Predicting survival in light chain amyloidosis

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In this issue of the Journal, Dittrich and coworkers report their systematic analysis of the performance of the three currently used staging systems for AL amyloidosis in a large population of 1,224 patients.[1] Their aim was to establish whether one of the available models had better discriminating ability and was preferable in the overall population and in subgroups of patients with potential interfering factors, such as renal failure and atrial arrhythmias.

In systemic AL amyloidosis a plasma cell clone produces light chains that misfold, aggregate and form deposits in tissues, causing dysfunction of the involved organs.[2] While the bone marrow clone is usually indolent and small, the amyloid light chains often give rise to rapidly progressive dysfunction and damage of one or more organs. The pattern of organ involvement determines the clinical presentation of the disease, which is fatal if recognized late or unsuccessfully treated. The heart and the kidneys are the most commonly involved organs. Cardiac and renal dysfunction also limit the access to intensive treatment. Survival is largely dependent on the presence and severity of heart involvement. Amyloid light chains cause direct toxicity to the myocardium, inducing p38 mitogen-activated protein kinase (MAPK) signaling and resulting in oxidative stress, impaired excitation-contraction coupling and cardiomyocyte death. Notably, MAPK signaling mediates transcription of the cardiac biomarker natriuretic peptide type-B (BNP), supporting a direct connection between light chain cardiotoxicity and BNP levels.[3] Indeed, the level of the amino-terminal portion of pro-BNP (NT-proBNP) can indicate clinically relevant heart involvement in 100% of cases and is a powerful prognostic marker in AL amyloidosis.[4,5] After chemotherapy targeting the plasma cell clone, the reduction of the concentration of the amyloid free light chain (FLC) results in decreased NT-proBNP levels that predict longer survival.[6] Validated criteria for cardiac response are based on the decrease of NT-proBNP level.[7] However, the clearance and, consequently, the serum concentration of natriuretic peptides are influenced by renal function. While BNP is also actively removed from the bloodstream, following binding with natriuretic peptide receptors and through protease hydrolysis, NT-proBNP appears to lack active clearance mechanisms and is almost exclusively removed through glomerular filtration. Thus, renal failure is a potential confounding factor when assessing cardiac dysfunction by natriuretic peptide levels. In AL amyloidosis, BNP is preferred over NT-proBNP in prognosticating survival of patients with an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2 (end-stage renal disease).[8] In addition, increased concentrations of natriuretic peptides are sensitive but not specific markers of heart dysfunction in AL amyloidosis, and certain common cardiac conditions, particularly atrial fibrillation, can contribute to their elevation.

Cardiac troponin (cTn) is another powerful predictor of survival in AL amyloidosis.[9] As well as NT-proBNP, cTn can be used to identify patients at higher risk of transplant-related mortality (those with NT-proBNP >5,000 ng/L and/or cTnT >0.06 ng/mL) who should not be considered candidates for autologous stem cell transplantation.[10] Levels of cardiac troponins and NT-proBNP can be combined to generate simple, yet accurate staging systems that sharply differentiate groups of patients with different survival (Table 1). Initially, a three-stage system was designed by Mayo Clinic investigators (Mayo2004).[11] Subsequently, two four-stage systems were devised. One of them, proposed by European collaborative studies, uses very high NT-proBNP levels to identify high-risk patients (Mayo2004/European).[12,13] The other was proposed by the Mayo Clinic group and included the difference between involved and uninvolved FLC (dFLC) as an indicator of clonal burden together with cardiac biomarkers (Mayo2012).[14] The use of BNP, cTnT, cTnI, and high-sensitivity troponin assays in these staging systems is now validated.[15-17]

