Diagnostic Challenges in Amyloid Light-Chain Amyloidosis

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ABSTRACT

Amyloid light-chain (AL) amyloidosis is a rare plasma cell disorder characterized by the extracellular deposition of misfolded immunoglobulin light chains, resulting in organ dysfunction and high mortality. Delayed and missed diagnoses are common owing to nonspecific, heterogeneous symptoms. Evidence shows that racial and ethnic minorities, individuals with low socioeconomic status, and patients without access to specialized centers are more likely to experience delayed diagnoses and reduced treatment access. This introduces the potential for populations affected by AL amyloidosis to be excluded from clinical cohorts. From a laboratory perspective, diagnosis relies heavily on serum and urine free light-chain assays. Reference intervals present an ongoing challenge as recommendations shift from population-specific to population-inclusive models and as organ dysfunction confounds urine-based assays. Refinement of reference intervals using diverse cohorts, development of novel assays targeting amyloidogenic light chains, risk-based stratification approaches, and artificial intelligence–based predictive models show promise for earlier disease recognition. Addressing diagnostic delays while minimizing unnecessary interventions requires coordinated improvements in laboratory testing, provider education, infrastructure, and population-based research.

ABBREVIATIONS: AI - artificial intelligence, AL - amyloid light chain, ATTR-CM - transthyretin amyloid cardiomyopathy, dFLC - difference between involved and uninvolved light chains, eGFR - estimated glomerular filtration rate, EHR - electronic health record, FLC - free light chain, MDT - multidisciplinary team, MGUS - monoclonal gammopathy of undetermined significance, SES - socioeconomic status, VistA - Veterans Health Information Systems and Technology Architecture.

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INTRODUCTION

Amyloidosis represents a family of rare disorders characterized by the extracellular deposition of misfolded protein fibrils (amyloid) in tissues and organs. The subtypes of amyloidosis vary in inheritance patterns, precursor proteins, and affected organs. Amyloid light-chain (AL) or primary amyloidosis is caused by the overproduction of abnormal light chains by a monoclonal plasma cell population in the bone marrow. These light chains misfold and form light-chain aggregates, which impact organ function. Cardiac involvement occurs in approximately 75% of cases and is the single most important predictor of survival.[1] In most cases, 2 or more organs are impaired.[2] The rarity of AL amyloidosis combined with the nonspecific presentation contributes to delayed diagnoses, high health care use, and substantial financial burden.

The epidemiology of AL amyloidosis reveals a potential disconnect between individuals with the disease and those who receive a diagnosis. Reported prevalence has steadily increased over time, with an 11.9% increase from 2007 to 2015 and a 35.7% annual increase from 2019 to 2021.[3,4] Although the 10% decrease in 6-month mortality from the 1980s to 2010s suggests that the rise in prevalence is caused by prolonged survival rather than increased incidence, improvements in outcomes are not equitably distributed.[5] Patients who experienced early mortality between 2010 and 2019 were more likely to be from an ethnic or racial minority and to present with advanced cardiac involvement at diagnosis.[5]

These disparities in diagnosis may contribute to the underrepresentation of racial and ethnic minority populations in clinical cohorts, which are frequently used to establish clinical criteria and laboratory reference standards. Because laboratory testing is central to the diagnosis and monitoring of AL amyloidosis, imbalances in represented populations may influence how the disease is detected and characterized across diverse groups. Thus, the goal of this literature review is to explore the intersection between diagnostic disparities in AL amyloidosis and laboratory testing decisions. First, it outlines how socioeconomic, health care system, and clinical

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barriers can limit access to appropriate testing. It then evaluates how laboratory practices, including assay and reference interval selection, can influence diagnostics. By reframing laboratory testing as an active component of diagnostic equity rather than a neutral step, this review seeks to identify opportunities to promote more equitable detection and care to all patients.

SOCIOECONOMIC BARRIERS

Population-level studies suggest that AL amyloidosis diagnosis and mortality patterns reflect differences in health care access. For example, Alexander et al[6] reported that mortality caused by amyloidosis of all subtypes was highest near amyloidosis centers and among Black men and women yet lowest in US states with a greater proportion of Black residents. Rather than reflecting true differences in disease burden, these patterns may reflect referral and ascertainment biases wherein proximity to referral centers increases the likelihood of diagnosis and inclusion in such studies. Similar disparities have been reported in a different subtype of amyloidosis, transthyretin amyloid cardiomyopathy (ATTR-CM), in which misfolded transthyretin proteins accumulate in the heart. Shankar et al[7] reported that Black patients were more likely to be diagnosed with ATTR-CM at a later disease stage than White patients, and Black patients with low socioeconomic status (SES) had worse outcomes regardless of disease severity. Additionally, they reported that most patients with an ATTR-CM diagnosis were from an area with high SES. These findings suggest that SES influences who has access to timely evaluation, diagnosis, and treatment.

