
Article:
Garg, M., Choudhuri, S., Parrish, C. et al. (2026) Early diagnosis of AL amyloidosis in haematology, cardiology, neurology, renal and general clinics: A British Society for Haematology Guideline. British Journal of Haematology, 208 (6). pp. 1931-1938. ISSN: 0007-1048

https://doi.org/10.1111/bjh.70472

Early diagnosis of AL amyloidosis in Haematology, Cardiology, Neurology, Renal and general clinics: A British Society for Haematology Good Practice Paper

Mamta Garg[1], Satarupa Choudhuri [2], Christopher Parrish [3], Stephen Hawkins [4], Helen Lachmann [5], Louise Clayton [1], Judith Richardson [6,7], Tom Jennis [6], YL Tracey Chan [8], Ashutosh Wechalekar [5]

Authors' affiliations: Name of NHS Trust

[1]University Hospitals Leicester, Leicester

[2]Northern Cancer Alliance NHS Foundation Trust, Manchester

[3]Leeds Institute of Clinical Trials Research, University of Leeds and Leeds Teaching Hospitals NHS Trust.

[4]The Clatterbridge Cancer Centre NHS Foundation Trust

[5]National Amyloidosis Centre, Royal Free London NHS Foundation Trust, London

[6] Myeloma UK

[7] University Health Service, Edinburgh

[8] University Hospitals Birmingham NHS Trust, Birmingham

Correspondence:

BSH Administrator, British Society for Haematology, 100 White Lion Street, London, N1 9PF, UK. E-mail: bshguidelines@b-s-h.org.uk

Methodology

This Good Practice Paper was compiled according to the BSH process at [https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

Literature review details

The literature search was undertaken with the help of BSH on 11th August 2023 using the PubMed database. The keywords used were: Amyloidosis with one or more of the following; cardiac failure HFpEF, nephrotic syndrome, peripheral neuropathy, autonomic neuropathy, MGCS, MGRS, MGUS, coagulopathy, macroglossia, soft tissue involvement, and hepatomegaly. The time period covered was from 1st January 1993 to 11th August 2023 and was further filtered using the following: inclusion criteria (Human, clinical trial), exclusion criteria (no papers published in non-English journals, no publications without an abstract).

Review of the manuscript

Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee Haem-Onc, the BSH Guidelines Committee and the sounding board of BSH. It was also on the members section of the BSH website for comment. It has also been reviewed by UKMS and Myeloma UK; these organisations do not necessarily approve or endorse the contents.

Introduction

Amyloidoses are conformational diseases caused by misfolding and aggregation of proteins that deposit in tissues in the form of amyloid fibrils.(1, 2) AL amyloidosis accounts for more than half of the patients with amyloidosis and is caused by a plasma cell clone that produces abnormal light chains that misfold and deposit as amyloid fibrils in tissues and thus affect organ function. The majority of patients with AL amyloidosis have plasma cell infiltration of the bone marrow of less than 10% (i.e. monoclonal gammopathy of uncertain significance (MGUS)-like phenotype). These low-grade, otherwise benign, clones that cause life-threatening end organ damage have been termed “small dangerous plasma cell clones”.(3)

The survival of patients with systemic AL amyloidosis largely depends on the extent of end organ damage. Patients with early stage disease can expect approximately 80% survival at 5 years with contemporary treatment, compared to less than 30% for those with advanced disease.(4, 5) Cardiac involvement remains the main cause of mortality but renal amyloidosis nonetheless causes significant morbidity, due to progressive renal failure; dialysis is required in 75% of patients with stage III renal disease at presentation (Table 3). (6, 7) AL amyloidosis is often diagnosed late: in a patient experience survey the diagnosis was made at least a year after the onset of symptoms in nearly 40% of the patients.(8)

