Gruppo Aziendale Amiloidosi dell'AOU Città della Salute e della Scienza di Torino dal 3 Dicembre 2014 come da Protocollo Aziendale n. 0118998

Amyloidosis 2019

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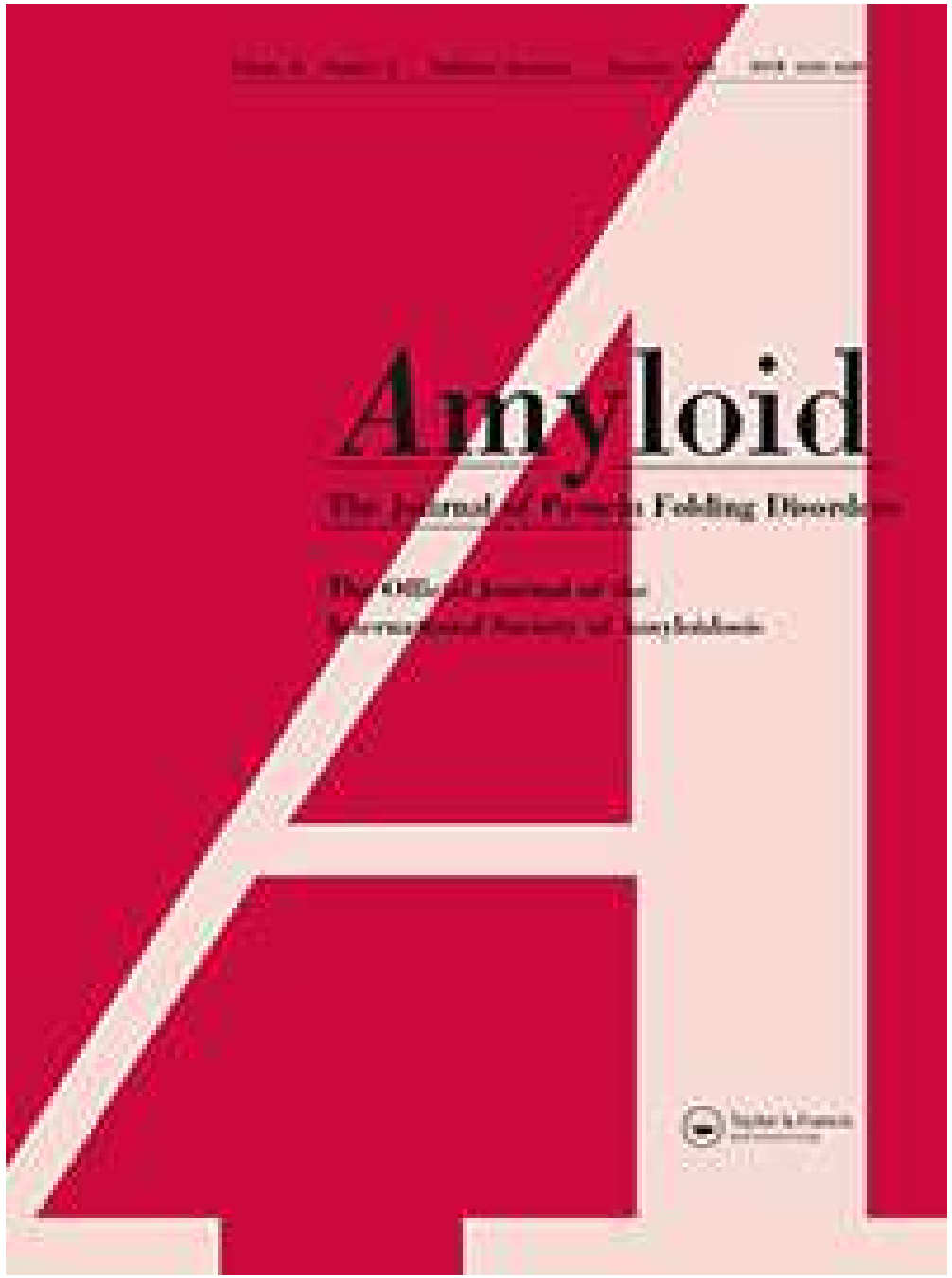
Amyloidosis

