Prognostic Assessment in Light Chain Amyloidosis: Emerging Models and Biomarkers

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THIS YEAR'S European Hematology Association (EHA) 2025 Congress spotlighted a transformative shift in the prognostic landscape of systemic light chain amyloidosis. Among more than 30 abstracts showcased, two studies stood out: one redefining ultra-high-risk cardiac disease through the Mayo Stage IIIc model, and another introducing circulating tumour cells as a non-invasive biomarker with independent prognostic value. Together, they delivered a clear message: in AL amyloidosis, the future of risk stratification lies at the intersection of refined cardiac imaging and cellular precision.

BACKGROUND

Systemic light chain (AL) amyloidosis is a rare plasma cell dyscrasia characterised by the extracellular deposition of misfolded Ig light chains, most commonly of the lambda (λ) type, as insoluble amyloid fibrils in various organs. Although virtually all organs except the brain may be affected, cardiac and renal involvement are the most frequent. Among these, cardiac involvement is the principal determinant of survival, making preservation and improvement of cardiac function the primary therapeutic goal. Another key prognostic factor is the size of the underlying bone marrow plasma cell clone at diagnosis.[1]

Despite significant therapeutic advances, including the introduction of daratumumab-based induction regimens and the increasing use of high-dose melphalan with autologous stem cell transplantation, AL amyloidosis remains incurable. Early mortality continues to pose a major challenge, particularly in those presenting with advanced cardiac dysfunction. Given the strong association between the depth and rate of haematologic response and subsequent organ recovery and survival, precise risk stratification at diagnosis is essential to inform treatment decisions.[2,3]

The Mayo Clinic staging systems stratify patients into prognostically distinct risk groups based on cardiac biomarkers, namely, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin, and the difference between involved and uninvolved serum free light chains (dFLC). However, in the modern treatment era, where therapies effectively target the

underlying plasma cell clone, the prognostic utility of dFLC appears to be diminishing.[4-7] Moreover, these traditional staging models, originally developed before the availability of current anti-plasma cell therapies, may inadequately capture early mortality risk and fail to identify ultra-high-risk patients.

In this feature, the author aims to highlight selected abstracts on AL amyloidosis presented at the 30th Congress of EHA; one of the largest global gatherings of researchers focused on haematologic disorders. This annual meeting provides a platform for investigators to share their latest findings with peers, clinicians, and patient advocates.

A search using the term 'AL amyloidosis' on the EHA 2025 Congress website revealed a total of 38 abstracts, including three oral presentations and 18 e-posters. Among these, the author has selected two abstracts that stood out due to their clinical relevance and potential impact on future practice.

REFINING CARDIAC RISK STRATIFICATION: THE MODIFIED MAYO STAGE IIIC MODEL

In the first abstract, a multinational cohort of 325 patients with newly diagnosed systemic AL amyloidosis from the a European collaboration were retrospectively evaluated to assess the applicability of a modified Mayo staging system, incorporating an ultra-poor risk category labelled as 'Mayo Stage IIIc' in the daratumumab-treated era.[8] This category is defined by the combination of three high-risk features at diagnosis: NT-proBNP ≥8,500 ng/L, high-sensitivity troponin T ≥50 ng/L, and myocardial global longitudinal strain >-9%, the latter reflecting advanced myocardial dysfunction.[8]

At diagnosis, the median age was 64 years, and the median bone marrow plasma cell infiltration was 15% (range: 0–90%). Cardiac involvement was observed in 81% of the cohort, with a substantial proportion also demonstrating renal (58%) and hepatic (19%) involvement. The cohort was heterogeneous in treatment exposure: 61% received daratumumab-based therapies, while 29% were treated with bortezomib-containing regimens. At a median follow-up of 29 months, the 2-year overall survival (OS) rate was 78%.[8]

