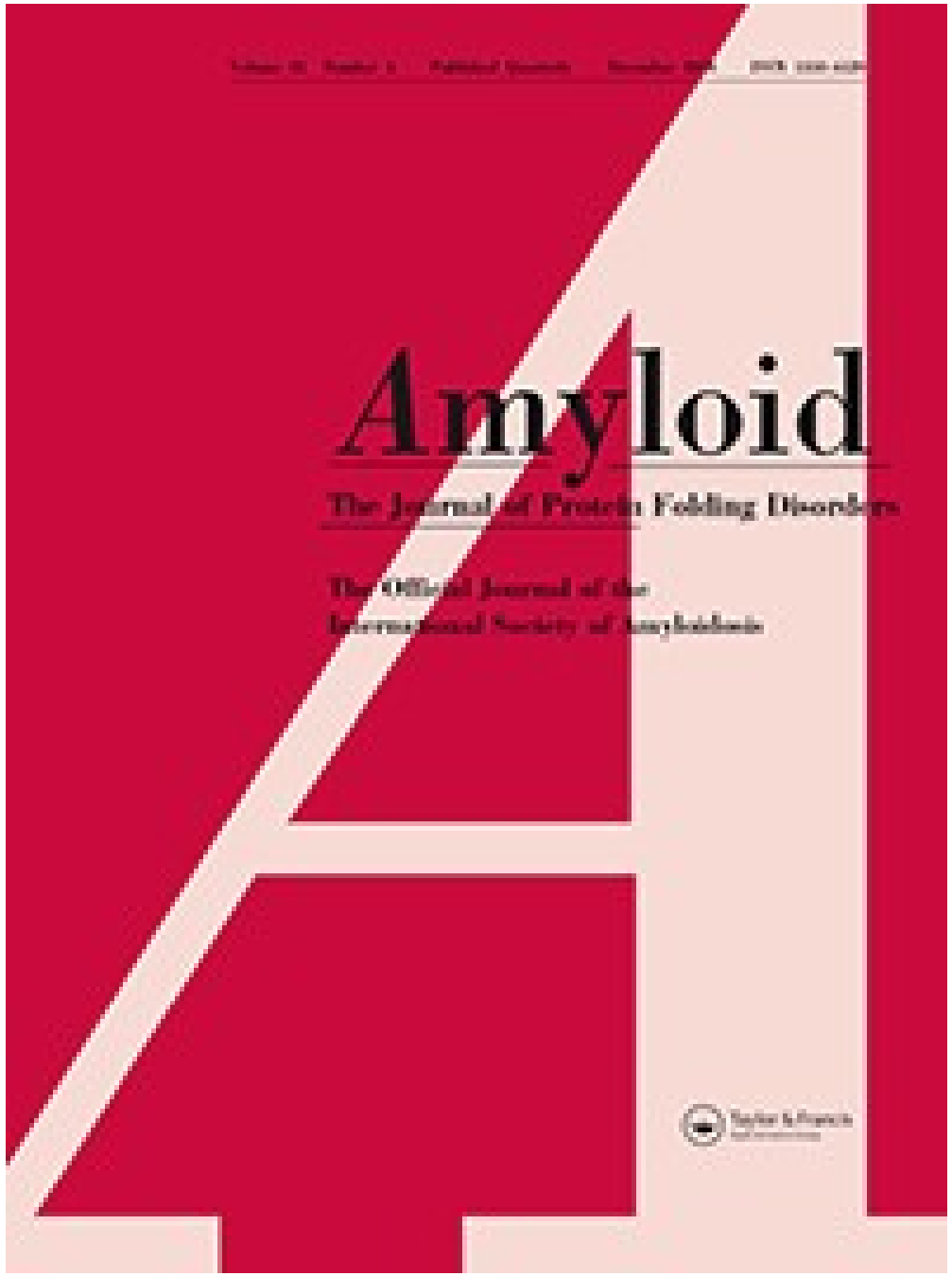
Amyloidosis

The term amyloidosis refers to a group of disorders in which protein fibrils accumulate in certain organs, disrupt their tissue architecture, and impair the function of the effected organ.

The clinical manifestations and prognosis vary widely depending on the specific type of the affected protein.

Amyloidosis has an overall estimated **incidence** of around **14 new cases per million person** per year and a **prevalence of less than 5 cases per 10,000 inhabitants**, which places them among the rare diseases.



Amyloid nomenclature 2018: recommendations by the International Society of Amyloidosis (ISA) nomenclature committee

Merrill D. Benson, Joel N. Buxbaum, David S. Eisenberg, Giampaolo Merlini, Maria J. M. Saraiva, Yoshiki Sekijima, Jean D. Sipe & Per Westermark

XVI International Symposium on Amyloidosis in Kumamoto, Japan, 25–29 March 2018

There are **more than 30 different** types of amyloidosis, each due to a specific protein misfolding.

Some are genetic while others are acquired.

Table 1. Amyloid fibril proteins and their precursors in human[a].

Fibril protein	Precursor protein	Systemic and/or localized	Acquired or hereditary	Target organs
AL	Immunoglobulin light chain	S, L	A, H	All organs, usually except CNS
AH	Immunoglobulin heavy chain	S, L	A	All organs except CNS
AA	(Apo) Serum amyloid A	S	A	All organs except CNS
ATTR	Transthyretin, wild type	S	A	Heart mainly in males, Lung, Ligaments, Tenosynovium
	Transthyretin, variants	S	H	PNS, ANS, heart, eye, leptomen.
Aβ2M	β2-Microglobulin, wild type	S	A	Musculoskeletal System
	β2-Microglobulin, variant	S	H	ANS
AApoAI	Apolipoprotein A I, variants	S	H	Heart, liver, kidney, PNS, testis, larynx (C terminal variants), skin (C terminal variants)
AApoAII	Apolipoprotein A II, variants	S	H	Kidney
AApoAIV	Apolipoprotein A IV, wild type	S	A	Kidney medulla and systemic
AApoCII	Apolipoprotein C II, variants	S	H	Kidney
AApoCIII	Apolipoprotein C III, variants	S	H	Kidney
Agel	Gelsolin, variants	S	H	PNS, cornea
ALys	Lysozyme, variants	S	H	Kidney
ALECT2	Leukocyte Chemotactic Factor-2	S	A	Kidney, primarily
AFib	Fibrinogen α, variants	S	H	Kidney, primarily
ACys	Cystatin C, variants	S	H	PNS, skin
ABri	ABriPP, variants	S	H	CNS
ADan*	ADanPP, variants	L	H	CNS
Aβ	Aβ protein precursor, wild type	L	A	CNS
	Aβ protein precursor, variant	L	H	CNS
AαSyn	α-Synuclein	L	A	CNS
ATau	Tau	L	A	CNS
APrP	Prion protein, wild type	L	A	CJD, fatal insomnia
	Prion protein variants	L	H	CJD, GSS syndrome, fatal insomnia
	Prion protein variant	S	H	PNS
ACal	(Pro)calcitonin	L	A	C-cell thyroid tumors
AIAPP	Islet amyloid polypeptide**	L	A	Islets of Langerhans, insulinomas
AANF	Atrial natriuretic factor	L	A	Cardiac atria
APro	Prolactin	L	A	Pituitary prolactinomas, aging pituitary
AIns	Insulin	L	A	Iatrogenic, local injection
ASPC***	Lung surfactant protein	L	A	Lung
AGal7	Galectin 7	L	A	Skin
ACor	Corneodesmosin	L	A	Cornified epithelia, hair follicles
AMed	Lactadherin	L	A	Senile aortic media
AKer	Kerato-epithelin	L	A	Cornea, hereditary
ALac	Lactoferrin	L	A	Cornea
AOAAP	Odontogenic ameloblast-associated protein	L	A	Odontogenic tumors
ASem1	Semenogelin 1	L	A	Vesicula seminalis
AEnf	Enfurvitide	L	A	Iatrogenic
ACatK****	Cathepsin K	L	A	Tumor associated

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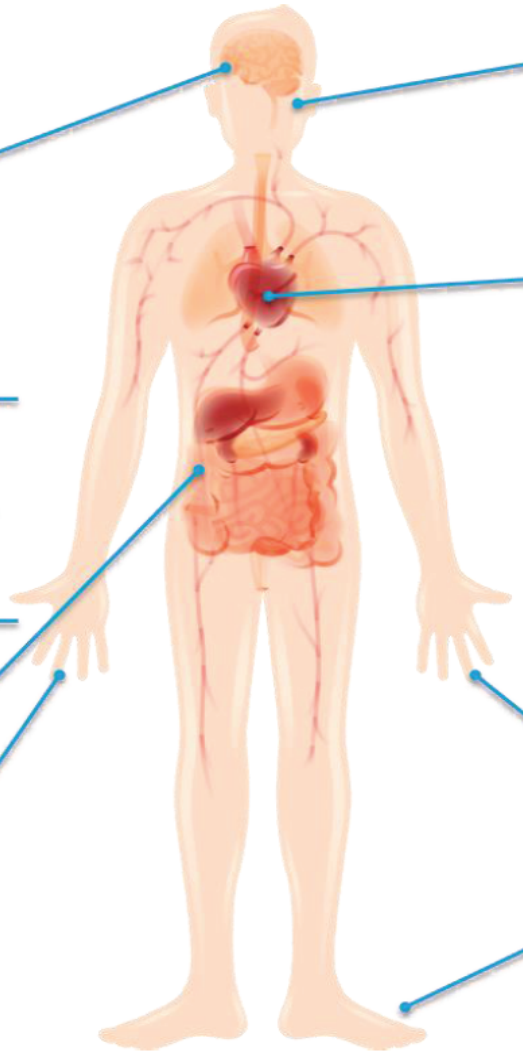
The acquired forms (AL, AH) are the most frequent, constituting 80-85% of the whole series, followed by the hereditary (ATTR) forms which represent 10-15% and by the reactive forms (AA), resulting from neoplasms, inflammatory diseases or chronic infections, which have progressively reduced over the last few decades to less than 5% of cases

