

Immunoglobulin Light Chain Amyloidosis: Diagnosis and Risk Assessment

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ABSTRACT

Immunoglobulin light chain (AL) amyloidosis is a clonal plasma cell disorder with multiple clinical presentations. The diagnosis of AL amyloidosis requires a high index of suspicion, making a delay in diagnosis common, which contributes to the high early mortality seen in this disease. Establishing the diagnosis of AL amyloidosis requires the demonstration of tissue deposition of amyloid fibrils. A bone marrow biopsy and fat pad aspirate performed concurrently have a high sensitivity for the diagnosis of AL amyloidosis and negate the need for organ biopsies in most patients. An accurate diagnosis requires amyloid typing via additional testing, including tissue mass spectrometry. Prognostication for AL amyloidosis is largely driven by the organs impacted. Cardiac involvement represents the single most important prognostic marker, and the existing staging systems are driven by cardiac biomarkers. Apart from organ involvement, plasma cell percentage on the bone marrow biopsy, specific fluorescence in situ hybridization findings, age at diagnosis, and performance status are important prognostic markers. This review elaborates on the diagnostic testing and prognostication for patients with newly diagnosed AL amyloidosis.

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The term “amyloid” refers to extracellular deposition of protein fibrils, with upward of 30 different types of amyloid fibrils having been identified in humans.^{1–3} Some of these amyloid fibrils are deposited systemically, leading to organ damage, whereas other types of amyloidosis have localized deposition.⁴ Systemic immunoglobulin light chain (AL) amyloidosis is a clonal plasma cell disorder arising from tissue deposition of insoluble β -pleated sheets of misfolded immunoglobulin light chains. Despite being the most frequently encountered systemic amyloidosis, AL amyloidosis is an uncommon entity with an estimated incidence of approximately 1 patient per 100,000 person-years.⁵ This translates to 3,500 to 4,500 new patients with AL amyloidosis being diagnosed in the United States each year.^{5,6} Immunoglobulin heavy chain (AH) amyloidosis, a rare immunoglobulin amyloidosis, presents with the clinical features and treatment responses that largely parallel AL amyloidosis, and as such are included in the discussion.^{7,8} Prognostication tools for AL amyloidosis have evolved over the past 2 decades. The heart is the most involved organ and is the most important determinant of outcome. This review addresses disease manifestations, diagnostic testing, and prognostic tools to aid clinicians in the initial steps of diagnosis.

Clinical Presentation of AL Amyloidosis

Establishing a diagnosis of AL amyloidosis is often challenging because there is no single test that conclusively establishes the diagnosis, but testing performed in the correct clinical context is needed. Delay in arriving at a diagnosis has been reported to range from 6 months to ≥ 2 years from time of symptom onset.^{9,10} The heterogeneous clinical phenotype for AL amyloidosis often leads to patients presenting with advanced disease after being evaluated in various specialties without a diagnosis.¹⁰ This delay in diagnosis is true even in patients with preexisting plasma cell disorders, who are known to be at risk for AL amyloidosis.¹¹ Fatigue is the commonest symptom in AL amyloidosis. In patients with coexisting/preexisting multiple myeloma or Waldenström’s macroglobulinemia, fatigue is often attributed to anemia or ongoing systemic therapy for these disorders.^{11,12}

Amyloid deposition can affect any organ system, and the presenting symptoms are largely driven by the organ