Studies specific to AL amyloidosis demonstrate similar trends. According to Staron et al,[5] the largest population-based studies of AL amyloidosis consist of predominately White patient populations. They reported that 86% of study participants from 1990 to 2020 were non-Hispanic White, suggesting that nonspecific symptoms such as nephrosis and cardiomyopathy are misattributed to conditions such as hypertension or diabetes mellitus in racial and ethnic minorities. Moreover, individuals who were unmarried or had lower educational attainment were more likely to experience delayed diagnosis and adverse outcomes independent of race or ethnicity. Access to advanced therapies such as high-dose melphalan and autologous stem cell transplantation were also influenced by SES and disease stage because racial and ethnic minorities were less likely to receive these treatments because of late-stage diagnoses.[5] These therapies are also costly; patients with limited insurance or high-deductible plans may be unable to pursue extensive diagnostic testing or specialized care. As such, household economic status is a consideration in treatment choice, alongside factors such as disease severity.[8] Collectively, these findings underscore the broader role of social determinants in access to diagnosis and treatment, thereby influencing which patients are captured in clinical datasets and research cohorts.

HEALTH CARE SYSTEM BARRIERS

Beyond individual-level socioeconomic barriers, structural features of the US health care system contribute to the delayed recognition of AL amyloidosis. Even among patients with health care access, the time to diagnosis can be prolonged by fragmented care pathways and variable provider familiarity with rare disorders. The nonspecific presentation of AL amyloidosis necessitates a multidisciplinary approach to patient care, which often requires travel to multiple specialist centers. According to one survey ($n = 248$), patients reported seeing a median of 3 physicians before receiving a diagnosis,[9] whereas McCausland et al[10] found that 27.9% of patients ($n = 341$) saw 6 or more physicians.

Additional barriers to care include distance to treatment centers, childcare costs, and limited ability to take leave from work. Telehealth could help to ease the burden of travel to specialist centers, but limited insurance reimbursement and regulation of appointments across state lines make this more challenging.[11] Evidence from the Veterans Health Information Systems and Technology Architecture (VistA) demonstrates both promise and limitations: patients who received a low proportion of primary care via telehealth had similar quality outcomes to those who received in-person care only, but the adjusted likelihood of quality outcomes decreased when telehealth usage was high.[12] Beyond primary care, complex disorders like AL amyloidosis require multidisciplinary team (MDT) coordination and in-person appointments for physical examination and testing.[13] With these limitations in mind, telehealth-facilitated MDT meetings combined with electronic health record (EHR) integration modeled after VistA could allow for real-time coordinated interpretation of complex cases among physicians. However, reliance on telehealth risks widening disparities for individuals with inequal access to technological literacy and resources.

CLINICAL BARRIERS

The heterogeneous patient presentation and nonspecific symptomatology of AL amyloidosis presents another challenge for individuals who can access medical care. According to a survey conducted by Abdallah et al[9] ($n = 98$), the most common initial symptoms reported by patients were fatigue or weakness (47%), swelling (38%), shortness of breath (28%), chest pain (23%), and foamy urine (22%). A median of 2 symptoms was reported per individual, whereas 31% reported only 1 symptom. Notably, one-third of participants reported a diagnostic delay of more than 12 months, and nearly half (48%) noted a lack of AL amyloidosis awareness among medical professionals. Overall, 59% felt their diagnosis was delayed,

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50% believed that this delay led to decreased treatment efficacy, and 25% felt that treatment itself was delayed.[9] These findings align with those from Li et al,[8] who observed that an average of 2 to 9 precursor diagnoses were made before reaching AL amyloidosis. Variability in provider awareness and familiarity with AL amyloidosis further compounds these challenges, particularly in rural settings where exposure to rare diseases may be limited.

Artificial intelligence (AI) and predictive algorithms show promise in mitigating the effects of inconsistent provider awareness in symptom recognition. One approach involves automatic flagging and reflex testing within EHRs triggered by laboratory values or other clinical patterns. Some studies have applied machine learning to differentiate AL amyloidosis from conditions with overlapping features, such as nephrotic syndrome and hypertrophic cardiomyopathy. Liu et al[14] used demographic data and laboratory results from 404 patients to create a predictive model to predict the likelihood of AL amyloidosis compared with other diseases with similar symptomatology.

