96.7%)	Cardiac referrals n=1,081 (9.4%)	Non-cardiac referrals n=10,446 (90.6%)	P-Value
Age, y	64 (51-73; 11,527)	75 (63-81; 1,081)	63 (51-72; 10,446)	<0.001
Sex, male, %	37.0 (11,527)	60.0 (1,081)	34.6 (10,446)	<0.001
BMI, kg/m ²	25.7 (22.9-29.4; 11,108)	26.6 (23.6-30.1; 1,052)	25.7 (22.8-29.3; 10,056)	<0.001
Cancer, %	73.6 (11,527)	19.9 (1,081)	79.1 (10,446)	<0.001
Arterial hypertension, %	40.9 (11,527)	60.3 (1,081)	38.9 (10,446)	<0.001
Diabetes, %	12.4 (11,527)	23.1 (1,081)	11.2 (10,446)	<0.001
Atrial fibrillation, %	9.1 (11,527)	34.2 (1,081)	6.5 (10,446)	<0.001
History of stroke, %	5.6 (11,527)	12.7 (1,081)	4.8 (10,446)	<0.001
CAD, %	12.9 (11,527)	47.6 (1,081)	9.3 (10,446)	<0.001
Previous MI, %	1.8 (11,527)	8.4 (1,081)	1.1 (10,446)	<0.001
Chronic heart failure, %	8.0 (11,527)	38.2 (1,081)	4.9 (10,446)	<0.001
PAD, %	1.5 (11,527)	3.7 (1,081)	1.3 (10,446)	<0.001
COPD, %	7.3 (11,527)	10.9 (1,081)	7.0 (10,446)	<0.001
CTS, %	0.9 (11,527)	1.9 (1,081)	0.8 (10,446)	<0.001
eGFR, ml/min/1.73m ²	78.9 (62.6-95.3; 6,325)	64.7 (46.3-82.0; 1,003)	81.2 (66.1-97.4; 5,322)	<0.001
LDL, mg/dl	103 (75-132; 2,611)	80 (58-109; 661)	110 (84-139; 1,950)	<0.001
Hemoglobin, mg/dl	12.8 (11.3-14.0; 6,103)	12.5 (10.8-14.1; 1,019)	12.9 (11.5-14.0; 5,084)	<0.001
Hematocrit, %	38.2 (34.1-41.2; 6,103)	37.4 (32.4-41.4; 1019)	38.3 (34.4-41.2; 5,084)	<0.001
HbA1c, %	5.7 (5.3-6.2; 1,932)	5.7 (5.3-6.5; 661)	5.7 (5.5-6.2; 1,271)	0.271
NT-proBNP, ng/dL	818 (212-2777; 1,904)	1726 (549-4273; 975)	321 (112-1157; 929)	<0.001
Hs-TnT, ng/L	21 (11-49; 1168)	31 (15-73; 580)	15 (9-30; 588)	<0.001

Creatine Kinase, mg/dl	94 (62-155; 4,150)	111 (75-201; 884)	90 (60-143; 3,266)	<0.001
CRP, mg/dl	0.7 (0.2-3.6; 5,945)	0.8 (0.3-3.9; 958)	0.7 (0.2-3.5; 4,987)	0.029
Perugini grading	(11,527)	(1,081)	(10,446)	<0.001
0	96.7	81.8	98.3	
1	1.8	6.8	1.3	
2/3	1.4	11.5	0.4	
Monoclonal protein, %	18.0 (1,474)	16.0 (75)	20.9 (123)	0.011
Left ventricular dysfunction, %	(2,027)	(910)	(1117)	<0.001
none	83.1	71.7	90.5	
≤mild	6.2	10.3	3.4	
≤moderate	5.5	8.1	3.8	
>moderate	5.2	9.6	2.4	
LVEDD, mm	44 (40-47; 2,027)	47 (40-49; 910)	44 (40-47; 1,117)	0.026
LAD, mm	53 (47-60; 2,027)	58 (53-65; 910)	50 (46-56; 1,117)	<0.001
RVEDD, mm	31 (28-35; 2,027)	33 (29-37; 910)	31 (28-34; 1,117)	<0.001
RAD, mm	51 (47-58; 2,027)	55 (50-62; 910)	49 (45-55; 1,117)	<0.001
IVS, mm	13 (11-16; 2,027)	16 (14-19; 910)	12 (10-13; 1,117)	<0.001

Brackets indicate number of patients with available data for each parameter.

