

# Light-Chain Amyloidosis: Orthopedic Manifestations and Clues to Early Diagnosis

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## Abstract

**Importance:** Systemic immunoglobulin light-chain (AL) amyloidosis is a clonal disorder in which survival depends largely on organ involvement at diagnosis. Musculoskeletal manifestations may precede recognition of cardiac or renal disease, but their overlap with common orthopedic disorders complicate early identification. **Objective:** To synthesize evidence on the musculoskeletal manifestations of AL amyloidosis, their temporal relationship with systemic diagnosis, and the diagnostic utility of tissues obtained during orthopedic procedures. **Evidence Review:** PubMed/MEDLINE was systematically searched for publications from January 1, 2016, through August 27, 2026. A total of 350 records were retrieved, and 13 publications were included in the AL-specific synthesis: two primarily addressing orthopedic manifestations and eleven primarily addressing diagnosis. Reviews and cohorts involving multiple amyloid types were used as contextual evidence and were not counted among the included publications. Heterogeneity in populations, tissues, typing methods, and outcomes required narrative synthesis. **Findings:** Clinical suspicion increases when orthopedic manifestations are bilateral, recurrent, or multifocal or coexist with monoclonal gammopathy or organ involvement. Interpretation of the reported temporal associations is limited by patient selection and retrospective documentation. In the orthopedic cohorts used as contextual evidence, deposits were predominantly transthyretin-derived, and new diagnoses of systemic AL amyloidosis were uncommon. Congo red positivity demonstrates amyloid but does not identify its precursor; a concomitant monoclonal gammopathy does not establish the composition of the deposit. Eval-

uation should integrate serum and urine immunofixation, serum free light-chain measurement, and tissue typing. A negative peripheral biopsy does not exclude AL amyloidosis when clinical suspicion remains high. **Conclusions and Relevance:** Musculoskeletal manifestations may facilitate recognition of AL amyloidosis but lack sufficient specificity in isolation. Suggestive patterns may prompt targeted, multidisciplinary diagnostic evaluation. Available evidence does not demonstrate a clinical benefit from screening orthopedic tissues or support its universal application; prospective studies are needed to assess its effects on disease stage at diagnosis and clinical outcomes.

## Keywords

Immunoglobulin Light-Chain Amyloidosis, Musculoskeletal Manifestations, Orthopedic Surgery, Carpal Tunnel Syndrome, Tissue Biopsy, Mass Spectrometry, Early Diagnosis

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## 1. Introduction

The amyloidosis comprise a heterogeneous group of diseases characterized by the extracellular deposition of misfolded proteins as insoluble fibrils, resulting in progressive disruption of tissue structure and function. Immunoglobulin light-chain (AL) amyloidosis is an acquired disorder caused by a clonal population of plasma cells or, less commonly, B cells that produces amyloidogenic light chains. Although its incidence is estimated at approximately 12 cases per million person-years, it remains an underdiagnosed and potentially fatal disease. A systematic review published in 2020 estimated that 25% of patients died within the first 6 months after diagnosis, primarily because of advanced organ damage, which limits the effectiveness of treatments directed against the underlying clone [1]. In a cohort of 592 patients with AL amyloidosis confirmed by mass spectrometry, 76% had cardiac involvement, 53% had renal involvement, 24% had neurologic involvement, and 17% had gastrointestinal involvement; 34% had single-organ disease, whereas 25% had involvement of more than 2 organs. Survival was determined primarily by cardiac involvement, irrespective of the total number of organs affected [2].

Early diagnosis is challenging because the initial manifestations are often non-specific, develop progressively, and may be evaluated separately by different medical specialties. In an electronic health record-based cohort of 1401 patients with AL amyloidosis, a median of 5 precursor diagnoses involving 4 organ systems were identified before the definitive diagnosis was established. Depending on the manifestation evaluated, its first documentation occurred between 3.2 and 21.4 months before the diagnosis of amyloidosis. Dyspnea, fatigue, neuropathy, chronic kidney disease, edema, and heart failure were the most frequent antecedent conditions. Carpal tunnel syndrome was documented in 10% of patients at the time of diagnosis and, among those with a newly recorded diagnosis during the

preceding 2 years, appeared a median of 6.7 months earlier [3]. These findings do not demonstrate that every precursor diagnosis was directly attributable to amyloid deposition because of the possible influence of comorbidities and coding errors. Nevertheless, they identify a clinical window during which the coexistence of multisystem findings could prompt an earlier evaluation.

Musculoskeletal manifestations warrant particular attention because they may precede recognition of cardiac or renal involvement and are often initially attributed to common orthopedic disorders. These manifestations include bilateral or recurrent carpal tunnel syndrome, lumbar spinal stenosis, rotator cuff and distal biceps tendon abnormalities, and amyloid deposition in synovial tissue, articular cartilage, tendons, and ligaments obtained during orthopedic procedures. A systematic review of 24 studies involving 3606 participants identified deposits in the transverse carpal ligament and flexor tenosynovium, ligamentum flavum, hip or knee synovium and articular cartilage, and rotator cuff tendons. However, among 2183 patients who underwent musculoskeletal biopsy, 410 samples contained transthyretin deposits and only 8 contained light-chain deposits. Furthermore, most studies provided level III or IV observational evidence and had insufficient follow-up to determine progression to systemic disease [4]. An orthopedic manifestation may therefore serve as a warning sign for amyloidosis but cannot independently establish the etiologic subtype or specifically attribute the deposit to AL amyloidosis.

Tissues obtained during orthopedic procedures provide a potential opportunity to detect amyloid before advanced organ dysfunction becomes clinically apparent. A meta-analysis of 21 studies involving 4482 patients undergoing carpal tunnel release, cited as contextual evidence and excluded from the AL-specific systematic synthesis, estimated a pooled prevalence of amyloid deposits in the tenosynovium or transverse carpal ligament of 11% in unselected US and European populations and 20% when clinical criteria were applied to identify patients at higher risk. Among patients with a positive biopsy who completed a cardiac evaluation, 5% to 20% were subsequently diagnosed with cardiac amyloidosis; however, most deposits were transthyretin-derived, and only a small number of patients were diagnosed with AL amyloidosis [5]. The etiologic interpretation of these findings is addressed in the subsection “Principles of Diagnostic Confirmation and Amyloid Typing.” In this context, the present systematic review aims to synthesize evidence on the musculoskeletal manifestations of AL amyloidosis, their temporal relationship with systemic diagnosis, associated gammopathies and differential diagnoses, and the diagnostic performance and limitations of biopsies obtained during orthopedic procedures. Based on these findings, we propose a clinical approach that enables orthopedic surgeons to recognize combinations of warning signs, initiate evaluation for a plasma cell disorder, and facilitate early histologic confirmation and amyloid typing.

