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ORIGINAL ARTICLE

Spinal amyloid deposits are common among older patients undergoing spinal stenosis decompression surgery

Avni Madhani BA[1] | Navya Kotturu BA[2] | Denise Fine MS[2] | Rabah Alreshq MD[2] | Aziz Saade MD[3] | Tony Tannoury MD[3] | Chadi Tannoury MD[3] | Frederick L. Ruberg MD[2,4]

[1]Boston University Chobanian & Avedisian School of Medicine, Boston, Massachusetts, USA

[2]Department of Medicine, Section of Cardiovascular Medicine, Boston University Chobanian & Avedisian School of Medicine, Boston Medical Center, Boston, Massachusetts, USA

[3]Department of Orthopedic Surgery, Boston University Chobanian & Avedisian School of Medicine, Boston Medical Center, Boston, Massachusetts, USA

[4]Amyloidosis Center, Boston University Chobanian & Avedisian School of Medicine, Boston Medical Center, Boston, Massachusetts, USA

Correspondence
Frederick L. Ruberg, Department of Medicine, Section of Cardiovascular Medicine, Boston University Chobanian & Avedisian School of Medicine, Boston Medical Center, 72 E Concord St., Boston, MA 02118, USA.
Email: frederick.ruberg@bmc.org

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Abstract

Background: Recent advances in the management of transthyretin amyloid cardiomyopathy (ATTR-CM) have highlighted the need for early identification. Studies have demonstrated amyloid deposits in orthopedic surgical specimens, prompting a diagnosis of concurrent ATTR-CM. We sought to determine the prevalence of spinal amyloid deposits among patients undergoing spinal stenosis decompression surgery and whether the presence of deposits was associated with ATTR-CM.

Methods: Patients >60 years of age undergoing spinal stenosis decompression surgery were enrolled as part of a prospective, single-center, cohort study. Samples from the disc and ligamentum flavum were obtained during surgery. Patients with amyloid deposition on Congo red staining returned for standard-of-care clinical assessment consisting of blood testing, a transthoracic echocardiogram, nuclear pyrophosphate imaging when indicated, and an evaluation with a cardiologist.

Results: Out of 54 enrolled patients, 24 patients (44%; 95% CI, 31%–59%) were found to have spinal amyloid deposits. Amyloid-positive patients were older than amyloid-negative patients (70 years vs. 63 years, $p < 0.01$). On follow-up testing, no amyloid-positive patients were found to have definitive ATTR-CM. However, 37% of amyloid-positive patients had abnormal cardiac biomarkers, and 36% of amyloid-positive patients had reduced global longitudinal strain on echocardiography, suggesting possible early disease.

Conclusions: Spinal amyloid deposits, in both the disc and ligamentum flavum, were found in 44% of older patients undergoing spinal stenosis decompression surgery. While none of these patients tested positive for ATTR-CM on early follow-up, subtle abnormalities in cardiac testing suggest that further follow-up testing is warranted to detect the advent of cardiac amyloidosis in the future.

KEYWORDS
amyloid, cardiac amyloidosis, spinal stenosis

1 | BACKGROUND

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an underdiagnosed cause of heart failure (HF) that may be present in approximately 10% of patients aged ≥60 years with HF.[1,2] ATTR-CM results from the misfolding and deposition of the transthyretin (TTR) protein in the myocardium and exists in both wild-type (normal *TTR* genotype) and hereditary (pathological *TTR* variant) forms.[2] The recent advent of ATTR amyloidosis therapies, which function by increasing TTR stability or suppressing TTR gene transcription, along with advances in noninvasive diagnosis of ATTR-CM have highlighted the need to diagnose ATTR-CM early when therapy is most efficacious.[3–6]