DPD indicates $^{99\text{m}}\text{Tc}$ -labeled 3,3-diphosphono-1,2-propanodicarboxylic acid bone scintigraphy; BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; CTS, carpal tunnel syndrome; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; hs-TnT, high sensitive troponin T; CRP, C-reactive protein; LVEDD, left ventricular enddiastolic diameter; LAD, left atrial diameter; RVEDD, right ventricular enddiastolic diameter; RAD, right atrial diameter; IVS, interventricular septum thickness; Bold values indicate $P \leq 0.05$.

Supplemental Table 2. Laboratory, echocardiographic, and histological baseline characteristics.

	DPD 0 n=11,151 (96.7%)	DPD 1 n=209 (1.8%)	DPD 2/3 n=167 (1.5%)	P value
eGFR, ml/min/1.73m ²	79.7 (63.9-95.9; 6,032)	60.4 (45.8-76.1; 155)*	61.4 (45.0-78.7; 138)†	<0.001
LDL, mg/dl	105 (77-134; 2,454)	81 (57-110; 72)*	76 (56-100; 85)†	<0.001
Hemoglobin, mg/dl	12.9 (11.3-14.0; 5,811)	12.3 (10.6-13.3; 152)*	12.9 (11.5-14.2; 140)‡	<0.001
Hematocrit, %	38.2 (34.1-41.3; 5,811)	36.6 (32.4-39.6; 152)*	38.3 (34.6-42.2; 140)‡	<0.001
HbA1c, %	5.7 (5.3-6.2; 1,789)	5.8 (5.4-6.5; 85)	5.9 (5.5-6.3; 115)	0.048
NT-proBNP, ng/dL	655 (185-2311; 1,704)	2117 (848-6364; 85)*	3043 (1562-6556; 115)†,‡	<0.001
Hs-TnT, ng/L	19 (10-41; 1058)	49 (25-148; 48)*	60 (33-104; 62)†	<0.001
Creatine Kinase, mg/dl	93 (62-153; 3,934)	114 (73-210; 108)*	106 (77-168; 108)†	0.003
CRP, mg/dl	0.7 (0.2-3.6; 5,663)	0.8 (0.3-2.9; 198)	0.5 (0.2-1.8; 163)†,‡	0.039
Monoclonal protein, %	17.8 (1,474)	32.0 (75)*	11.4 (123)‡	0.001
Left ventricular dysfunction, %	(1,827)	(85)*	(115)†	<0.001
none	86.1	59.7	45.0	
≤mild	5.4	9.0	20.0	
≤moderate	4.5	16.4	15.0	
>moderate	4.0	14.9	20.0	

LVEDD, mm	44 (40-47; 1,827)	47 (41-52; 85)*	41 (37-44; 115)†‡	<0.001
LAD, mm	31 (28-35; 1,827)	34 (32-37; 85)*	34 (29-39; 115)†	<0.001
RVEDD, mm	52 (47-59; 1,827)	62 (58-67; 85)*	63 (57-68; 115)†	<0.001
RAD, mm	51 (46-56; 1,827)	61 (53-65; 85)*	62 (55-68; 115)†	<0.001
IVS, mm	13 (11-15; 1,827)	14 (13-17; 85)*	20 (17-23; 115)†‡	<0.001
Tissue biopsy for amyloid	-	7.7 (16)	16.8 (28)‡	0.005
Heart	-	68.8 (11/16)	78.6 (22/28)	
Kidney	-	25.0 (4/16)	14.3 (4/28)	
Other	-	12.5 (2/16)	25.0 (7/28)	
Amyloid confirmation on biopsy	-	93.8 (15/16)	92.9 (26/28)	0.91
ATTR	-	26.7 (4/15)	76.9 (20/26)‡	0.002
AL	-	73.3 (11/15)	15.4 (4/26)‡	<0.001
ATTR/AL combined	-	0.0 (0/15)	7.7 (2/26)	0.27

*) DPD grade-1 vs. DPD grade-0: $P \leq 0.05$

†) DPD grade-2/3 vs. DPD grade-0: $P \leq 0.05$

‡) DPD grade-2/3 vs. DPD grade-1: $P \leq 0.05$

Brackets indicate number of patients with available data for each parameter.

DPD indicates ^{99m}Tc -labeled 3,3-diphosphono-1,2-propanodicarboxylic acid bone scintigraphy; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; hs-TnT, high sensitive troponin T; CRP, C-reactive protein; LVEDD, left ventricular enddiastolic diameter; LAD, left atrial diameter; RVEDD, right ventricular enddiastolic diameter; RAD, right atrial diameter; IVS, interventricular septum thickness; ATTR, transthyretin amyloidosis; AL, light-chain amyloidosis; Bold values indicate $P \leq 0.05$.

Supplemental Table 3: Uni- and multivariate Cox regression analyses assessing the association of parameters with cardiovascular mortality.