Amyloidosis -clinical



CNS MANIFESTATIONS
- Progressive dementia
- Headache
- Ataxia
- Seizures
- Spastic paresis
- Stroke-like episodes

GASTROINTESTINAL MANIFESTATIONS
- Nausea and vomiting
- Changes in GI motility (ie, diarrhea, constipation, gastroparesis, early satiety)
- Unintentional weight loss

NEPHROPATHY
- Proteinuria
- Renal Failure

CARPAL TUNNEL SYNDROME

OCULAR MANIFESTATIONS
- Vitreous opacification
- Glaucoma
- Abnormal conjunctival vessels
- Papillary abnormalities

CARDIOVASCULAR MANIFESTATIONS
- Conduction block
- Cardiomyopathy
- Palpitations and arrhythmia
- Mild regurgitation
- Shortness of breath
- Edema

AUTONOMIC NEUROPATHY
- Orthostatic hypotension
- Recurrent urinary tract infection (due to urinary retention)
- Sexual dysfunction
- Sweating abnormalities

PERIPHERAL SENSORY-MOTOR NEUROPATHY
- Neuropathic pain
- Altered sensation (ie, change in sensitivity to pain and temperature)
- Numbness and tingling
- Muscle weakness
- Impaired balance
- Difficulty walking

AL Amyloidosis

AL → clonal population of bone marrow PC that produces a clonal light chain of κ or λ type as either an intact molecule or a fragment

Prevalence of AL amyloidosis in patients with MM: 12-15%
Increased in recent years → increased survival of PCD

The median age at diagnosis is 63 years, and 1.3% of patients are under the age of 34 years.

There is a male predominance, with men accounting for 55% of patients.

45-55% IgG or IgA; 7% IgM

AL amyloidosis occurs in all races and geographic locations, but data are limited regarding the incidence of AL amyloidosis across different ethnic groups

AL Amyloidosis -hearth

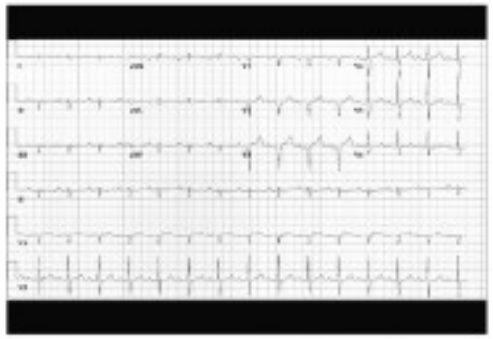
Heart involvement is the most important prognostic factor in AL amyloidosis patients and occurs in 71% of AL amyloid patients.

The patients present with **fatigue, dyspnea at exertion, peripheral edema, jugular venous distention and pleural effusion**.

Other manifestations can include arrhythmia causing sudden death or syncope, and rarely myocardial infarction due to the accumulation of amyloid in the coronary arterioles.

Amyloidosis AL -hearth

A ECG



ECG → Amiloide= elettricamente inerte

45% bassi voltaggi QRS (derivazioni periferiche <5mm) → early stage, worse prognosis

Onde Q pseudoinfartuali (QS) in almeno 2 derivazioni precordiali consecutive

Blocchi di branca

BAV I-II-III grado

Allungamento QT

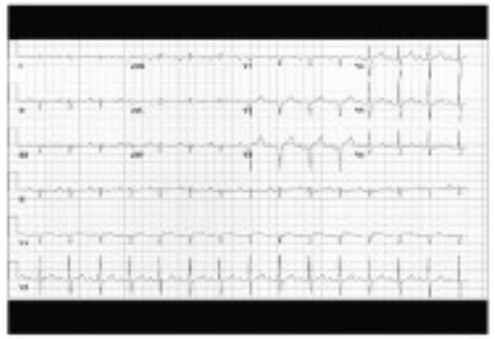
Tachiaritmie

ECG Holter

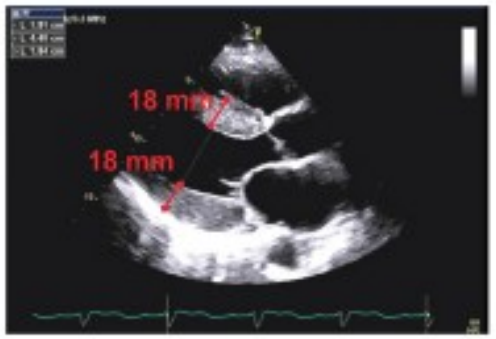
Grogan M et al. Heart 2017

Amyloidosis AL -hearth

A ECG



B ECHO



Echo → Aumento spessore parietale del Vsx con distribuzione uniforme dell'ipertrofia e peculiare ecoriflettenza miocardica con aspetto «a vetro smerigliato» (**granular sparkling**)

Disfunzione diastolica di grado II-IV

Aumento dello spessore della parete libera del VDx

Dilatazione biatriale con presenza di trombi intracavitari (35%)

Aumento di spessore del setto interatriale

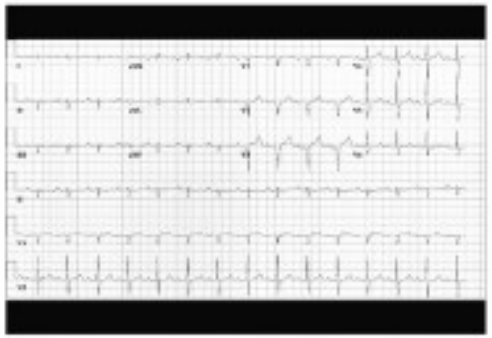
Ispessimento delle valvole atrio-ventricolari

Versamento pericardico e pleurico

Grogan M et al. Heart 2017

Amyloidosis AL -hearth

A ECG



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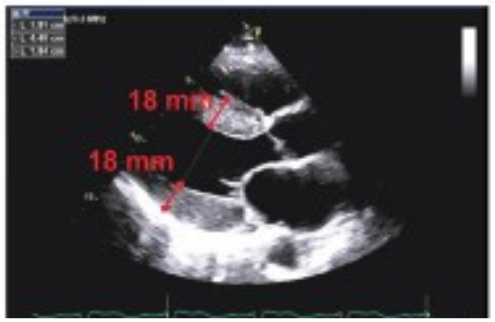
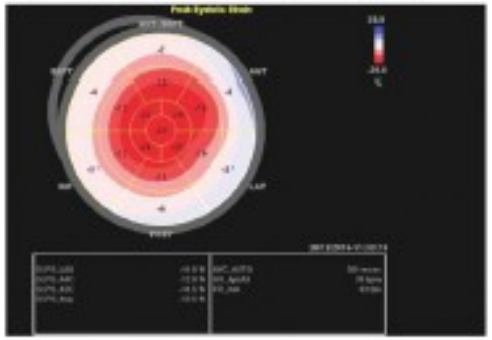


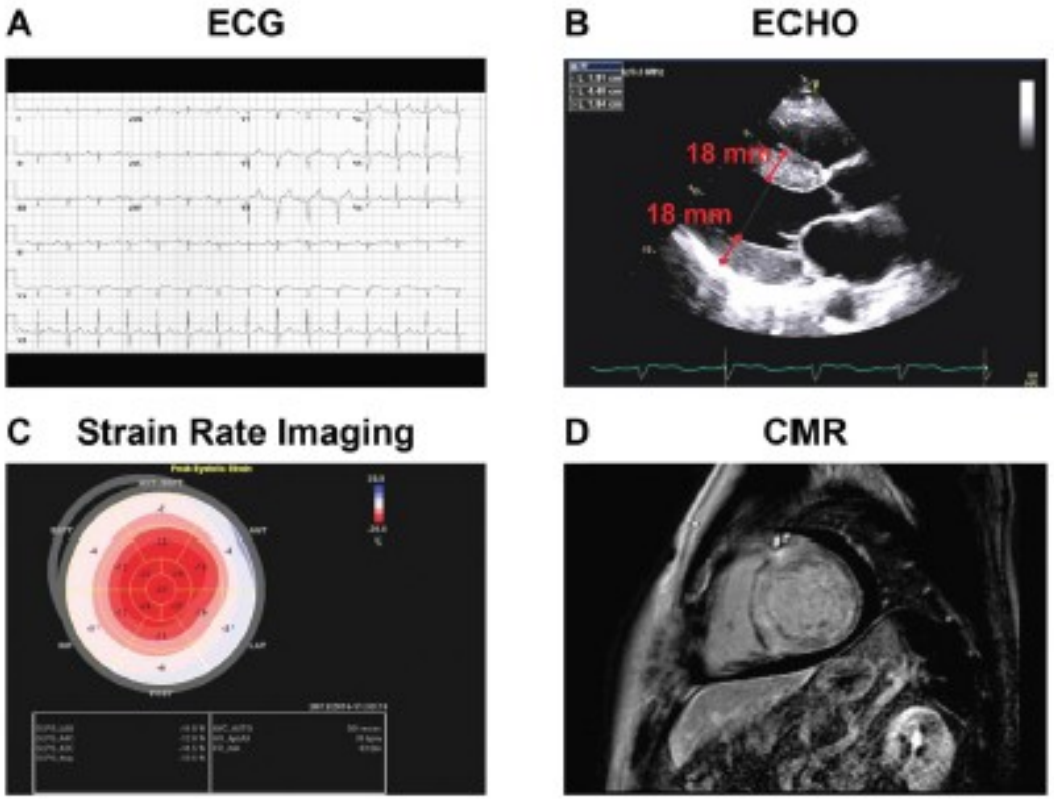
C Strain Rate Imaging



STRAIN → A characteristic LV strain pattern with preservation of the apex **(bull's eye)** is often an indication of the disease
Abnormalities of longitudinal ventricular function demonstrated by strain imaging are independent predictors of survival.
Furthermore, abnormal right ventricular strain may be an early diagnostic clue.
The severity of echocardiographic abnormalities and the rapidity at which they develop may correlate with worse prognosis.