Until now, there was no indication on which of the available staging systems performed better and should be preferred in different settings. This can be particularly relevant in determining eligibility for clinical trials and in specific patient populations with confounding factors, such as renal failure and atrial arrhythmia, which can interfere with the assessment of cardiac dysfunction. Dittrich and coworkers adopted a 50 mL/min/1.73 m^2 cutoff to discriminate patients with reduced eGFR based on the current stratification of renal involvement in AL amyloidosis.[18] In the overall population all the staging systems provided a sharp discrimination of survival between subgroups. However, the Mayo2004/European system was superior in identifying low-risk and very high-risk patients. Notably, reduced eGFR and atrial arrhythmia predicted poorer survival *per se*, besides being associated with higher concentrations of cardiac biomarkers. Thus, patients with impaired eGFR and atrial arrhythmia were correctly assigned to higher stages. Importantly, the impact of low eGFR on prognosis appeared to be associated with heart involvement, mainly because of prerenal kidney injury. At multivariate analysis, decreased eGFR retained an independent prognostic value with the Mayo2004 and Mayo 2012 staging systems, but not with the Mayo2004/European system. Atrial arrhythmia reduced the discriminating ability of all three staging systems, with a more pronounced impact on the Mayo2012 system. Moreover, the very high levels of NT-proBNP (>8,500 ng/L) used in the Mayo2004/European model to identify high-risk patients portended a very poor outcome irrespective of decreased renal function and atrial arrhythmia.

A similar study in 1,005 patients was recently published by the Mayo Clinic investigators.[19] Overall, they did not

Table 1. Staging systems for AL amyloidosis.

Models	Variables and cutoffs	Stages
Mayo2004	• NT-proBNP, 332 ng/L (or BNP, 81 ng/L) • cTnT, 0.035 ng/mL (or cTnI, 0.1 ng/mL)	Stage I: both variables below the cutoffs Stage II: one variable above the cutoff Stage III: both variables above the cutoffs
Mayo2004 European	Mayo 2004 stage III is divided into two groups according to • NT-proBNP, 8500 ng/L (or BNP, 700 ng/L)	Stage IIIa: Mayo2004 stage III and NT-proBNP (or BNP) below the cutoff Stage IIIb: Mayo2004 stage III and NT-proBNP (or BNP) above the cutoff
Mayo2012	• NT-proBNP, 1800 ng/L • cTnT, 0.025 ng/mL (or cTnI 0.1 ng/mL, or hs-cTnT 40 ng/L) • dFLC, 180 mg/L	Stage I: all markers below the cutoffs Stage II: one marker above the cutoffs Stage III: two markers above the cutoffs Stage IV: all markers above the cutoffs

NT-proBNP, amino-terminal portion of pro-brain natriuretic peptide type B; BNP, natriuretic peptide type-B; cTnT, cardiac troponin T; cTnI, cardiac troponin I; hs-cTnT, high sensitivity cardiac troponin T; dFLC, difference between involved and uninvolved free light chain concentration.

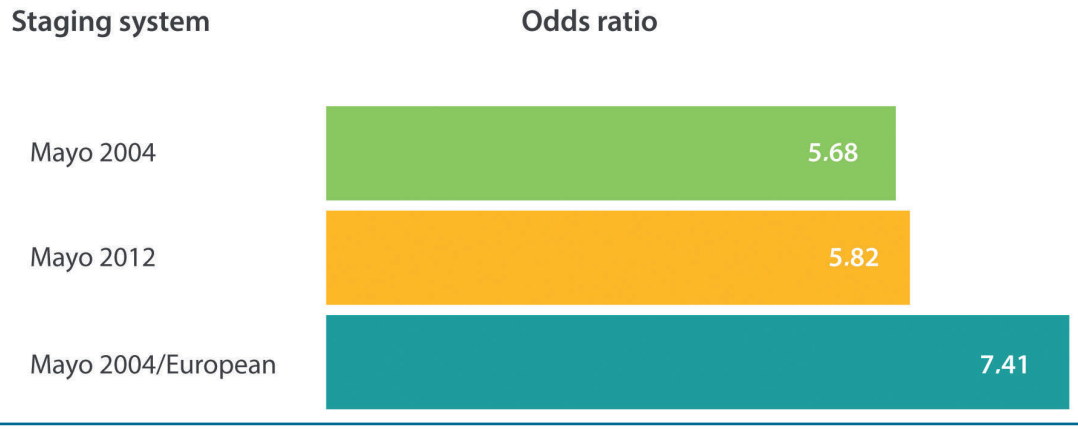

Figure 1. Odds ratio for very early death (within 6 months of diagnosis) of patients classified as being at highest risk by the three staging systems. Data from 1,065 patients with AL amyloidosis diagnosed between 2004 and 2015 at the Pavia Amyloidosis Research and Treatment Center. Mayo 2004 stage III. Odds ratio 5.68 (95% confidence interval: 4.03- 8.00). Mayo 2012 stage IV. Odds ratio 5.82 (95% confidence interval: 4.22- 8.05). Mayo 2004/European stage IIIb. Odds ratio 7.42 (95% confidence interval: 5.24- 10.51).