Parameter	Univariate		Multivariate	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age, per 10y increase	3.303 (2.913-3.744)	<0.001	2.776 (2.431-3.171)	<0.001
Male Sex	2.760 (2.191-3.476)	<0.001	1.495 (1.176-1.901)	0.001
Cancer	0.444 (0.353-0.559)	<0.001	0.533 (0.421-0.675)	<0.001
Arterial hypertension	3.011 (2.365-3.833)	<0.001	0.987 (0.743-1.309)	0.925
Diabetes	2.971 (2.293-3.851)	<0.001	1.289 (0.974-1.706)	0.076
Atrial fibrillation	5.575 (4.325-7.186)	<0.001	1.255 (0.944-1.668)	0.117
Chronic heart failure	6.329 (4.905-8.167)	<0.001	1.761 (1.300-2.385)	<0.001
CAD	7.185 (5.694-9.067)	<0.001	1.852 (1.381-2.486)	<0.001
Past MI	5.384 (3.336-8.686)	<0.001	1.346 (0.814-2.226)	0.247
Past stroke	5.498 (4.160-7.267)	<0.001	1.802 (1.326-2.448)	<0.001
PAD	3.959 (2.269-6.908)	<0.001	1.051 (0.592-1.866)	0.866
COPD	2.768 (2.014-3.803)	<0.001	1.225 (0.882-1.702)	0.226
DPD positivity	5.651 (3.944-8.097)	<0.001	1.785 (1.255-2.540)	0.001

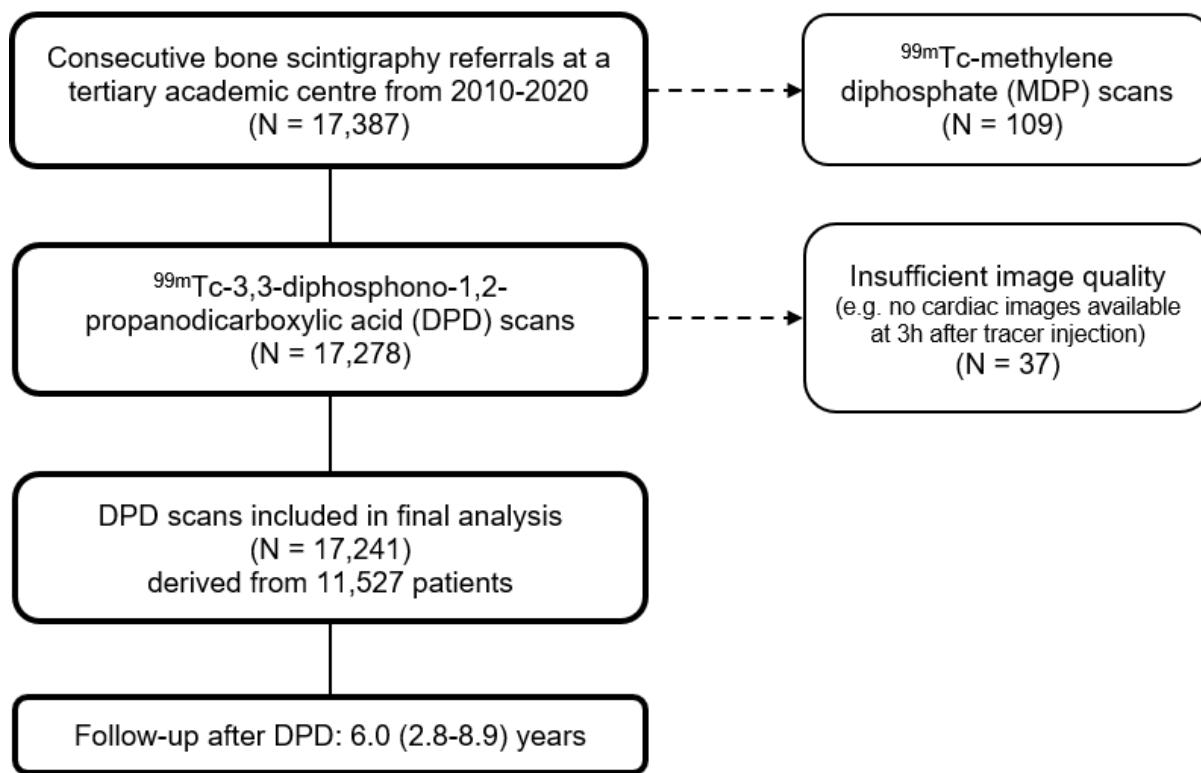
For abbreviations see Table 1. Bold values indicate $P \leq 0.05$.