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

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

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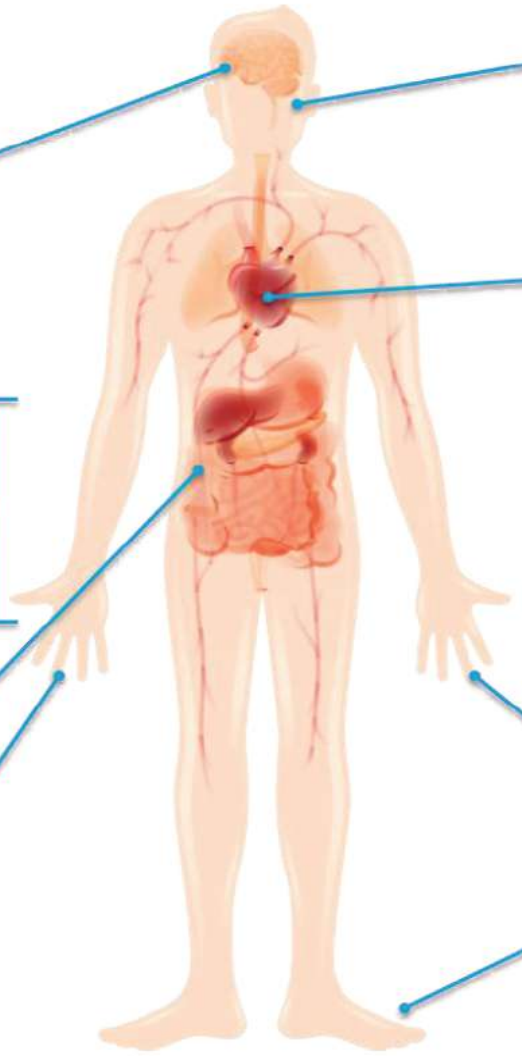
The acquired forms (AL, AH) are the most frequent, constituting 80-85% of the whole series, followed by the hereditary (ATTR) forms which represent 10-15% and by the reactive forms (AA), resulting from neoplasms, inflammatory diseases or chronic infections, which have progressively reduced over the last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

VOLUME 31 · NUMBER 34 · DECEMBER 1 2013
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Coexistent Multiple Myeloma or Increased Bone Marrow Plasma Cells Define Equally High-Risk Populations in Patients With Immunoglobulin Light Chain Amyloidosis

Taxiarchis V. Kourelis, Shaji K. Kumar, Morie A. Gertz, Martha Q. Lacy, Francis K. Buadi, Suzanne R. Hayman, Steven Zeldenrust, Nelson Leung, Robert A. Kyle, Stephen Russell, David Dingli, John A. Lust, Yi Lin, Prashant Kapoor, S. Vincent Rajkumar, Arleigh McCurdy, and Angela Dispenzieri

AL amyloidosis: from molecular mechanisms to targeted therapies

Giampaolo Merlini

Amyloidosis Research and Treatment Center, Foundation Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Department of Molecular Medicine, University of Pavia, Pavia, Italy

Review

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Recent Advances in the Diagnosis, Risk Stratification, and Management of Systemic Light-Chain Amyloidosis

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[a]Division of Hematology, Mayo Clinic, Rochester, MN, USA; [b]Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel; [c]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

European Collaborative Study Defining Clinical Profile Outcomes and Novel Prognostic Criteria in Monoclonal Immunoglobulin M–Related Light Chain Amyloidosis

Sajitha Sachchithanantham, Murielle Roussel, Giovanni Palladini, Catherine Klersy, Shameem Mahmood, Christopher Paul Venner, Simon Gibbs, Julian Gillmore, Helen Lachmann, Philip N. Hawkins, Arnaud Jaccard, Giampaolo Merlini, and Ashutosh D. Wechalekar

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.