## 2. Methods

PubMed/MEDLINE was searched on October 4, 2026, for publications from Jan-

uary 1, 2016, through August 27, 2026, without language restrictions. The MeSH terms “Immunoglobulin Light-chain Amyloidosis,” “Musculoskeletal Diseases,” “Carpal Tunnel Syndrome,” “Biopsy,” and “Sensitivity and Specificity” were combined with free-text terms related to orthopedic manifestations, monoclonal protein detection, amyloid typing, and diagnostic delay, using MeSH and title/abstract fields and the Boolean operators AND and OR.

Eligible designs included cohort, case-control, cross-sectional, clinical registry, and diagnostic studies involving adults that evaluated carpal tunnel syndrome, other compressive neuropathies, arthropathy, myopathy, tendon or ligament lesions, bone involvement, spinal stenosis, clonal detection, biopsies, or time to AL diagnosis. Orthopedic manifestations were defined as the listed musculoskeletal and compressive nerve disorders documented clinically or through imaging, neurophysiologic studies, or histology. Eligibility of AL cases required an author-reported histologic diagnosis of systemic AL amyloidosis, together with hematologic and organ assessment. The typing method and its reported coverage, serum and urine immunofixation, free light-chain testing, available clonal studies, and organ involvement were recorded; studies meeting the required histologic-systemic diagnostic criterion were retained despite incomplete reporting of typing or monoclonal protein testing, with this limitation documented as diagnostic uncertainty. Neither positivity of all monoclonal protein tests nor involvement of multiple organs was required. A localized deposit was defined as light-chain amyloid confined to a single site, without evidence of systemic involvement after the reported hematologic and organ assessment. When this assessment was incomplete or only normal monoclonal protein test results were reported, the case was classified as “systemic AL amyloidosis not confirmed.” Localized deposits and unconfirmed cases were not counted as systemic AL cases. Diagnostic studies could include controls without AL if confirmed AL cases and their results were identifiable. Exclusions comprised localized deposits without systemic confirmation, untyped deposits without an explicit histologic diagnosis of AL, pediatric or pregnant populations, nonhuman studies, individual case reports, small noncomparative descriptive case series, and studies focused exclusively on treatment or prognosis. Secondary sources and cohorts involving multiple amyloid types, including AL/ATTR, were used as contextual evidence and were not counted in the AL synthesis.

A total of 350 records were retrieved, and 12 duplicates were removed; of the 338 records screened, 280 were excluded after title and abstract review. Full texts were sought for 58 reports, of which 24 could not be retrieved. Of the 34 reports assessed, 21 were excluded: 10 because of insufficient confirmation of systemic AL, 9 because their populations involved multiple amyloid types, 1 because AL results could not be extracted separately, and 1 because it was a small noncomparative descriptive case series. Thirteen publications were included: two primarily addressing orthopedic manifestations and eleven primarily addressing diagnosis.

### 3. Definition, Classification, and Hematologic Basis of AL Amyloidosis

The term *amyloidosis* does not denote a single etiology but rather a group of diseases characterized by tissue deposition of proteins that adopt a fibrillar structure rich in cross- $\beta$  sheets. The International Society of Amyloidosis nomenclature identifies fibril protein using the letter A followed by an abbreviation of its precursor. Accordingly, AL denotes amyloid derived from immunoglobulin light chains and, strictly speaking, not the disease itself; the correct term is *AL amyloidosis*. This form may be localized or systemic. Classification depends on the site at which the precursor is produced: the deposit is considered localized when it forms near the clone producing the light chain, whereas systemic disease occurs when the circulating precursor deposits at distant sites and may involve one or more organs [6].

Systemic AL amyloidosis is an immunoglobulin deposition disorder caused by a plasma cell clone or, less commonly, a lymphoplasmacytic or B-cell clone. These cells produce a complete or fragmented monoclonal  $\kappa$  or  $\lambda$  light chain capable of misfolding, forming fibrils, and depositing extracellularly. Unlike multiple myeloma, the extent of organ damage does not necessarily depend on extensive cellular proliferation: the median bone marrow plasma cell proportion is approximately 10%, and some patients have even smaller clones. The underlying hematologic disorders form a continuum that includes monoclonal gammopathy of undetermined significance, particularly light-chain monoclonal gammopathy, smoldering multiple myeloma, and symptomatic multiple myeloma. AL amyloidosis may also be associated with Waldenström macroglobulinemia and other immunoglobulin-producing B-cell neoplasms [7].

Although AL amyloidosis and multiple myeloma belong to the spectrum of plasma cell neoplasms and paraprotein-associated disorders, they should not be considered equivalent diagnoses. Multiple myeloma requires at least 10% clonal plasma cells in the bone marrow or a biopsy-proven plasmacytoma accompanied by organ damage or a myeloma-defining biomarker. AL amyloidosis, by contrast, is defined by the presence of an amyloid deposition-related syndrome in which the light-chain composition of the deposits has been confirmed. The 2 diseases may occur simultaneously or sequentially. In a prospective registry of 141 patients with AL amyloidosis, 7 had localized disease and 134 had systemic disease. Among those with systemic disease, 25 of 134 patients, representing 18.7%, met International Myeloma Working Group criteria for multiple myeloma; 23 had synchronous diagnoses, and 2 had a history of smoldering multiple myeloma. The mean bone marrow plasma cell proportion was 37.16% among patients with both myeloma and amyloidosis, compared with 18.02% among those with amyloidosis without myeloma, with  $P < .001$ . These findings demonstrate the need to apply the diagnostic criteria for each disease independently but do not provide a generalizable prevalence estimate. The data originated from a referral center, covered an extended period, and included a cohort in which cardiac involvement occurred

in 90.3%, indicating substantial clinical selection [8].