Such tools could also be useful for risk stratification. Disease progression occurs on a spectrum—monoclonal gammopathy of undetermined significance (MGUS) can precede plasma cell disorders like AL amyloidosis. More often, however, MGUS is a benign monoclonal expansion that can arise because of impaired renal function, a temporarily heightened immune state, or rise naturally with age. One major clinical trial (iStopMM) sought to determine the clinical utility of screening for MGUS. They reported that 4.94% of adults had MGUS, but the majority of these cases were classified as low risk (38%) or low–intermediate risk (36%).[15] Because a high proportion of cases do not require excessive follow-up, risk stratification permits early diagnosis while reducing overtesting and patient anxiety caused by increased follow-ups. Excessive appointments and health care use associated with unnecessary testing could also widen disparities among individuals who cannot afford to take time off work or travel for appointments.

Combining these risk stratification tools with other predictive algorithms could help identify which patients may be at risk of progressing to AL amyloidosis, thus improving patient outcomes and resource allocation. Examples of potential applications include using next-generation sequencing and cytogenetics to enhance early detection of AL amyloidosis progression in MGUS and patients with smoldering multiple myeloma,[16] using clustering algorithms on clinical signs and baseline laboratory values to categorize AL amyloidosis patients into low-, intermediate-, and high-risk outcome groups[17] or using machine learning to predict the amyloidogenic potential of specific light-chain mutations.[18] Despite these advances, AI models require large, diverse datasets for validation, and the complexity of light-chain characteristics and molecular signatures can limit generalizability. Furthermore, technical and logistical barriers, such as integration into EHR systems and simplicity for provider use, make integration a complex process. Nevertheless, AI and predictive algorithms could eventually help to mitigate discrepancies in provider education, reduce misdiagnosis, and support equitable care across diverse patient populations.

THE ROLE OF THE LABORATORY

On clinical recognition of AL amyloidosis, the diagnostic process relies heavily on laboratory evaluation to detect monoclonal proteins and excess free light chains (FLCs). A full panel including serum protein electrophoresis, serum immunofixation by electrophoresis, and serum FLC quantification as well as supplementation with urine protein electrophoresis, urine immunofixation electrophoresis, and bone marrow aspirate and biopsy are recommended by the International Myeloma Working Group and National Comprehensive Cancer Network for the diagnosis of monoclonal gammopathies.[19] FLC assays use antisera directed against epitopes exposed only on unbound κ and λ light chains, thereby distinguishing FLCs from those incorporated into intact immunoglobulins. Because laboratory testing is central to staging and therapeutic monitoring, differences in assay selection and interpretation directly influence clinical decision-making and, potentially, equity of care.

Several FLC assays are currently approved for clinical use, including Freelite (The Binding Site, Birmingham, United Kingdom), N Latex (Siemens Healthineers, Erlangen, Germany), Diazyme (Diazyme Laboratories, Poway, California), and Sebia (Sebia, Lisses, France). Diazyme FLC, Sebia FLC, and Freelite (the first and most widely adopted assay) use polyclonal antisera to recognize multiple epitopes on κ and λ FLCs. In contrast, N Latex uses monoclonal antisera, targeting a specific epitope on each light-chain type.[20] Each assay design has pros and cons; for example, polyclonal antisera may allow broader recognition of structurally heterogeneous proteins but exhibit greater lot-to-lot variation.[20,21] Discrepant results may be produced among assays owing to varying binding affinities for monomeric vs dimeric or oligomeric proteins, which is an important consideration in the context of light-chain aggregation. This has more of an impact on λ FLC detection because these light chains more often build dimeric and oligomeric complexes; although kappa correlation is excellent among assays, lambda correlation exhibits lower concordance.[20-22] This interassay variability also requires the same test to be used over the course of patient treatment monitoring for consistent results.

Most risk scores, such as Mayo staging and therapeutic response criteria, were originally validated using the Freelite assay. Palladini et al[23] compared Freelite and N Latex measurements of the difference between involved and uninvolved light chains (dFLC) and found that the prognostic cutoff for hematological response differed between assays; a more than 33% decrease using the N Latex FLC corresponded to a more than 50% decrease using Freelite. Although assay-specific thresholds are

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applied to adjust interpretation, these differences underscore a broader lack of analytical harmonization. There is currently no international reference standard available for FLC assays. Unlike other analytes, FLCs are not a uniform target; they vary in sequence, conformation, and degree of aggregation from patient to patient. This inherent biological variability complicates standardization and contributes to interassay discordance.

Additionally, measuring samples with extreme protein concentrations confers analytical susceptibility to the nonlinearity and to the prozone phenomenon in which an unequal antigen-to-antisera ratio leads to falsely low measurements.[20] Although FLC testing should be considered as part of the larger clinical picture, ensuring that laboratory tests are reflective and predictive of a patient's disease state is paramount.