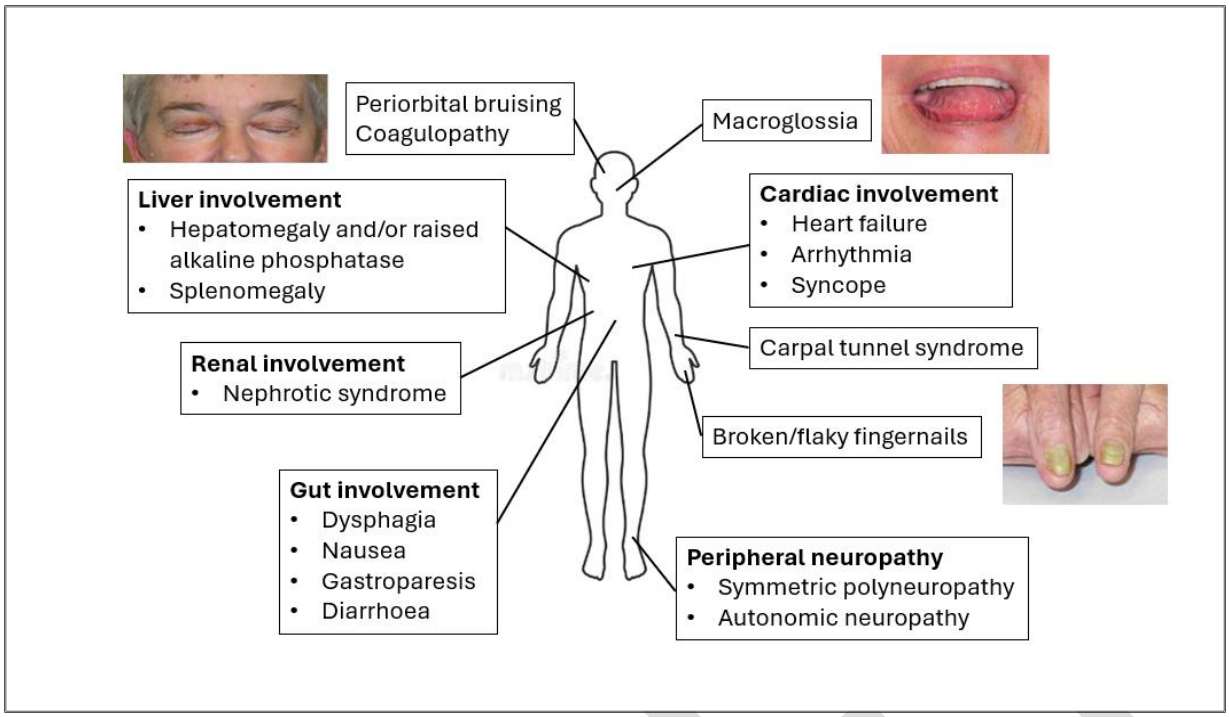
At the UK National Amyloidosis Centre, 45% of all newly diagnosed patients with AL amyloidosis have stage III disease and 20% have very advanced stage IIIb disease. (9) These patients presenting with advanced irreversible organ involvement have a very high risk of death in the first few months despite modern treatments. No improvement has yet been seen in early mortality in these patients due to established advanced cardiac damage. (2)

The availability of highly sensitive biomarkers of clonal and organ involvement as well as better imaging have allowed for accurate risk stratification of the disease and is reshaping the approach to patients with AL amyloidosis (10, 11). Biomarkers can also be used as tools for early identification of the disease.

The clinical manifestations of systemic AL amyloidosis are protean and a consequence of advanced organ damage. Most organs can be involved by AL amyloidosis (Figure 1) and a key diagnostic clue is the involvement of two or more systems. The clinical presentation and outcomes depend upon the pattern and severity of organ involvement by the amyloidogenic monoclonal protein i.e. light chain. (11) Diagnosis can be difficult as symptoms can mimic more common conditions. (12)

The aim of this guideline is to facilitate recognition or suspicion of amyloidosis. It is important to recognise that amyloidosis can present in any clinic, including general medicine/care of the elderly and general practice. The screening investigations for amyloidosis are listed in Table 1. Early diagnosis is paramount in improving outcomes as shown in tables 2 and 3..