Grogan M et al. Heart 2017

Amyloidosis AL -hearth



RMN cardiaca →

aumento globale del volume extracellulare

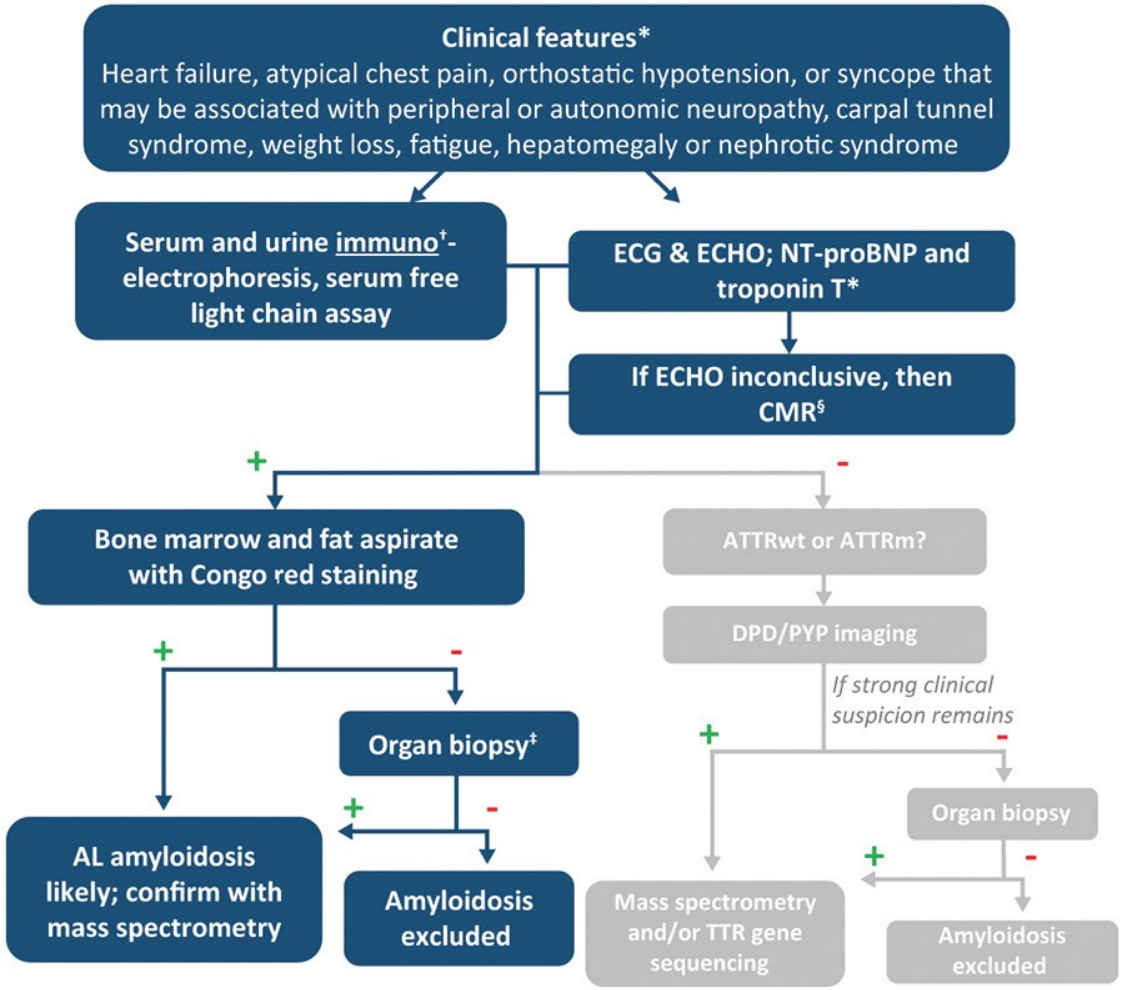
Immagine tipica di «late enhancement» del subendocardio del Vsx e del VDx (aspetto "a zebra" del SIV) ma spesso alterazione a tutto spessore; la misura dell'espansione dell'interstizio potrebbe quantificare l'entità del danno cardiaco

Le alterazioni RMN possono precedere le alterazioni eco e correlano con la prognosi

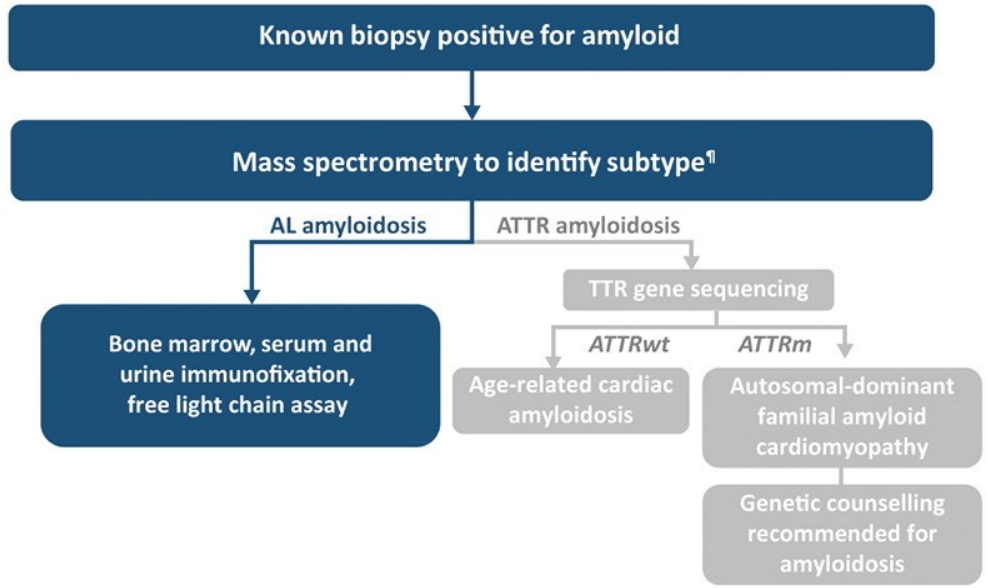
Grogan M et al. Heart 2017

Amyloidosis AL -hearth

A Algorithm for diagnosis in patients with suspected cardiac amyloidosis*

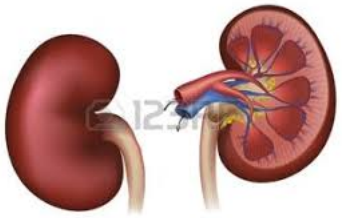


B Algorithm for diagnosis in patients with amyloidosis established by biopsy



Grogan M et al. Heart 2017

Amyloidosis AL -kidney



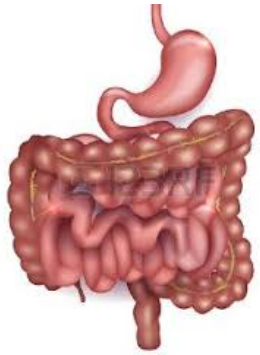
Renal involvement occurs in 58% of AL amyloidosis;
patients and usually presents as a **nonselective proteinuria or nephrotic syndrome**.

The patient may present with **peripheral edema, anasarca, foaming urine, or symptoms of uremia**.

Laboratory tests may show elevated lipid levels, hypoalbuminemia, and nonselective proteinuria.

Ultrasound or CT may demonstrate enlarged kidneys.

Amyloidosis AL –GI tract



GI involvement manifests itself as **constipation, diarrhea, early satiety, GI bleeding, heartburn, nausea and vomiting due to gastroparesis, and weight loss**.

Laboratory testing may show hypoalbuminemia and anemia, and imaging tests may demonstrate a dilated esophagus and signs of decreased peristalsis, as well as thickening of the stomach wall or small intestine.

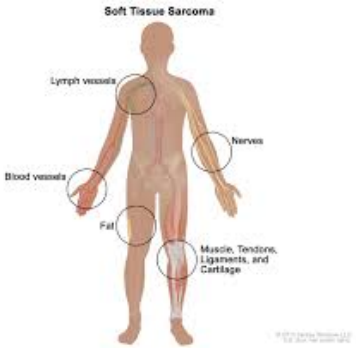
Amyloidosis AL –nervous system

Mixed sensory and motor peripheral neuropathy (20%) and **autonomic neuropathy** (15%) are prominent features in AL amyloidosis.

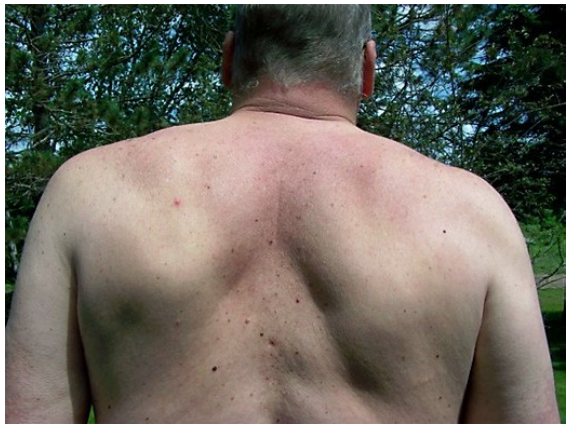
Symptoms of **numbness, paresthesia, and pain** are frequently noted resulting from the involvement of peripheral nerves, especially the median nerve within the carpal tunnel.
Symptoms of **bowel or bladder dysfunction** and **orthostatic hypotension** are caused by autonomic nervous system damage.

