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Screening for Transthyretin Cardiac Amyloidosis in Patients with Bilateral Carpal Tunnel Syndrome: Identifying Missed Opportunities for Early Detection and Treatment

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Abstract

Purpose: Transthyretin cardiac amyloidosis (ATTR-CA) has been linked to many extra-cardiac manifestations including bilateral carpal tunnel syndrome (CTS). The aim of this study is to analyze patients with bilateral CTS to identify patients with high-risk features or "red flags" for ATTR-CA, identify if systematic screening was done for ATTR-CA and define opportunities for improved detection. **Methods:** Out of >5000 patients with bilateral CTS evaluated in a single tertiary care center in Southeast Michigan (2010-2016), we retrospectively studied a focused population of patients: men > 50 years and women > 60 years old with bilateral CTS and atrial fibrillation (n = 295). Baseline demographic, comorbidities, and electrocardiographic and echocardiographic findings were analyzed. A high-risk group suspicious for ATTR-CA was identified as patients with bilateral CTS, atrial fibrillation, and concomitant "red flags" including heart failure and left ventricular hypertrophy. **Results:** Out of 295 patients, 51.2% were female, 75.6% were White, and 22.4% were African American. Upon comparing the high-risk group (n = 67) with the remaining study population (n = 228), both diagnosis of ATTR-CA and mortality were higher among the high-risk group (7.5% vs 0.4% and 43.3% vs 24.6%, respectively, P = 0.003). **Conclusions:** A substantial number of bilateral CTS patients had additional "red flags" warranting formal evaluation for ATTR-CA; however, systematic evaluation for cardiac amyloidosis was not

performed in many patients. This emphasizes that Multidisciplinary collaboration is needed to create a systematic workflow and to raise awareness amongst cardiologists and other physicians for suspecting ATTR-CA in bilateral CTS patients who have additional "red flags".

Keywords

Bilateral Carpal Tunnel Syndrome, Morality, Prevalence, Red Flags, Transthyretin Cardiac Amyloidosis

1. Introduction

Our understanding of cardiac amyloidosis (CA) has substantially evolved over the past decade with new insights into disease prevalence as well as advances in diagnostic and therapeutic strategies. However, CA still remains an under- recognized and under-diagnosed disease, and for many patients, the diagnosis happens late in the process of cardiac involvement. [1] Although CA is still considered rare, it is responsible for significant cardiovascular morbidity and mortality. CA is seen in less than 1 in 200,000 patients in the USA and less than 1 in 2000 patients in Europe. [1] Among the different types of amyloidosis, cardiac involvement is primarily seen in light chain amyloidosis and transthyretin cardiac amyloidosis (ATTR-CA).

Patients with ATTR-CA may present with either a hereditary form (related to mutations in the transthyretin gene) or a non-hereditary age-related protein misfolding form (wild-type). ATTR-CA has been found to coexist alongside many extra-cardiac manifestations, particularly bilateral carpal tunnel syndrome (CTS) and spinal stenosis. [1] It is now recognized that bilateral CTS precedes the onset of cardiac involvement by 5 - 10 years. [2] CTS is also seen in approximately 13% of patients who have heart failure with preserved ejection fraction (HFpEF), 16% of patients with degenerative aortic stenosis (particularly the paradoxical low gradient aortic stenosis subtype), and in almost 25% of autopsies of patients above the age of 85 years. [3] [4] Early identification of ATTR-CA is challenging because the extra-cardiac manifestations that may serve as clues to the presence of disease are not widely appreciated by clinicians, and most patients already have established ATTR-CA at the time of diagnosis. The hereditary form of ATTR-CA has further come into importance with the availability of genetic testing, and increased prevalence of certain mutations such as V14p21 (formerly Val122Ile), which is seen in 3% - 10% of African American patients. [1] Screening patients who are at risk of having ATTR-CA, such as patients with bilateral CTS, and identifying those with the subclinical or early disease could potentially allow timely initiation of specific therapies, such as tafamidis, which is the most beneficial in the early stages of the disease. [5] Also, identifying hereditary ATTR-CA could help with appropriate family counseling and screening. Currently, no guidelines have been established for screening patients who have

bilateral CTS for ATTR-CA.