Figure 1: Clinical manifestations of AL amyloidosis


Periorbital bruising
Coagulopathy
Macroglossia
Liver involvement
• Hepatomegaly and/or raised alkaline phosphatase
• Splenomegaly
Cardiac involvement
• Heart failure
• Arrhythmia
• Syncope
Renal involvement
• Nephrotic syndrome
Carpal tunnel syndrome
Broken/flaky fingernails
Gut involvement
• Dysphagia
• Nausea
• Gastroparesis
• Diarrhoea
Peripheral neuropathy
• Symmetric polyneuropathy
• Autonomic neuropathy

92

Table 1. Screening investigations for AL amyloidosis in non-haematology clinics

- Immunoglobulin levels and serum protein electrophoresis (SPE) and immunofixation (IFE)
- Serum free light chain (FLC) assay to measure serum kappa and lambda levels and calculate the FLC ratio
- Urine electrophoresis and immunofixation looking for urinary Bence Jones protein (BJP)
- Urine albumin:creatinine ratio (ACR) & protein:creatinine ratio (PCR)
- U&E (urea and electrolytes)
- LFTs (liver function tests)
- Bone profile
- Coagulation screen (PT/APTT)
- NT-proBNP (N-terminal pro-B-type natriuretic peptide) or BNP
- Troponin (TnT or TnI)*
- ECG (electrocardiogram)

* The scoring systems for AL predominantly used TnT, however many centres will now use alternative assays e.g. TnI and we recommend using whichever test is available locally. For the purposes of screening, elevation above the reference range of your local test (corrected for renal function) should raise concern. Care should be taken if TnT is requested outside of a specialist clinic setting as a raised result may prompt concern about acute coronary syndromes. The patient should also be informed that this test is being used as a staging blood test for a different condition.

Table 2:	**STAGING OF CARDIAC AMYLOIDOSIS (23)**	**Median Survival**
Stage I	NT-proBNP <332 ng/L and Troponin T <0.035 ng/L	Not reached at 5 years
Stage II	NT-proBNP > 332 ng/L but < 8500 ng/L OR Troponin T ≥ 0.035 ng/L	Not reached at 5 years
Stage III A	NT-proBNP < 8500 ng/L and Troponin T ≥ 0.035 ng/L	76 months
Stage III B	NT-proBNP >8500 ng/L and Troponin T ≥ 0.035 ng/L	26 months
Stage III C (25)	NT-proBNP >8500 ng/L, Troponin T ≥ 0.035 ng/L and global longitudinal strain >-9%	4 months

98

99

Table 3:	**STAGING OF RENAL AMYLOIDOSIS (24)**	Risk of going on dialysis/renal survival
Stage 1	Proteinuria ≤5 g/24h and eGFR ≥50	none
Stage 2	either proteinuria >5 g/24 h or eGFR <50	11-25% at 2 years
Stage 3	both proteinuria >5 g/24 h and eGFR <50	60- 75% at 2 years

100

When to suspect AL amyloidosis in patients with a paraprotein or abnormal free light chains:

AL amyloidosis is commoner than often appreciated and is a well-established complication of monoclonal gammopathies. Patients with lambda light chain disease are at particular risk, but AL amyloidosis can occur in those with kappa light chain disease or an intact paraprotein without light chain excess. (2)

Biomarker based screening can help identify pre-symptomatic patients with monoclonal gammopathies who are developing AL amyloidosis.(13) Initial investigations for patients referred with a paraproteinemia should include urine protein:creatinine ratio and albumin:creatinine ratio (PCR & ACR), N-terminal pro-B-type natriuretic peptide (NT-proBNP) and a troponin assay to screen for early renal and cardiac involvement. A detailed clinical history to identify other organ involvement should be part of the assessment.

NT-proBNP is always raised in cardiac AL amyloidosis and high levels can precede development of clinically evident cardiac AL amyloidosis by many years. In an MGUS/myeloma clinic, unexplained high NT-proBNP, or progressively rising levels, should raise a high suspicion of cardiac amyloidosis. (14)

The first manifestation of renal amyloidosis is frequently albuminuria. Urine PCR and ACR have superseded 24-hour urine collection as easier tests in practice. Urine PCR is non-specific and will detect all proteinuria (including monoclonal light chains i.e. Bence Jones protein). In contrast, ACR specifically detects albuminuria and is a better test for assessing glomerular disease. (15, 16)

Healthcare professionals who monitor patients with MGUS for progression should be aware that patients can progress to AL amyloidosis with minimal or no increase in clonal light chains and clinical vigilance is of the utmost importance.

