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Prior Carpal Tunnel Syndrome and Early Concomitant Echocardiographic Findings Among Patients with Cardiac Amyloidosis

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Abstract

We aimed to characterize patients with systemic amyloidosis stratified by a prior diagnosis of carpal tunnel syndrome (CTS) and to describe early echocardiographic parameters concomitant with CTS. Patients with suspected amyloidosis during CTS diagnosis were excluded. Our cohort included 108 patients with systemic amyloidosis of which 36% had a prior CTS at a median of 4 (IQR 2.8, 6.7) years before disease diagnosis. Patients with prior CTS were more likely to present subsequently with cardiac amyloidosis (78% versus 53%, p =0.013), yet overall survival was comparable between groups (53% versus 61%, p=0.825). Prior CTS was more commonly diagnosed in subsequent transthyretin (ATTR) patients (62%) than in immunoglobulin light chain (AL) patients (24%; p <0.001). Furthermore, in a sub-analysis of patients subsequently diagnosed with cardiac amyloidosis, findings at CTS diagnosis (n=17) demonstrated a mild increase in septal thickness 1.3 (IQR 1.2, 1.5) cm, increased relative wall thickness 0.46 (IQR 0.45, 0.58) and increased left ventricular mass index 155 (IQR 92, 177) grams/m^2 compared to age-adjusted normal range echocardiographic values. Doppler mitral flow data was supportive of left ventricular diastolic dysfunction. In conclusion, early echocardiographic findings at CTS diagnosis, preceding the diagnosis of cardiac amyloidosis in several years, are suggestive of increased wall thickness and diastolic dysfunction.

Introduction

The cardiac infiltration of either immunoglobulin light chain (AL) or amyloid transthyretin (ATTR) is responsible for the majority of cases of cardiac amyloidosis (CA). Amyloid-induced cardiomyopathy results from the cytotoxic circulating amyloid oligomers and amyloid fibrils, which distort the structure of the cardiac tissue causing impaired contractility [1, 2]. Unfortunately, the prognosis for AL and ATTR is poor, partially due to the high frequency of late-diagnosis and misdiagnosis of these patients, leading to established organ dysfunction by the time the correct diagnosis is made [3]. Early diagnosis is even more important nowadays due to availability of therapies for ATTR which prevent the deposition of amyloid oligomers [4, 5] rather than targeting already existing amyloid deposits. In AL, novel agents (proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, venetoclax) and autologous stem cell transplantation, all used for eliminating the underlying plasma cell clone, have shown promising results in improving clinical outcomes. However, the prognosis for patients with advanced cardiac involvement at presentation is still grave.

Amyloid deposits have been reported in the flexor tenosynvium and transverse carpal ligament of the hand [6-9], and carpal tunnel syndrome (CTS) was associated with a future diagnosis of systemic amyloidosis in a large cohort of patients who underwent surgical repair [10]. The recognition that CTS often precedes the diagnosis of systemic amyloidosis [11], raises the potential for early diagnosis and timely treatment of the latter. Descriptive echocardiographic data at CTS diagnosis are lacking.

In this study we aimed to characterize a cohort of patients diagnosed with systemic amyloidosis (AL or ATTR) stratified by the presence of prior CTS. Furthermore, by

focusing our analysis on patients with CTS subsequently diagnosed with CA we aimed to explore the possibility that echocardiographic features at the time of prior CTS diagnosis are suggestive of early cardiac amyloid involvement.

Materials and Methods

Study population- The population of the current study was comprised of consecutive AL and ATTR patients treated at our institution (Rabin Medical Center, Israel) between the years 2008-2018. For all patients, electronic medical records, echocardiographic and nuclear scintigraphy scans were reviewed.