AL amyloidosis associated with a monoclonal IgM protein represents an uncommon and heterogeneous hematologic phenotype. In a cohort of 1174 patients with newly diagnosed systemic AL amyloidosis, 75 patients, representing 6%, had an IgM monoclonal protein. A preexisting clonal disorder had been recognized in 31%, primarily IgM monoclonal gammopathy, smoldering lymphoplasmacytic lymphoma, or previously treated lymphoplasmacytic lymphoma. Review of 70 bone marrow biopsies identified a neoplasm with lymphoplasmacytic morphology in 44 patients, a pure plasma cell neoplasm in 16, and other patterns in 10, corresponding to 63%, 23%, and 14%, respectively. The 2 groups had distinct molecular profiles: none of the evaluated lymphoplasmacytic cases had t(11;14), whereas this alteration was identified in 60% of pure plasma cell neoplasms. Conversely, the *MYD88* L265P variant was present in 84% of lymphoplasmacytic cases and in none of the plasma cell cases, whereas *CXCR4* variants were observed in 29% and 0%, respectively. Patients with IgM-associated AL amyloidosis also had more frequent soft tissue and peripheral nerve involvement but less frequent cardiac involvement than patients with non-IgM AL amyloidosis. An IgM paraprotein should therefore prompt targeted bone marrow evaluation using morphologic assessment, immunophenotyping, cytogenetics, and, when appropriate, *MYD88* and *CXCR4* testing. These findings should be interpreted in light of the retrospective, single-center design and incomplete availability of molecular testing [9].

#### 4. Principles of Diagnostic Confirmation and Amyloid Typing

After Amyloid identification, deposit typing, and confirmation of systemic disease are distinct diagnostic steps. Congo red staining and characteristic birefringence under polarized light demonstrate amyloid but do not identify its precursor protein. The term *characteristic birefringence* is more precise than the traditional expression *apple-green birefringence* because the observed color may vary among green, yellow, orange, and red. A monoclonal gammopathy may coexist incidentally with deposits of another origin, particularly in older adults; its presence alone does not establish the AL subtype. Diagnosis requires the integration of a compatible clinical syndrome, histologic demonstration of amyloid, and confirmation of the light-chain composition of the deposits. Even when a musculoskeletal deposit has been typed as light-chain amyloid, hematologic and organ assessment is required to determine whether the disease is localized or systemic [6] [7].

Immunohistochemistry and immunofluorescence can be used to type deposits, although interpretation may be limited by incomplete antibody panels, loss or alteration of epitopes in fragmented or misfolded light chains, and nonspecific antibody binding. Laser microdissection followed by liquid chromatography-tandem mass spectrometry identifies proteins within Congo red-positive areas without prespecifying an amyloid type and can be applied to archived, paraffin-em-

bedded tissue. Mass spectrometry is the reference method for amyloid typing when adequate material and access to an experienced laboratory are available [7] [10].

As contextual evidence, a reference laboratory reported proteomic typing of 16 175 specimens over 11 years and identified 21 amyloid types; 59.0% of the specimens were classified as AL. This experience illustrates the method's ability to identify different precursor proteins, including uncommon types that are not routinely included in immunohistochemical panels. These proportions describe specimens referred for amyloid typing and do not represent population prevalence or findings from the AL-specific systematic synthesis [10].

## 5. Systemic Presentation and Diagnostic Journey

AL amyloidosis usually presents as a systemic disease in which the organs affected and the sequence of symptom onset vary among patients. In a retrospective cohort of 63 patients treated at 3 tertiary care centers in Colombia, renal involvement was present in 66%, cardiac involvement in 61%, peripheral nervous system involvement in 34%, soft tissue involvement in 26%, and hepatic involvement in 25%; 61% had involvement of at least 2 organs. Median overall survival was 45.1 months, and cardiac involvement was associated with greater mortality in multivariable analysis (HR, 3.27; 95% CI, 1.23 - 8.73). These findings demonstrate that the disease may already be advanced and involve multiple organs when it is recognized, but they should not be interpreted as population-level estimates because of the small sample, retrospective design, and selection of patients referred to specialized centers. In addition, the absence of mass spectrometry-based typing introduces the possibility that some cases were misclassified [11].

The nonspecific nature of the initial manifestations contributes to a prolonged and fragmented diagnostic journey. In a mixed-methods study that included interviews with physicians and patients and a community-based survey of 341 individuals with AL amyloidosis, fatigue was the most frequent initial symptom and coexisted with dyspnea, edema, orthostatic dizziness, early satiety, weight loss, and neuropathy. Overall, 71.8% received the diagnosis at least 6 months after symptom onset, 43.4% waited 1 year or longer, and 27.9% had consulted 6 or more physicians before receiving the diagnosis. Predominant cardiac involvement was associated with a greater likelihood of diagnostic delay than predominant renal involvement (relative risk, 1.43; 95% CI, 1.21 - 1.69), probably because proteinuria and other renal abnormalities more readily prompt objective testing and biopsy, whereas fatigue and dyspnea have broader differential diagnoses. Participants also described uncertainty and emotional distress during this process. However, recruitment through patient organizations, reliance on self-reported information, and participation of physicians experienced in amyloidosis may limit the representativeness of the findings [12].

The consequences of diagnostic delay are particularly relevant in patients with cardiac involvement. In a retrospective cohort of 77 patients with histologically

confirmed cardiac AL amyloidosis, the median interval from the first symptoms of heart failure to diagnosis was 7 months, and 26% were diagnosed after the first year. A longer diagnostic interval correlated with more advanced disease according to both the modified 2004 Mayo staging system and the revised 2012 system. Compared with diagnosis within the first 12 months, intervals of 13 to 18 months and at least 19 months were associated with greater mortality in the final multivariable model (HR, 3.20; 95% CI, 1.38 - 7.42; and HR, 5.05; 95% CI, 1.78 - 14.41, respectively). Patients with advanced cardiac disease also received lower-intensity treatment regimens and had less favorable hematologic and cardiac responses. Although measuring survival from symptom onset reduced the potential for lead-time bias, the retrospective single-center design, small groups, and reconstruction of symptom onset from patient recall preclude interpreting 12 months as a causal or universally applicable threshold [13].