Therefore, in addition to monitoring for more usual criteria for progression to myeloma such as bone pain, anaemia and renal impairment, one must be watchful for unexpected symptoms, signs or investigation findings that could be consistent with AL amyloidosis as described in Figure 1. For example, new symptoms such as pedal oedema, unexplained severe fatigue, weight loss, dry mouth, difficulty in chewing or swallowing, postural hypotension, frothy urine and shortness of breath are of equal importance as the classical features of myeloma. We advise adding urine ACR and PCR, and NT-proBNP to standard tests for assessment and monitoring of MGUS (serum protein electrophoresis (SPE), immunofixation (IFE) and serum free light chains (SFLC), full blood count (FBC), Urea and Electrolytes (U&E), bone profile and liver function tests (LFT)), as recommended by the recent MGUS and smouldering myeloma Good Practice Papers. A troponin assay should be considered if the NT-proBNP is abnormal. (17, 18)

If AL amyloidosis is suspected, a histological diagnosis should be sought and appropriate amyloid typing undertaken. Congo red positivity in biopsy from any site (including bone marrow) should prompt detailed assessment for end organ involvement. Although beyond the specific remit of this guideline, other M-protein associated disorders should also be borne in mind such as monoclonal gammopathy of renal significance (MGRS), light chain deposition disease (LCDD) and POEMS syndrome (polyneuropathy, oedema/organomegaly, endocrinopathy, monoclonal gammopathy, skin changes).

When to suspect AL amyloidosis in patients with unexplained cardiac impairment:

The key features that should raise a suspicion for amyloidosis in patients with heart failure with or without a known monoclonal gammopathy:

- Low serum albumin (<30 g/L)
- Unexplained persistent proteinuria (urine PCR or ACR >50 mg/mmol)

- Autonomic or peripheral neuropathy
- Unexplained persistent high (or rising) troponin without significant coronary artery disease
- Significant persistent hypotension or unexplained worsening of heart failure symptoms after starting angiotensin converting enzyme inhibitors ((ACE-I) or angiotensin receptor blockers (ARBs), beta-blockers or angiotensin receptor-neprilysin inhibitor (ARNi)
- Previously hypertensive patient developing unexplained low or low normal blood pressure despite reduction of anti-hypertensives
- Heart failure with preserved ejection fraction (HFpEF) on echocardiogram (ECHO)
- Low voltage complexes on electrocardiogram
- History of bilateral carpal tunnel surgery; biceps (or other) tendon rupture; spinal canal stenosis
- Echocardiographic features:
    - “Left ventricular hypertrophy” with normal or low voltage ECG
    - Loss of longitudinal function i.e. abnormal global longitudinal strain (GLS) with apex to base gradient with a preserved apical compared to basal function)

A high index of suspicion should be maintained whilst interpreting echocardiograms and cardiac magnetic resonance imaging (MRI). Radiographic changes may be subtle, and it is important that imaging is undertaken by a practitioner with expertise in imaging of cardiac amyloidosis. An alternative aetiology for cardiac amyloidosis is transthyretin amyloidosis (ATTR). ATTR and MGUS may co-exist. There are guidelines for differentiation and evaluation of types of cardiac amyloidosis.(19) Screening investigations

for monoclonal gammopathy should be undertaken in all patients with suspected AL amyloidosis, as listed in Table 1.

When to suspect AL amyloidosis in patients with renal impairment

Testing for myeloma and screening for AL amyloidosis (see box 1) should be undertaken in all the following groups:

- Unexplained persistent proteinuria
- Urine PCR/ACR >50 mg/mmol
- Progressive renal impairment after the age of 40 (**https://bestpractice.bmj.com/topics/en-gb/875**)
- High clinical suspicion of AL amyloidosis

Up to 50% of patients with a monoclonal gammopathy with proteinuria >1.5 g/L or microscopic haematuria (for non-AL MGRS), particularly associated with an abnormal FLC ratio, will have a monoclonal protein related renal disorder. Unless there is a contraindication or a high suspicion of AL amyloidosis, all patients should be referred for a kidney biopsy. In suspected non-AL MGRS, a kidney biopsy is more informative than a bone marrow biopsy, whereas, in AL a bone marrow test or fat pad biopsy is less invasive and can be undertaken before a kidney biopsy. A renal biopsy is not routinely indicated in patients with monoclonal gammopathy and a significant proteinuria, if the bone marrow shows congo red positivity and the amyloid type is confirmed to be AL type as the kidney involvement is most likely to be due to renal amyloidosis. Unexpected features like blood in the urine or non proteinuric chronic kidney disease (CKD) need further investigations.