The diagnosis of AL was made in the presence of a monoclonal protein (identified by serum and urine protein immunofixation plus serum free light chain assay) and histological evidence of amyloid deposition in tissue biopsy by Congo red staining. Further protein analysis confirming light chain deposits was performed by immunohistochemistry [12]. Mass spectrometry proteomic analysis was undertaken in selected cases. Cardiac amyloid involvement in AL was based on either cardiac magnetic resonance (CMR) imaging or endomyocardial biopsy (EMB). Only patients who were considered by their caring physician unsuitable to undergo CMR (either due to the presence of magnetic resonance incompatible electrical device or claustrophobia) or EMB (high-risk patients) had the diagnosis of CA based solely on echocardiographic features (concentric hypertrophy and diastolic dysfunction), as previously reported [11, 13]. The diagnosis of ATTR was established based on either (1) an EMB with confirmed amyloid deposits via Congo red staining with further subtyping, or, (2) a technecium pyrophosphate nuclear scintigraphy (99mTc-PYP) with myocardial tracer uptake analysis using the semi-quantitative visual score ($\geq$2) and the quantitative heart to contralateral ratio $\geq$1.5 [14, 15]. The exclusion of light

chain monoclonality by serum free light chain and serum and urine immunofixation was mandatory in all patients diagnosed with ATTR [15]. Following a histological or non-invasive diagnosis of ATTR, all patients underwent TTR genetic testing to differentiate between mutant ATTR and wild-type ATTR.

The diagnosis of prior CTS was based on the documentation of either CTS release surgery, a positive electromyography study or a clinical diagnosis by a hand surgeon. We reviewed factors possibly contributing to the development of idiopathic CTS in order to evaluate possible confounders [16].

Study exclusion criteria- Patients were excluded from this study if the diagnosis of AL or ATTR was questionable based on the above criteria. We also excluded patients who were diagnosed with CTS during an evaluation for already suspected systemic amyloidosis or after an established diagnosis.

Echocardiographic analysis- We analyzed the resting echocardiographic parameters of patients with CA and a prior diagnosis of CTS by screening the electronic database for examinations performed at 2 different time-points: (i) at CTS diagnosis and (ii) at the initial diagnosis of systemic amyloidosis. Referral echocardiography indications at CTS diagnosis were reviewed in order to exclude patients undergoing an evaluation for already suspected cardiomyopathy. The left atrial and ventricular diameters and left ventricular (LV) ejection fraction (LVEF) were obtained according to accepted guidelines [17]. Right ventricular (RV) function was evaluated qualitatively by visual assessment [18]. Relative wall thickness (RWT) was calculated as 2 times left posterior wall diastolic thickness divided by LV diastolic diameter [17]. LV mass was calculated according to the Devereux formula [19]: 1.04 ((LV diastolic diameter + interventricular septal diameter + LV posterior wall diastolic thickness)^3- (LV diastolic diameter^3)-13.6. The pulmonary artery

systolic pressure was derived from summing up the peak velocity of the tricuspid regurgitation jet and the systolic right atrial pressure. Cut-offs for defining abnormalities in these variables in comparison to the age-adjusted values in the general population were chosen according to published reference guidelines [17, 20-24]. LV diastolic function was assessed by recording mitral flow with standard pulsed Doppler technique, and measurements of early diastolic peak flow velocity (E), late diastolic peak flow velocity (A) and the ratio of early to late flow velocity peaks (E/A ratio) [25]. We graded LV diastolic function in the absence of more than mild mitral regurgitation as followed: Grade 1 (impaired relaxation pattern), E/A ratio <0.8; Grade 2 (pseudo-normal pattern), E/A ratios between 0.8 and 2; Grade 3 (restrictive pattern), E/A ratio> 2 [20, 25].

Mortality during follow-up was determined for all patients through the Israeli National Population Registry. Patient management was at the discretion of the attending physicians. The study protocol was approved by our Institutional Review Board.

Statistical analysis- The statistical analysis for this paper was generated using SAS Software, Version 9.4 (SAS Institute Inc., Cary, NC). Continuous variables were presented by median and interquartile 25th, 75th range. Categorical variables were presented by (N, %). T-Test was used to compare the value of continuous variables, which were deemed to have a normal distribution between study groups and the Wilcoxon test was used for non-normal variables. Chi-Square (for more than two categorical values) or Fisher's exact test (for two categorical values) were used to compare the value of categorical variables between study groups. Univariate Odds Ratios (OR) were evaluated by logistic regression The cumulative incidence of death

during study follow-up was assessed by Kaplan-Meier survival analysis, with the log-rank test. Two sided p values less than 0.05 were considered statistically significant.