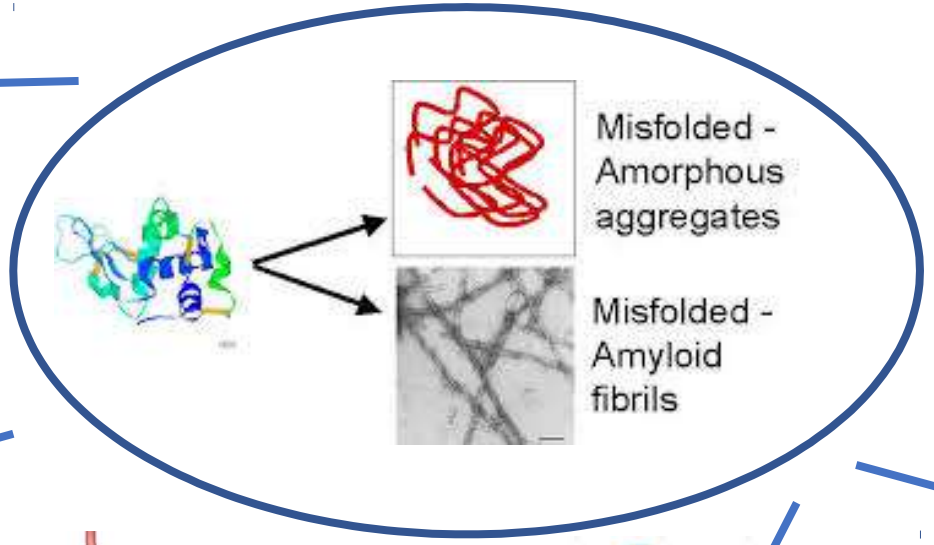
There is a male predominance, with men accounting for 55% of patients.