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dysfunction caused by the amyloid deposition. Cardiac amyloidosis presents with signs and symptoms of heart failure and the initial suspicion is commonly raised by cardiologists during echocardiographic evaluation with findings suggesting infiltrative cardiomyopathy.¹³ A combination of concentric cardiac hypertrophy, increase in interventricular septal thickness, and normal-to-low voltage on electrocardiogram (ECG) has been classically described in AL amyloidosis, but multiple confounders limit the sensitivity of these findings.¹⁴ The cardiac hypertrophy tends to be biventricular, unlike in systemic hypertension in which it is commonly left-sided. More specific abnormalities on echocardiogram for cardiac amyloidosis include an abnormal strain pattern with a base-to-apex gradient.¹³ Cardiac MRI in amyloidosis demonstrates late gadolinium enhancement (LGE), which occurs due to the disruption of the tight junctions in between the myocytes from the expanding interstitial amyloid. Transmural LGE correlates to an advanced cardiac involvement.¹⁵ Apart from heart failure, electromechanical dissociation and ventricular arrhythmias are a common cause of cardiac mortality in patients with AL amyloidosis, especially sudden cardiac death.¹⁶ Nephrotic range proteinuria without an obvious etiology merits evaluation for AL amyloidosis.⁹ Patients presenting with a symmetric distal painful peripheral neuropathy with or without an autonomic component often have an extensive neurologic evaluation performed before ultimately being diagnosed with AL amyloidosis.¹⁷ In a study of peripheral neuropathy as the first manifestation of AL amyloidosis, a median delay of 21 months from symptom onset to diagnosis of AL amyloidosis was reported.¹⁸ It is important to recognize other causes of peripheral neuropathy that may be associated with a monoclonal protein (eg, cryoglobulinemia, POEMS syndrome, IgM neuropathy) as well as common causes of peripheral neuropathy that can have an incidental presence of a monoclonal protein (eg, chronic inflammatory demyelinating polyneuropathy). Presentation with other organ involvement, including liver (eg, hepatomegaly, elevated alkaline phosphatase) and gastrointestinal tract (eg, diarrhea from malabsorption, constipation, early satiety, weight loss), and other manifestations such as musculoskeletal pathologies (eg, arthralgias/arthritis, myopathy), endocrinopathies (eg, hypothyroidism, hypogonadism), and coagulopathy (eg, bleeding diathesis), tend to be nonspecific and require a high index of suspicion. Other classic clinical findings, including macroglossia, bilateral carpal tunnel syndrome, and periorbital ecchymoses (“raccoon eyes”), may trigger an evaluation for systemic amyloidosis, but are uncommon.¹⁹ Incidental detection of amyloid deposits on bone marrow or fat specimens without a clinical syndrome has a low risk of progression to systemic amyloidosis with organ involvement (2.7%) and does not require treatment.²⁰

Common signs and symptoms that should raise suspicion for AL amyloidosis are depicted in Figure 1.

Diagnostic Testing for AL Amyloidosis

The first step in diagnosing AL amyloidosis is to establish the presence of a monoclonal protein, because the absence of a monoclonal protein makes the diagnosis of AL amyloidosis extremely unlikely. In a Mayo Clinic study, among 522 evaluable patients, only 1 (0.2%) had AL amyloidosis with normal results of all monoclonal protein studies.²¹ For full evaluation, serum electrophoresis and immunofixation, 24-hour urine protein collection for electrophoresis/immunofixation, and serum free light chain assay should be ordered. Once a suspicion of AL amyloidosis is entertained, a biopsy demonstration of Congo red–positive amorphous deposits with apple green birefringence on polarized light microscopy is necessary.²² Alternate stains, including thioflavin T or sulfated alcian blue, can be used in place of Congo red staining to demonstrate the amyloid fibrils. A bone marrow biopsy is typically the most common source for tissue specimen evaluation, but has a sensitivity of only 56% to 70% for establishing a diagnosis.^{23,24} The next most used biopsy is a fat pad aspiration, which when performed alone has a diagnostic sensitivity for AL amyloidosis of 70% to 80%.^{25,26} When a bone marrow biopsy and a fat pad aspiration are performed concurrently, the diagnostic sensitivity for AL amyloidosis reaches 80% to 90%.^{27,28} Thus, an organ biopsy is unnecessary in most patients. For example, although renal biopsy is the gold standard for confirming renal involvement, nonselective proteinuria (>0.5 g/24 h) and documented extrarenal amyloid deposits eliminate the need for a renal biopsy.²⁹ Approximately 10% to 20% patients can have a negative fat pad aspirate and bone marrow study. If the clinical suspicion for amyloidosis remains elevated, biopsy of the suspected involved organ should be considered, with careful attention paid to the adequacy of the specimen to avoid false-negative results.²⁷ Apart from providing tissue for Congo red staining, a bone marrow biopsy is needed to assess the underlying B-cell disease (typically pure plasma cell clone, as well as occasionally other monoclonal protein–secreting disorders, such as Waldenström macroglobulinemia).^{19,30} Fluorescence in situ hybridization (FISH) testing can have important prognostic and therapeutic implications, as discussed later, and should be performed on the bone marrow specimen at diagnosis.²²

Amyloid Typing

The importance of typing the amyloid fibrils cannot be overstated. This is true even when there is evidence of a monoclonal protein in the serum, because a monoclonal gammopathy may be unrelated to the amyloid process. Mass spectrometry–based proteomic assay is considered