Results

Study population

In total, 112 patients with systemic amyloidosis were identified during the study period. Four patients were excluded due to suspected or confirmed amyloidosis at time of CTS diagnosis. Therefore, our study population included 108 patients of whom 82 (76%) had AL and 26 (24%) had ATTR. Cardiac amyloid involvement was diagnosed in 61% (n=66) of patients with systemic amyloidosis (**Table 1**). Among the 82 patients with AL, 41 (50%) had cardiac involvement as determined by one or more modality: CMR (n=29), EMB (n=8) or echocardiography (n=7). Among the 26 patients with ATTR, 25 (96%) had cardiac involvement as determined by one or more modality: technetium pyrophosphate scan (n=19), CMR (n=17) or EMB (n=1). Twenty patients had wild-type ATTR and 6 had hereditary ATTR**.** The median age for the diagnosis of systemic amyloidosis was 68 (25th, 75th interquartile (IQR) range 61, 78) years with male predominance (**Table 2**).

CTS in patients subsequently diagnosed with systemic amyloidosis

Prior CTS was diagnosed in 33% (n=36) of patients with systemic amyloidosis. Patients' characteristics stratified by a diagnosis of prior CTS are presented in **Table 2**. The median age for the diagnosis of CTS was 63 (IQR 56, 73) years, approximately 4 (IQR 2.8, 6.7) years before the diagnosis of systemic amyloidosis. The prevalence of diabetes mellitus and hypothyroidism, both common etiologies for the development of idiopathic CTS, were 14% and 3%, respectively.

Prior diagnosis of CTS was more prevalent in the group of patients with ATTR compared to patients with AL (62% versus 24%, respectively, p <0.001) (**Figure 1**). A non-statistically significant trend (p =0.09) for a longer time lag from the diagnosis of CTS to systemic amyloid disease was noted in patients with ATTR versus AL.

The rate of cardiac amyloid involvement was higher in patients with a prior diagnosis of CTS versus patients without prior CTS (78% vs. 53%, OR 3.1, 95% CI 1.3-7.8), p=0.013, **Table 2**). However, the cumulative incidence of survival (53% of patients with prior CTS versus 61% of patients with no prior CTS, p=0.825, **Figure 2**) and the time interval from the diagnosis of systemic amyloidosis to death were comparable between patients with or without prior CTS.

CTS in patients subsequently diagnosed with CA

We performed a separate analysis which included only CA patients with a prior diagnosis of CTS (n=28, **Figure 3**). Stratified by the misfolded amyloid protein, the rates of cardiac amyloid involvement were 60% (12/20) in the AL subgroup and 100% (16/16) in the ATTR subgroup (**Table 1**). The different modalities used to determine cardiac amyloid involvement are presented in **Figure 3**. We did not found an association between a diagnosis of prior CTS and the subsequent development of CA in AL patients (OR 1.7, 95% CI 0.6-4.8, p=0.441). All patients with ATTR and prior CTS diagnosis subsequently presented with CA, thus, OR was not calculated in this subgroup.

Echocardiographic findings at CTS diagnosis

We evaluated early echocardiographic features at CTS diagnosis preceding the diagnosis of CA (**Table 3**). Sixty-one percent (17/28) of patients with CA and a prior