ATTR amyloid deposition has been found in various joint and ligament pathologies, including carpal tunnel syndrome, lumbar spinal stenosis, and rotator cuff tears.[7–9] In addition, patients with ATTR-CM may have a higher rate of orthopedic procedures, such as total hip and total knee arthroplasty, prior to diagnosis of cardiomyopathy.[10] Evidence also suggests that orthopedic manifestations, particularly carpal tunnel syndrome, frequently precede cardiac amyloidosis by 5–10 years.[11,12] Such findings raise the question of whether tissue samples from orthopedic surgeries can be used to identify subclinical ATTR-CM. Specifically, in a small (98 patient) prospective study of biopsies of the tenosynovial tissue performed during carpal tunnel release surgery, 10 patients with amyloid-positive biopsies were identified, and one of these patients was found to have undiagnosed ATTR-CM.[13]

Lumbar spinal stenosis, frequently resulting from thickening of the ligamentum flavum, has been identified as a potential avenue for early identification of ATTR-CM. Studies have demonstrated ATTR amyloid deposits in the ligamentum flavum of up to 59% of individuals with spinal stenosis, and the presence of amyloid fibrils has been found to correlate with the thickness of the ligamentum flavum.[14,15] Furthermore, the specific C-terminal TTR fragment involved in the pathogenesis of ATTR-CM is frequently found in the ligamentum flavum of spinal stenosis patients.[14,16,17] A limited number of studies exist that inform the prevalence of ATTR-CM in individuals with TTR amyloid deposits in the ligamentum flavum, with estimates ranging from 0% to 10%.[15,18–20] It is important to note that most of these studies have focused on stenosis of the lumbar spine, and none have explored nonligamentous spinal tissue (e.g., disc components) for amyloid deposits. Given that over 65,000 patients are surgically treated for lumbar spinal stenosis annually, examination of surgical specimens may provide an opportunity for widespread screening and detection of subclinical ATTR-CM.[21] In addition to serving as an early marker of systemic ATTR disease, it is plausible that amyloid deposits in different spinal structures may interfere with surgical efficacy. The primary aim of this study was to determine the prevalence of amyloid deposits in ligamentum flavum and disc tissue samples from patients undergoing decompression surgery for spinal stenosis. Among individuals with spinal amyloid deposition, we assessed the presence of concurrent ATTR-CM by standard-of-care clinical testing.

2 | METHODS

2.1 | Study overview

Patients undergoing spinal stenosis decompression surgery at Boston Medical Center were enrolled as part of a prospective, single-center, cohort study. Inclusion criteria consisted of patients >60 years of age undergoing decompression surgery for spinal stenosis, irrespective of spinal level. Patients were excluded if they had any type of systemic amyloidosis at baseline. Patients undergoing surgery between October 1, 2020, and December 31, 2021, were screened for study inclusion. Two spine-trained orthopedic surgeons at Boston Medical Center (CT and TT) conducted preoperative evaluation for surgical indication and performed the surgeries. The study was approved by the Institutional Review Board of Boston Medical Center, and all patients provided written informed consent.

2.2 | Study procedures

Samples were obtained from the ligamentum flavum or disc (annulus fibrosus and/or nucleus pulposus) during cervical or lumbar spinal stenosis decompression surgery. Tissue specimens were placed in 10% neutral buffered formalin and transferred to the Boston Medical Center pathology laboratory, where processing and Congo red staining were performed. Amyloid deposition was determined by characteristic apple-green birefringence when viewed under polarized light and was graded on a scale of 0–2. Study samples were analyzed by a single pathologist.

2.3 | Cardiac evaluation

Patients with evidence of amyloid deposition in spinal specimens were contacted for standard-of-care follow-up and clinical testing consisting of laboratory testing, a transthoracic echocardiogram (echo), and an evaluation with a cardiologist. Laboratory tests included renal function, N-terminal pro-B-type natriuretic peptide (NT-proBNP), B-type natriuretic peptide (BNP), troponin I, and prealbumin. To exclude light-chain (AL) amyloidosis, serum and urine immunofixation electrophoresis (IFE) and serum free light chain (FLC) concentration were measured following consensus recommendations.[22] If the initial evaluation demonstrated echocardiographic (increased wall thickness, unexplained diastolic dysfunction) or cardiac biomarker testing abnormalities, a technetium-99 m-pyrophosphate (Tc99m-PYP) scan was performed to further assess cardiac amyloid deposition, with a diagnostic scan interpreted according to consensus recommendations.[23] Patients with abnormal results, such as abnormal plasma cell testing, were referred to the appropriate follow-up standard-of-care testing.