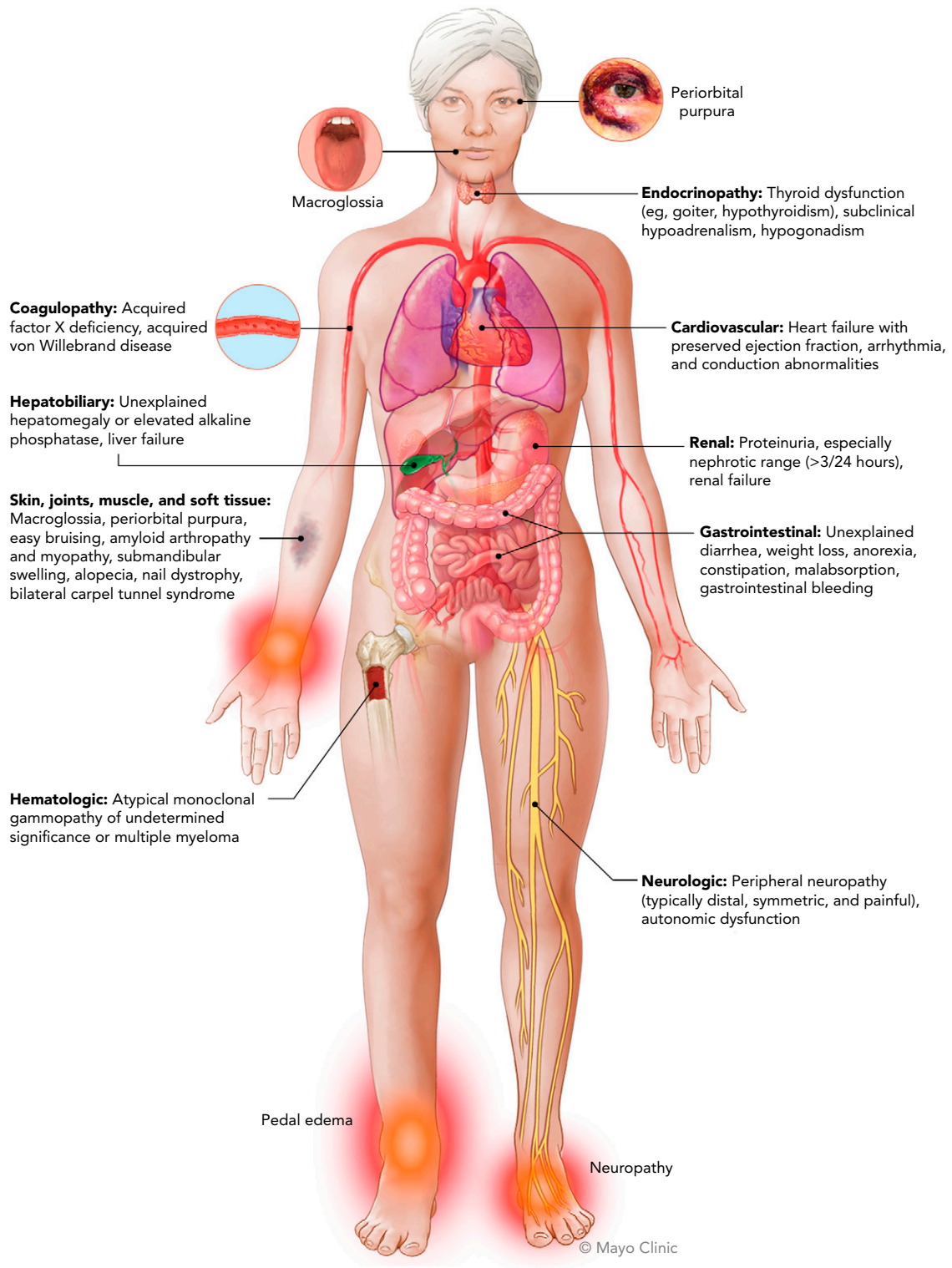


Figure 1. Common presenting signs and symptoms that should raise clinical suspicion for immunoglobulin light chain amyloidosis.

the gold standard testing to establish the type of amyloid fibril.³¹ A major advantage of mass spectrometry is the high sensitivity/specificity for all types of amyloidosis with a single test, even with a small amount of tissue. Other techniques used for typing of amyloidosis include immunohistochemistry, immunofluorescence, and immunogold electron microscopy (IEM). These typing techniques, however, are less accurate, because antibodies are available only for common amyloid types, the antigen-antibody chemistry is nonspecific, and IEM is not readily available.^{22,32} In a study of 320 specimens that were Congo red–positive and –negative by immunohistochemistry testing, mass spectrometry was able to detect the amyloid protein in 255 (80%).³²