diagnosis of CTS underwent echocardiography at a median of 1.6 (IQR -3, +10) months from time of CTS diagnosis. The referral indications for echocardiography are presented in **Supplementary Table 1**. At the diagnosis of CTS, patients had normal biventricular systolic function expressed as median LVEF 60 (IQR 60, 60)% with no evidence of RV dysfunction by visual assessment. Median wall thickness was 1.1 (0.9, 1.4) cm in the posterior wall and 1.3 (IQR 1.2, 1.5) cm in the intraventricular septum. The latter was abnormally increased as compared to published reference standards [17, 20]. The incidence of diabetes mellitus, hypertension and significant aortic stenosis, all possible competing etiologies for the echocardiographic phenotype of concentric hypertrophy are presented in **Supplementary Table 2**. Importantly, median wall thickness at time of CTS diagnosis remained increased (septum 1.4 (IQR 1.2, 1.6) cm, posterior wall 1.4 (IQR 1.0, 1.5) cm) in the 11 patients without these comorbidities. LV mass (234 (IQR 177, 292) grams) and LV mass index (155 (IQR 92, 177) grams)/m^2) were moderately increased at CTS diagnosis as compared to published reference standards [17, 22]. We also observed an increase in the relative wall thickness (0.46 (0.45, 0.58)) at CTS diagnosis, altogether compatible with LV concentric hypertrophy [17]. Doppler mitral flow evaluation at CTS diagnosis demonstrated impaired relaxation (Grade 1 LV diastolic dysfunction) in 40% of patients, and pseudo-normal or restrictive pattern (Grade 2 or Grade 3 LV diastolic dysfunction) in 60% of patients (**Figure 4**). Diastolic dysfunction was further supported by an increased left atrial area. Doppler mitral flow evaluation was missing in 41% of the echocardiographic exams performed (7/17 exams; one patient had atrial fibrillation during the examination, Doppler mitral flow evaluation was not pursued in the other 6 patients).

Echocardiographic findings at the diagnosis of amyloidosis

Echocardiographic features obtained at the subsequent diagnosis of systemic amyloidosis are presented in **Table 3** and **Figure 4**. At disease diagnosis, we found a significant increase in wall thickness relative to values obtained at CTS diagnosis with median posterior wall thickness of 1.5 (IQR 1.3, 1.6) cm and septal wall thickness of 1.4 (IQR 1.2, 1.6) cm. Similarly, we observed a significant increase in both LV mass index (292 (IQR 243, 342)grams/m^2) and RWT (0.65 (IQR 0.58, 0.79)). Moreover, LV diastolic function further deteriorated showing Grade 2 or Grade 3 diastolic patterns in 72% of patients. Interestingly, at the diagnosis of amyloidosis we observed a mild LV systolic impairment (median LVEF 55 (IQR 47, 60)%) and RV systolic dysfunction was present in 19% of patients. Moreover, systolic pulmonary artery pressures were elevated (37 (27, 42) mmHg) and a higher rate of patients (29%) presented with moderate or severe tricuspid regurgitation compared to values obtained at CTS diagnosis.

Discussion

This study evaluated the incidence of prior CTS diagnosis as well as concomitant echocardiographic parameters in a cohort of patients with systemic amyloidosis comprised of both AL and ATTR patients. We found that: (1) CTS is a common finding (62%) in ATTR, and to a lesser extent AL (24%), and precedes the diagnosis of systemic amyloidosis by a median of 4 years; (2) Early echocardiographic findings concomitant with CTS diagnosis demonstrate increased wall thickness, LV mass and LV diastolic dysfunction.

The association between CTS and systemic amyloidosis, particularly ATTR, is not novel, yet the reported prevalence range vary [2, 3, 26]. We demonstrated that prior CTS was found in 33% of patients with systemic amyloidosis with even higher rate in the subgroup of patients with ATTR (62%) preceding the diagnosis of systemic disease in a median of 4 (IQR 2.8, 6.7) years. These findings are in agreement with the study published by Nakagawa et al. which described CTS as the most common initial symptom in 55% of patients with ATTR [27]. Importantly, prior CTS was diagnosed in 24% of our AL cohort several years before the diagnosis of systemic disease. Although CTS is a much less common manifestation of AL compared to ATTR it was evident in a substantial number of AL patients, as reported here and by others [26, 28, 29]. Taking together the rapidly progressive nature of AL and the prognostic significance of cardiac involvement in the disease [2], early recognition of CTS in these patients may pave the way for an earlier diagnosis of AL, thus possibly allowing a change in disease course. A recent study by Milandri et al. [30] which evaluated the prevalence of CTS in an Italian population of amyloid patients reported a much lower prevalence of CTS among patients with systemic amyloidosis and among the sub-populations of ATTR and AL patients (12% (55/469), 18% (50/273) and 3% (5/196), respectively). This discrepancy may resulted from reporting bias and the different definitions used for CTS diagnosis (CTS release surgery was the defining criteria in the latter and was only performed in 69% of patients with prior CTS in our study).