The aim of this study is to retrospectively analyze patients in our database with bilateral CTS to identify patients with high-risk features or "red flags" for ATTR-CA based on clinical and imaging findings, identify if systematic screening was done for ATTR-CA and define opportunities for improved awareness and early detection.

2. Methods

2.1. Study Design and Population

We performed a retrospective cross-sectional study of older adult patients from a single tertiary care center in Southeast Michigan between January 2010 and December 2016. Out of over 5000 patients with bilateral CTS, we identified 295 patients (males older than 50 years old and females older than 60 years old) with a concomitant diagnosis of atrial fibrillation. All patients with unilateral CTS were excluded. We further identified a high-risk group (HRG) where clinical suspicion for ATTR-CA would be high: patients with bilateral CTS, atrial fibrillation, and heart failure with echocardiographic evidence of left ventricular hypertrophy (LVH). The study and waiver of informed consent were approved by the Institutional Review Board (#15454). This manuscript was prepared in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

2.2. Data Collection, Study Definitions, and Outcomes

All data were gathered through chart review and manual abstraction of the electronic health records (Epic, Epic Systems, Verona, WI). The following baseline demographics and underlying comorbidities were collected: age, race, sex, body mass index, medical history of coronary artery disease, myocardial infarction, lumbar spinal stenosis, biceps tendon rupture, and peripheral neuropathy. Electrocardiographic findings were also collected, including the presence of Q wave and low voltage QRS in addition to the following specific echocardiographic data: ejection fraction, diastolic dysfunction, interventricular septum thickness, posterior wall thickness, left atrial volume index, right ventricular size and function, and global longitudinal strain, if available. All information was de- personalized and study numbers were assigned to each patient. We reviewed the following types of evaluations that were performed for identifying ATTR-CA: technetium- 99m pyrophosphate (PYP) scan, cardiac magnetic resonance imaging (cMRI), echocardiography with strain, and genetic testing for mutations in the transthyretin gene.

In this study, heart failure with reduced ejection fraction was defined as patients with ejection fraction < 50% and HFpEF as ≥50%. [6] Left ventricular hypertrophy was identified by interventricular septal or posterior wall thickness ≥ 12 mm. The primary outcome was to evaluate if the HRG underwent evaluation for CA, especially ATTR-CA and identify opportunities for systematic

evaluation of these patients.

2.3. Statistical Analysis

Continuous variables were described as mean and standard deviation, and categorical/discrete variables were described as counts and frequencies. Group comparisons were done with the two-sided Wilcoxon test for continuous variables and the chi-square test for categorical/discrete variables. A 2-sided $\alpha < 0.05$ was considered statistically significant.

3. Results

Of more than 5000 patients with bilateral CTS treated at our institution, 295 patients had bilateral CTS with concomitant atrial fibrillation and met the age criteria. There were 153 (51.2%) female patients, 142 (48.1%) male patients, 66 (22.4%) were Black/African American, and 223 (75.6%) were White. There were 273 patients who had previously undergone echocardiography, among which 132 (48.3%) had either systolic or diastolic heart failure and 126 (46.1%) had LVH. All patients included had a high amyloid prediction score, which is a score described by Bukhari *et al.* to predict the positivity of the PYP scan used to diagnose ATTR-CA. [7]

There were 228 (77.3%) patients in the non-HRG and 67 (22.7%) patients in the HRG (additional heart failure and left ventricular hypertrophy). Table 1 and Table 2 demonstrate all differences in baseline characteristics and outcomes between HRG and non-HRG.

Patients who had a diagnosis of ATTR-CA were significantly overrepresented in the HRG. Of the 6 (2.0%) patients in the entire cohort with an ATTR-CA diagnosis, proportionately more were in the HRG (5 of 67) than in the non-HRG

Table 1. Baseline characteristics of patients with bilateral carpal tunnel syndrome and atrial fibrillation.

