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Original Article

Clinical experience of a systemic algorithm for diagnosis of cardiac amyloidosis

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ABSTRACT

INTRODUCTION. Cardiac amyloidosis is an underdiagnosed disease, and its prevalence is probably higher than previously estimated. We aimed to investigate the effect of introducing a systemic diagnostic algorithm for cardiac amyloidosis in clinical practice.

METHODS. A systematic diagnostic algorithm was developed and clinically applied in two hospitals in Eastern Denmark. Elderly patients (males > 60 years, females > 70 years) with left ventricular hypertrophy (≥ 12 mm) and diastolic dysfunction leading to a suspicion of cardiac amyloidosis were referred for standardised workup, including biochemistry and bone scintigraphy.

RESULTS. A total of 224 patients (median age 76 years (70-83); 65% males) were included in the analysis. In total, 43 (19%) patients (84% males) were diagnosed with cardiac amyloidosis. Among the 43 diagnosed patients, 38 had transthyretin wild-type amyloidosis, one had the hereditary form and four had monoclonal-immunoglobulin-light-chain amyloidosis. Patients with cardiac amyloidosis were significantly older (81 versus 75 years old, $p < 0.001$) and more often male (84% versus 61%, $p = 0.004$) than the overall screened population.

CONCLUSIONS. Systematic screening for cardiac amyloidosis in older patients with cardiac hypertrophy and echocardiographic signs of diastolic dysfunction is feasible and shows a diagnostic yield of 19% in the assessed population.

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Cardiac amyloidosis (CA) is an underrecognised cause of heart failure and arrhythmias [1]. CA is characterised by extracellular deposits of misfolded proteins (amyloid fibrils) within the myocardium, leading to left ventricular hypertrophy, impaired systolic and diastolic function and risk of arrhythmias. Major types of the disease include wild type (ATTRwt) and hereditary transthyretin (ATTRv) amyloidosis and monoclonal immunoglobulin light chain amyloidosis (AL) [2, 3].

CA may appear as the only manifestation of amyloidosis or with a constellation of extracardiac symptoms or signs, such as renal insufficiency, carpal tunnel syndrome, spinal stenosis and polyneuropathy. The typical cardiac and extracardiac symptoms and signs are often referred to as red flags, and awareness of these should

increase the suspicion of CA and lead to further diagnostic testing [2, 4, 5].