Supplemental Table 4: Uni- and multivariate Cox regression analyses assessing the association of parameters with hospitalization for heart failure.

Parameter	Univariate		Multivariate	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age, per 10y increase	2.787 (2.389-3.252)	<0.001	1.830 (1.541-2.173)	<0.001
Male Sex	2.255 (1.676-3.033)	<0.001	0.900 (0.656-1.235)	0.514
Cancer	0.349 (0.260-0.469)	<0.001	0.558 (0.408-0.763)	<0.001
Arterial hypertension	6.106 (4.234-8.807)	<0.001	1.449 (0.953-2.203)	0.083
Diabetes	4.571 (3.363-6.214)	<0.001	1.742 (1.247-2.433)	0.001
Atrial fibrillation	15.01 (11.15-20.21)	<0.001	2.355 (1.661-3.339)	<0.001
Chronic heart failure	32.14 (23.44-44.08)	<0.001	10.51 (7.09-15.59)	<0.001
CAD	8.165 (6.062-10.998)	<0.001	0.913 (0.634-1.316)	0.626
Past MI	7.598 (4.534-12.732)	<0.001	1.306 (0.751-2.270)	0.344
Past stroke	4.826 (3.333-6.989)	<0.001	1.210 (0.810-1.807)	0.352
PAD	3.833 (1.884-7.796)	<0.001	0.735 (0.355-1.521)	0.406
COPD	3.923 (2.729-5.638)	<0.001	1.294 (0.889-1.883)	0.179
DPD positivity	11.26 (7.84-16.18)	<0.001	2.254 (1.510-3.365)	<0.001

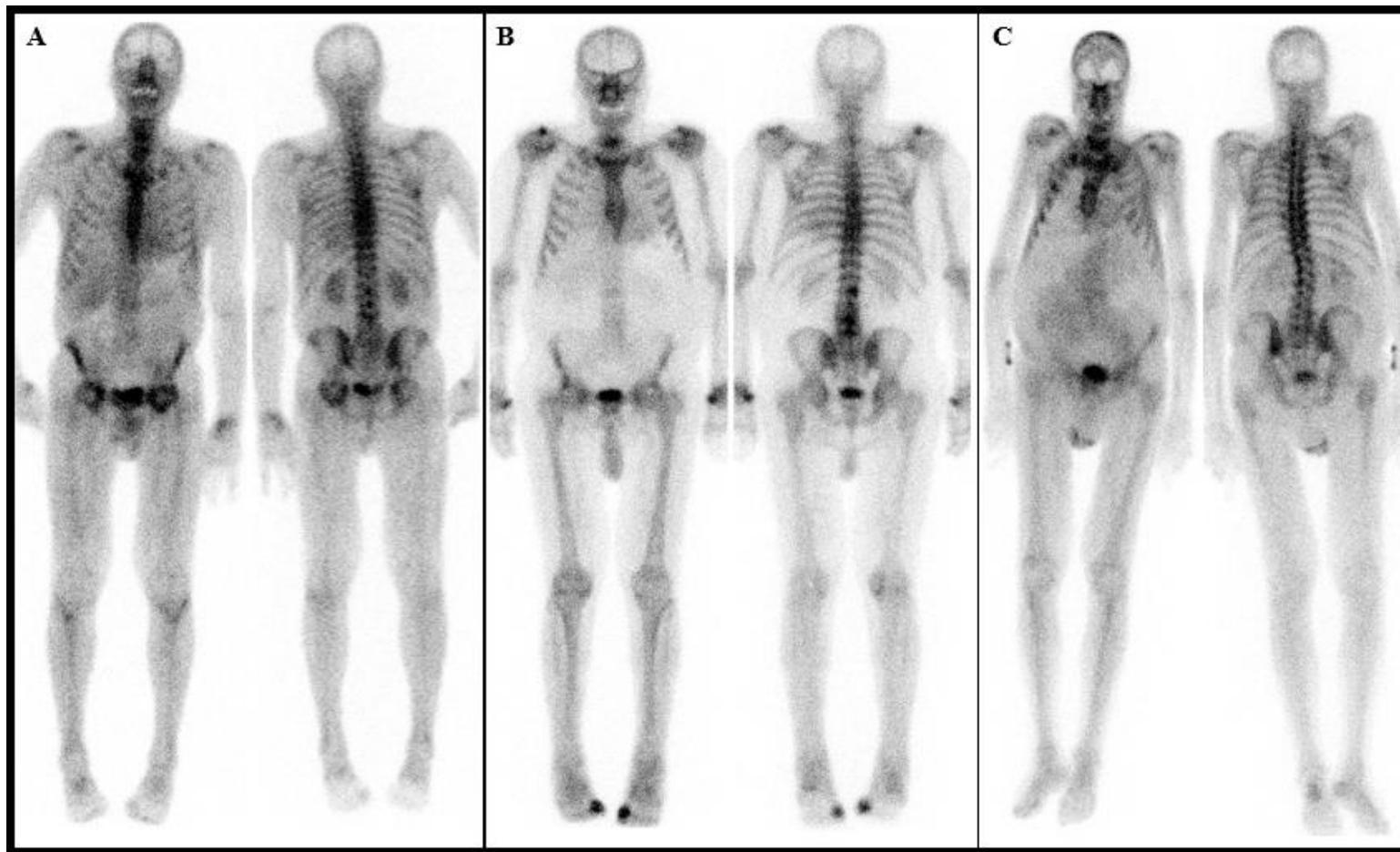
For abbreviations see Table 1. Bold values indicate $P \leq 0.05$.