2.4 | Data analysis

Data regarding patients' preexisting health conditions, baseline laboratories, and baseline echo were obtained from reviewing the electronic health records. Data were analyzed for differences between the amyloid-positive and amyloid-negative groups. Differences in categorical variables, including patients' age, sex, race, ethnicity, and pre-existing health conditions, were analyzed with a chi-squared test or, where applicable, Fisher's exact test. Continuous variables, including baseline laboratories, baseline echo data, and follow-up laboratory data and echo parameters for amyloid-positive patients, were assessed for normality with the Shapiro–Wilk test, Anderson–Darling test, and histograms. Normal data with equal variance were compared with the *t*-test and are reported as mean (standard deviation). When the assumption of normality was not met, data were analyzed with the Wilcoxon rank-sum test and are reported as median (Q_1, Q_3). All tests were two-sided and considered significant at $p < 0.05$. Data analysis was performed with JMP Pro Version 17.2.0.

3 | RESULTS

3.1 | Overview

Between October 1, 2020, and December 31, 2021, 128 patients >60 years of age underwent spinal stenosis decompression surgery and were screened for inclusion. Fifty-four patients were enrolled in the study, with the remainder of eligible patients declining consent (Figure 1). Of note, study enrollment occurred during the COVID-19 pandemic, which resulted in a decrease in elective surgeries. The prevalence of patients with amyloid deposits in ligamentum flavum or disc specimens was 44% (95% CI, 31%–59%; $n = 24$ amyloid-positive cases). A total of 96 surgical specimens were obtained from the 54 patients, of which 89% ($n = 85$) were from the disc and 11% ($n = 11$) were from the ligamentum flavum (Figure 2). Testing demonstrated that 38% ($n = 32$) of the disc samples were positive, and 18% (n = 2) of the ligamentum flavum samples were positive for amyloid deposits ($p = 0.32$). Of the 96 samples, 35% ($n = 34$) were from the cervical spine, and 65% ($n = 62$) were from the lumbar spine. Testing demonstrated that 47% ($n = 16$) of the cervical samples were positive, and 29% ($n = 18$) of the lumbar samples were positive for amyloid deposits ($p = 0.12$). Finally, in a semiquantitative assessment of the degree of amyloid deposition, of the 34 positive samples, 85% ($n = 29$) had 1+ Congo red staining, and 9% ($n = 3$) had 2+ Congo red staining. There were two Congo red positive samples that were missing a staining grade. Although amyloid type identification was not routinely performed as a part of study procedures, two patients had amyloid typing by liquid chromatography tandem mass spectrometry as a part of clinical follow-up. Both of these studies showed indeterminate amyloid type.

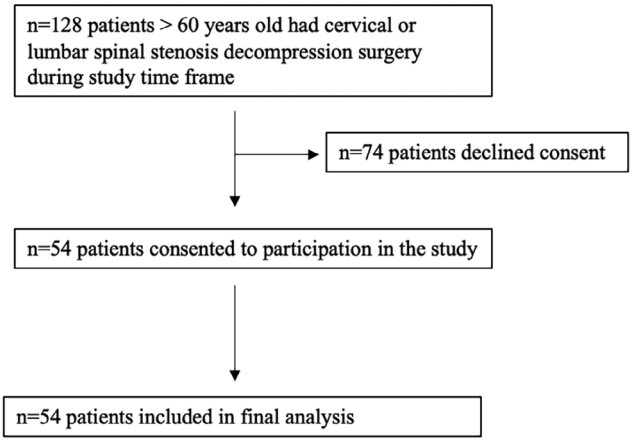

FIGURE 1 Patient flowchart.