Patients with neurologic symptoms should be evaluated with electromyography, bearing in mind that this test can be normal because the neuropathy is most typically due to damage to the small unmyelinated nerve fibers.

Amyloidosis AL –soft tissue

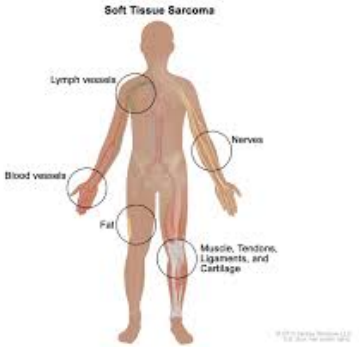


AL amyloidosis patients may present with **hoarseness, dysarthria, obstructive sleep apnea, periorbital purpura** often occurring after mild trauma or physical activity, **submandibular gland swelling, xerostomia**, and periarticular involvement causing the **shoulder pad sign** (enlargement of the anterior shoulder due to fluid in the glenohumeral joint or amyloid infiltration of the synovial membrane and surrounding structures).

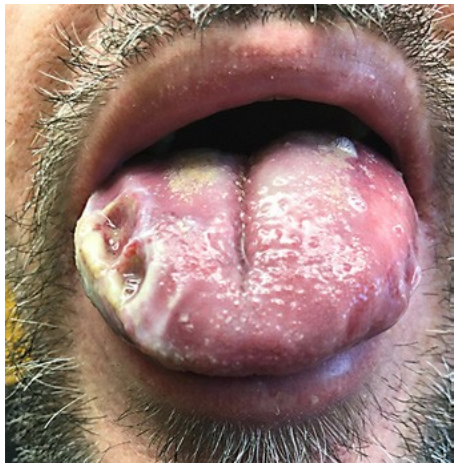


Shoulder pad sign

Amyloidosis AL –soft tissue

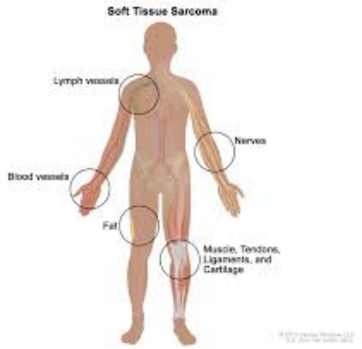


Macroglossia can cause significant morbidity due to problems with breathing, talking, and chewing, resulting in the need for feeding tubes and tracheostomy.



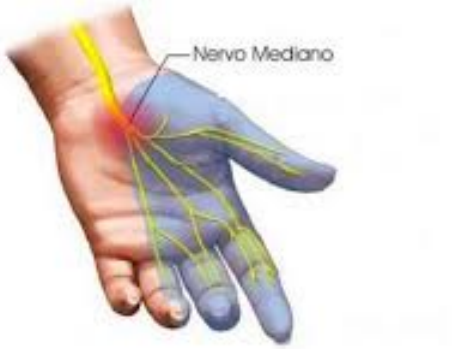
Macroglossia

Amyloidosis AL –soft tissue



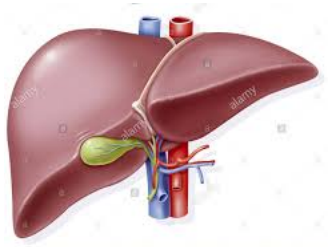
Jaw claudication (pain while chewing) reflects vascular amyloid deposition and may cause a great deal of morbidity.

Carpal tunnel syndrome sometime precedes the tissue diagnosis of AL amyloidosis by years (range 1 month to 9.3 years).



Carpal tunnel syndrome

Amyloidosis AL –liver and coagulation



AL amyloidosis may be associated with a **bleeding diathesis**.

Subnormal factor X activity is found in 14%
The proposed mechanisms include factor X deficiency due to binding to amyloid fibrils, decreased synthesis of coagulation factors due to advanced liver disease, and acquired von Willebrand disease.

However, some patients with abnormal bleeding have no abnormality in any coagulation test. In such cases amyloid infiltration of blood vessels should be suspected.

Amyloidosis AL -diagnosis

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

SVincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, María-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosinol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Beksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

Systemic AL amyloidosis‖** [11,18]	Presence of an amyloid-related systemic syndrome (eg, renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement) Positive amyloid staining by Congo red in any tissue (eg, fat aspirate, bone marrow, or organ biopsy) Evidence that amyloid is light-chain-related established by direct examination of the amyloid using mass spectrometry-based proteomic analysis, or immunoelectronmicroscopy, and Evidence of a monoclonal plasma cell proliferative disorder (serum or urine monoclonal protein, abnormal free light-chain ratio, or clonal plasma cells in the bone marrow)

Amyloidosis AL -diagnosis

The diagnosis of AL amyloidosis requires the **demonstration of amyloid fibrils** in a tissue sample taken from the **suspected affected organ** (heart, kidney, liver, etc.) or from a **surrogate site** (abdominal fat pad, bone marrow).

Biopsy of the iliac crest bone marrow combined with abdominal subcutaneous fat aspiration will identifyamyloid deposits in 85% of patients with AL amyloidosis.

Table 1. The sensitivity of various biopsy sites in detecting amyloid fibrils

Organ	Sensitivity reported, %
Abdominal fat pad	60–80
Rectal biopsy	50–70
Bone marrow biopsy	50–55
Skin biopsy	50
Kidney	90
Liver	90

Immunofixation of serum
Immunofixation of urine
Ig free light chain assay

IF NEG AND κ:λ (0.26-1.65)
→ AL UNLIKELY

Bone marrow biopsy
Abdominal subcutaneous fat aspiration

NEG → 15% AL LIKELIHOOD
Biopsy of involved organ

Amyloidosis AL -diagnosis

Table 2. Suggested diagnostic evaluation for a newly diagnosed amyloid patient

Blood tests	Urinary tests	Imaging and invasive tests	Others
Complete blood count	Electrophoresis of the serum and urine	Unilateral bone marrow aspirate and biopsy with immunohistochemical staining for κ and λ and Congo red staining for amyloid and FISH[1]	Blood pressure to asses for orthostatic hypotension
Liver and renal function	24-h urinary protein	Bone imaging[2]	Fertility preservation
Protein electrophoresis		Electrocardiogram	
Immunofixation of the serum		Echocardiogram	
FLC assay		Cardiac MRI optional	
Troponin T and NT-proBNP		Electromyography and nerve conduction studies if symptomatic	
Thyroid-stimulating hormone		Gastric emptying test if pseudo-obstruction	
Prothrombin time and partial thromboplastin time			

[1] Suggested FISH panel: t(11;14), t(4;14), t(14;16), t(14;20), trisomies, 1q+, and del(17p).
[2] Should be performed in patients with ≥10% bone marrow plasma cells.

Amyloidosis AL –localized vs systemic

Localized amyloidosis occurs in a variety of organ systems, including the **skin and nails, larynx**, **lung, bowel**, **orbit**, or **urinary tract**, including the renal pelvis, ureter, bladder, and urethra.
Evolution of localized amyloidosis to systemic amyloidosis is rare.
The course of the disease is relatively benign in most patients with no effect on life expectancy, but severe damage to the affected organ can ultimately occur. If symptomatic, localized amyloidosis can be treated by radiotherapy or by local excision using either classic surgical techniques or laser-based excision.
Coexisting autoimmune diseases were reported in 7% of patients.

Amyloidosis AL - Chromosomal Abnormalities

Fluorescence in situ hybridization (**FISH**) is prognostic in untreated AL amyloidosis and may guide therapeutic decisions.
Often the amyloidogenic clone is characterized by chromosomal abnormalities.
The most frequent genetic abnormalities in AL amyloidosis are **t(11;14)** (50%), **monosomy 13/del(13q)** (36%), and **trisomies** (26%).

The presence of **t(11; 14)** is associated with poorer outcomes with bortezomib-based and immunomodulatory (IMiD)-based therapy. These patients have a lower rate of very good partial response (VGPR) or better, and an inferior overall survival (OS) when treated with bortezomib. Patients should be considered for autologous stem cell transplantation (ASCT) or standard-dose melphalan at diagnosis because the survival disadvantage may be abrogated.

Trisomies were associated with a shorter OS, reaching statistical significance only for patients treated with melphalan.

Amyloidosis AL – Chromosomal Abnormalities

t(4; 14) and t(14; 16) were rarely found in AL, accounting only for 3% and 4% of patients, respectively. The frequency of **del(17p)** in AL amyloidosis is 3%. These MM high-risk FISH aberrations, t(4; 14), t(14; 16), and del(17p), conferred no adverse prognosis in patients treated with bortezomib.

Gain of 1q21 is less frequent in AL amyloidosis than in MM, being found in less than 20% of patients. Gaining 1q21 conferred no adverse prognosis in patients treated with bortezomib.