A possible mechanistic association between CTS and the development of CA in patients with systemic amyloidosis has been recently suggested by demonstrating that CTS is an incremental risk factor for cardiac involvement in ATTR [30]. This

finding is limited by the fact that wild-type ATTR patients and a substantial rate of hereditary ATTR patients ("cardiogenic mutations") invariably present with cardiac involvement regardless of CTS diagnosis [3, 31]. Accordingly, although an association between prior CTS and CA was established in the overall systemic amyloidosis cohort of our study, such association was not demonstrated in the sub-population of AL patients. Thus, it is likely that CTS is an early manifestation of amyloid deposition rather than an independent risk factor for cardiac involvement.

Nevertheless, the early diagnosis of CTS often years before the diagnosis of systemic and cardiac amyloidosis gives rise to questions regarding possible early cardiac amyloid involvement. In a recent prospective study by Zegri-Reiriz et al. who investigated the prevalence of CA in patients who underwent CTS surgery the prevalence of concomitant CA was relatively low (1.2%) [32]. However, the cohort included mainly female patients, while, as shown here and by others [2, 3, 26], CA is characterized by male predominance (ATTR>AL). In another recent work done by Sperry and colleagues which described a cohort of 98 patients who underwent surgical repair for CTS [29], 10% were diagnosed with positive-stained amyloid biopsies of the tenosynovium, and 2 of these patients were found to have previously unknown CA (2% prevalence). However, since cardiac evaluation was only performed in those with positive-stained amyloid, the true prevalence and extent of concomitant cardiac amyloid involvement may have been underestimated due to caveats of limited tissue sample and low biopsy yield [33]. Herein, by retrospectively reviewing a cohort of patients with confirmed CA, we were able to investigate early echocardiographic findings concomitant with CTS diagnosis. A recently published study by Boldrini et al. [21] described the development of multiparametric scores to

diagnose CA in patients with AL or in those with increased heart wall thickness suspected for amyloidosis. In both groups of patients the presence of CA was characterized by greater wall thickness and LV mass, greater extent of concentric remodeling and higher degree of diastolic dysfunction. In our cohort of subsequently diagnosed CA patients we found an increase in wall thickness and a higher prevalence of abnormal diastolic function at CTS diagnosis relative to the age-adjusted general population. These findings, which were detected several years before the diagnosis of systemic amyloidosis, potentially match the earlier stages of CA and may help shed new light on the natural history of cardiac amyloid involvement. Nevertheless, as our study lacks further support to this hypothesis by other imaging modalities or cardiac tissue histology, it merits further validation.

The remaining questions involve the characterization of the CTS patient in whom the diagnosis of amyloidosis should be further investigated. First, idiopathic CTS has two peak frequencies: the first and higher of them between 45 and 59 years of age; and the second between 75 and 84 years [16]. As shown, the median age for CTS diagnosis in patients who subsequently develop amyloidosis is 63 (IQR 56, 73) years, thus possibly allowing to define age screening criteria. Second, as opposed to the common female phenotype of idiopathic CTS (65-75%) [16], we show that the majority of patients with CTS who were subsequently diagnosed with amyloidosis were male. Third, as reported by others [26, 32], bilaterality of CTS is another red-flag for the subsequent diagnosis of amyloidosis. A proposed algorithm for the consideration of a tenosynovial biopsy at time of CTS release surgery has been suggested [29]. We believe that our findings, and dependent upon their future validation in larger-scale studies, support the incorporation of an echocardiography

examination to this algorithm. Moreover, the addition of CA biomarkers, specifically troponin and pro-brain natriuretic peptide (pro-BNP) should also be evaluated.