find a significant advantage in discriminating ability of one model over the others. However, the Mayo2004/European staging system had the greatest ability to identify patients who died within the first year after diagnosis. In a landmark analysis including patients who survived at least 1 year, there was no difference in discriminating ability between the Mayo2004/European and the Mayo2012 staging systems. Interestingly, however, in a 3-year landmark analysis, the Mayo 2012 model performed better than the Mayo2004/European staging system.

How do these studies help in selecting the best way to stratify patients with AL amyloidosis? Clearly, four-stage models perform better than the Mayo2004 staging system. Not surprisingly, the Mayo2004/European model, which was designed to detect very high-risk subjects, has the best performance in identifying patients who die early. In a series of 1,065 patients diagnosed with AL amyloidosis at the Pavia Amyloidosis Research and Treatment Center, subjects classified as stage IIIb with the Mayo2004/European model had the highest odds ratio for death within 6 months of diagnosis (Figure 1). Moreover, the Mayo2004/European staging system performs better in patients with atrial arrhythmia and low eGFR. Thus, the Mayo2004/European model, which is powerful, simple (based on only 2 markers), and less influenced by confounding factors, appears to be generally preferable, and particularly useful in assessing eligibility for clinical trials. Stage IIIb patients identified by the Mayo2004/European staging system are at the highest risk of early death and should only be enrolled in clinical trials specifically designed for these extremely fragile subjects. However, while early deaths are mainly caused by severe cardiac dysfunction at presentation, long-term survival is probably influenced by the tendency of the amyloid plasma cell clone to relapse. Indeed, the Mayo2012 model, which includes a marker of clonal disease burden, has better discriminating ability 3 years after diagnosis. Nevertheless, when relapse occurs, restaging with either the Mayo2004/European or the Mayo2012 staging system can reliably stratify patients with different survival.[20]

The fact that patients' survival can be very effectively predicted by staging systems entirely or mainly based on cardiac biomarkers emphasizes the peculiarity of AL amyloidosis: a hematologic disease causing multiorgan dysfunction in which death most often occurs as a consequence of cardiac involvement. Thus, the workup of patients with AL

amyloidosis should be multidisciplinary, choice of treatment should be risk-adapted, and the treatment plan should be frequently verified and reconsidered based on evaluation of hematologic and organ responses.[2] For these reasons, patients with AL amyloidosis should be referred to specialized centers whenever possible.

We are now able to prognosticate survival easily and accurately in patients with AL amyloidosis both at diagnosis and at relapse. However, there is still room for improvement. For instance, it is possible that more advanced renal dysfunction has a greater impact on the performance of the staging systems than a reduction of eGFR below 50 mL/min/1.73 m^2. It is likely that patients with end-stage renal failure need a different approach for stratification of survival, possibly based on BNP rather than on NT-proBNP. Moreover, it is uncertain whether dFLC is the best possible marker for assessing the likelihood of late relapse, particularly given the availability of novel, powerful treatments. Staging systems incorporating other markers of clonal disease, for instance bone marrow plasma cell infiltration or chromosomal abnormalities, should be tested for their ability to predict relapse and long-term survival. Finally, the novel advanced imaging tools for the evaluation of amyloid cardiac involvement (e.g. cardiac magnetic resonance, assessment of longitudinal strain at echocardiography, positron electron tomography-computed tomography with amyloid-specific tracers) should be tested for their ability to add prognostic information to the existing staging system. International collaborative studies are the ideal setting for answering these questions quickly and reliably.

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