3.2 | Differences in baseline characteristics, laboratories, and Echo parameters

Amyloid-positive patients were older with a median age of 70 years (IQR, 63–74 years) when compared to amyloid-negative patients with a median age of 63 years (IQR, 61–67 years; $p < 0.01$). No other significant differences were noted in gender, self-identified race, ethnicity, or baseline comorbidities between the amyloid-positive and amyloid-negative groups, as illustrated in Table 1. Notably, the rate of baseline peripheral neuropathy was not significantly different between the amyloid-positive and amyloid-negative groups. Of the 24 amyloid-positive patients, five patients (21%; 95% CI, 7%–42%) had a prior diagnosis of carpal tunnel syndrome, seven patients (29%; 95% CI, 13%–51%) had trigger finger, and two patients (8%; 95% CI 1%–27%) had biceps tendon rupture. No differences in baseline laboratory testing or echo parameters were present between the amyloid-positive and amyloid-negative groups, as illustrated in Table 1. Renal function was similar between the two groups, with a median creatinine of 0.87 mg/dL (IQR, 0.76–1.04) in the amyloid-positive group and 0.86 mg/dL (IQR, 0.76–0.96) in the amyloid-negative group ($p = 0.67$). Baseline preoperative echo data were limited to eight amyloid-positive patients and nine amyloid-negative patients. No significant differences in left ventricular (LV) wall thickness or left ventricular ejection fraction (LVEF) were seen between amyloid-positive and amyloid-negative patients at baseline.

3.3 | Overview of follow-up for amyloid-positive patients

Out of the 24 amyloid-positive patients, $n = 21$ had follow-up laboratories, Tc99m-PYP scan, and/or echo. Fourteen patients had both follow-up laboratories and echo (of whom three underwent Tc-99 m-PYP imaging), five patients had only follow-up laboratories, and two patients had only follow-up echo. The

FIGURE 2 Overview of samples.

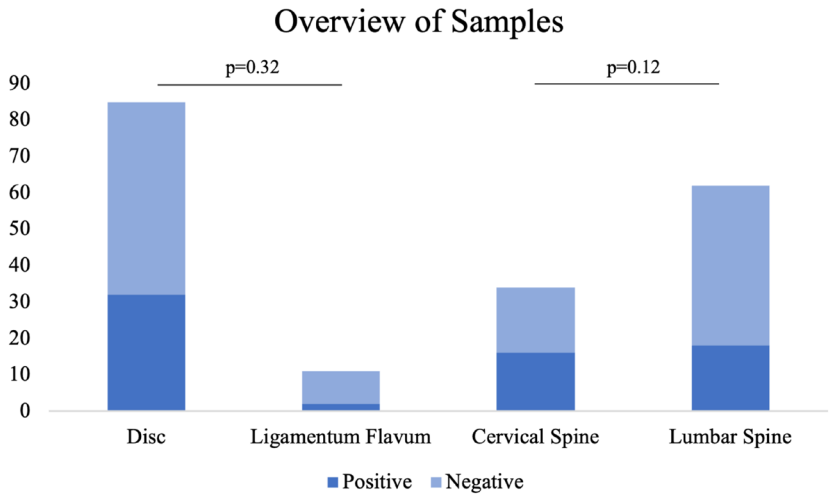

TABLE 1 Demographics, comorbidities, and baseline labs and echocardiographic parameters by amyloid status.

Variable	Amyloid-negative $n=30$	Amyloid-positive $n=24$	p-value
Age (years)	63 (61, 67)	70 (63, 74)	**0.008**
Male Sex	11 (36.7%)	13 (54.2%)	0.27
Self-identified Race			
White	19 (63.3%)	14 (58.3%)	
Black or African American	7 (23.3%)	5 (20.8%)	
Asian	1 (3.3%)	0	0.63
American Indian/Alaskan Native	0	1 (4.2%)	
Other/Not Reported	3 (10%)	4 (16.7%)	
Hispanic/Latino	2 (6.7%)	3 (12.5%)	0.65
Comorbidities			
Type 2 Diabetes	6 (20%)	9 (37.5%)	0.22
Hyperlipidemia	19 (63.3%)	14 (58.3%)	0.78
Hypertension	19 (63.3%)	19 (79.2%)	0.24
Obesity	6 (20%)	11 (45.8%)	0.08
Bicep Tendon Rupture	1 (3.3%)	2 (8.3%)	0.58
Carpal Tunnel Syndrome	10 (33.3%)	5 (20.8%)	0.37
Trigger Finger	4 (13.3%)	7 (29.2%)	0.19
Peripheral Neuropathy	5 (16.7%)	6 (25%)	0.51
Chronic Kidney Disease	6 (20%)	3 (12.5%)	0.72
Anemia	11 (36.7%)	6 (25%)	0.39
Creatinine (mg/dl)	0.86 (0.76, 0.96)	0.87 (0.76, 1.04)	0.67
Echocardiogram	**$n=9$**	**$n=8$**	
IVSd (mm)	9.6 (2.3)	9.8 (1.2)	0.83
PWd (mm)	9.3 (2.2)	9.5 (1.4)	0.86
EF (%)	61.3 (3.5)	62.5 (10.5)	0.77