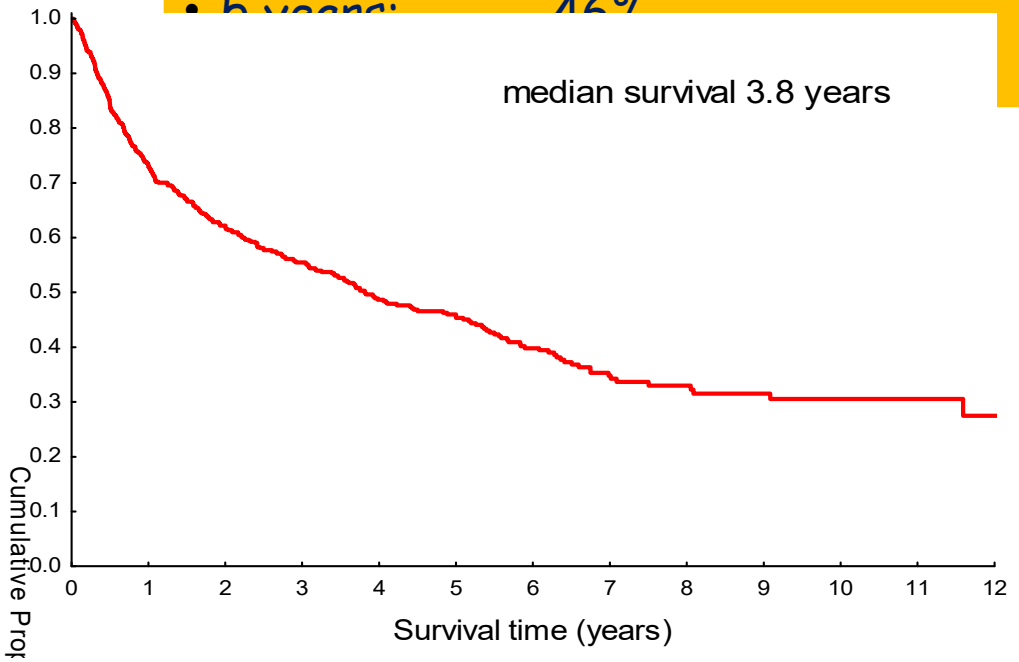
AL Amyloidosis - prognosis

AL amyloidosis

Cumulative proportion surviving:

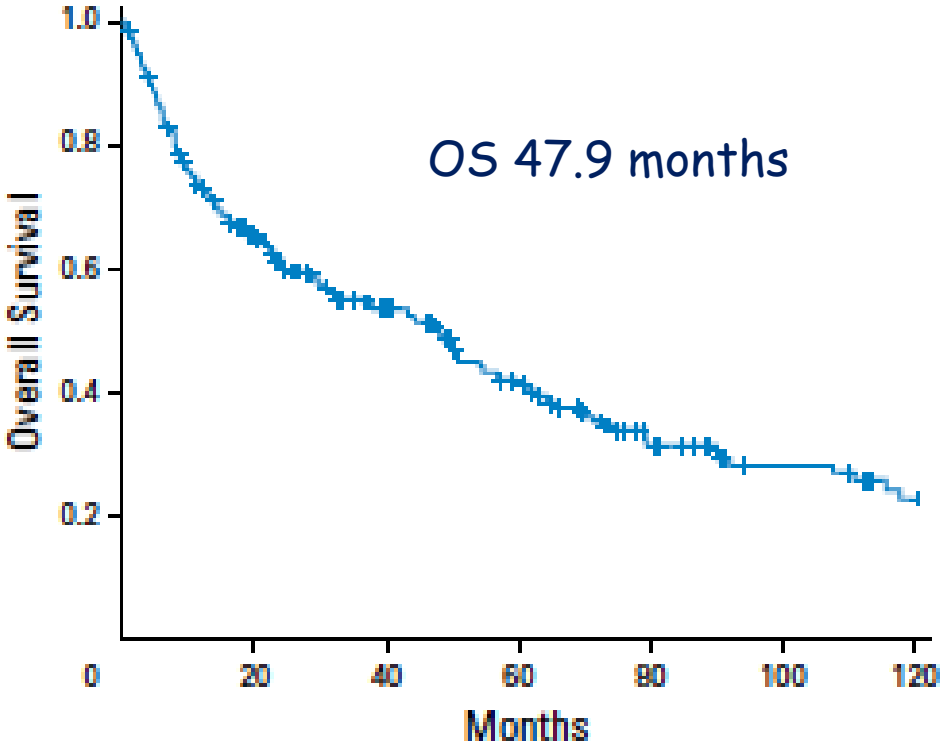
- 1 year: 73%
- 5 years: 46%

Survival of 868 patients with AL amyloidosis



Merlini G, et al JCO 2011 (29) 14: 1924-1933

IgM –AL amyloidosis

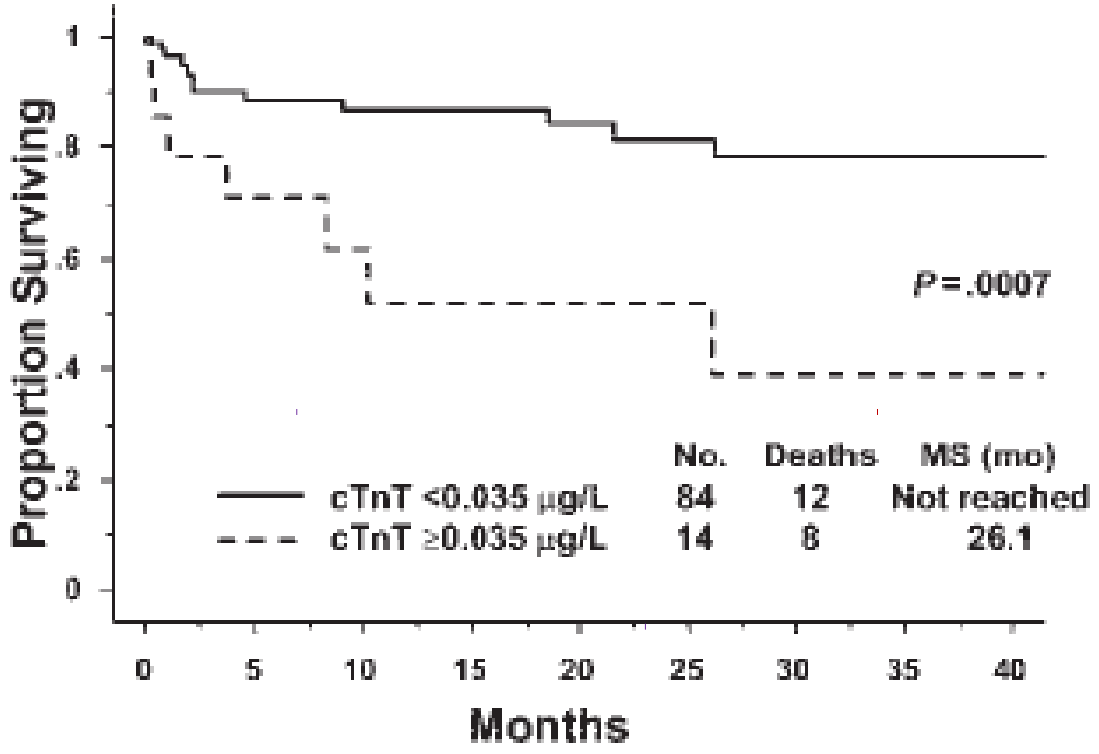


Sachchithanantham S et al. JCO 2016;34:2037-2045

AL Amyloidosis - risk stratification

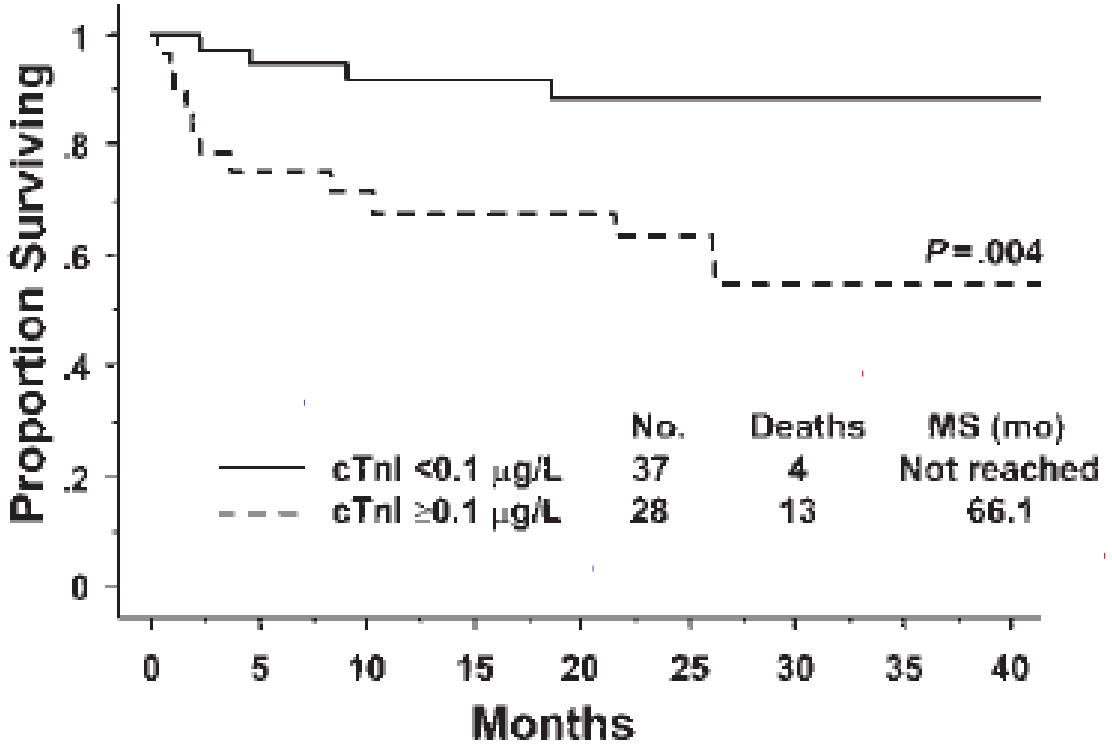
Troponin T

14% of patients



Troponin I

43% of patients

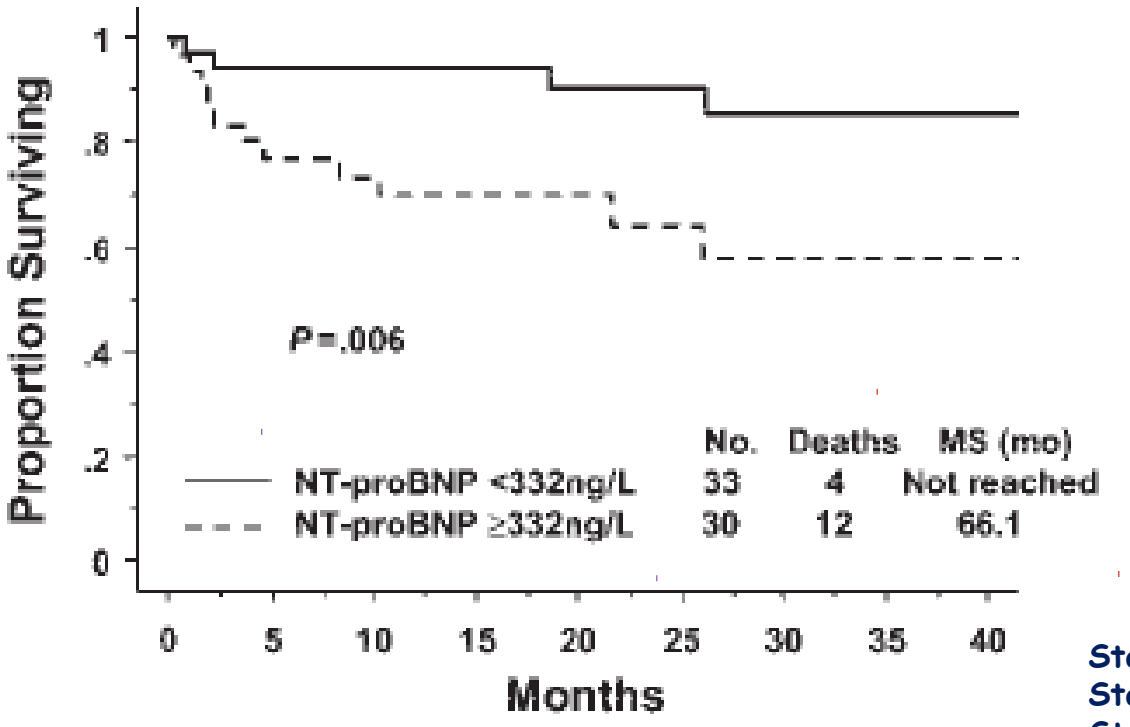


Dispenzieri A et al. JCO 2004;22:3751-3757

AL Amyloidosis - risk stratification

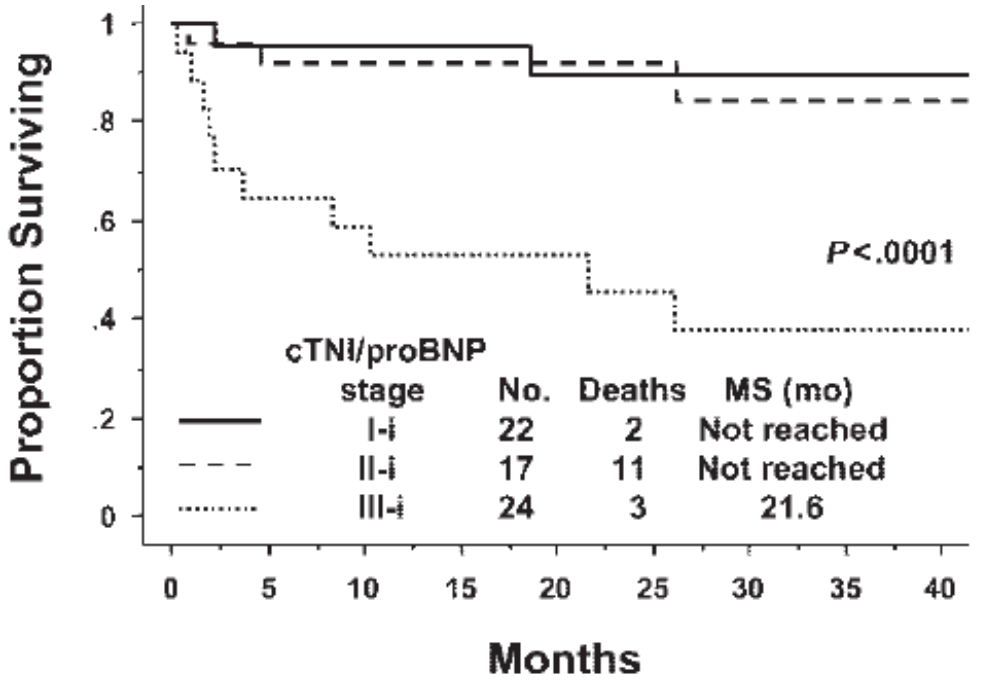
NTproBNP

48% of patients



Dispenzieri A et al. JCO 2004;22:3751-3757

Mayo Clinic stagin system



Stage I-i is when both are below threshold.
Stage II-i is when either is greater than or equal to threshold value.
Stage III-i is when both are greater than or equal to threshold value.
Threshold values for cTnI and NT-proBNP are less than 0.1 g/L and less than 332 ng/L, respectively.

AL Amyloidosis - risk stratification

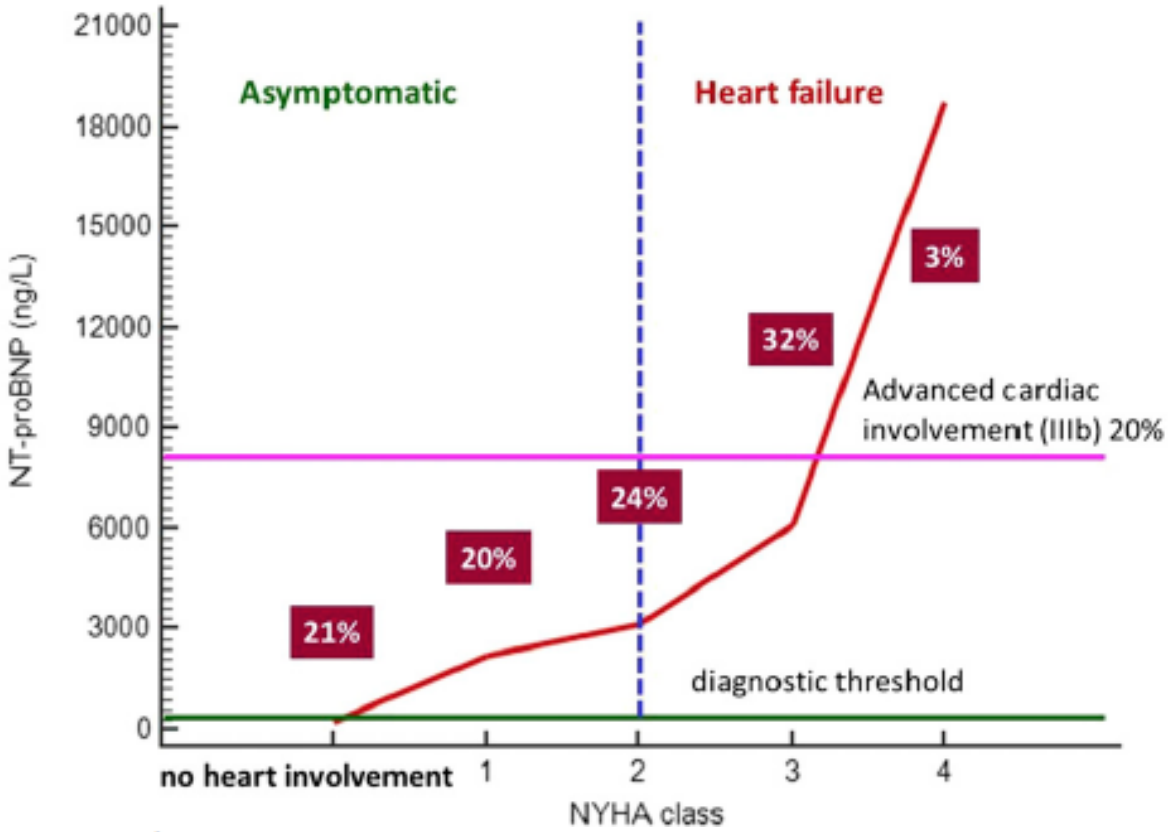
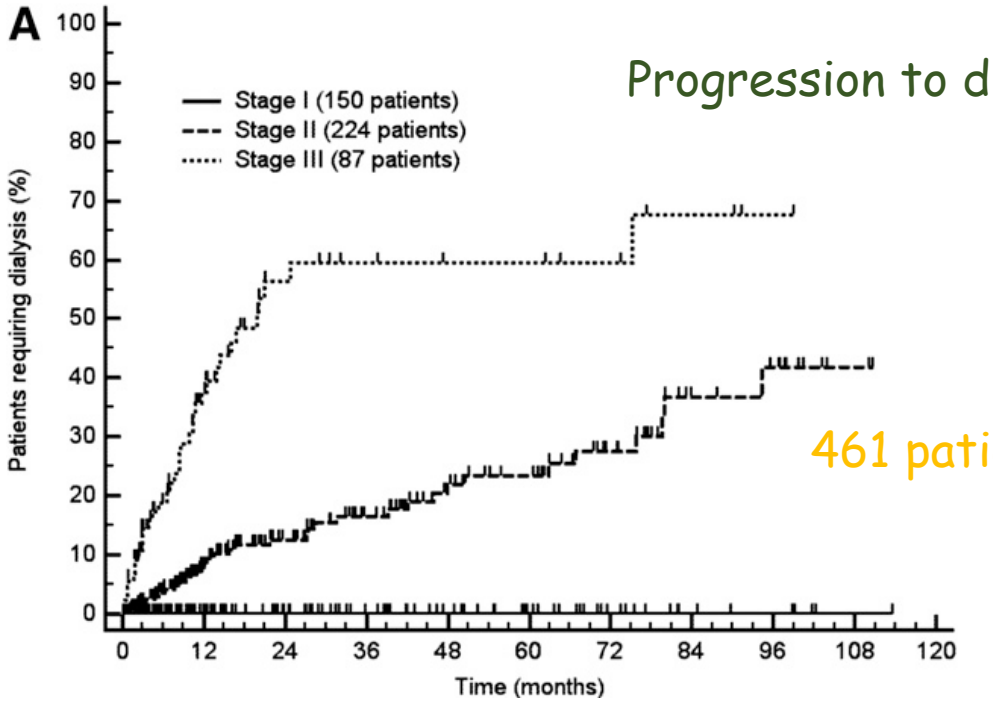


Figure 2. NT-proBNP increase above the threshold of 332 ng/L anticipates symptomatic cardiac failure. NT-proBNP concentration at diagnosis in 1065 patients is plotted versus cardiac symptoms (New York Heart Association [NYHA] class). The cardiac biomarker NT-proBNP can detect cardiac involvement before the appearance of symptoms of cardiac failure in one-fifth of patients. This biomarker could be used for screening patients for initial amyloid cardiac involvement in populations at risk to reduce the still-disheartening 20% of patients who are diagnosed with very advanced cardiac damage with NT-proBNP >8500 ng/L.