Limitations: First, our study is limited by its relatively small sample size and single center nature potentially limiting generalizability. Second, protein analysis confirming light chain deposits was mostly performed by immunohistochemistry, which can be misleading due to both low sensitivity and specificity [34]. Mass spectrometry was not in routine use in our Institute throughout most of the study observation period. Third, echocardiographic exams during CTS diagnosis were not performed in 39% of our CA cohort allowing a possible selection bias. This gap was due to the retrospective nature of the study. Fourth, although all patients' echocardiography exams were available for the extraction of data, echocardiographic reports were incomplete. Moreover, the spectrum of echocardiographic parameters used to assess cardiac amyloid involvement and diastolic dysfunction was limited in the current study due to its retrospective nature and the fact that specific evaluation techniques such as global longitudinal strain were not in routine use at the time of CTS diagnosis. However, the primary parameter used, the increased trans-mitral flow, was supported by confirming the absence of significant mitral disease and an increased left atrial size. Fifth, several echocardiographic findings at CTS diagnosis such as increased wall thickness could potentially be explained by other comorbidities such as hypertension. However, a separate analysis which excluded patients with diabetes and hypertension from the cohort demonstrated similar findings. Finally, a possible bias could result if the initial indication for performing echocardiographic examination was due to already suspected systemic amyloidosis. However, we

carefully reviewed the electronic medical records of the study patients and excluded patients with clinically suspected CA.

In conclusion, this study described a high prevalence of prior CTS in patients with amyloidosis, particularly ATTR, several years before disease diagnosis, and identified echocardiographic features that potentially match the early stages of CA. Larger-scale studies are warranted in order to confirm our findings and to further define the diagnostic yield of incorporating echocardiography exams in the assessment of patients with CTS. Increased awareness for the possibility of systemic amyloidosis in patients presenting with CTS and abnormal echocardiographic findings may pave the way for early diagnosis and treatment.

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Figure legends

Figure 1: Study population of systemic amyloidosis

A flow-chart of patients with systemic amyloidosis stratified by their misfolded amyloid protein and by the diagnosis of prior CTS. Time intervals between CTS diagnosis and systemic amyloidosis diagnosis are also presented for each amyloid sub-population (median (25th, 75th IQR) years).

Abbreviations: AL, immunoglobulin light-chain; ATTR, amyloid transthyretin; CTS, carpal tunnel syndrome

* we excluded patients with an established diagnosis of amyloidosis or under the evaluation of cardiomyopathy during CTS diagnosis (n=4)

Figure 2: Kaplan-Meier curve of 10-year survival of patients with systemic amyloidosis stratified by prior CTS diagnosis.

Abbreviations: CTS, carpal tunnel syndrome.

Figure 3: Study population of cardiac amyloidosis and prior CTS

Flow-chart of patients with systemic amyloidosis and prior CTS stratified by their misfolded amyloid protein and by amyloid cardiac involvement. The modalities used to confirm cardiac involvement are presented for each subgroup of amyloidosis patients (N (%)).

Abbreviations: AL, immunoglobulin light-chain; ATTR, amyloid transthyretin; CMR; cardiac magnetic resonance; CTS, carpal tunnel syndrome; EMB, endomyocardial biopsy; TTE, trans-thoracic echocardiography.

Figure 4: Diastolic function during CTS diagnosis and at systemic amyloidosis

diagnosis

Diastolic function graded by pulsed-Doppler mitral flow assessment in the population

of patients with CA and prior CTS at (A) CTS diagnosis and at (B) systemic

amyloidosis diagnosis.

Abbreviations: CA, cardiac amyloidosis; CTS, carpal tunnel syndrome.

*Doppler mitral flow evaluation was only available for 10/17 (58%) of

echocardiographic exams

Table 1: Rates of CA in the different amyloidosis subtype populations

	All patients	**AL**	**ATTR**
Amyloidosis	66/108 (61%)	41/82 (50%)	25/26 (96%)
Amyloidosis and prior CTS	28/36 (78%)	12/20 (60%)	16/16 (100%)

Data are presented as Number (percentages).