Supplemental Figure 1: Patient population.



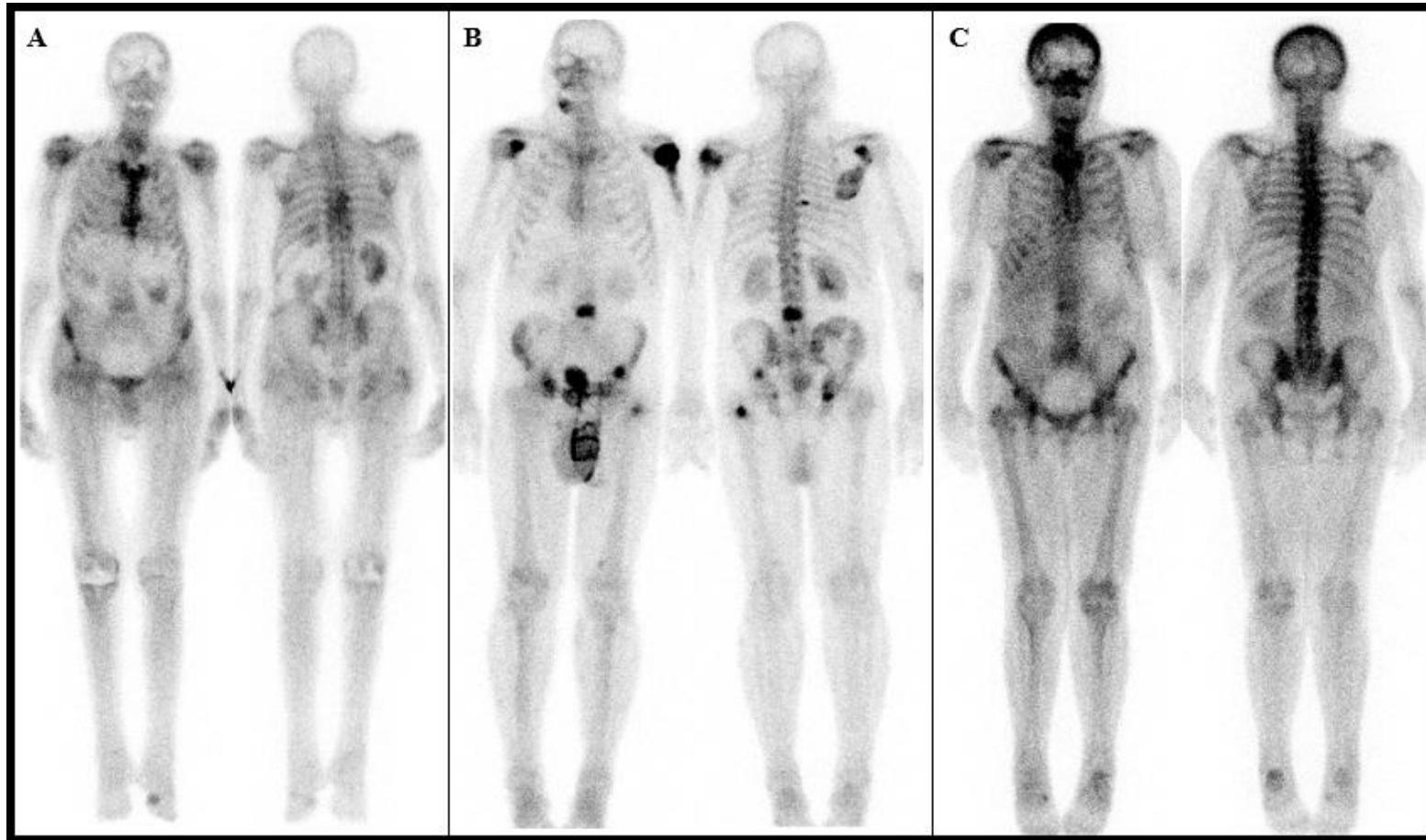
Bone scintigraphy scans with insufficient image quality or performed with ^{99m}Tc -methylene diphosphonate (MDP) were excluded. DPD indicates ^{99m}Tc -3,3-diphosphono-1,2-propanodicarboxylic acid.