Merlini G et al. Educational ASH 2017

AL Amyloidosis - risk stratification



Progression to dialysis according to renal stage

461 patients; P <.001

Renal stage I: both proteinuria <5 g/24 h and eGFR >50 mL/min per 1.73 m2.

Renal stage II: either proteinuria >5 g/24 h or eGFR <50 mL/min per 1.73 m2.

Renal stage III: both proteinuria >5 g/24 h and eGFR <50 mL/min per 1.73 m2.

Table 3. Cox analysis of the impact of proposed response and progression criteria on renal survival (6-month landmark analysis)

		Testing cohort (n = 301)		Validation cohort (n = 171)	
Criteria	**Definition**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Renal progression	≥25% decrease in eGFR	4.56 (2.44-8.52)	<.001	4.74 (2.64-8.50)	<.001
Renal response	≥30% decrease in proteinuria or drop of proteinuria below 0.5 g/24 h in the absence of renal progression	0.15 (0.05-0.49)	<.001	0.25 (0.06-0.98)	.039
Target hematologic response	VGPR (dFLC <40 mg/L in patients with baseline dFLC ≥50 mg/L) or CR (negative serum and urine immunofixation and normal FLC ratio)	0.47 (0.25-0.87)	.014	0.24 (0.13-0.48)	<.001

Palladini G et al. Blood. 2014;124(15):2325-2332.

AL Amyloidosis - risk stratification

Table 3. Staging of cardiac and renal damage in AL amyloidosis.

Staging system	Markers and thresholds	Stages	Outcomes*
Cardiac[54,55]	NT-proBNP >332 ng/L cTnT >0.035 ng/mL (or cTnI > 0.01 ng/mL)	I. no markers above the cutoff II. one marker above the cutoff IIIa. both markers above the cutoff and NT-proBNP <8500 ng/L IIIb. both markers above the cutoff and NT-proBNP ≥8500 ng/L	I. median survival not reached, 60% surviving 10 years II. median survival 49 months IIIa. median survival 14 months IIIb. median survival 5 months
Revised Mayo Clinic [139]	NT-proBNP >1800 ng/L cTnT >0.025 ng/mL dFLC >180 mg/L	I. 0 markers above the cutoff II. 1 marker above the cutoff III. 2 markers above the cutoff IV. 3 markers above the cutoff	I. median survival not reached, 55% surviving 10 years II. median survival 57 months III. median survival 18 months IV. median survival 6 months
Renal[60]	eGFR <50 mL/min per 1.73 m^2 proteinuria >5 g/24h	I. both eGFR above and proteinuria below the cutoffs II. either eGFR below or proteinuria above the cutoffs III. both eGFR below and proteinuria above the cutoffs	I. 1% risk of dialysis at 2 years II. 12% risk of dialysis at 2 years III. 48% risk of dialysis at 2 years

cTn, cardiac troponin; dFLC, difference between involved (amyloidogenic) and uninvolved circulating free light chain; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-natriuretic peptide type-B. *Observed in 1065 patients with AL amyloidosis newly diagnosed at the Pavia Amyloidosis Research and treatment center.

IgM AL Amyloidosis - risk stratification

Table A2. Proposed New Prognostic Model for Patients With IgM-Related AL Amyloidosis

Factors	Score	Median OS (months)
NT-proBNP > 332 ng/L	1	
cTnT > 0.035 µg/L or cTnI > 0.1 µg/L	1	
Liver involvement	1	
Involvement of PNS/ANS	1	
Mayo stage		
1	0	90
2	1	33
3	2 or more	16

Abbreviations: AL, light chain; ANS, autonomic nervous system; cTnI, cardiac troponin I; cTnT, cardiac troponin T; IgM, immunoglobulin M; NT-proBNP, N-terminal pro-brain natriuretic peptide; OS, overall survival; PNS, peripheral nervous system.

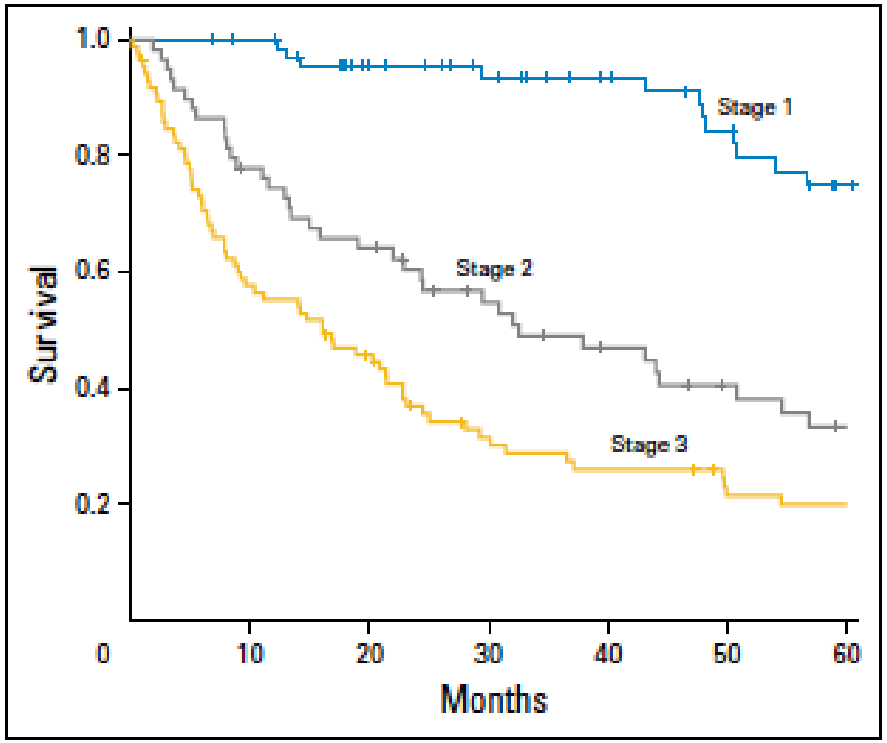


Fig A2. Shows survival curve for prognostic model with PNS involvement, abnormal BNP, abnormal Troponin T/Troponin I and liver involvement for patients with IgM-related AL amyloidosis. Stage 1, no abnormal features; stage 2, one abnormal feature; and stage 3, two or more abnormal features.

Sachchithanantham S et al. *JCO* 2016;34:2037-2045

AL Amyloidosis – response criteria

Table 2. New Hematologic and Cardiac Response and Progression Criteria*

Criteria	HR	95% CI	*P*
Hematologic response†			
aCR (negative serum and urine immunofixation and normal FLC ratio)	1		—
VGPR (dFLC < 40 mg/L)	2.67	1.26 to 5.66	.01
PR (dFLC decrease > 50%)	6.24	2.96 to 16.15	< .001
NR	12.34	6.03 to 25.35	< .001
Cardiac response and progression			
NT-proBNP response (> 30% and > 300 ng/L decrease if baseline NT-proBNP ≥ 650 ng/L)	0.23	0.14 to 0.38	< .001
NT-proBNP progression (> 30% and > 300 ng/L increase)	4.36	3.24 to 5.89	< .001
cTn progression (≥ 33% increase)	2.27	1.57 to 3.27	< .001
NYHA class response (≥ two-class decrease if baseline NYHA class 3 or 4)	0.28	0.13 to 0.60	.001
EF progression (≥ 10% decrease)	1.95	1.20 to 3.17	.007

Abbreviations: aCR, complete response; cTn, cardiac troponin; dFLC, difference between involved and uninvolved free light chain; EF, ejection fraction; FLC, free light chain; HR, hazard ratio; NT-proBNP, *N*-terminal pro-natriuretic peptide type B; NR, no response; NYHA, New York Heart Association; PR, partial response; VGPR, very good partial response.

*Cox univariable analysis.