Emerging technologies could improve analytical consistency for FLC testing. For example, AmyLite, a new FLC assay undergoing research and validation, detects a unique light-chain fragment (dimeric light-chain constant domain) exposed only in misfolded or amyloidogenic proteins.[20] This would allow clinicians to distinguish between pathogenic and benign light chains. However, AmyLite only targets λ light chains, which are present in most AL amyloidosis cases but not all (75%).[20] Mass spectrometry is another approach to improving FLC detection. Matrix-assisted laser desorption/ionization identified monoclonal proteins in 50% of patients who tested negative by conventional methods.[20] This increased analytical sensitivity, or the ability to detect smaller analyte concentrations, can be useful for monitoring treatment response in patients with a dFLC under the limit of detection of traditional assays. However, small monoclonal peaks are not always clinically relevant, as noted with patients with low-risk MGUS.

REFERENCE INTERVALS AND RENAL CONFOUNDING

Importantly, although FLC reference intervals are used globally, they were established through studies of predominately White individuals. MGUS may be overdiagnosed in Black individuals when using these intervals. This introduces unnecessary financial, psychological, and medical burdens.[24] Bertamini et al[24] proposed an adjusted reference interval that was designed using a more diverse group of patients ($n = 10\,035$). Using this adjusted reference interval, light-chain MGUS in Black patients decreased from 10.7% to 0.97%. It is important to note that a decrease in false-positive rates may result in increased false-negative rates. Another study that applied refined reference intervals from the iStopMM trial reclassified 32% of patients with "abnormal FLC ratio" MGUS to having "normal" ratio with no increased risk of progression.[25] However, most participants in the iStopMM trial were White. When reference intervals are derived from predominantly White cohorts, applying these thresholds universally may result in false-positive or false-negative rates across racial groups.

Renal function is another important consideration in the design of "normal" reference intervals because declining kidney function can naturally increase FLC concentrations. Thus, patients with poor kidney function have a different "normal" FLC interval than those without. Renal reference intervals based on estimated glomerular filtration rate (eGFR) have been proposed by Long et al[26] (0.46–2.62 for eGFR 45–59, 0.48–3.38 for eGFR 30–44, and 0.54–3.30 for eGFR <30).

Hutchison et al[27] proposed a generally wider "normal" interval of FLC for patients with GFR of less than 60. Neither have been officially tested in patients with concurrent AL amyloidosis and kidney dysfunction. When stratifying reference intervals based on patient characteristics, it is important to consider lessons learned from the race-based eGFR coefficient. Historically, eGFR values were artificially raised in Black individuals because it was thought that Black patients had higher levels of creatinine that biased eGFR calculations downward. As a result, a race-based coefficient was added to "correct" eGFR calculations for Black patients. In 2021, the National Kidney Foundation and American Society of Nephrology recommended a new equation that removed the race-based coefficient. They demonstrated that because race is not a true biological variable (genetic variation within groups is greater than between them), its inclusion delayed the diagnosis of chronic kidney disease and led to disparities in access to treatment. The new race-free equation performed equally well across racial groups, thus avoiding these inequities.[28] As such, adjusted reference intervals should be employed with caution. Broad race-based adjustments risk worsening health disparities; using diverse study groups to establish reference intervals is a much stronger approach.

CONCLUSIONS

AL amyloidosis exemplifies how rare diseases with nonspecific presentations can result in disproportionate outcomes among patient populations. Socioeconomic barriers influence access to care, health care system fragmentation shapes the efficacy of diagnostic pathways, and variability in provider awareness determines when confirmatory testing is pursued. Because laboratory assays are central to diagnosis and reference intervals are often validated within limited populations, diagnostic inequities may ultimately shape how a disease is defined and detected in future patient populations.

Emerging strategies to mitigate these inequities include telehealth-supported multidisciplinary care, EHR-integrated automated clinical decision support, and inclusive reference interval development. However, these methods must be implemented in a manner that avoids reinforcing existing disparities. Although new developments show promise, there are inherent delays between

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advances in clinical research and implementation into clinical practice. For example, novel disease prediction algorithms require years to assess patient outcomes and to establish provider awareness.

Ultimately, ensuring equitable access to AL amyloidosis diagnoses will require a multifaceted approach. Future research should focus on large-scale validation of emerging assays and AI tools and inclusion of diverse populations in clinical studies. Most importantly, the most reliable tools should be available to all patients rather than limited to those with access to specialized centers. By addressing these shortcomings and allocating funding to AL amyloidosis research, accurate and timely diagnosis can be accessible to all patients.

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