Abbreviations: EF, ejection fraction; IVSd, interventricular septal thickness at end diastole; PWd, posterior wall thickness at end diastole.

median duration between surgery and follow-up laboratories was 286 days, and the median duration between surgery and follow-up echo was 359 days. For the three patients with follow-up Tc-99 m-PYP scans, the durations between surgery and the scan were 204 days, 512 days, and 738 days. No patients were found to have cardiac amyloidosis on evaluation. All patients had normal

TABLE 2 Follow-up laboratory data for amyloid-positive group.

Patient	NTproBNP (pg/ml)	BNP (pg/ml)	Troponin I	Prealbumin (mg/dl)	Serum IFE	Urine IFE	FLC ratio	Follow up Echo
1	94	36	Normal	22	–	–	1.67	No
2	146	68	Normal	28	–	N/A	1.06	Yes
3	<50	12	Normal	25	+	–	1.7	Yes
4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes
5	77	42	Normal	25	–	–	2.24	Yes
6	150	61	Normal	25	–	–	1.34	Yes
7	<50	<10	normal	24	–	N/A	2	No
8	200	59	Normal	44	–	N/A	1.24	Yes
9	97	31	Normal	31	–	N/A	1.83	Yes
10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes
11	155	50	Normal	29	–	–	1.02	No
12	N/A	17	Normal	28	–	N/A	1.54	Yes
13	N/A	17	Normal	23	–	N/A	1.54	No
14	**804**	106	Normal	14	–	N/A	0.87	Yes
15	<50	13	Normal	29	–	N/A	1.1	No
16	<50	15	N/A	28	–	+	1.4	Yes
17	**724**	187	Normal	29	–	N/A	1.29	Yes
18	53	13	Normal	27	–	N/A	1.14	Yes
19	306	88	Normal	19	–	N/A	1.51	Yes
20	N/A	128	Normal	32	+	N/A	1.52	Yes
21	91	36	Normal	29	+	N/A	0.88	Yes

Note: Bolded text indicates abnormally elevated lab values. Three patients were lost to follow-up.

Abbreviations: BNP, B-type natriuretic peptide; FLC, ratio, kappa/lambda free light chain ratio; IFE, immunofixation electrophoresis; N/A, not acquired; NTproBNP, N-terminal pro-brain natriuretic peptide.

troponin values, and only one patient had an abnormal prealbumin. All Tc-99 m-PYP scans were Grade 0 or 1, and the highest heart to contralateral chest uptake (H/CL) ratio was 1.4, thereby not reaching the threshold for ATTR-CM diagnosis of Grade 2 or 3 uptake.

3.4 | Amyloid-positive group: free light chain and immunofixation electrophoresis abnormalities

No patients were found to have AL amyloidosis by FLC or serum or urine IFE analysis. Most patients (58% of patients) had normal FLC and IFE testing excluding a monoclonal process. Of the four patients (Patients 1, 5, 7, 9; Table 2) with an isolated elevation in kappa/lambda FLC ratio (normal: <1.65), two patients had chronic kidney disease, leading to impaired clearance and elevated FLC ratio, and one patient had kappa light chain monoclonal gammopathy of undetermined significance (MGUS). One patient with abnormal FLC ratio was lost to follow-up. Three patients (Patients 16, 20, and 21) had positive serum and/or urine IFE's without elevated FLC ratio, and one of these patients was found to have a low-risk MGUS, as evaluated by hematologic consultation. Two patients with IFE testing abnormalities were lost to follow-up. One patient (Patient 3) had both a mildly elevated FLC ratio and a positive serum IFE and was diagnosed with IgM MGUS. Thus, a majority of abnormalities in FLC and IFE were secondary to previously undiagnosed MGUS as opposed to AL amyloidosis.