Variable	All Patients (N = 295)		Non-High-Risk (n = 228)		*High-Risk (n = 67)		P value
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Age, years	295	76.7 (8.6)	228	76.0 (8.8)	67	79.0 (8.6)	0.016
Female age, years	153	78.8 (7.8)	116	78.3 (8.1)	37	80 (6.7)	0.358
Male age, years	142	74.4 (9.1)	112	73.5 (9.1)	30	78 (8.6)	0.015
BMI, kg/m^2	295	30.9 (7.2)	228	31.0 (6.9)	67	30.5 (8.3)	0.199
BNP, pg/mL	235	718.05 (990.07)	174	562.57 (885.54)	61	1161.52 (1136.59)	0.001
Ejection fraction, %	273	55.47 (11.65)	206	57.65 (10.01)	67	48.75 (13.69)	0.001
Left atrial volume index	224	36.63 (15.27)	163	34.34 (14.06)	61	42.75 (16.74)	0.001
Interventricular septal diameter, cm	257	1.20 (0.30)	190	1.13 (0.28)	67	1.42 (0.24)	0.001
Posterior wall thickness, cm	257	1.15 (0.24)	190	1.09 (0.22)	67	1.31 (0.23)	0.001
APS score	295	0.31 (0.22)	228	0.29 (0.22)	67	0.38 (0.24)	0.013

APS, amyloid prediction score; BMI, body mass index; BNP, B-type natriuretic peptide; SD, standard deviation. *Patients in the high-risk group also had heart failure with echocardiographic evidence of left ventricular hypertrophy.

Table 2. Additional baseline characteristics and outcomes in patients with bilateral carpal tunnel syndrome and atrial fibrillation.

Variable	All Patients (N = 295) n (%)	Non-High-Risk (n = 228) n (%)	*High-Risk (n = 67) n (%)	P value
Sex				0.531
Female	153 (51.9)	116 (50.9)	37 (55.2)	
Male	142 (48.1)	112 (49.1)	30 (44.8)	
Race				
Black/African American	66 (22.4)	44 (19.3)	22 (32.8)	0.019
White	223 (75.6)	179 (78.5)	44 (65.7)	0.123
Comorbidity				
AV block	44 (14.9)	33 (14.5)	11 (16.4)	0.695
Chronic kidney disease	182 (61.7)	139 (61.0)	43 (64.2)	0.634
Coronary artery disease	132 (44.8)	101 (44.3)	31 (46.3)	0.776
Defibrillator	11 (5.4)	10 (4.4)	6 (9.0)	0.147
Diabetes mellitus	123 (41.7)	93 (40.8)	30 (44.8)	0.561
Hypertension	258 (87.5)	198 (86.8)	60 (89.6)	0.556
Myocardial infarction	68 (23.1)	52 (22.4)	17 (25.4)	0.608
Neuropathy	136 (46.1)	105 (46.1)	31 (46.3)	0.975
Orthostatic hypotension	45 (15.3)	33 (14.5)	12 (17.9)	0.492
Pacemaker	47 (15.9)	33 (14.5)	14 (20.9)	0.207
Spinal stenosis	87 (29.5)	69 (30.3)	18 (26.9)	0.592
Stroke	50 (17.0)	30 (13.2)	20 (29.9)	0.001
Clinical Features				
Diastolic dysfunction				0.001
None	144/239 (60.3)	132/175 (75.4)	12/64 (18.8)	
Grade 1	50/239 (20.9)	23/175 (13.1)	27/64 (42.2)	
Grade 2	31/239 (13.0)	15/175 (8.6)	16/64 (25.0)	
Grade 3	14/239 (5.9)	5/175 (2.9)	9/64 (14.1)	
Low QRS voltage	37/285 (13.0)	27/218 (12.4)	10/67 (14.9)	0.589
Q wave	28/285 (9.8)	21/218 (9.6)	7/67 (10.5)	0.845
Right ventricular dysfunction				0.001
None	222/264 (84.1)	174/188 (87.9)	48/66 (72.7)	
Mild	24/264 (9.1)	15/198 (7.6)	9/66 (13.6)	
Moderate	14/264 (5.3)	5/198 (2.5)	9/66 (13.6)	
Severe	4/264 (1.5)	4/198 (2.0)	0/66 (0)	
Outcomes				
ATTR-CA diagnosis	6 (2.0)	1 (0.4)	5 (7.5)	0.003
Death	85 (28.8)	56 (24.6)	29 (43.3)	0.003

ATTR-CA, transthyretin cardiac amyloidosis; AV, atrioventricular. *Patients in the high-risk group also had heart failure with echocardiographic evidence of left ventricular hypertrophy.