A known monoclonal gammopathy should lower the threshold for screening for myeloma, AL amyloidosis and MGRS. However, in a large published series of patients with unexplained proteinuria undergoing a kidney biopsy who subsequently were

diagnosed with MGRS, 29% of patients were not known to have a monoclonal paraprotein prior to the biopsy and >70% patients with a subsequent diagnosis of amyloidosis were not known to have a monoclonal protein prior to biopsy.(20)

When to suspect AL amyloidosis in unexplained neuropathy

Both AL amyloidosis and ATTR can involve the peripheral nervous system. In addition, monoclonal gammopathies, particularly IgM gammopathies, may result in paraproteins with direct anti-neuronal antibody activity. (21) We therefore recommend that assessment for a monoclonal protein (see table 1) forms part of the routine diagnostic work-up for patients with unexplained polyneuropathy. A clinical haematologist should be involved if AL amyloidosis is suspected.

A combination of peripheral and autonomic neuropathy is a hallmark of systemic amyloidosis (AL or ATTR). The presence of both without an apparent cause (e.g. long standing uncontrolled diabetes), should prompt a detailed search for amyloidosis. Conversely, isolated non-progressive or very slowly progressive neuropathy with a monoclonal protein but normal serum free light chains is rarely caused by amyloid deposition. .

When to refer urgently to a haematology clinic:

Consideration should be given to referring patients urgently for haematology review with a confirmed (or highly likely) diagnosis of AL amyloidosis with the following clinical manifestations:

- Hypoalbuminaemia <25 g/L
- Falling estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2
- All cases of cardiac amyloidosis.

- Autonomic neuropathy with postural hypotension >20 mmHg
- Hepatic amyloidosis with high bilirubin (>2 × upper limit of normal) (22)
- Factor X deficiency

Summary

AL amyloidosis is a chameleon of clinical medicine; its aetiology is complex, manifestations myriad and management subspecialised. It is not, however, particularly rare. It is therefore important that clinicians who may encounter patients with this disorder are aware of the disease and able to detect it. We have here summarised key features of the disease and outlined suggested investigations that will aid diagnosis and enable early referral which improves outcomes for patients with this condition.

Acknowledgements

The authors wish to thank Niche for help in undertaking the initial literature review.

The authors would like to thank the BSH Haemato-oncology task force, the BSH sounding board, and the BSH guidelines committee for their support in preparing this guideline.

Disclaimer

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the publishers accept any legal responsibility for the content of this guidance.

References:

1. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med. 2003;349(6):583-96.
2. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet. 2016;387(10038):2641-54.
3. Merlini G, Stone MJ. Dangerous small B-cell clones. Blood. 2006;108(8):2520-30.
4. Kastritis E, Misra A, Gurskyte L, Kroi F, Verhoek A, Vermeulen J, et al. Assessing the prognostic utility of hematologic response for overall survival in patients with newly diagnosed AL amyloidosis: results of a meta-analysis. Hematology. 2023;28(1):2157581.
5. Palladini G, Schonland S, Merlini G, Milani P, Jaccard A, Bridoux F, et al. The management of light chain (AL) amyloidosis in Europe: clinical characteristics, treatment patterns, and efficacy outcomes between 2004 and 2018. Blood Cancer J. 2023;13(1):19.
6. Dispenzieri A. Renal risk and response in amyloidosis. Blood. 2014;124(15):2315-6.
7. Palladini G, Hegenbart U, Milani P, Kimmich C, Foli A, Ho AD, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood. 2014;124(15):2325-32.
8. Lousada I, Comenzo RL, Landau H, Guthrie S, Merlini G. Light Chain Amyloidosis: Patient Experience Survey from the Amyloidosis Research Consortium. Adv Ther. 2015;32(10):920-8.
9. Ravichandran S, Cohen OC, Law S, Foard D, Fontana M, Martinez-Naharro A, et al. Impact of early response on outcomes in AL amyloidosis following treatment with frontline Bortezomib. Blood Cancer J. 2021;11(6):118.
10. Palladini G, Campana C, Klersy C, Balduini A, Vadacca G, Perfetti V, et al. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. Circulation. 2003;107(19):2440-5.
11. Palladini G, Milani P. Advances in the treatment of light chain amyloidosis. Curr Opin Oncol. 2022;34(6):748-56.
12. Gertz MA, Dispenzieri A. Systemic Amyloidosis Recognition, Prognosis, and Therapy: A Systematic Review. JAMA. 2020;324(1):79-89.
13. Palladini G, Merlini G. What is new in diagnosis and management of light chain amyloidosis? Blood. 2016;128(2):159-68.
14. Wechalekar AD, Gillmore JD, Wassef N, Lachmann HJ, Whelan C, Hawkins PN. Abnormal N-terminal fragment of brain natriuretic peptide in patients with light chain amyloidosis without cardiac involvement at presentation is a risk factor for development of cardiac amyloidosis. Haematologica. 2011;96(7):1079-80.

15. Guy M, Borzomato JK, Newall RG, Kalra PA, Price CP. Protein and albumin-to-creatinine ratios in random urines accurately predict 24 h protein and albumin loss in patients with kidney disease. Ann Clin Biochem. 2009;46(Pt 6):468-76.
16. Guy M, Newall R, Borzomato J, Kalra PA, Price C. Diagnostic accuracy of the urinary albumin: creatinine ratio determined by the CLINITEK Microalbumin and DCA 2000+ for the rule-out of albuminuria in chronic kidney disease. Clin Chim Acta. 2009;399(1-2):54-8.
17. Stern S, Chaudhuri S, Drayson M, Henshaw S, Karunanithi K, Willis F, et al. Investigation and management of the monoclonal gammopathy of undetermined significance: A British Society for Haematology Good Practice Paper. Br J Haematol. 2023;202(4):734-44.
18. Hughes D, Yong K, Ramasamy K, Stern S, Boyle E, Ashcroft J, et al. Diagnosis and management of smouldering myeloma: A British Society for Haematology Good Practice Paper. Br J Haematol. 2024;204(4):1193-206.
19. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation. 2016;133(24):2404-12.
20. Klank D, Hoffmann M, Porubsky S, Bergner R. Histological Findings in Kidney Biopsies of Patients with Monoclonal Gammopathy-Always a Surprise. Diagnostics (Basel). 2022;12(8).
21. Nobile-Orazio E, Barbieri S, Baldini L, Marmiroli P, Carpo M, Premoselli S, et al. Peripheral neuropathy in monoclonal gammopathy of undetermined significance: prevalence and immunopathogenetic studies. Acta Neurol Scand. 1992;85(6):383-90.
22. Park MA, Mueller PS, Kyle RA, et al. Primary (AL) hepatic amyloidosis: clinical features and natural history in 98 patients. Medicine 2003;82:291–8.
23. Dispenzieri A, Gertz MA, Kyle RA et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol 2004; 22 (18):3751-3757
24. Palladini G, Hegenbart U, Milani P, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood. 2014;124:2325–2332. doi: 10.1182/blood-2014-04-570010

25. Jahanzaib Khwaja, Sriram Ravichandran, Joshua Bomsztyk, Oliver Charles Cohen, Darren Foard, Ana Martinez-Naharro, Lucia Venneri, Marianna Fontana, Carol Whelan, Philip N Hawkins, Julian Gillmore, Helen J Lachmann, Shameem Mahmood, Amy A Kirkwood, Ashutosh D. Wechalekar; Defining a New “Mayo Stage IIIc” Ultra Poor Risk Category in Systemic AL Amyloidosis: Incorporating Echocardiographic Global Longitudinal Strain to the European Modified Mayo Staging System. *Blood* 2024; 144 (Supplement 1): 890.