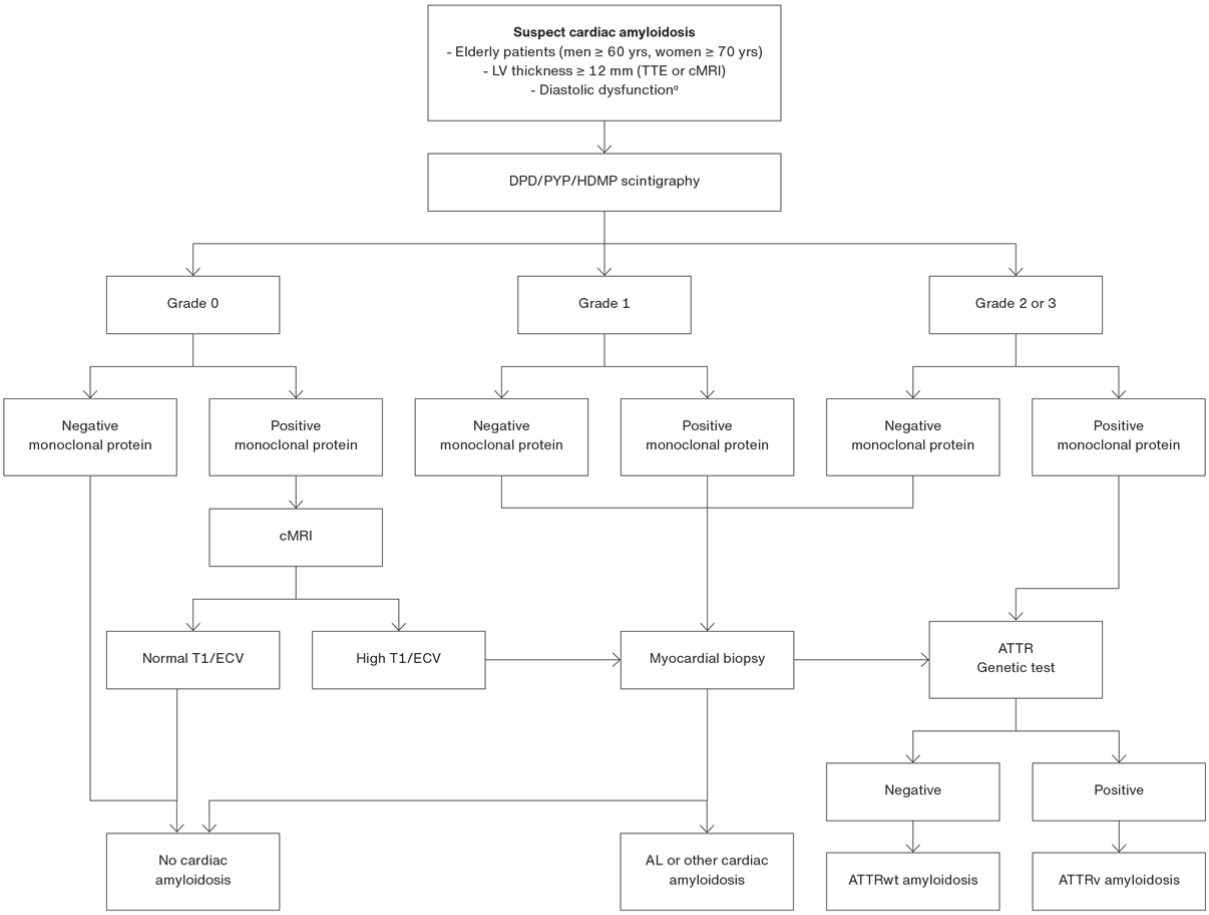
Advances in non-invasive diagnostic testing and the introduction of disease-modifying treatments have made it simpler to diagnose CA and have increased awareness of the disease [4]. Until recently, CA could be diagnosed only with an endomyocardial biopsy, but now nuclear scintigraphy using bone-avid radio-tracers has been confirmed as a sensitive and specific modality for diagnosing ATTR-CA, even early in the disease course [2, 4, 6, 7]. ATTR-CA can thus safely be diagnosed with a scintigraphy showing grade 2 or grade 3 cardiac uptake and in the absence of monoclonal proteins [4, 8, 9]. However, increased awareness among clinicians and implementation of diagnostic guidelines are needed since a considerable diagnostic delay is often seen, which together with the risk of misdiagnosis, can lead to inappropriate patient management [10].

In 2018, a diagnostic algorithm for patients with possible CA was approved for the Capital Region of Copenhagen; the algorithm was very similar to the one later included in the European heart failure guidelines [4]. In this paper, we present the clinical implementation of the algorithm and describe its diagnostic yield when applied in a clinical setting.

Methods

An algorithm was introduced to screen patients suspected of CA (**Figure 1**) who presented either in the outpatient clinic or as in-hospital patients. We present data from two major hospitals in the Greater Copenhagen Area with a combined catchment population of approximately one million people. We performed a retrospective chart review of all patients referred for a bone scintigraphy on suspicion of CA from September 2018 to January 2022. Review boards at both hospitals approved the project (19087531).

FIGURE 1 Diagnostic algorithm for when to suspect and diagnose cardiac amyloidosis.



AL = amyloid light chains; ATTR = amyloid transthyretin; cMRI = cardiac MR imaging; DPD = 3,3-diphosphono-1,2-propanodicarboxylate; ECV = extracellular volume; HDMP = hydroxymethylene diphosphonate; LV = left ventricle; PYP = pyrophosphate; TR = tricuspid regurgitation; TTE = transthoracic echocardiography; v = hereditary; wt = wild type.
a) ≥ 2 of the following criteria: 1) E/e' >14 (e': mean value of septal and lateral e'), 2) septal e' < 7 cm/sec or lateral e' < 10 cm/sec, 3) TR gradient > 2.8 m/sec (32 mmHg), 4) left atrium volume index > 34 ml/m^2.

The diagnostic algorithm: Older patients (males ≥ 60 years, females ≥ 70 years) with ventricular hypertrophy (interventricular septal thickness in diastole (IVSd) ≥ 12 mm) measured by echocardiography and signs of diastolic dysfunction were suspected of having CA (Figure 1). Diastolic dysfunction was defined as ≥ 2 of the following criteria: 1) E/e' >14 (e': mean value of septal and lateral e'), 2) septal e' < 7 cm/sec or lateral e' < 10 cm/sec, 3) tricuspid regurgitation (TR)-gradient > 2.8 m/sec (32 mmHg) or 4) left atrium volume index > 34 ml/m^2.