Contemporary administrative data confirm that diagnostic opportunities are missed even after repeated encounters with specialists. A US health care claims database identified 470 patients with AL amyloidosis who had received treatment within 6 months after diagnosis. During the preceding 24 months, 86% had cardiovascular manifestations and 74% had renal manifestations. Overall, 72% had been evaluated by a cardiologist, and each patient visited a mean of 4 different cardiologists; nevertheless, hematology or oncology established 49.8% of the diagnoses, whereas cardiology established only 7%. A total of 179 patients (38.1%) had a cardiovascular manifestation recorded more than 1 year before diagnosis. During the 6 months after diagnosis, these patients had a greater likelihood of cardiovascular emergency department visits (adjusted OR, 1.98; 95% CI, 1.21 - 3.24) and cardiovascular hospitalization (adjusted OR, 1.65; 95% CI, 1.10 - 2.46). These associations suggest a greater clinical burden related to delayed diagnosis but do not establish causality. Administrative codes cannot confirm that each manifestation was attributable to amyloidosis, and the selection of insured individuals with continuous follow-up who received early treatment excluded patients who died before treatment initiation or followed different health care trajectories [14].

A Japanese hospital database provided additional information on the interval between initial evaluation and diagnostic confirmation. Among 323 adults with AL amyloidosis, the median age was 73 years. In the 228 patients with an evaluable interval from the initial visit for suspicious manifestations, the median time to diagnosis was 81.5 days. This interval was longer among patients aged at least 65 years than among younger patients (105.5 vs 69.5 days) and reached 150 days among those with a Charlson Comorbidity Index of 4 or higher. Hematology involvement was associated with a substantially shorter interval, with a median of 7.5 days to diagnostic confirmation. Recorded prodromal manifestations included heart failure, constipation, nephrotic syndrome, arrhythmias, peripheral neuropathy, and carpal tunnel syndrome, although the latter occurred in only 5 patients and does not permit estimation of its actual frequency. In-hospital survival tended

to be higher when diagnosis occurred during the first year, but the differences were not statistically significant. The descriptive design, absence of multivariable adjustment, exclusive capture of hospital-based care and mortality, and inclusion only of ultimately confirmed cases may have underestimated both the duration and consequences of diagnostic delay [15].

## 6. Musculoskeletal and Orthopedic Manifestations

Musculoskeletal involvement in light-chain amyloidosis may affect peripheral nerves, tendon sheaths, synovium, periarticular structures, the spine, and skeletal muscle. Although these manifestations are less frequent than cardiac or renal involvement, they are clinically relevant because they may bring patients to orthopedic attention several years before systemic disease is recognized. Their interpretation requires caution: carpal tunnel syndrome, lumbar spinal stenosis, trigger finger, tendon ruptures, and degenerative arthropathy are also common among older adults, and much of the evidence linking these conditions to amyloidosis is derived predominantly from patients with transthyretin deposits. An isolated orthopedic manifestation therefore rarely provides sufficient grounds to suspect AL amyloidosis. The diagnostic probability increases when manifestations are bilateral or recurrent, involve multiple structures, lack an adequate mechanical explanation, or coexist with neuropathy, macroglossia, periarticular abnormalities, or other indicators of systemic disease.

Carpal tunnel syndrome is the most extensively studied orthopedic manifestation, but its association with AL amyloidosis is less consistent than its association with transthyretin amyloidosis (ATTR). In a cohort of 538 individuals, including 196 patients with AL amyloidosis, 273 with ATTR amyloidosis, and 69 asymptomatic carriers of *TTR* variants, the frequency of surgical carpal tunnel release among patients with AL amyloidosis was comparable with that expected in the age- and sex-adjusted general population. In contrast, it reached 20.3% among patients with ATTR amyloidosis and cardiac involvement, and the increase in incidence between 5 and 9 years before the diagnosis of amyloid cardiomyopathy was essentially restricted to ATTR amyloidosis. In addition, 42 of the 57 participants with a history of carpal tunnel surgery had bilateral involvement, although this finding applied to the combined etiologic groups and cannot be attributed specifically to AL amyloidosis [16]. A second cohort of 108 patients documented a history of carpal tunnel syndrome in 36 participants, corresponding to 33.3% of the study population. Its frequency was lower in AL than in ATTR amyloidosis—24% vs 62%—but the temporal association remained noteworthy: in the AL subgroup, carpal tunnel syndrome preceded the diagnosis of systemic amyloidosis by a median of 4.2 years. Within this subgroup, however, a history of carpal tunnel syndrome was not significantly associated with subsequent cardiac involvement. These findings indicate that carpal tunnel syndrome may precede AL amyloidosis, but its usefulness as a warning sign depends on additional clinical features and should not be extrapolated from the stronger evidence available for ATTR amy-

loidosis [17].

Other manifestations involving the hand and upper extremity include flexor tenosynovitis, trigger finger, entrapment neuropathies, and spontaneous distal biceps tendon rupture. Shoulder synovial proliferation, rotator cuff thickening, and tendon tears have also been described. However, most surgical series and tissue deposits supporting these associations involve ATTR amyloidosis, particularly among older men. The coexistence of multiple trigger fingers, bilateral carpal tunnel release, or a low-energy tendon rupture may justify a broader evaluation, but none of these findings has demonstrated sufficient specificity to independently identify AL amyloidosis [18]. In AL amyloidosis, the soft tissue manifestations with the greatest clinical value include macroglossia, periorbital purpura, the shoulder pad sign—caused by periarticular deposition around the shoulders—synovial enlargement, carpal tunnel syndrome, and firm lymphadenopathy. The combination of macroglossia or periorbital purpura with a musculoskeletal abnormality is particularly suggestive of AL amyloidosis, although the absence of these findings does not exclude the disease. Hip or knee arthropathy and tendon ruptures should be interpreted more cautiously because they are nonspecific and the available evidence primarily associates them with ATTR amyloidosis [19].

Peripheral neurologic involvement may produce musculoskeletal symptoms that are mistaken for radiculopathy, joint disease, or focal neuropathies. In a retrospective cohort of 155 consecutive patients with biopsy-confirmed systemic AL amyloidosis, 49.0% had at least 1 of 4 neurologic manifestations: peripheral polyneuropathy in 36.8%, carpal tunnel syndrome in 12.9%, clinically relevant lumbar spinal stenosis in 7.1%, and amyloid myopathy in 3.9%. Carpal tunnel syndrome was bilateral in 45% of cases. Polyneuropathy predominantly followed a symmetric, length-dependent axonal sensorimotor pattern, with hypoesthesia, paresthesias, and small-fiber pain that was more pronounced in the lower extremities; it was also closely associated with autonomic dysfunction. Recognition of this diffuse pattern may help distinguish systemic involvement from an isolated entrapment neuropathy, although diabetes, nutritional deficiencies, alcohol use, and medication-related neurotoxicity must be excluded. Lumbar spinal stenosis was defined by compatible symptoms and imaging findings after alternative explanations were excluded, but the absence of a control group precludes determining how much of its prevalence was directly attributable to amyloid deposition [20].