3.5 | Amyloid-positive group: cardiac biomarker abnormalities

Follow-up cardiac laboratory testing for amyloid-positive patients included NT-proBNP, BNP, troponin I, and prealbumin (Table 2). The median NT-proBNP (normal: <125 pg/mL for <75 years, <450 pg/mL for >75 years) was 95.5 pg/mL (IQR, 50.75–188.75) with 38% of patients with results above the upper limit of normal. The median BNP (normal: <100 pg/mL) was 36 pg/mL (IQR, 15–68) with 16% patients with results above the upper limit of normal. No patients had an abnormal troponin I. The median prealbumin (normal: >16 mg/dL) was 28 mg/dL (IQR, 24–29). Only one patient (Patient 14) had a low prealbumin of 14 with concurrent elevation in NT-proBNP, BNP, and LV wall thickness on echo; however, this patient unfortunately did not follow-up for further evaluation.

TABLE 3 Follow-up imaging data for amyloid-positive group.

Patient	IVSd (mm)	PWd (mm)	LVEF (%)	GLS (%)	Average E/e'	PYP	Perugini grade
2	8	11	64	N/A	9.8	No	N/A
3	10	11	62	−18	N/A	No	N/A
4	10	6	64	N/A	7.8	No	N/A
5	10	9	70	−19.8	10.3	No	N/A
6	9	9	64	−21.2	14.2	No	N/A
8	8	9	40	−8.5	N/A	No	N/A
9	7	6	58	−16	10.5	No	N/A
10	8	9	68	−17	9.5	No	N/A
12	9	9	58	−17	11.3	Yes	1
14	15	14	60	N/A	13.4	No	N/A
16	N/A	N/A	63	−16	N/A	No	N/A
17	10	10	53	−15	12.9	Yes	0
18	11	10	51	N/A	6.6	No	N/A
19	9	9	56	N/A	N/A	No	N/A
20	12	12	55	−21	20.6	Yes	0
21	11	10	65	−21	5.1	No	N/A

Abbreviations: GLS, global longitudinal strain; IVSd, interventricular septal thickness at end diastole; LVEF, left ventricular ejection fraction; PWd, posterior wall thickness at end diastole; PYP, Technetium-99 m-pyrophosphate imaging.

3.6 | Amyloid-positive patients: cardiac imaging abnormalities

Echocardiographic parameters assessed on follow-up included interventricular septal thickness (IVSd), posterior wall thickness (PWd), LVEF, global longitudinal strain (GLS), and average E/e' (Table 3). Mean IVSd and PWd (normal: <10 mm for males, <9 mm for females) were 9.7 mm (SD, 2.0 mm) and 9.6 mm (SD, 2.0 mm), respectively. The percentage of patients with abnormal IVSd and PWd was 40%. Mean LVEF (normal: >52% for males, >54% for females) was 59.5% (SD, 7.4%) with 13% of patients having an LVEF below the normal limit. Average global longitudinal strain (normal: >17%) was 17.3% (SD, 3.7%), and 36% of patients had a lower value than the reference range. Finally, average E/e' (normal: <15) was 11 (SD, 4.1) with 8% of patients having an abnormal E/e'. A majority of patients with abnormal cardiac biomarkers and echo parameters had known cardiovascular comorbidities, particularly hypertension. Three patients had Tc99m-PYP scans, with H/CL ratios ranging between 0.94 and 1.4 and Perugini scores between 0 and 1. Thus, no scans were interpreted as suggestive of ATTR-CM.