Supplemental Figure 2: Images of patient examples considered as low-grade uptake.



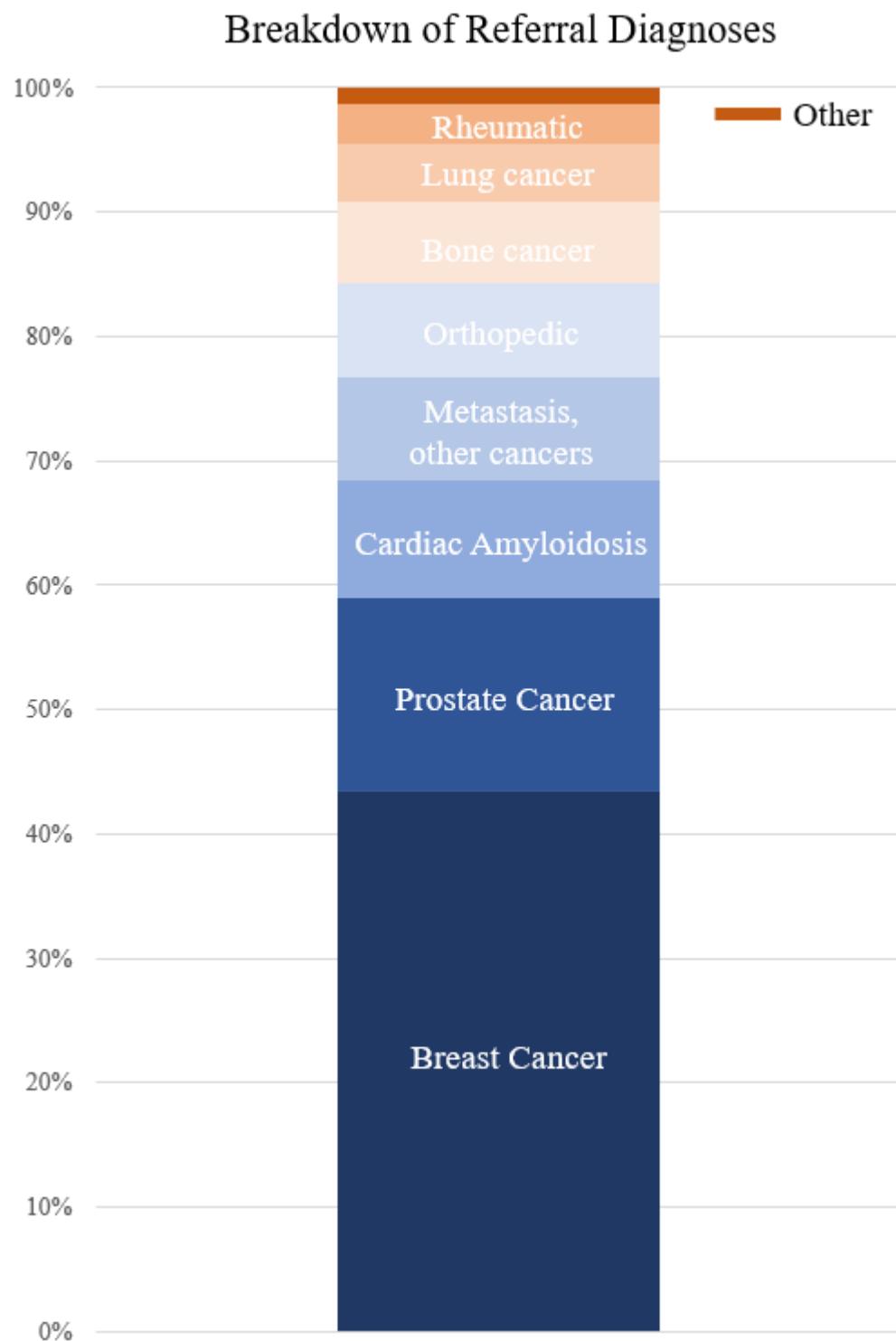
This figure highlights 3 patients with a final diagnosis of low-grade uptake (Perugini grade-1). Endomyocardial biopsy results were available for the patient depicted in **Panel B** demonstrating ATTR-CA as the underlying pathology.

Supplemental Figure 3: Images of patient examples considered as questionable.