Amyloid myopathy is an uncommon but probably underdiagnosed presentation. In a series of 3434 patients with AL amyloidosis evaluated over 20 years, only 51 (1.5%) had biopsy-confirmed muscle deposition. Muscle weakness was present in 96% and was predominantly proximal; 45% also had distal weakness. Other manifestations included dysphagia in 45%; myalgia and macroglossia in 33% each; muscle atrophy and jaw claudication in 25% each; dysphonia in 18%; and muscle pseudohypertrophy in 12%. The median interval from symptom onset to diagnosis was 23 months, with a range of 2 to 120 months. Creatine kinase levels were elevated in only 11 of the 32 patients with available measurements; therefore, a

normal concentration does not exclude muscle involvement. Among the 27 patients who underwent muscle biopsy before referral to the specialized center, only 16 initially received the correct diagnosis. Review of 8 specimens previously interpreted as nonspecific demonstrated amyloid deposits in 7. Twelve patients had received inappropriate treatments, primarily glucocorticoids for presumed inflammatory myopathy. Progressive proximal weakness accompanied by dysphagia, macroglossia, jaw claudication, neuropathy, or pseudohypertrophy should therefore prompt consideration of amyloid myopathy even when muscle enzyme levels are normal. For the orthopedic clinician, the principal clue is not an isolated lesion but the convergence of compressive, neurologic, tendinous, periarticular, or muscular manifestations that are not adequately explained by a common mechanical or degenerative disorder [21].

## 7. Biopsy of Orthopedic Tissues and the Opportunity for Early Diagnosis

Surgical carpal tunnel release provides an opportunity to investigate amyloid deposits in the transverse carpal ligament and flexor tenosynovium, tissues that can be obtained without substantially modifying the procedure. These findings should be interpreted according to the principles outlined in the subsection “Principles of Diagnostic Confirmation and Amyloid Typing” before establishing a diagnosis of systemic AL amyloidosis. Positive biopsies obtained during carpal tunnel surgery are considerably more frequent than new diagnoses of systemic disease requiring treatment.

The most relevant initial evidence comes from a prospective study of 98 patients—men aged 50 years or older and women aged 60 years or older—undergoing release for idiopathic carpal tunnel syndrome. Ten tenosynovial biopsies were Congo red-positive, and mass spectrometry identified 7 ATTR deposits, 2 light-chain deposits, and 1 deposit that could not be typed. One light-chain deposit was identified in a woman with a known monoclonal gammopathy,  $\lambda$  light-chain amyloid, and previously unrecognized cardiac involvement; she received plasma cell clone-directed therapy and achieved a complete hematologic response. The second deposit contained  $\kappa$  light chains but was not accompanied by a detectable monoclonal protein or cardiac involvement; therefore, the tissue finding did not constitute a confirmed diagnosis of systemic AL amyloidosis. Subsequent evaluation also identified 1 case of wild-type ATTR cardiac amyloidosis and allowed disease-specific treatment to be initiated in 3 participants. This study demonstrates that biopsy may occasionally anticipate a clinically relevant diagnosis of AL amyloidosis, although its observed yield was 1 clearly documented systemic case among 98 selected procedures [22].

A subsequent implementation study examined 185 tenosynovial biopsies obtained from patients who met age-based criteria. Although 55 specimens were initially Congo red-positive, only 54 were confirmed by the reference laboratory, corresponding to a histologic positivity rate of 29%. Mass spectrometry identified

wild-type ATTR in 44 specimens, hereditary ATTR in 1, and a combination of wild-type ATTR and  $\kappa$  light chains in 1; 6 specimens were insufficient for typing, and 2 contained nonspecific peptides. No exclusively light-chain deposits were identified, and no new diagnosis of systemic AL amyloidosis was documented. No complications were attributed to tissue collection. The study supports the feasibility of incorporating biopsy into the procedure, but its follow-up did not determine how many isolated deposits subsequently progressed to systemic disease [23].

A prospective cohort of 246 consecutive patients without prior selection by age or sex compared transverse carpal ligament and synovial specimens. Amyloid was detected in 28 ligament specimens (11.4%) and 31 synovial specimens (12.6%); 3 patients had positive findings only in the synovium. Immunohistochemistry identified transthyretin in all but 1 case, in which the deposit was  $\lambda$  light-chain-positive and was classified by the investigators as light-chain amyloidosis. However, the publication did not provide sufficient clonal and organ characterization to determine whether this case represented systemic AL amyloidosis or a localized deposit. Age, bilateral symptoms, and trigger finger were independent predictors of a positive biopsy. Subsequent evaluation identified 8 patients with ATTR and grade 2 or 3 cardiac tracer uptake, whereas most deposits remained confined to the carpal tissues or lacked unequivocal evidence of cardiac involvement [24].

Application of a selection algorithm across 156 procedures illustrates the difference among eligibility, tissue positivity, and clinically actionable disease. Seventy-five patients met the proposed criteria, 62 agreed to undergo biopsy, and 14 had amyloid deposits, corresponding to a positivity rate of 22.5% among those actually biopsied. All deposits were wild-type ATTR, and all patients with positive findings had bilateral carpal tunnel syndrome. Only 1 patient was diagnosed with asymptomatic cardiac amyloidosis and began treatment with tafamidis. No cases of AL amyloidosis were identified. Patient attrition between screening, acceptance of biopsy, and cardiac evaluation also demonstrates that a detection program requires multidisciplinary coordination and a predefined follow-up pathway [25].

Tissue selection was evaluated in 148 procedures with paired specimens. Amyloid was detected in 31 tenosynovial biopsies (21%) and 33 transverse carpal ligament biopsies (22%), with concordant results in 138 cases (93%). Among the 10 discordant results, 6 were positive only in the ligament and 4 only in the tenosynovium. Although the authors calculated a sensitivity of 87% and a specificity of 95% for the ligament specimen, they used the tenosynovial biopsy as the reference. These figures describe agreement between 2 sampling sites rather than sensitivity or specificity for diagnosing systemic amyloidosis because neither tissue serves as an independent reference standard and not all patients underwent a uniform systemic evaluation. Biopsy of a single site appears reasonable, whereas the incremental benefit of dual-site sampling should be weighed against its costs and the clinical relevance of the additional deposits identified [26].