4 | DISCUSSION

In this study, we report the prevalence of amyloid deposits in the ligamentum flavum and disc tissue of individuals undergoing decompression surgery for cervical or lumbar spinal stenosis. In addition, we tested those with spinal amyloid deposits for ATTR-CM. Our study cohort is distinct from prior publications for two important reasons. First, the majority of our tissue samples (89%) were disc material, in which we demonstrated amyloid deposits, thereby representing a new finding. Second, a third of our tissue samples (35%) were from the cervical spine, while prior studies have focused nearly exclusively on the lumbar spine. The primary findings of this study are that (1) 44% of patients >60 years of age undergoing decompression surgery for cervical or lumbar spinal stenosis had amyloid deposits in either the ligamentum flavum or disc tissue; (2) patients with amyloid deposits in spinal tissue were significantly older than those without amyloid deposits. Finally, we found that 37% of amyloid-positive patients with follow-up laboratories had abnormal cardiac biomarkers, and 36% of patients had low echo GLS, suggesting the possibility of early ATTR-CM disease (Figure 3).

Prior studies have reported a broad range (19%–100%) for the prevalence of amyloid deposits in the ligamentum flavum of patients with spinal stenosis. A percentage of these deposits represented ATTR deposition, while in a large proportion the misfolded protein could not be determined.[14,15,18–20] Our finding of a prevalence of 44% amyloid deposits is, to our knowledge, the first to capture both the ligamentum flavum and disc tissue (annulus fibrosus and nucleus pulposus). Our study is the first to our knowledge to systematically examine disc tissue specimens for amyloid deposits. The presence of amyloid deposits in the disc tissue suggests that deposition is not restricted to the ligamentum. Spinal stenosis owing to amyloid deposits has been construed as a ligamentous pathophysiology, but our observations suggest that a disc component may also contribute to the disease process. Those with amyloid deposits were found to be significantly older than those without amyloid deposits, consistent with the known pathophysiology of wild-type ATTR, which is the

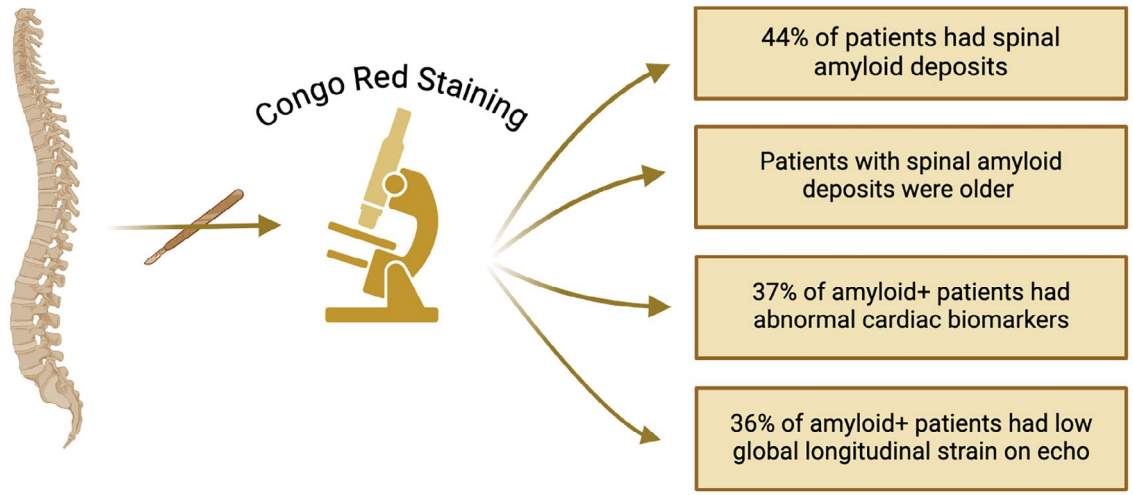

FIGURE 3 Primary findings of study.

likely etiology of the misfolded protein given that it is a disease of aging.[2]

Although no individuals who followed up were found to have cardiac manifestations of amyloidosis, this does not preclude the possibility of future development of ATTR-CM. Fosbøl et al. demonstrated that individuals who underwent surgery for carpal tunnel syndrome had a higher incidence of future amyloidosis and heart failure when compared to controls from an age- and sex-matched cohort. The median durations from carpal tunnel surgery to amyloid diagnosis and heart failure diagnosis were 3.1 years and 3.7 years, respectively.[24] Debonnaire et al. reported that among patients diagnosed with ATTR-CM, 40% of patients had a prior diagnosis of spinal stenosis at an average of 7.4 years prior to the diagnosis of ATTR-CM.[25] Thus, detection of amyloid deposits in soft tissue structures may precede diagnosis of ATTR-CM by a number of years.