Assessing Organ Involvement

Given that the heart is the most common organ involved in AL amyloidosis and cardiac involvement is the most important prognostic marker, assessing for heart involvement is crucial. Echocardiographic findings of concentric hypertrophy with a restrictive filling pattern and abnormal base-to-apex strain gradient are consistent with cardiac amyloidosis in the right clinical context (ie, compatible clinical syndrome with biopsy proof of AL amyloid from a different site) and negate the need for endomyocardial biopsy.¹³ Artificial intelligence–based ECG assessment can aid in diagnosing cardiac amyloidosis and may improve the rate of early diagnosis, based on the findings of a single-center study.³³ Its impact on early diagnosis of cardiac amyloidosis is being explored, and it currently has limited access in clinical practice. The role of nuclear imaging of the heart is primarily reserved for identifying transthyretin (TTR) cardiac amyloidosis, an amyloid entity not related to a clonal plasma cell disorder. The technetium-99m pyrophosphate (PYP) single-photon emission CT (SPECT) scan has demonstrated excellent sensitivity (85%–97%) and specificity (97%–100%) in the diagnosis of TTR amyloidosis, and is used as a confirmatory study for cardiac TTR amyloidosis without the need for biopsy confirmation.³⁴ However, PYP-SPECT can also be positive in AL cardiac amyloidosis. Therefore, in the presence of a monoclonal protein, this nuclear imaging test cannot be used to validate typing, and tissue-based typing should be pursued.^{35,36} Because the most commonly involved organs are the heart and kidneys, followed by the nerves, liver, and gastrointestinal tract, the minimal evaluation for organ involvement in patients with AL amyloidosis should include ECG, echocardiogram, cardiac biomarkers (as will be discussed later), serum creatinine, albumin, and alkaline phosphatase.²² If suspicion exists for nerve involvement, then nerve conduction studies, electromyography, and autonomic nerve studies should be performed. Gastrointestinal involvement can only be ascertained by biopsy

confirmation and should be considered in the right clinical context. Screening for coagulopathy can be performed using prothrombin time and partial thromboplastin time and by directly measuring factor X level. In patients with AL amyloidosis and a bleeding disorder, acquired von Willebrand disease should also be ruled out, especially if prothrombin time and factor X level are normal.³⁷

Prognostic Markers for AL Amyloidosis

Advances in plasma cell–directed therapies and improved supportive care have resulted in an improvement in overall survival (OS) for patients with AL amyloidosis over the past 2 decades.^{38,39} However, despite a reduction in early mortality rate, up to 30% patients die within 6 months of diagnosis.^{28,40} Much of the early mortality is driven by cardiac amyloidosis, whereas the long-term prognosis is determined by organ involvement and characteristics of the underlying plasma cell clone.^{22,39,41,42}

Cardiac Prognostication

Cardiac biomarkers, troponin and natriuretic peptide, have been incorporated into well-validated prognostic models. The Mayo 2004 prognostic model for AL amyloidosis incorporates NT-proBNP (*N*-terminal pro-B-type natriuretic peptide; ≥ 332 ng/L) and cardiac troponin T (cTnT; ≥ 0.035 μ g/L), with 1 point for each biomarker above the mentioned thresholds (Table 1).⁴³ The European modification of the Mayo 2004 model further stratifies Mayo 2004 stage III into stages IIIa and IIIb based on NT-proBNP levels $>8,500$ ng/L (stage IIIb), which identifies patients with poorest outcomes with median OS of <6 months.⁴⁴ The serum light chain burden has been incorporated with the cardiac biomarkers into the revised Mayo 2012 model.⁴⁵ Work by researchers at Boston University established a BNP of 81 ng/L to be most closely comparable to the cutoff of 332 ng/L for NT-proBNP used in the Mayo 2004 model.⁴⁶ Although there are limited head-to-head comparison data for BNP and NT-proBNP, the longer half-life, greater stability (even on frozen samples), and less stringent preanalytical requirements for NT-proBNP make it the routine choice of biomarker in clinical practice.⁴⁷ The commonly used prognostic staging systems for AL amyloidosis and the expected survival with staging are depicted in Table 1. High-sensitivity cTnT (hs-cTnT) is now the cardiac biomarker of choice. To harmonize the previously used 4th generation troponin T assay used for modeling with the currently used hs-cTnT, a conversion tool has been developed (Table 2).⁴⁸