In a more recent prospective cohort of 100 consecutive patients, amyloid deposits were identified in 62: 61 were typed as ATTR and one as  $\kappa$  light-chain am-

ylloid. In the patient with the  $\kappa$  deposit, serum and urine immunofixation and serum free light-chain testing were normal; systemic AL amyloidosis was not confirmed by the assessment performed. Among the 93 patients whose specimens were submitted separately, concordance between the tenosynovium and ligament was 91%; four cases would have been missed if only one of these tissues had been analyzed. Eight patients with ATTR had asymptomatic myocardial tracer uptake; three met the criteria for cardiac amyloidosis and initiated treatment, whereas five remained in a preclinical stage. The high histologic positivity rate of 62%, observed at a single Japanese center, limits the generalizability of the findings. The study illustrates that a light-chain deposit in orthopedic tissue does not independently confirm systemic AL amyloidosis [27].

Overall, biopsies obtained during carpal tunnel release frequently detect amyloid deposits, but most are ATTR and only exceptionally lead to a new diagnosis of systemic AL amyloidosis. Available evidence does not support universal biopsy or permit calculation of its sensitivity for AL amyloidosis. Biopsy appears more justifiable in older patients with bilateral or recurrent disease, multiple trigger fingers, spinal stenosis, biceps tendon rupture, unexplained cardiomyopathy, or a history of monoclonal gammopathy. Every positive specimen should undergo reliable amyloid typing, preferably by mass spectrometry when available. Identification of  $\kappa$  or  $\lambda$  light chains should prompt hematologic evaluation but should not be labeled systemic AL amyloidosis without demonstration of a producing clone and compatible organ involvement. Orthopedic tissue biopsy therefore functions as a warning signal that activates further diagnostic evaluation rather than as an isolated test capable of establishing the definitive diagnosis.

## 8. Diagnostic Pathway for Suspected AL Amyloidosis: From an Orthopedic Finding to Systemic Confirmation

The identification of suggestive orthopedic manifestations or amyloid deposits in tissue obtained during a surgical procedure should trigger a systemic evaluation but does not independently permit attribution of the deposit to immunoglobulin light chains. The priorities are to confirm the presence of amyloid, accurately identify the precursor protein, and determine whether a monoclonal disorder capable of producing it is present. The importance of avoiding diagnostic delay was demonstrated in a cohort of 36 patients with predominantly cardiac AL amyloidosis, in which the median interval from symptom onset to diagnosis was 4 months, with a range of 1 to 55 months. In 10 patients (28%), the initial biopsy had been reported as negative despite suggestive clinical and ancillary findings; subsequent review of the tissue at specialized centers confirmed the deposits, primarily after technical difficulties with Congo red staining were corrected. In addition, 31% died within the first 5 months after diagnosis. Although the concentration of patients with cardiac involvement limits the generalizability of these findings, they demonstrate that an initially negative biopsy should not terminate the evaluation when clinical suspicion remains high [28].

Evaluation for a monoclonal component should be performed concurrently with the histologic assessment and should include serum immunofixation, urine immunofixation, and serum free light-chain measurement with determination of the  $\kappa:\lambda$  ratio. Serum protein electrophoresis alone lacks sufficient sensitivity and should not be used to exclude AL amyloidosis. In a meta-analysis of diagnostic accuracy studies, the pooled sensitivity for detecting the plasma cell disorder associated with AL amyloidosis was 68% for serum immunofixation, 77% for urine immunofixation, and 82% for the serum free light-chain ratio. Combined serum and urine immunofixation achieved a sensitivity of 89%, whereas the combination of all 3 tests reached 99%. However, the certainty of the evidence was low to moderate, and many studies originated from tertiary care centers and used case-control designs. This panel therefore provides high-sensitivity screening for monoclonality, but a positive result does not demonstrate that the monoclonal protein is responsible for the tissue deposit and does not replace amyloid typing [29].

Interpretation of serum free light chains requires consideration of age, kidney function, the analytical method, and laboratory-specific reference intervals. Reduced renal clearance increases the concentrations of both light chains and may broaden the  $\kappa:\lambda$  ratio in the absence of an amyloid-producing clone. In a comparison of 1705 patients with AL amyloidosis and 675 with wild-type ATTR amyloidosis, use of reference intervals adjusted for age and estimated glomerular filtration rate maintained an overall sensitivity for monoclonal component detection comparable with that obtained using the conventional interval—99.1% vs 99.2%—when combined with serum and urine immunofixation. Among patients with wild-type ATTR amyloidosis and negative immunofixation results, the proportion with an abnormal ratio decreased from 26.5% with the conventional interval to 2% with the adjusted intervals. Accordingly, a mild isolated abnormality in the ratio, particularly in an older adult or a patient with chronic kidney disease, should not automatically be interpreted as evidence of AL amyloidosis [30].

Detection of the monoclonal component also depends on the combination of tests and the analytical method. In a cohort of 126 patients with AL amyloidosis, Zhang *et al.* reported that serum protein electrophoresis, serum and urine immunofixation, and serum free light-chain testing together detected a monoclonal component in 124 patients, corresponding to a detection rate of 98.4% [31]. Mahmood *et al.* compared Freelite and N Latex in 90 baseline serum samples and found discrepancies in  $\kappa:\lambda$  ratio classification, limiting the interchangeability of their results [32]. In 40 untreated patients with renal AL amyloidosis, Wang *et al.* evaluated the heavy/light chain (HLC) assay for intact immunoglobulins, which provided additional detection in some cases with negative serum immunofixation or a normal serum free light-chain ratio [33]. These findings were obtained in selected populations with AL amyloidosis, and their applicability to orthopedic screening remains unestablished.

The histologic strategy depends on tissue availability. If tenosynovium, ligament, joint capsule, bone, or periarticular tissue obtained during surgery demon-

strates characteristic birefringence under polarized light after Congo red staining, the paraffin block should be preserved and submitted for amyloid typing. Another biopsy is not required solely to demonstrate amyloid again unless the original material is insufficient or the finding is uncertain. When no positive tissue specimen is available, abdominal fat pad aspiration and bone marrow evaluation provide less invasive initial biopsy sites. In 600 patients with confirmed cardiac amyloidosis, fat pad aspiration detected deposits in 181 of 216 patients with AL amyloidosis, corresponding to a sensitivity of 84%. Performance depended on total-body amyloid burden, decreasing from 100% among patients with a large burden to 78% among those with a small burden. Furthermore, immunohistochemistry of fat tissue correctly typed the deposit as AL in only 47% of the complete cohort. These findings distinguish 2 outcomes that should not be conflated: detecting amyloid and identifying its precursor. A negative peripheral tissue biopsy does not exclude the disease; when suspicion remains high, biopsy of the clinically affected organ should be considered [34].