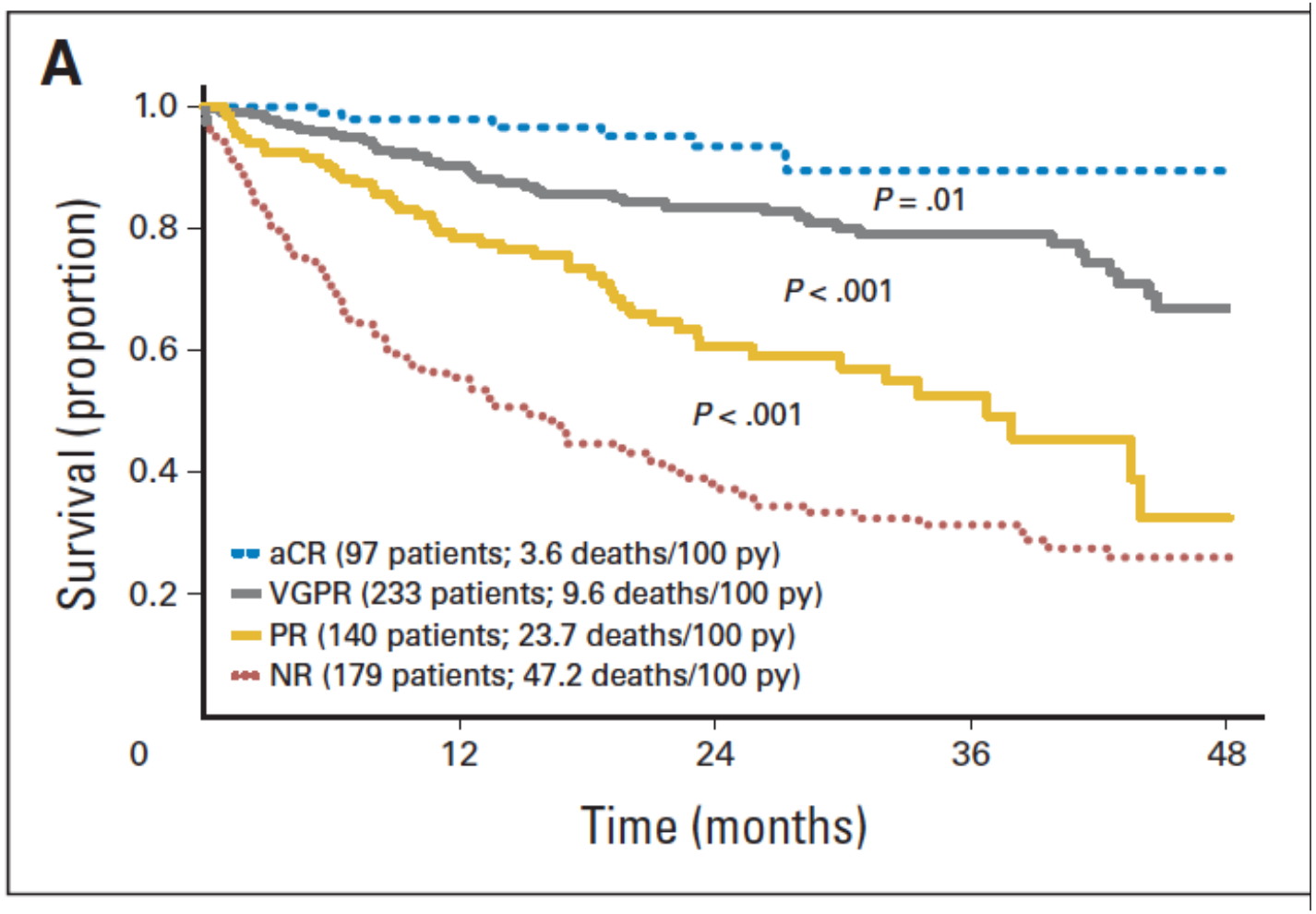
†For the model: $P < .001$; Harrel C = 0.72; Royston explained variation = 0.33.

The aim of treatment is to achieve at least a VGPR.

Further improvement of cardiac or renal function after CR can be achieved by obtaining a status of **negativity for minimal residual disease**, as assessed by nextgeneration flow cytometry

Palladini G et al J Clin Oncol. 2012;30(36):4541-4549.

AL Amyloidosis – hematologic response



(A)Survival at 6-month in 649 patients

Palladini G et al. JCO 2012;36:4541-4549

AL Amyloidosis – therapy

Table 2. Outcome of AL amyloidosis treated with selected upfront regimens according to disease severity

Disease severity	Treatment	Patients	Hematologic response % (CR %, VGPR %)	Organ response %	PFS (median months)*	Overall survival (median years)
Fit patients (15%–20%), age <65 y, stage I/early II, NT-proBNP <5000 ng/L, cTnT <0.06 ng/mL, ECOG 0-1, eGFR >50 mL/min, no gastrointestinal bleeding	ASCT[58]					
	ASCT[61]					
Intermediate fit (50%–60%), stage II and stage IIIa, ECOG 1-2, SBP >100 mm Hg, NT-proBNP <8500 ng/L	CyBorD[68]	128 Stages II and IIIa	66 (20, 27)	H 22 K 25	13	5
	BMDex[66]	87 (19 stage IIIb)	69 (42, 13)	H 16 K 16	39	53% at 5 y
	MDex[63]	119 (12 stage IIIb)	76 (31, 29)	H 37 K 24	30	7.4
Frail (15%–20%), stage IIIb, NT-proBNP >8500 ng/L, SBP <100 mm, ECOG 4, NYHA 3–4	CyBorD attenuated[68]	43	42 (14, 9)	H 4	NR	7 mo
	MDex attenuated†	62	37 (9, 15)	H 18	NR	7 mo

In patients with >10% PCs in the bone marrow, induction therapy with bortezomib-based regimens significantly improve the quality of response after ASCT.
Consolidation with bortezomib-based regimens in subjects who fail to achieve a CR after ASCT increases the CR rate to almost 60%

cTnT, cardiac troponin T; ECOG, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; H, heart; K, kidney; NR, not reported; NYHA, New York Heart Association classes of heart failure; PFS, progression-free survival; SBP, systolic blood pressure.
*There are no validated progression criteria in AL amyloidosis and PFS is defined differently in different studies.

AL Amyloidosis – therapy

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	ASCT[61]	629	— (35, —) 45 CR with Mel 200 34 CR with Mel 100-140	—	NR	7.6
Intermediate fit (50%–60%), stage II and stage IIIa, ECOG 1-2, SBP >100 mm Hg, NT-proBNP <8500 ng/L	CyBorD[68]					
	BMDex[66]					
	MDex[63]	(12 stage IIIb)		K 24		
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An international, randomized phase 3 study comparing MDex and BMDex that BMDex induced a VGPR or better in 62% of patients, compared with 40% withMDex (P =.016), with ~40% cardiac and renal responses

cTnT, cardiac troponin T; ECOG, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; H, heart; K, kidney; NR, not reported; NYHA, New York Heart Association classes of heart failure; PFS, progression-free survival; SBP, systolic blood pressure.

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AL Amyloidosis – therapy

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*There are no validated progression criteria in AL amyloidosis and PFS is defined differently in different studies.

AL Amyloidosis – therapy

Table 3. Outcome of relapsed/refractory AL amyloidosis patients who received salvage therapy with different treatment regimens

Treatment	No. of patients	Hematologic response % (CR %/VGPR %)	Organ response %	Median PFS	Median overall survival
Bortezomib[64]	70	60 (24/—)	H 13, K 29	77% at 1 y	90% at 1 y
Lenalidomide-dexamethasone[90]	84	61 (20/8)	H 12; K 40	73% at 2 y	84% at 2 y
Pomalidomide-dexamethasone[74]	28	68 (4/25)	K 17	16 mo	26 mo
Bendamustine[77]	125*	36 (2/8)	H 13; K 15	NR	21 mo
Ixazomib[75]	27	52 (10/33)	H 45; K 45	15 mo	85% at 1 y
Carfilzomib[76]	24	63 (13/33)	5 (21%): 3 K, 1 GI, 1 liver	20 mo	NR
Daratumumab[80]	25	76 (36/24)	NR	NR	NR

Since t(11; 14) is the most common cytogenetic abnormality in AL amyloidosis, it is logical that **venetoclax** will be important in the therapy of AL amyloidosis. In a case report of a patient with AL amyloidosis with t(11; 14) who plateaued at a partial response with CyBorD therapy, the addition of venetoclax to bortezomib resulted in a complete response. The duration of response was short, and the κ-FLC began increasing within 3 months of stopping treatment along with serum creatinine. The patient quickly responded to venetoclax upon reintroduction. A trial of venetoclax given at one of four escalating doses (100, 200, 400, or 800 mg/day) and dexamethasone is currently ongoing (NCT03000660).

IgM AL Amyloidosis - therapy

Table 2 Hematologic Response, Median OS, 2-Year Survival, and TTNT for Each Treatment Group

Treatment Type	Patients		Proportion With Cardiac Involvement (Mayo stage 3)		VGPR/PR or Better		Median OS (months)	2-Year Survival (%)	TTNT (months)
	No.	%	No.	%	No.	%			
Autologous stem cell transplantation	4	1.8	25	0	100	33	NR	100	NR
Chlorambucil or cyclophosphamide	62	27.1	41	25	46	7	50.8	73	11
CHOP/COP/VAD	14	6.1	21	33	62	0	49.8	79	21
Melphalan with or without dexamethasone	53	23	58	28	70	26	22.9	49	8
Fludarabine, cyclophosphamide, or cladribine	12	5	42	25	40	0	31.4	58	10
Fludarabine, cyclophosphamide, and rituximab	11	4.8	27	0	70	30	69.4	73	63
R-CD/R-CHL/R-CVP/ R-CHOP/R-TD	45	19.7	44	23	63	15	91.9	63	20
Bortezomib	8	3.5	50	25	57	42	NR	88	NR
Rituximab plus bortezomib	8	3.5	50	25	86	29	30.2	75	19
Thalidomide	11	4.8	36	27	63	9	37.9	55	5

Abbreviations: CHOP, cyclophosphamide, vincristine, doxorubicin, and prednisolone; COP, cyclophosphamide, vincristine, and prednisolone; NR, not reached; OS, overall survival; PR, partial response; R-CD, rituximab plus cyclophosphamide and dexamethasone; R-CHL, rituximab and chlorambucil; R-CHOP, rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisolone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisolone; R-TD, rituximab plus thalidomide; TTNT, time to next treatment; VAD, vincristine, doxorubicin, and dexamethasone; VGPR, very good partial response.

Sachchithanantham S et al. *JCO* 2016;34:2037-2045