Renal Prognostication

Kidneys are involved in 50% to 70% of patients with AL amyloidosis, and end-organ damage is a major source of morbidity.⁴⁹ In patients with coexistent cardiac and renal AL amyloidosis, OS is largely dictated by the cardiac

Table 1. Prognostic Models in AL Amyloidosis

Prognostic Model	NT-proBNP	Cardiac Troponin	dFLC	Stage	Median OS by Stage
Mayo 2004 model ⁴³	≥332 ng/L	cTnT ≥0.035 µg/L or cTnI ≥0.1 µg/L	NA	I: no marker above threshold II: 1 marker above threshold III: 2 markers above threshold	I: 26.4 mo (HR, ref) II: 10.5 mo (HR, 2.5 mo) III: 3.5 mo (HR, 6.7 mo)
European modification of Mayo 2004 model ^{28,44}	≥332 ng/L (>8,500 ng/L identifies higher risk)	cTnT ≥0.035 µg/L or cTnI ≥0.1 µg/L	NA	I: no marker above threshold II: 1 marker above threshold IIIa: 2 markers above threshold; NT-proBNP 332–8,500 ng/L IIIb: 2 markers above threshold and NT-proBNP >8,500 ng/L	I: Median OS, NR; 10-y OS, 57% (HR, ref) II: 67 mo (HR, 2.5 mo) IIIa: 15 mo (HR, 4.9 mo) IIIb: 4 mo (HR, 11.1 mo)
Mayo 2012 model ⁴⁵	≥1,800 pg/mL	cTnT ≥0.025 µg/L or cTnI ≥0.1 µg/L	≥18 mg/dL	I: no marker above threshold II: 1 marker above threshold III: 2 markers above threshold IV: 3 markers above threshold	I: 94.1 mo (HR, ref) II: 40.3 mo (HR, 1.7 mo) III: 14 mo (HR, 4.1 mo) IV: 5.8 mo (HR, 6.3 mo)

Abbreviations: AL, immunoglobulin light chain; cTnI, cardiac troponin I; cTnT, cardiac troponin T; dFLC, difference in serum free light chains; HR, hazard ratio; NR, not reached; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OS, overall survival.

involvement, and most patients succumb to the disease before end-stage renal disease ensues.^{43,49} Single-organ renal involvement has a favorable outcome, with 8-year OS of 80%.²¹ Palladini et al⁵⁰ proposed a renal staging system for predicting progression to dialysis, the more pertinent endpoint for renal amyloidosis. In this staging system, proteinuria >5 g/24 hours and estimated glomerular filtration rate (eGFR) <50 mL/min per 1.73 m² were identified as independent predictors of progression to dialysis. Patients with both of these risk factors were demonstrated to have a risk of progression to dialysis of 60% to 85%, compared with 0% to 4% among patients with proteinuria ≤5 g/24 hours and eGFR ≥50 mL/min per 1.73 m² (Table 3).⁵⁰

Plasma Cell Burden and Interphase FISH

Average bone marrow plasma cell (BMPC) involvement in AL amyloidosis on bone marrow biopsy is approximately 10%, and although multiple studies have demonstrated that patients with a higher BMPC (>10%) have adverse outcomes, this is not universal.^{51–53} More recently, a Mayo Clinic study demonstrated that coexistent plasma cell burden of ≥20% at diagnosis had a markedly inferior median OS of 12 months compared with 33 months in patients with 5% to 19% BMPCs and 81 months in patients with <5% BMPCs.⁵⁴ A higher BMPC percentage was

associated with increased cardiac involvement, and the prognostic impact of ≥20% BMPCs was independent of other commonly used prognostic markers.⁵⁴ The frequency of high-risk FISH [eg, del(17p), t(4;14), and t(14;16)] as well as myeloma CRAB features was also more prevalent in patients with a higher BMPC percentage. Compared with multiple myeloma, the presence of clonal heterogeneity is much lower in AL amyloidosis. This is likely due to the high prevalence of t(11;14) in AL amyloidosis (seen in 40%–60% of AL), which can suppress subclonal disease, rather than an effect of the disease itself.⁵⁵

Translocation t(11;14) is present in 40% to 60% of patients with AL amyloidosis and is associated with inferior response and survival in patients treated with bortezomib-based therapy.^{56–59} This treatment-dependent adverse marker can be overcome with autologous transplant and daratumumab-based treatments.¹⁹ In addition, t(11;14) serves as a predictive marker for response to BCL-2 inhibition with venetoclax, although venetoclax is currently not FDA-approved for this indication.⁶⁰ Patients with trisomies (identified in up to 30% of patients with AL amyloidosis) and those with high-risk FISH cytogenetics have poor outcomes, but the latter are infrequently encountered in patients with AL amyloidosis.^{56,61}