However, significant survival stratification was evident when patients were categorised according to the revised staging system. Median OS for the modified Mayo Stage IIIc patients was only 9 months, compared to 76 months for Stage IIIb (excluding IIIc), while Stages I through IIIa had not yet reached a median survival threshold. The hazard ratio for mortality in Stage IIIc compared to Stage I was 24.33 (95% CI: 5.67–104.00), indicating a profoundly adverse prognosis. This updated model effectively identified an ultra-high-risk subgroup within Stage III and demonstrated improved discriminative capacity (Harrell's C=0.70). These findings suggest that a combination of global longitudinal strain and cardiac biomarkers provides a valuable tool for early identification of patients at greatest risk of early death, thus supporting more aggressive or tailored interventions in this subgroup.[8]

> **Median OS for the modified Mayo Stage IIIc patients was only 9 months, compared to 76 months for Stage IIIb**

CIRCULATING TUMOUR CELLS AS A PROGNOSTIC BIOMARKER IN LIGHT CHAIN AMYLOIDOSIS

In the second abstract, Kostopoulos et al.,[9] Athens, Greece, prospectively evaluated the prognostic role of circulating tumour cells (CTC) in 218 patients with newly diagnosed, treatment-naïve AL amyloidosis. CTCs were quantified in peripheral blood using highly sensitive next-generation flow cytometry in accordance with EuroFlow guidelines. Detectable CTCs were present in 59% of patients, with a wide range of tumour burden (0.0002–11.4%). The presence of CTCs was significantly associated with higher levels of involved free light chains, elevated NT-proBNP, and increased bone marrow infiltration. Notably, the correlation between CTC levels and bone marrow plasma cell percentage was modest, suggesting that peripheral tumour burden may provide unique prognostic information distinct from marrow involvement.[9]

> **The correlation between CTC levels and bone marrow plasma cell percentage was modest**

Importantly, baseline CTC levels were not significantly associated with the depth of haematological or organ response. However, a higher CTC burden was independently predictive of inferior event-free survival (EFS) and OS in multivariate analysis. CTCs retained prognostic significance even after adjusting for Mayo stage, difference in uninvolved free light chains, and daratumumab exposure. The most discriminatory thresholds were identified as ≥10^{-4} for OS, and the assay's limit of detection for EFS. Furthermore, patients without detectable CTCs achieved significantly higher rates of measurable residual disease negativity, implying that the absence of CTCs may serve as a surrogate marker for deeper and more durable treatment responses. These findings position CTC quantification as a promising non-invasive biomarker that could enhance risk stratification and guide therapeutic decision-making in the early stages of AL amyloidosis, prior to the onset of irreversible organ damage.[9]

CONCLUSION

Systemic AL amyloidosis remains an incurable disease; however, early diagnosis and the advent of novel therapies have significantly improved patient outcomes. All patients require prompt treatment at diagnosis due to the risk of progressive organ dysfunction. As a multisystem disorder, AL amyloidosis necessitates multidisciplinary management, especially in the context of cardiac and renal involvement. Simple, biomarker-based staging systems, using NT-proBNP and cardiac troponin, are widely accessible and clinically useful. Nonetheless, selecting the optimal first-line therapy is critical. The daratumumab, bortezomib, cyclophosphamide, and dexamethasone regimen remains the preferred approach due to its superior haematologic and organ response rates. It is strongly recommended that patients be referred to specialized centers with experience in amyloidosis and autologous hematopoietic stem cell transplantation.

Data presented at the 30th EHA Congress reinforce the importance of refining prognostic stratification in AL amyloidosis. The modified Mayo Stage IIIc model effectively identifies an ultra-high-risk subgroup with poor treatment strategies survival, highlighting the need for tailored or intensified in this population. Additionally, the presence and burden of CTCs emerged as an independent prognostic biomarker, associated with inferior EFS and OS, even after adjusting for established staging criteria.

Taken together, these findings support a paradigm shift toward multimodal risk assessment in AL amyloidosis, incorporating cardiac function, tumour biology, and emerging cellular markers. Continued prospective validation of these tools is essential. Ultimately, a more nuanced understanding of individual patient risk will enable personalised treatment strategies aimed at improving survival while minimising treatment-related toxicity in this complex and heterogeneous disease.

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