Abbreviations: AL, immunoglobulin light-chain; ATTR, amyloid-transthyretin; CA, cardiac amyloidosis; CTS, carpal tunnel syndrome.

Table 2: Characteristics of patients with systemic amyloidosis stratified by a prior diagnosis of CTS

	All amyloidosis patients (n=108)	Amyloidosis patients with **no prior CTS** (n=72)	Amyloidosis patients **with prior CTS** (n=36)	**p-value**
Age at systemic amyloidosis diagnosis (years)	68 (61, 78)	68 (62, 76)	68 (60, 80)	0.704
Women (%)	40 (36)	29 (40)	10 (28)	0.288
Cardiac amyloid involvement (%)	66 (61)	38 (53)	28 (78)	0.013
Interval from systemic amyloidosis diagnosis to death (months)	19 (8, 45)	20 (6, 50)	19 (10, 39)	0.401
Age at CTS	NR	NR	63 (56, 73)	

diagnosis (years)				
Interval from CTS diagnosis to systemic amyloidosis (years)	NR	NR	4.3 (2.8, 6.7)	
CTS release surgery (%)	NR	NR	25 (69)	
Diabetes mellitus (%)	NR	NR	5 (14)	
Hypothyroidism (%)	NR	NR	1 (3)	

Data are presented as medians (25th, 75th quartiles) or as percentages, as appropriate.

Abbreviations: AL, immunoglobulin light-chain; ATTR, amyloid-transthyretin; CTS, carpal tunnel syndrome; NR, non-relevant.

Table 3: Echocardiographic findings among patients with CA and prior CTS at CTS diagnosis and at systemic amyloidosis diagnosis

	At CTS diagnosis (n=17)	At systemic amyloidosis diagnosis (n=28)
LVEF (%)	60 (60, 60)	55 (47, 60)
RV dysfunction (%)	0	5 (19)
Posterior wall (cm)	1.1 (0.9, 1.4)	1.5 (1.3, 1.6)
Intraventricular septum (cm)	1.3 (1.2, 1.5)	1.4 (1.2, 1.6)
LVEDD (cm)	4.8 (4.2, 4.8)	4.5 (4.1, 4.6)
LVESD (cm)	3.0 (2.8, 3.2)	3.0 (2.6, 3.3)
RWT	0.46 (0.45, 0.58)	0.65 (0.58, 0.79)
LA area (cm^2)	20 (18, 28)	25 (23, 29)
LV mass (grams)	234 (177, 292)	292 (243, 342)
LV mass index (grams/m^2)	155 (92, 177)	166 (153, 189)
E/A	1.6 (0.8, 2.1)	2.1 (1.6, 3.3)
E/e'	NA	17 (11, 20)
Moderate or severe TR (%)	2 (7)	8 (29)
SPAP (mmHg)	28 (25, 40)	37 (27, 42)

Data are presented as medians (25th, 75th quartiles) or as percentages, as appropriate.

Abbreviations: CA, cardiac amyloidosis; CTS, carpal tunnel syndrome; LA, left atria, LV, left ventricular; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; NA, non-available; RV, right ventricular; RWT, relative wall thickness; SPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.

Systemic amyloidosis (n=108)

n=36	n=72
33%	67%

CTS to amyloidosis interval
5.3 (IQR 3.6, 9.2) years

CTS to amyloidosis interval
4.2 (IQR 2.3, 6.0) years

AL (n=82, 76% amyloidosis cohort)

ATTR (n=26, 24% amyloidosis cohort)

n=10	n=16
38%	62%

n=20	n=62
24%	76%

■ Prior CTS
■ No prior CTS

Systemic amyloidosis patients with prior CTS (n=36)

n=8	n=28
22%	78%

ATTR and prior CTS (n=16)

0	n=16
	100%

AL and prior CTS (n=20)

n=12	n=8
60%	40%

Evaluation for cardiac amyloid involvement:

Scintigraphy = 16
CMR = 11
EMB = 1
TTE only = 0

CMR = 10
EMB = 3
TTE only = 3

Cardiac amyloidosis
No Cardiac amyloidosis