In a cohort of 612 patients with AL amyloidosis, Muchtar *et al.* reported sensitivities for amyloid detection by Congo red staining of 69% for bone marrow biopsy, 75% for fat aspiration, and 89% when both sites were combined [35]. Li *et al.* studied 224 patients with AL amyloidosis confirmed by renal biopsy; among the 90 patients in the primary study group who underwent both abdominal skin and subcutaneous fat biopsy and rectal mucosal biopsy, combined sampling detected deposits in 89, corresponding to a sensitivity of 98.9% [36]. These estimates describe amyloid detection in patients with confirmed AL amyloidosis. Patient selection, unequal availability of tissue samples, and the absence of negative controls limit their applicability to orthopedic screening.

In the diagnostic pathway, amyloid deposit typing should follow the principles outlined in the subsection “Principles of Diagnostic Confirmation and Amyloid Typing,” particularly when the clinical phenotype, monoclonal protein studies, and immunohistochemical findings are discordant. Archived tissue from previous orthopedic procedures can be reanalyzed by mass spectrometry if sufficient material is available [10].

The need to confirm the precursor protein has also been demonstrated outside highly specialized centers. In a Brazilian cohort of 79 patients with biopsies obtained from 13 tissue types, mass spectrometry identified the amyloid subtype in 91% of specimens and was inconclusive in 9%. A model integrating clinical, laboratory, imaging, and pathologic data correctly classified 80% of cases but incorrectly identified 3 ATTR cases as AL amyloidosis, and 1 of these patients received plasma cell-directed treatment; a case of heavy-chain amyloidosis was also classified as AL. Among 47 specimens evaluated using a 4-antibody immunohistochemical panel, the precursor protein was correctly identified in 28%, and sensitivity for AL amyloidosis was 10%. This performance should not be extrapolated to expert laboratories using extensive panels and validated techniques, but it illustrates the risks of relying on limited immunohistochemistry or clinical inference.

It also demonstrates that mass spectrometry may be inconclusive and requires adequate material, quality control, and specialized interpretation [37].

Exploratory approaches have also been investigated for early detection. Zhou *et al.* studied 21 individuals with  $\lambda$  monoclonal gammopathies and documented two cases of AL amyloidosis confirmed by biopsy and mass spectrometry following an evaluation guided by free light-chain testing and IGLV gene analysis [38]. Wu *et al.* evaluated tissue clearing and three-dimensional imaging of tongue biopsies in 17 participants with suspected systemic AL amyloidosis, including seven cases initially confirmed by histology and light-chain typing [39]. The small size of these cohorts and targeted or incomplete verification limit the assessment of their diagnostic accuracy and the clinical benefit of screening.

Operationally, the pathway begins with recognition of a suggestive orthopedic pattern or detection of amyloid in surgical tissue. Serum and urine immunofixation, serum free light-chain measurement, and typing of the deposit should then be performed concurrently. If the orthopedic specimen is insufficient, fat pad and bone marrow specimens may initially be evaluated. A negative biopsy requires reassessment of the clinical probability and, when suspicion remains high, tissue sampling from an affected organ. Detection of a monoclonal component without tissue typing does not confirm AL amyloidosis, just as demonstration of amyloid without identification of its precursor does not determine treatment. Once a light-chain deposit has been documented, bone marrow aspiration and biopsy, flow cytometry, and cytogenetic studies allow characterization of the responsible clone. In a cohort of 63 patients with newly diagnosed AL amyloidosis, Lisenko *et al.* identified clonal cell populations by multiparameter flow cytometry in 61, supporting its contribution to characterization of the underlying hematologic disorder [40]. The assessment should be completed by targeted evaluation for cardiac, renal, hepatic, neurologic, and other organ involvement using biomarkers, urine studies, electrocardiography, and selected imaging modalities. Confirmed or strongly suspected AL amyloidosis requires urgent referral to hematology or a specialized amyloidosis center because timely diagnosis depends on integrating the orthopedic finding with hematologic, histologic, and proteomic evidence.

## 9. Implications for Orthopedic Practice and Future Priorities

The reviewed evidence places orthopedic surgeons in a potentially important position for the early recognition of AL amyloidosis but does not support using isolated musculoskeletal manifestations as diagnostic markers. Carpal tunnel syndrome, trigger fingers, lumbar spinal canal stenosis, shoulder abnormalities, tendon injuries, and arthropathies are highly prevalent in the general population and are more commonly attributable to degenerative, metabolic, or mechanical causes. Their clinical value increases when they are bilateral or recurrent, affect multiple anatomic regions, require multiple procedures, or coexist with a monoclonal gammopathy, peripheral neuropathy, proteinuria, heart failure of unexplained cause,

orthostatic hypotension, weight loss, macroglossia, periorbital purpura, or other compatible systemic manifestations.

The objective should not be to automatically attribute these disorders to amyloidosis but to identify a combination of findings that justifies broader evaluation. Pretest probability is particularly important because most deposits incidentally identified in orthopedic tissues from older adults are transthyretin-derived, whereas only a small proportion are related to immunoglobulin light chains. In addition, the presence of a monoclonal gammopathy does not demonstrate that the amyloid is AL because the 2 conditions may coexist incidentally. Therefore, the orthopedic phenotype, detection of a monoclonal component, and positive staining for amyloid should not be interpreted independently.

When tissue obtained during orthopedic surgery is selected for analysis, the usefulness of the procedure depends on specimen quality and the availability of a defined pathway for processing and acting on the results. Tissue should be fixed and preserved in a manner that permits Congo red staining, examination under polarized light, and subsequent precursor protein typing. A positive result without typing may generate unnecessary investigations or lead to etiologic misclassification, whereas a negative result from a small, poorly vascularized, or inadequately processed specimen does not exclude systemic disease. Before implementing screening programs, institutions should establish coordination mechanisms among orthopedic surgery, pathology, hematology, and reference laboratories capable of performing mass spectrometry.