Based on these criteria, the clinicians were encouraged to suspect CA and enroll the patients in the diagnostic algorithm (Figure 1) with referral to bone scintigraphy serum-free light chain (FLC) ratio, and serum/urine protein electrophoresis with immunofixation (SPIE/UPIE). According to the result of the bone scintigraphy and the haematological tests, the diagnostic algorithm further suggested a cardiac magnetic resonance imaging (cMRI), myocardial biopsy or genetic test, Figure 1.

Bone scintigraphy: Patients were intravenously injected with 500-700 MBq ^{99m}Tc-3,3-diphosphono-1,2-pyrophosphate (^{99m}Tc-DPD) or ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HDP). Subsequently, 2-3 hours after injection, anterior and posterior planar recordings of ten minutes of the thorax and abdomen were obtained using either Philips SKYLight SPECT gamma camera (Philips Medical Systems, Eindhoven, The Netherlands) or Symbia SPECT/CT (Siements Healthineers, Erlangen, Germany) with low energy, high resolution collimators. Planar images were supplemented with SPECT/CT of the thorax in case of doubt that cardiac uptake

was derived from a blood pool or focal infarctions. The bone scintigraphy was assessed according to established criteria from grade 0-3. Grade 0; absences of myocardial uptake and normal bone uptake. Grade 1; myocardial uptake in a lower degree than in bones. Grade 2; a similar myocardial and bone uptake. Grade 3; myocardial uptake greater than bone with reduced/absent bone uptake [9].

Haematological test: Positive results of monoclonal proteins, in either serum (SPIE) or urine (UPIE), or an abnormal ratio of kappa/lambda (< 0.26 or > 1.65) regardless of scintigraphy findings, were consulted with a haematologist to assess for underlying AL amyloidosis or other haematologic disease, including monoclonal gammopathy of undetermined significance (MGUS).

We retrospectively reviewed the electronic patient charts of all patients referred for bone scintigraphy on suspicion of CA. We collected data on basic demographics, symptoms and the results of diagnostic tests (electrocardiograms (ECGs), standard biochemistry tests and echocardiograms). In addition, we recorded the results of bone scintigraphy and biochemical screening for AL amyloidosis, cMRI, biopsy results and the final diagnosis.

According to the algorithm (Figure 1), the diagnosis of ATTR amyloidosis was established if patients had a scintigraphy with grade 2 or grade 3 cardiac uptake and absence of monoclonal protein in plasma/urine, or by demonstration of transthyretin amyloid deposits on myocardial biopsy. According to the diagnostic algorithm, all patients diagnosed with ATTR were intended for genetic testing (ATTRv versus ATTRwt). The diagnosis of AL amyloidosis was dependent on findings of abnormal monoclonal proteins or an abnormal FLC ratio, which required further histology showing amyloid, and most often a myocardial biopsy [4]. The established diagnostic algorithm included referral to cMRI in the presence of monoclonal proteins and DPD scintigraphy grade 0 (Figure 1). However, some patients may have had a cMRI for other diagnostic reasons.

Statistics: Continuous variables are presented as mean ± standard deviation if normally distributed, and as medians and IQR if non-normally distributed. Categorical variables are reported as counts with percentages. Patients with CA were compared to patients without CA (ATTR and AL were grouped together). Baseline characteristics of the groups according to CA were compared using χ^2 and the Wilcoxon tests. In addition, patients were divided into three groups according to cardiac uptake on scintigraphy (grade 0, grade 1 and grade 2-3). Baseline characteristics of the groups were compared with the test for trend for categorical variables and Spearman's test for continuous variables. Grade 0 served as the reference in all analyses unless otherwise stated. A two-sided $p < 0.05$ was considered statistically significant. All analyses were performed with SAS software version 9.4 (SAS Institute, Copenhagen, Denmark).

Trial registration: not relevant.