(1 of 228) (7.5% vs 0.4%; P = 0.0003). In addition, overall mortality was significantly higher in the HRG than in the non-HRG (43.3% vs 24.6%; P = 0.003). A review of the approach to ATTR-CA evaluation among the 5 patients in the HRG with an ATTR-CA diagnosis showed that workup was variable: 3 patients had a positive PYP scan, one of whom also underwent a genetic study positive for transthyretin gene mutation, 1 patient had a positive cMRI and positive gene study, and 1 patient had a positive echocardiography with strain study. The 1 patient in the non-HRG who had an ATTR-CA diagnosis was evaluated with PYP scan which was positive.

Among the 67 patients in the HRG, 47 (70%) had been evaluated by a cardiologist, but only 9 (13.4%) patients had an evaluation appropriate for assessing ATTR-CA. These included 3 (4%) patients who had undergone a PYP scan, 3 (4%) patients who had cMRI, and 3 (4%) patients who had echocardiography with strain. Only 2 patients underwent a genetic study after having either a positive PYP scan or cMRI. Among the 228 patients in the non-HRG, 179 (78%) had been evaluated by a cardiologist and only 10 (4%) patients had an evaluation for ATTR-CA, with PYP scan performed in 2 (0.8%) patients, cMRI in 3 (1%) patients and echocardiography with strain performed in 5 (2%) patients, suggesting a substantially low rate of screening and evaluation for CA, even amongst cardiologists.

4. Discussion

In this retrospective cross-sectional analysis of older adults with bilateral CTS and atrial fibrillation, we looked for clinical "red flags" indicative of ATTR-CA and evaluated whether patients with high-risk features would be more likely to have had a diagnosis of ATTR-CA and what types of evaluations they had received. We observed a higher prevalence of ATTR-CA in the HRG. However, we also observed a low rate of clinical evaluation for CA in the patients at highest risk. Our findings suggest that systematic screening for CA is low, even amongst cardiologists, and that cardiac imaging studies for the evaluation of CA are underutilized.

In Figures 1-7, we provided an illustrative example for two patients with

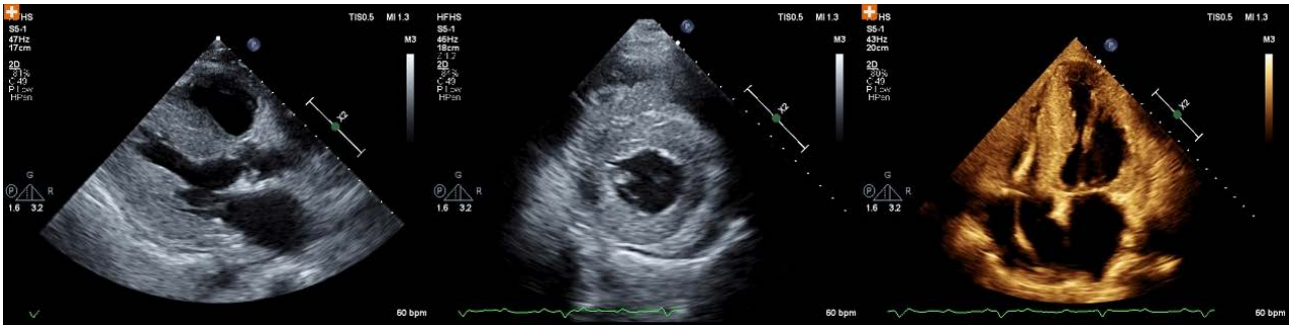

Figure 1. Two-dimensional echocardiographic images of parasternal long, parasternal short and apical 4-chamber views, respectively, showing diffuse severe increase left ventricular wall thickness with increased backscatter appearance suspicious of infiltrative cardiomyopathy in patient 1.

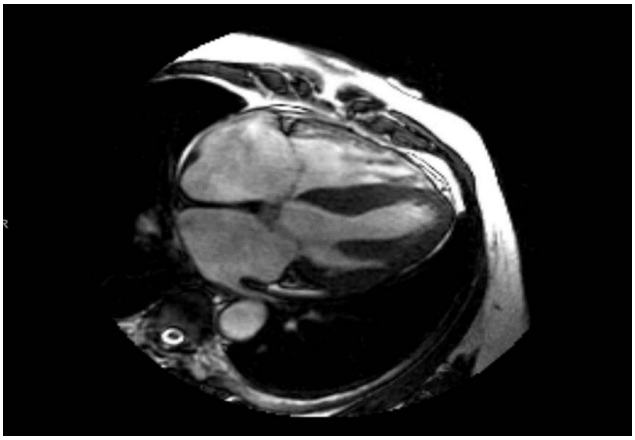

Figure 2. Axial 4 chamber still image of cardiac magnetic resonance imaging (steady sate free precession cine) showing bi-atrial enlargement and diffuse increased left ventricular wall thickness in patient 1.