Furthermore, the cohort in our study may not have captured those with the highest risk of concurrent ATTR-CM. The CASS study, which assessed the prevalence of ATTR deposits in the ligamentum flavum in 82 patients undergoing spinal stenosis surgery and the prevalence of ATTR-CM, found that three out of the 48 patients with ATTR spinal deposits had concurrent ATTR-CM. Amyloid deposits were graded on a scale of 1 to 4, and all three patients with cardiac amyloidosis had grade 4 deposition.[15] In our study, amyloid deposits were graded on a 2-point scale, and a majority of patients had grade 1 deposits, suggestive of earlier-stage disease. Thus, amyloid deposition may not have progressed to a significant enough degree for cardiac presentation. This is further supported by the median age of the amyloid-positive cohort in our study of 70 years, which is earlier than the typical age of diagnosis of ATTR-CM attributable to wild-type ATTR at approximately 75 years.[26]

Given the high prevalence of spinal stenosis in older individuals, it is important for primary care physicians, who often follow patients for this pathology, to consider systemic amyloidosis as an underlying cause, regardless of whether spinal stenosis is at the cervical or lumbar level. Specific therapies for ATTR-CM are most effective at early stages of the disease, and standard cardiac medications may not be effective in patients with ATTR-CM. Thus, early identification is crucial for referral and optimal treatment, and preexisting spinal stenosis should increase index of suspicion for ATTR-CM in older individuals.

4.1 | Limitations

Our study is limited by a relatively small number of patients, largely owing to the decrease in elective surgeries during the COVID-19 pandemic during which this study was performed. For this reason, some patients did not return for further evaluation resulting in missing follow-up data. Missing data are an important limitation as three patients with spinal specimens positive for amyloid deposits were lost to follow-up and may have had ATTR-CM. Detection of ATTR-CM may have also been falsely decreased by the identification of individuals with clinically significant cardiac disease during preoperative evaluation, whose surgeries would have likely been delayed. Additionally, given the abstraction of baseline data from the electronic health record, a majority of patients did not have a baseline echo. Finally, because of processing constraints and funding limitations, mass spectrometry was not systematically performed, and the isolated amyloid protein was not routinely typed. Thus, the number of individuals with spinal TTR deposits remains undefined.

5 | CONCLUSION

In this study, we demonstrate that 44% of patients >60 years undergoing elective spinal stenosis decompression surgery had amyloid deposits in their ligamentum flavum or spinal disc material. We also found that none of the individuals with amyloid deposits with follow-up testing had concurrent manifestations of ATTR-CM. Clinicians caring for older patients with spinal stenosis should

consider systemic amyloidosis as a potentially contributing factor. Although symptomatic spinal stenosis alone is insufficient to infer the presence concurrent ATTR-CM, further studies are warranted to determine the time span between the development of spinal stenosis and ATTR-CM to inform the development of screening protocols.

AUTHOR CONTRIBUTIONS

Avni Madhani: Data curation; formal analysis; visualization; writing – original draft. **Navya Kotturu:** Data curation. **Denise Fine:** Data curation; project administration. **Rabah Alreshq:** Data curation. **Aziz Saade:** Data curation. **Tony Tannoury:** Investigation. **Chadi Tannoury:** Investigation. **Frederick L. Ruberg:** Conceptualization; funding acquisition; investigation; methodology; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

FLR received funding for this study from Akcea (award number: 4100143001). The funding source had no role in the design, practice or analysis of this study. CT holds stock in 4webmedical and patents with DePuy Synthes. TT is a consultant for Johnson & Johnson and receives publishing royalties from Wolters Kluwer Health.

ETHICS STATEMENT

The study was approved by the Institutional Review Board of Boston University Medical Campus (protocol H-39175), and all patients provided written informed consent.

ORCID

Avni Madhani https://orcid.org/0009-0000-5747-6948

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