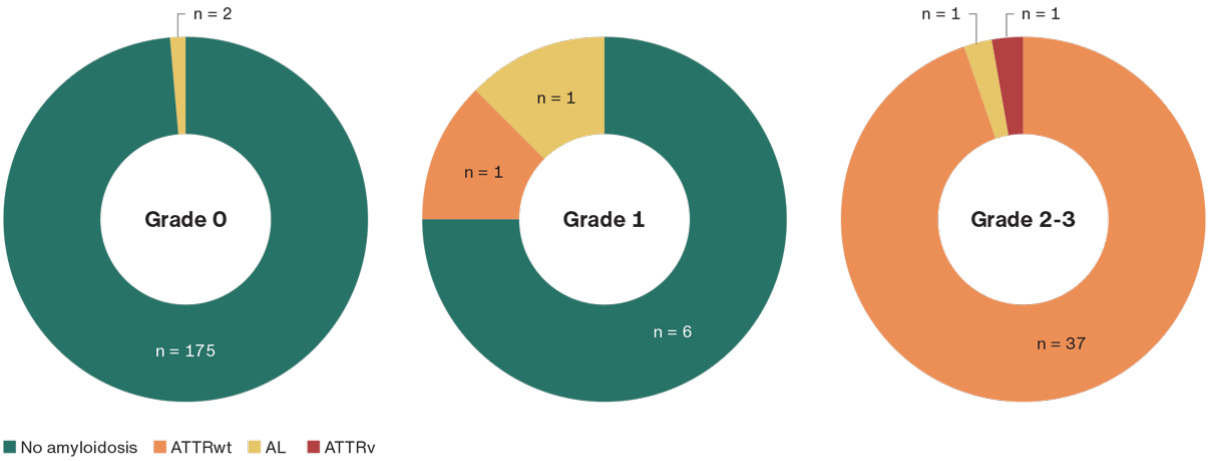
Results

In the period from September 2018 to January 2022, a total of 228 patients were referred for bone scintigraphy on suspicion of CA. One patient died before examination, two patients never showed up and one patient declined use of his electronic health record for research.

In total, 224 patients, median age 76 years (IQR: 70-83; 65% males), completed a bone scintigraphy and were available for analysis.

Figure 2 shows the results of the bone scintigraphy; 177 patients had grade 0 uptake, eight patients had grade 1 uptake and 39 patients had grade 2-3 uptake (see **Table 1** for baseline characteristics).

FIGURE 2 Final diagnosis according to grade of cardiac uptake on scintigraphy.



AL = amyloid light chains; ATTR = amyloid transthyretin; v = hereditary; wt = wild type.

TABLE 1 Baseline characteristics subgrouped by cardiac uptake on scintigraphy.