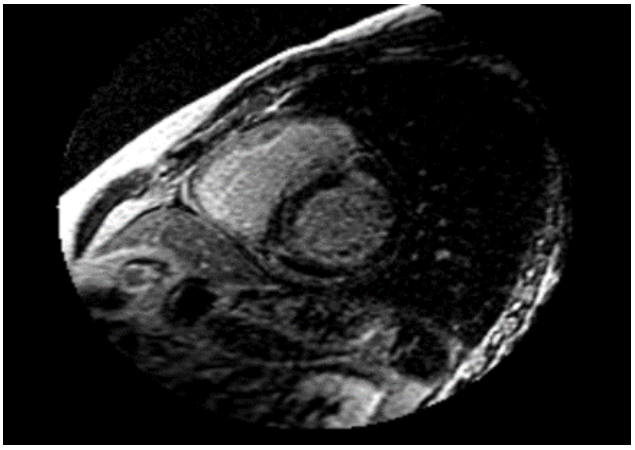

Figure 3. Late gadolinium enhancement cardiac magnetic resonance image showing diffuse subendocardial uptake in the left ventricle and along right ventricular free wall in patient 1.

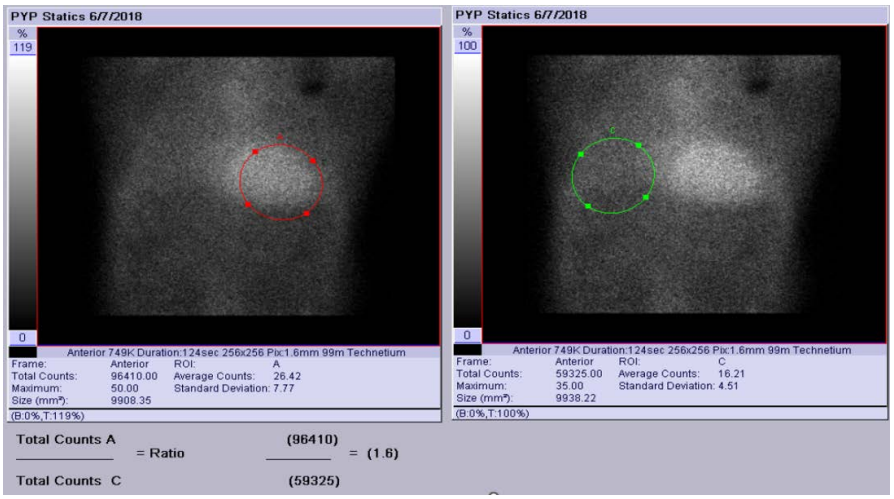

Figure 4. Planar Technetium-99m pyrophosphate image with heart/contralateral ratio > 1.5 suggestive of transthyretin cardiac amyloidosis in patient 1.

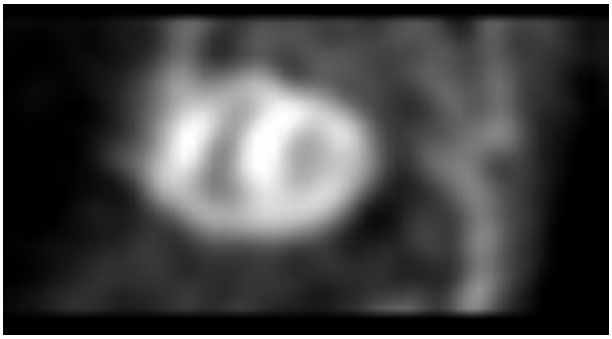

Figure 5. Technetium-99m pyrophosphate single-photon emission computerized tomography short axis image showing diffuse left and right ventricular uptake confirming abnormal myocardial uptake of isotope confirming the diagnosis of transthyretin cardiac amyloidosis in patient 1.