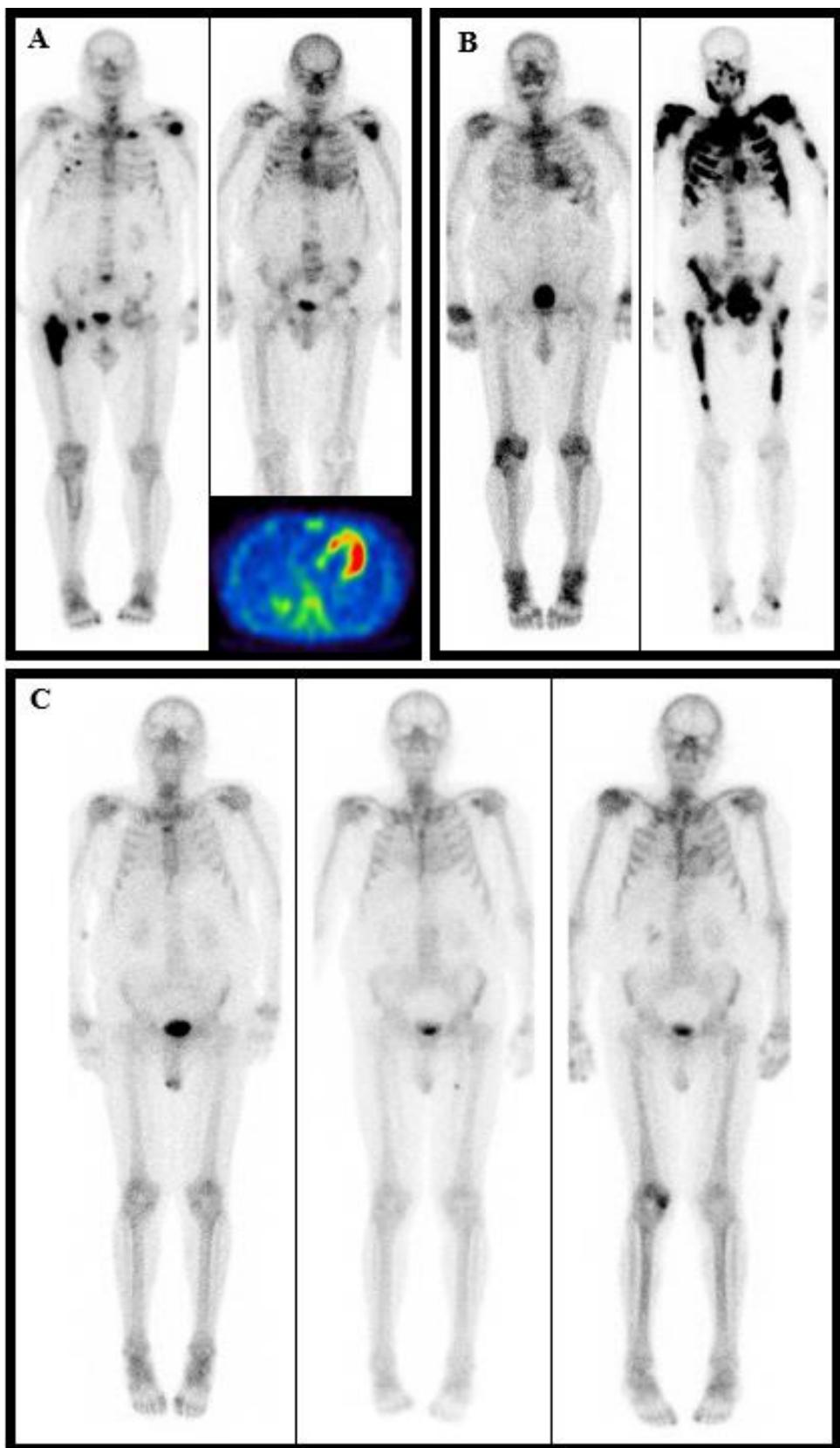


Three patients with questionable Perugini grading are shown. In these borderline cases, scans were reviewed by a third nuclear imaging specialist and a final diagnosis was reached by consensus. Final diagnoses for the respective patients were grade-1 (**Panel A**, appreciate also subtle uptake in cardiac region seen on dorsal acquisition), and grade-0 (**Panels B** and **C**).

Supplemental Figure 4: Indications for bone scintigraphy referrals.