	Grade 0 (n = 177)	Grade 1 (n = 8)	Grade 2-3 (n = 39)	All (N = 224)	p value
Men, n (%)	107 (60)	6 (75)	33 (85)	146 (65)	0.01
Age, median (IQR), yrs	75 (69-81)	85 (80-89)	81 (77-86)	74.5 (70-83)	< 0.0001
Medical history, n (%)					
Hypertension	106 (60)	4 (50)	24 (62)	134 (59)	0.85
Ischaemic heart disease	47 (27)	1 (13)	9 (23)	57 (25)	0.78
Atrial fibrillation or atrial flutter	81 (46)	7 (88)	24 (62)	112 (50)	0.02
Diabetes mellitus	28 (16)	0	8 (21)	36 (16)	0.40
Carpal tunnel syndrome	7 (4)	2 (25)	9 (23)	18 (8)	0.0002
Spinal stenosis	9 (5)	0	6 (15)	15 (7)	0.06
Pacemaker	24 (14)	1 (13)	11 (28)	36 (16)	0.08
Implantable cardioverter defibrillator	8 (5)	0	0	8 (4)	0.50
Symptoms, n (%)					
Dyspnoea	109 (62)	6 (75)	29 (74)	144 (64)	0.30
NYHA III-IV	19 (11)	1 (13)	9 (23)	29 (13)	0.11
Chest pain	41 (23)	1 (13)	6 (15)	48 (21)	0.60
Palpations	10 (6)	0	2 (5)	12 (5)	1.00
Peripheral oedema	34 (19)	3 (38)	14 (36)	51 (23)	0.04
Dizziness	25 (14)	1 (13)	3 (8)	29 (13)	0.60
Syncope	6 (3)	1 (13)	3 (8)	10 (4)	0.11
ECG, n (%)					
Sinus rhythm	109 (64)	2 (25)	9 (24)	120 (54)	< 0.0001
Atrial fibrillation	47 (28)	6 75)	19 (50)	72 (32)	0.0009
Low voltage	13 (7)	3 (38)	2 (5)	18 (8)	0.03
Hypertrophy	33 (19)	1 (13)	0	34 (15)	0.003
Transthoracic echocardiography					
Left ventricular ejection fraction, median (IQR), %	50 (40-60)	55 (48-60)	45 (30-50)	50 (40-60)	0.003
Interventricular septum in diastole, median (IQR), mm	14 (12-16)	13 (11-16)	15 (12-17)	14 (12-16)	0.08
Left atrial volume index, median (IQR), ml/m^2	40 (28-52)	49 (46-50)	43 (29-54)	42 (28-52)	0.25
Elevated e'[a], n (%)	168 (95)	8 (100)	39 (100)	215 (96)	0.54
Tricuspid valve regurgitation gradient, median (IQR), mmHg	27 (31-33)	33 (31-41)	28 (20-38)	28 (21-33)	0.15
Aortic stenosis[b], n (%)	32 (19)	1 (14)	3 (9)	36 (16)	0.34
Pericardial effusion, n (%))	10 (6)	0	1 (3)	11 (5)	0.80
Biochemistry					
Elevated troponin[c], n (%)	61 (34)	4 (50)	20 (51)	85 (38)	0.12
Pro-BNP, median (IQR), pmol/l	117 (43-413)	342 (165-6,929)	453 (158-1,510)	161 (54-556)	0.0006
Creatinine, median (IQR), mmol/l	87 (70-107)	96 (83-127)	100 (84-131)	99 (72-110)	0.004
Abnormal free light chain ratio[d], n (%)	32 (25)	2 (29)	6 (17)	40 (24)	0.60
Monoclonal protein component in plasma, n (%)	17 (13)	1 (20)	7 (21)	25 (15)	0.50
Monoclonal protein component in urine, n (%)	4 (10)	0	0	4 (7)	0.40
Abnormal free light chain ratio or monoclonal protein in plasma or urine, n (%)	39 (29)	3 (43)	10 (29)	52 (30)	0.70

BNP = brain natriuretic peptide; ECG = electrogardiogram; NYHA = New York Heart Association Classification.
a) Septal < 7 or lateral < 10.
b) Defined as gradient > 2.5 m/sec.
c) Troponin T > 14 ng/l, troponin I > 45 ng/l.
d) Free light chain ratio < 0.26 or > 1.65.

Haematological tests: FLC was measured in 171 patients (76%), SPIE in 167 patients (75%) and UPIE in 58 patients (26%), see Table 1 and **Table 2**. According to the diagnostic algorithm, all patients with bone scintigraphy grade 0 and abnormal haematological tests were intended to undergo cMRI; however, only 31/39 completed a cMRI. The lack of full implementation was due to patient decline and patients who were too sick to participate or had magnetic material implanted. Some of the patients may have had a cMRI on other indications, e.g. diagnostic workup of cardiomyopathy. All patients were referred for specialised haematologic follow-up. In the 31 patients with grade 0 uptake and a cMRI, two patients showed an elevated T1 value, and seven patients had abnormal gadolinium kinetics (one also with high T1 values). Five of the eight patients with either elevated T1 or abnormal gadolinium kinetics had a myocardial biopsy performed; all were negative for amyloid and

therefore not diagnosed with CA.

TABLE 2 Baseline characteristics according to diagnosis.