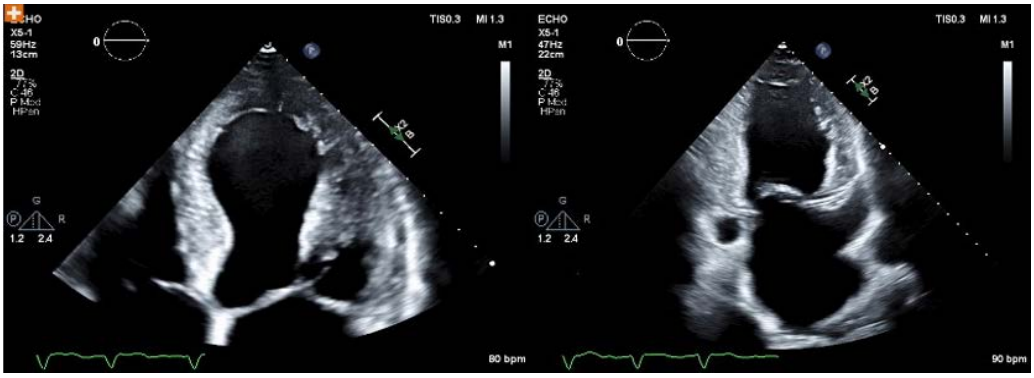

Figure 6. Two-dimensional echocardiographic images demonstrating diffuse increase left ventricular wall thickness and left atrial dilation in patient 2.

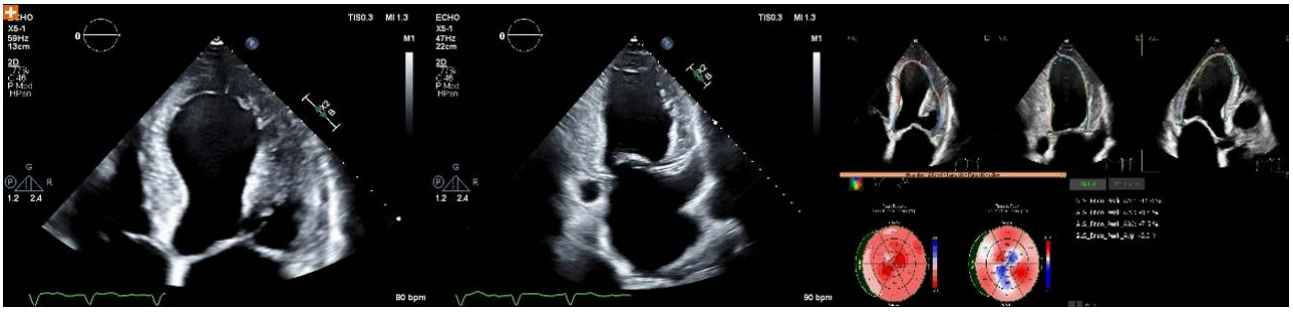

Figure 7. Echocardiography with speckle tracking strain showing severe global reduction in strain with mild apical sparing pattern in patient 2.

higher risk features for ATTR-CA who underwent variable workup. The first patient had a complete cardiac imaging workup including echocardiography, cMRI, and PYP scan leading to a diagnosis of ATTR-CA (**Figures 1-5**), while the second patient had an incomplete workup despite the abnormal echocardiographic findings (**Figure 6** and **Figure 7**) and red flags. Both patients were within HRG and had high amyloid prediction score secondary to bilateral CTS, atrial fibrillation and LVH.

Our study suggests that many physicians, including cardiologists, appear to be

unaware of the red flags that may indicate the presence of CA, especially the strong association between CTS and ATTR-CA. While 70% of the patients in the highest risk group had been seen by a cardiologist, most of them had not undergone a systematic evaluation for CA. Our study supports a critical need for formal education and collaborative efforts to disseminate information about the non-cardiac clues indicative of CA. This paper sheds some light on the necessity of more research on CA to spread awareness about the early signs of this disease among physicians and enhance early detection.

As HFpEF is more prevalent in patients who are beyond the sixth decade of life, exploring the coexisting conditions in this patient age group that could point to a specific underlying cause, such as ATTR-CA, is important. Previous studies have suggested that 44% - 57% of patients with hereditary ATTR-CA and 39% of patients with wild-type ATTR-CA have received a misdiagnosis, and up to 69% of patients with ATTR-CA had seen 3 or more doctors before their diagnosis was made. [8] [9] A common reason for misdiagnosis appears to be that physicians who attribute HFpEF to coexisting hypertension may automatically not perform a comprehensive evaluation that would identify ATTR-CA.