Table 2. Comparable Threshold for Cardiac Biomarkers Used in AL Amyloidosis Prognostic Systems

Model	cTnT	cTnI	HS-cTnT	NT-proBNP	BNP ⁴⁶
Mayo 2004 model ⁴³	≥0.035 µg/L	≥0.1 µg/L	≥50 ng/L	≥332 ng/L	≥81 ng/L
European modification of Mayo 2004 model ⁴⁴	≥0.035 µg/L	≥0.1 µg/L	≥50 ng/L	≥332 ng/L >8,500 ng/L (stage IIIb)	≥81 ng/L >700 ng/L (stage IIIb)
Mayo 2012 model ⁴⁵	≥0.025 µg/L	NA	≥40 ng/L	≥1,800 ng/L	≥400 ng/L

Abbreviations: AL, immunoglobulin light chain; BNP, brain natriuretic peptide; cTnI, cardiac troponin I; cTnT, cardiac troponin T; HS-cTnT, high-sensitivity cardiac troponin T; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide. Adapted from Muchtar E, Kumar SK, Gertz MA, et al. Staging systems use for risk stratification of systemic amyloidosis in the era of high-sensitivity troponin T assay. *Blood* 2019;133:765; with permission.

Table 3. Renal Staging in AL Amyloidosis

Renal Staging ⁵⁰	eGFR <50 mL/min per 1.73 m ²	Proteinuria >5 g/24 h	Progression to Dialysis
Low risk (stage I)	Absent	Absent	0% and 4% at 3 years in testing and validation cohort, respectively
Intermediate risk (stage II)	Present	Absent	7% and 30% at 3 years in testing and validation cohort, respectively
	Absent	Present	
High risk (stage III)	Present	Present	60% and 85% at 3 years in testing and validation cohort, respectively

Abbreviations: AL, immunoglobulin light chain; eGFR, estimated glomerular filtration rate.

Depth of Response and Prognosis

Serum free light chains are the primary assay used for assessment of hematologic response to therapy in AL amyloidosis.^{62–64} The greater the reduction in the amyloidogenic light chain supply, the better the survival. Greater than 50% reduction in dFLC (difference between involved and uninvolved free light chains) is consistent with partial response, whereas dFLC <40 mg/L qualifies as a very good partial response (VGPR).⁶² Hematologic complete response, defined as a negative serum and urine immunofixation with a normal free light chain ratio, is the level of response that is consistently associated with superior outcomes, and should be the target goal if it can be safely achieved.^{62–66} Hematologic VGPR is an acceptable response. Together, hematologic complete response and VGPR can be achieved with first-line therapy in approximately 65% to 80% of patients.⁶⁷ Patients with a baseline dFLC of <50 mg/L are considered nonevaluable for hematologic response. In these patients, achievement of dFLC <10 mg/L after treatment has been demonstrated to be of prognostic value in multiple studies, and is termed *low-dFLC partial response*.^{68,69} Hematologic response should be achieved as early as possible to improve chances of organ response and survival. Multiparameter flow cytometry–based minimal residual disease negativity at the end of treatment is associated with improved progression-free survival, and additional studies are needed to better define its role in response assessment and management.^{70,71}

Organ response, the ultimate goal of therapy, is typically delayed, occurring 6 to 12 months from the start of therapy. This is a limitation in its utility for early prognostication.⁷² Depth of organ response is also prognostic, and deeper responses are associated with improved OS for both cardiac and renal responses.^{72–74} Other

important prognostic parameters include advanced physiologic age at diagnosis (>65 to 70 years), poor performance status (ECOG performance status >2), and autonomic involvement.^{38,75–77}

Summary

Patients with systemic AL amyloidosis present with a varied constellation of symptoms driven by the underlying organ involvement. Establishing the diagnosis requires a high index of suspicion. Diagnosis confirmation requires biopsy-proven Congo red–positive material followed by accurate typing of the amyloid fibril. Prognosis in AL amyloidosis is driven by organ involvement, with the currently prevalent staging systems relying heavily on the baseline cardiac biomarkers. Apart from organ involvement, plasma cell burden and FISH findings carry prognostic value. Even with advances in treatment, high early mortality rates remain a major hurdle, further underscoring the need for early diagnosis.

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