	Amyloidosis (n = 43)	No amyloidosis (n = 181)	p value
Men, n (%)	36 (84)	110 (61)	0.004
Age, median (IQR), yrs	81 (77.0-86.0)	75 (69.0-81.0)	0.0002
Past history, n (%)			
Hypertension	26 (60)	108 (60)	1
Ischaemic heart disease	9 (21)	48 (27)	0.6
Atrial fibrillation, atrial flutter	25 (58)	87 (48)	0.3
Diabetes mellitus	9 (21)	27 (14)	0.4
Carpal tunnel syndrome	10 (23)	8 (4)	< 0.0001
Spinal stenosis	6 (14)	9 (5)	0.03
Polyneuropathy	3 (7)	10 (5)	0.70
Pacemaker	12 (28)	24 (13)	0.03
Implantable cardioverter defibrillator	0	8 (4)	0.40
Symptoms, n (%)			
Dyspnoea	31 (72)	113 (62)	0.03
NYHA III-IV	9 (21)	20 (47)	0.08
Chest pain	6 (14)	42 (23)	0.22
Palpations	2 (5)	10 (6)	0.81
Peripheral oedema	15 (35)	36 (20)	0.04
Dizziness	4 (9)	25 (14)	0.43
Syncope	4 (9)	6 (3)	0.09
ECG, n (%)			
Sinus rhythm	12 (29)	108 (62)	0.0001
Atrial fibrillation	20 (48)	52 (30)	0.30
Low voltage	3 (7)	15 (8)	1.00
Hypertrophy	0	34 (19)	0.0006
Transthoracic echocardiography			
Left ventricular ejection fraction, median (IQR), %	45 (30-55)	50 (40-60)	0.01
Interventricular septum in diastole, median (IQR), mm	15 (12-17)	14 (12-16)	0.02
Left atrium volume index, median (IQR), ml/m^2	43 (31-52)	41 (28- 52)	0.50
Elevated e'[a], n (%)	43 (100)	172 (95)	0.21
Tricuspid valve regurgitation gradient, median (IQR), mmHg	28 (20-35)	27.5 (21-33)	0.60
Aortic stenosis[b], n (%)	3 (8)	33 (19)	0.15
Pericardial effusion, n (%)	1 (3)	10 (7)	0.37
Biochemistry			
Elevated troponin[c], n (%)	22 (51)	63 (35)	0.047
Pro-BNP, median (IQR), pmol/l	450 (158-973)	121 (42-478)	0.0003
Creatinine, median (IQR), mmol/l	101 (84-131)	87 (70-105)	0.001
Free light chain ratio in abnormal range[d], n (%)	9 (23)	31 (23)	0.95
Monoclonal protein component in plasma, n (%)	18 (14)	7 (19)	0.40
Monoclonal protein component in urine, n (%)	0	4 (9)	0.22
Abnormal free light chain ration or monoclonal protein in plasma or urine, n (%)	13 (33)	39 (28)	0.6

BNP = brain natriuretic peptide; ECG = electrogardiogram; NYHA = New York Heart Association Classification.
a) Septal < 7 or lateral < 10.
b) Defined as gradient > 2.5 m/sec.
c) Troponin T > 14 ng/l, troponin I > 45 ng/l.
d) Free light chain ratio < 0.26 or > 1.65.

Myocardial biopsy: Three patients with grade 0 uptake had a myocardial biopsy taken. All were without amyloid, and the patients were, therefore, not diagnosed with CA. One of the three patients with grade 1 uptake and positive FLC/ SPIE/UPIE had a myocardial biopsy taken, which was also without amyloid.

In total, 43 patients were diagnosed with CA, including both ATTR and AL amyloidosis, leading to a prevalence of 19.2% in the selected population. Please see Figure 2 for CA according to the scintigraphy results. Table 2 presents baseline characteristics for patients with versus without CA.

The patients with CA were significantly older (81 versus 75 years old, p = 0.0002) and more often males (84% versus 61%, p = 0.004). A significantly higher percentage of the patients with CA had a previous history of carpal tunnel syndrome (p < 0.0001) and spinal stenosis (p = 0.03). The clinical examination showed a higher percentage of peripheral oedema (p = 0.04), atrial fibrillation (48% vs 30%, p = 0.03) and left ventricular hypertrophy ((IVSd) – 15 mm vs 14 mm, p = 0.02) among the patients with CA compared to the screened patients without CA. The biochemistry tests revealed a significantly higher percentage of patients with elevated troponin (51% versus 35%, p = 0.047) and a significantly higher level of pro-brain natriuretic peptide (pro-BNP) (450 pmol/l versus 121 pmol/l, p = 0.0003) among patients with CA.

Among the 43 patients diagnosed with CA, 39 patients (91%, mean age 80.6 ± 8.3 years) were found to have ATTR-CA. Genetic tests were performed in 30 patients, one of whom had ATTRv; a female aged 66 years, and therefore actually younger than the target patients for the diagnostic algorithm (> 70 years for women). The remaining four patients had AL amyloidosis (mean age 74.5 ± 15.9 years, 50% males). One patient diagnosed with ATTR-CA had concurrent MGUS. Two patients never completed the full diagnostic algorithm; both had a bone scintigraphy with a cardiac uptake of grade 2-3. The National Amyloidosis Centre (NAC) stages for the 39 patients with ATTR-CA were as follows: 22 patients in NAC stage 1, ten patients in NAC stage 2, and two patients in NAC stage 3.