Furthermore, previous studies have highlighted that bilateral CTS may precede ATTR-CA by 5 - 10 years. [10] [11] [12] One study showed that the probability of having bilateral CTS was the highest 5 to 9 years prior to ATTR-CA diagnosis; however, the authors also mentioned that screening performed too early might not detect cardiac involvement, and that long-term follow-up testing might be required, suggesting a need for long-term surveillance of patients with CTS. [13] Current ATTR-CA therapies cannot reverse the damage that has already been done by deposited amyloid fibrils in the myocardium; therefore, early identification and initiation of treatment to prevent significant cardiac damage are essential to limit the clinical impact of CA. Previous studies suggested a median survival of 3.5 - 5 years, particularly when cardiac involvement is present at the time of diagnosis. [14]

Among patients who undergo carpal tunnel release surgery, biopsies of tenosynovium are not routinely obtained by most hand surgeons to evaluate for amyloid deposits. In at least 11 different studies, amyloid deposits have been identified in 3% - 30% of patients who have had carpal tunnel release surgery. [10] A workflow algorithm has been developed to guide hand surgeons in targeting patients who are potentially at high-risk for ATTR-CA and to promote performing tenosynovial biopsy to evaluate for amyloidosis at the time of carpal tunnel release surgery. [10] It is worth noting that based on this algorithm, all patients in our study would have had an indication for tenosynovial or transverse carpal ligament biopsy to evaluate for amyloid deposits.

Our findings highlight that multidisciplinary efforts among different specialists, including primary care physicians, orthopedic/hand surgeons, and cardiologists, are still needed to raise awareness of the red flag features indicative of CA in patients with bilateral CTS. Efforts, such as holding regular multidisciplinary meetings and identifying a workflow for referral, are encouraged. Patients with CTS and underlying cardiomyopathy, specifically those with additional high-risk

features like atrial fibrillation, heart failure and left ventricular hypertrophy, may benefit from a referral to a cardiologist and a formal screening workup for ATTR-CA, as well as potential long-term surveillance for CA. Other collaborations with neurologists and neurosurgeons to systematically screen patients with neuropathy and spinal stenosis could also prove valuable for the early identification of ATTR-CA.

We acknowledge several limitations to the generalizability of our study. First, retrospective studies are prone to selection and detection and misclassification bias. Additionally, patients were included from a single center, which may not reflect the standard of care at different institutions. Furthermore, the timing of bilateral CTS diagnosis was not well documented, and we did not determine the amount of time that the CTS diagnosis had preceded the onset of cardiac manifestations. Lastly, a systematic approach to workup and workflow was not available, and since the completion of this study, our institution has embarked on a collaborative effort within the orthopedics department to identify patients being evaluated for carpal tunnel release surgery to undergo biopsy and evaluation for amyloidosis.

In conclusion, a substantial number of patients with bilateral CTS and atrial fibrillation had additional red flag features warranting an evaluation for ATTR-CA, with about 23% having additional cardiomyopathy warranting formal screening for CA. Few patients in the highest risk group for CA had undergone systematic evaluation for this rare but serious condition, highlighting the importance of raising awareness amongst cardiologists and other physicians of the association between CTS within the context of cardiomyopathy and ATTR-CA. We believe that multidisciplinary collaborations are needed to create a systematic workflow for identifying patients with bilateral CTS and CA red flag features and referring these patients for ATTR-CA evaluation. As a result of our findings, we have embarked on a collaborative effort with our orthopedics department to initiate a prospective systematic evaluation of patients with bilateral CTS and CA red flags to undergo tenosynovial biopsy testing for amyloid deposits during their planned carpal tunnel release surgery, in which patients with positive results would be referred to cardiology for a formal ATTR-CA evaluation.

Conflicts of Interest

Dr. Ananthasubramaniam has received research grants from Alnylam Pharmaceuticals and has served on the advisory board of Alnylam Pharmaceuticals. The other authors declare that they have no relevant financial or non-financial interests to disclose.

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