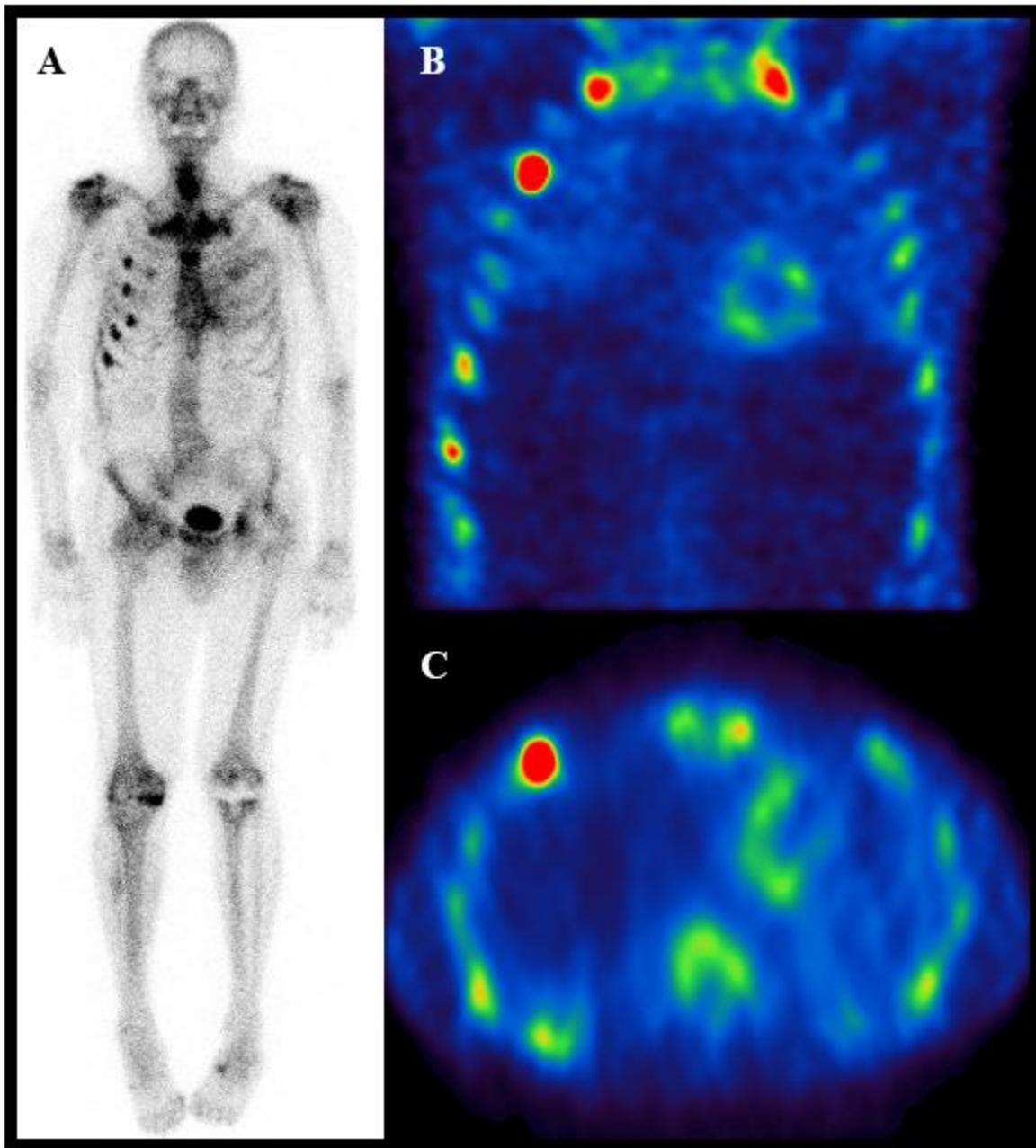


Supplemental Figure 5: Trajectories of cardiac tracer uptake.



This figure highlights 3 patients with changes in Perugini grading over time. **Panel A** shows a 75 y/o male, who developed grade 2 cardiac tracer uptake confirmed by SPECT 6 years following a negative scan result,. Conversely, one 80 y/o male with prostate cancer experienced a decline from Perugini grade 2 to grade 1 within 2 years based on tracer competition due to excessive bone metastasis (**Panel B**). Finally, progressive increase in cardiac tracer uptake from grade 0 to grade 1 to grade 2 was observed in one 82 y/o male 3 and 4 years, respectively, following an initial negative scan (**Panel C**).

Supplemental Figure 6. Utility of additional SPECT in the diagnosis of CA.



In this 76 y/o male patient referred for suspected CA, planar images were inconclusive regarding the presence of cardiac tracer uptake (**Panel A**). Additional SPECT from the chest was pivotal to discriminate uptake from the myocardium vs. the sternovertebral region (**Panels B and C**). The presence of a plasma cell dyscrasia was ruled out by laboratory testing, yielding a final diagnosis of subclinical ATTR-CA (grade 1 cardiac uptake).