Only one patient with grade 1 cardiac uptake on scintigraphy (normal FLC and negative SPIE/UPIE) was diagnosed with ATTRwt (Figure 2). A cardiac biopsy was never performed to confirm the diagnosis as the patient opted out of the clinical follow-up. However, the history and clinical evaluation of the patient revealed several red flags for CA.

Discussion

This study shows the feasibility of introducing a non-invasive diagnostic algorithm for CA. In recent years, new improved treatment strategies have been introduced, making the diagnosis of CA even more important to ensure that relevant patients receive treatment.

The present retrospective study found that in a population of elderly suspected of CA based on the findings of left ventricular hypertrophy and diastolic dysfunction, a systematic algorithm found a 19% prevalence of CA with a high ratio of ATTR-CA. The most frequent type of CA in the presented data was ATTRwt (88%). Only one patient had ATTRv (2% of the patients with CA), and AL-CA was found in 9% (four patients) of all patients with CA. Since the study only reviewed patients included in the algorithm, the true prevalence of ATTR-CA in the catchment population remains unknown. AL-CA may have been underdiagnosed since 24% of the patients had missing haematological tests.

The prevalence of CA in our study is thought to be comparable to the results of previous studies. Thus, among patients with heart failure with preserved ejection, the prevalence of ATTR-CA was shown to be 13-17%, and autopsy studies have shown the same prevalence to be 20-25% in octogenarians [11-13]. The patients with CA in our cohort aligned with the usual presentation of CA; They were older, more often male, had thicker ventricular wall thickness and higher myocardial biomarkers [3, 14, 15].

In the present population, two out of eight patients with grade 1 uptake of cardiac tracer on bone scintigraphy were diagnosed with CA, one of whom with ATTR-CA. This highlights the importance of referring such patients for cMRI and/or myocardial biopsy, as illustrated by the applied diagnostic algorithm. Similarly, one case of AL-CA was found in the group with grade 2-3 cardiac uptake, illustrating the importance of haematological screening in all patients. In the present study, haematological tests were missing in 24% of the patients for unknown causes, which may have produced underdiagnosis of AL-CA.

One substantial caveat of screening patients for monoclonal haematological disease is the high prevalence of abnormal findings. Among patients who were not diagnosed with AL amyloidosis, we found a 22% prevalence of any monoclonal abnormality, which is higher than results from previous studies with a 3-6% prevalence of MGUS among patients older than 50 years [16].

We want to stress how important the clinicians' awareness of CA is and highlight the awareness of diagnostic tools for CA. To find all patients, a setup should be in place where referral for screening for CA follows a single and simple pathway. The algorithm used in this study to determine when to suspect and how to diagnose CA is highly comparable to a diagnostic algorithm in a recently published statement paper by the ESC Working Group on Myocardial and Pericardial Disease [4]. However, our data highlight the issues with creating a clinical setting in which all necessary tests and referrals are routinely incorporated into clinical practice.

With increasing awareness of CA and more feasible diagnostics, the prevalence of ATTR-CA, in particular, is likely to increase in the coming years.

Over the past decade, not only has awareness increased, but progress has also been made in the treatment of CA. New treatment options have been developed, halting and delaying amyloid deposition, which is expected to play an essential role in the future treatment of CA [4]. However, in the presented study period, tafamidis was not yet reimbursed for patients with ATTRwt in Denmark, which was reflected in the data showing only one patient with ATTRv receiving active treatment (tafamidis).

The results of the study were limited by the retrospective design of the study. Furthermore, patients were only referred for the diagnostic workup if the physicians suspected CA - and there may therefore have been borderline cases where patients were not referred. Only three-fourths of the patients underwent haematologic screening, which might have underestimated the prevalence of CA and MGUS. Not all patients had genetic testing, which may have underdiagnosed ATTRv. Data demonstrating how many patients met the criteria for enrolment in the diagnostic algorithm but were not referred are unavailable and would have been informative.

Conclusions

A standard algorithm for when to suspect CA is useful and feasible in a routine clinical setting. Furthermore, we confirm that CA has a relatively high 19% prevalence in a selected population of elderly patients with ventricular hypertrophy and signs of diastolic dysfunction.

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References can be found with the article at ugeskriftet.dk/dmj

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