Available evidence also does not justify universal screening of all tissues obtained during carpal tunnel release, arthroplasty, spinal surgery, or other orthopedic procedures. Such a strategy would primarily identify deposits unrelated to AL amyloidosis and could increase misdiagnosis, patient anxiety, additional biopsies, and costs. A selective approach appears more reasonable and should consider age, bilateral or recurrent manifestations, multiple procedures, a history of monoclonal gammopathy, systemic symptoms, and the results of cardiac, renal, or neurologic evaluations. However, no validated score currently identifies which patients should undergo biopsy or hematologic assessment.

Future research should move beyond retrospective series and establish prospective multicenter cohorts with clearly defined denominators. Studies should use standardized protocols for patient selection, specimen collection, Congo red staining, and mass spectrometry-based typing. They should also distinguish among histologic positivity, identification of the precursor protein, presence of a hematologic clone, and confirmation of systemic disease because these outcomes represent different stages of the diagnostic process. Reporting an overall biopsy positivity rate without specifying how many deposits are AL or how many lead to a new systemic diagnosis overestimates the clinical usefulness of orthopedic screening.

Another priority is the prospective reconstruction of the temporal disease trajectory. Studies should record the first musculoskeletal manifestation, timing of

the orthopedic intervention, emergence of systemic signs, and date of AL amyloidosis confirmation. This information would help determine whether a reproducible diagnostic window exists and whether recognition in orthopedic practice reduces the cardiac or renal stage at diagnosis. Studies should also evaluate quality of life, number of procedures avoided, safety, costs, and survival rather than limiting outcomes to deposit detection. Finally, predictive models should undergo external validation and demonstrate greater clinical utility than usual assessment before being recommended for screening.

## 10. Limitations

**Studies** This review has limitations related to both its methodological strategy and the nature of the available evidence. The search was restricted to PubMed/MEDLINE and the period from January 1, 2016, through August 27, 2026; therefore, publications indexed exclusively in other databases and earlier studies relevant to the historical description of musculoskeletal manifestations may have been omitted. Excluding case reports and small case series reduced the risk of overemphasizing exceptional presentations but may also have omitted uncommon orthopedic phenotypes of AL amyloidosis. Studies focusing exclusively on transthyretin amyloidosis were excluded except when they provided information necessary for differential diagnosis or interpretation of orthopedic tissue findings.

The synthesis was limited by substantial clinical and methodological heterogeneity. The studies evaluated populations from hematology, cardiology, orthopedic surgery, or specialized amyloidosis centers, with markedly different pretest probabilities of disease. Tissues from the carpal tunnel, tendons, synovium, joint capsules, bone, intervertebral discs, and ligaments were analyzed using nonuniform methods. Some studies were limited to Congo red staining, others used immunohistochemistry, and only a subset performed proteomic typing. Consequently, positivity rates are not directly comparable, and a reliable quantitative synthesis could not be performed.

The qualitative assessment identified a risk of selection and referral bias in cohorts from specialized centers, together with uncertainty regarding the diagnostic reference standard when amyloid typing was incompletely described. Studies involving patients with previously confirmed AL amyloidosis, without negative controls, allow estimation of sensitivity in those populations but not specificity or the performance of orthopedic screening. Retrospective documentation of symptom onset limits the precision of intervals to diagnosis and the interpretation of temporal associations. In orthopedic cohorts used as contextual evidence, the predominance of ATTR, the small number of AL cases, and nonuniform systemic evaluation limit extrapolation of their findings to systemic AL amyloidosis. Accordingly, estimates of diagnostic performance should be interpreted in light of the population and reference standard used; temporal associations do not establish causality, and biopsy positivity alone does not demonstrate a clinical benefit from screening.

Definitions of localized disease, incidental deposits, and systemic amyloidosis also varied. Identification of amyloid in orthopedic tissue was not always followed by serum and urine immunofixation, serum free light-chain measurement, bone marrow evaluation, or systematic organ assessment. In other cases, the subtype was inferred from the clinical context or presence of monoclonal gammopathy without direct typing of the deposit. These variations limit estimation of the number of new AL amyloidosis diagnoses attributable to orthopedic surgery.

Finally, temporal evidence was insufficient. Although some studies suggest that musculoskeletal manifestations may precede the systemic diagnosis by several years, symptom onset, the date of orthopedic intervention, and the time of AL confirmation were not always documented accurately. It has also not been demonstrated that screening orthopedic tissues reduces diagnosis at advanced stages, improves treatment response, or prolongs survival. The findings should therefore be interpreted as a basis for increasing clinical suspicion and developing prospective research rather than as definitive evidence supporting universal screening programs.

## 11. Conclusions

AL amyloidosis can produce diverse musculoskeletal manifestations, and in some patients these manifestations appear before the organ involvement that ultimately leads to diagnosis. Carpal tunnel syndrome, shoulder involvement, tendon injuries, arthropathy, axial abnormalities, and bone lesions become more relevant when they are bilateral, recurrent, or multifocal or are accompanied by systemic or hematologic findings. However, no isolated orthopedic manifestation has sufficient specificity to confirm or exclude the disease.

Tissue obtained during orthopedic procedures provides a diagnostic opportunity, but its usefulness depends on distinguishing three stages: demonstration of amyloid by Congo red staining, identification of the precursor protein, and confirmation of systemic disease. Histologic positivity is not equivalent to AL amyloidosis, and the coexistence of a monoclonal component does not establish causality. Mass spectrometry-based typing, when available, reduces the risk of confusing AL with ATTR or other forms of amyloidosis.

When a suggestive orthopedic pattern or a confirmed tissue deposit is identified, the evaluation should integrate serum and urine immunofixation, serum free light-chain measurement, tissue typing, clone characterization, and targeted assessment for cardiac, hepatic, and neurologic involvement. A negative peripheral tissue biopsy does not exclude the disease when clinical suspicion remains high. Early referral to hematology or a specialized center facilitates completion of the diagnostic evaluation without delay.

Available evidence supports considering targeted diagnostic evaluation when combinations of warning signs are present but does not demonstrate that screening orthopedic tissues reduces advanced organ involvement or improves survival. Limitations in patient selection, diagnostic verification, and follow-up restrict ex-

trapolation of the findings. Prospective studies with standardized protocols, amyloid typing, and adequate follow-up are needed to establish the clinical benefit of this approach.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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