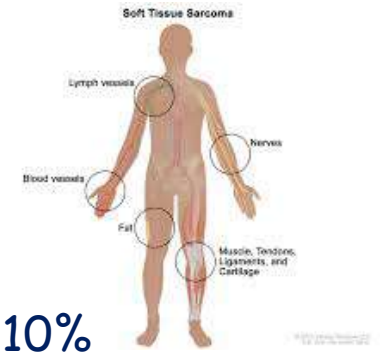
45-55% IgG or IgA; 7% IgM

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

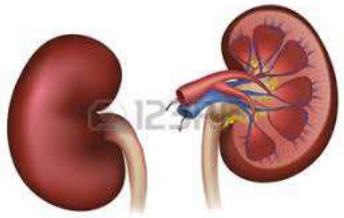
AL Amyloidosis

Hearth 71%

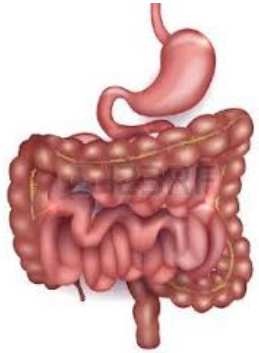




Soft tissue 10%

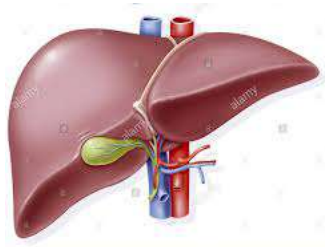


Kidney 58%



GI tract 22%

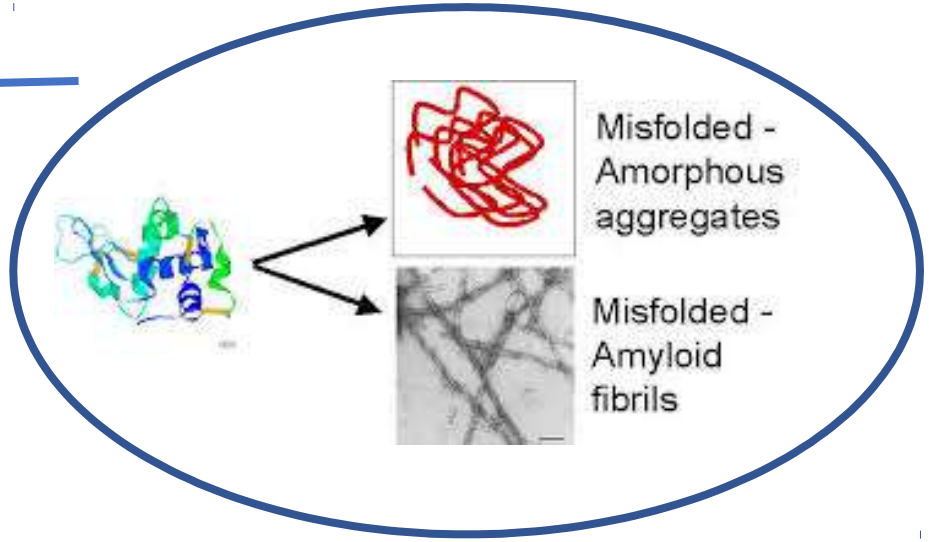
Nervous system 23%



Liver 16%

AL Amyloidosis

Hearth 71%



AL Amyloidosis -hearth

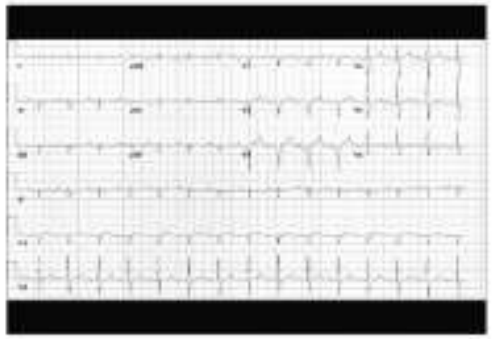
Heart involvement is the most important prognostic factor in AL amyloidosis patients and occurs in 71% of AL amyloid patients.

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

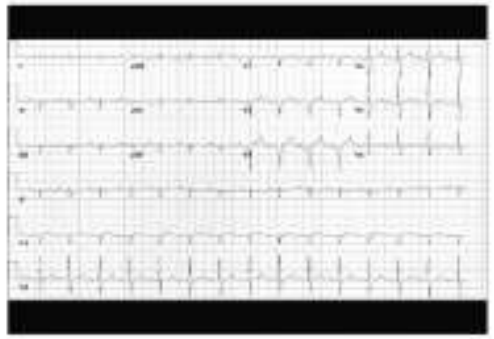
Tachiaritmie

ECG Holter

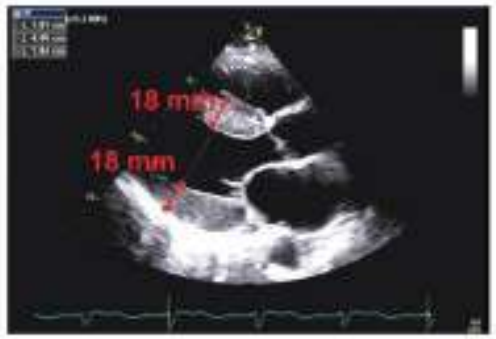
Grogan M et al. Heart 2017

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

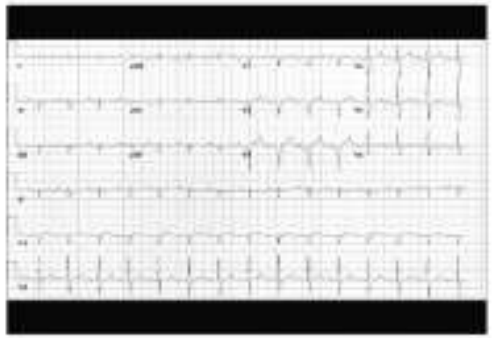
Ispessimento delle valvole atrio-ventricolari

Versamento pericardico e pleurico

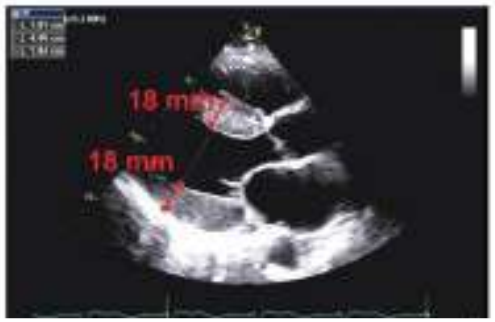
Grogan M et al. Heart 2017

Amyloidosis AL -hearth

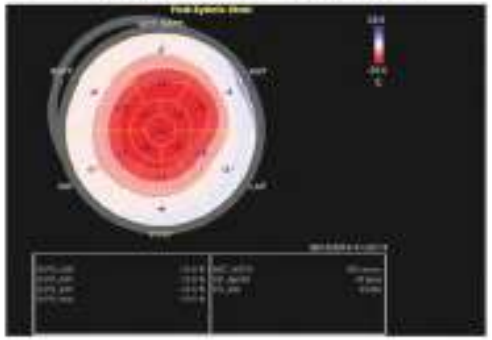
A ECG



B ECHO



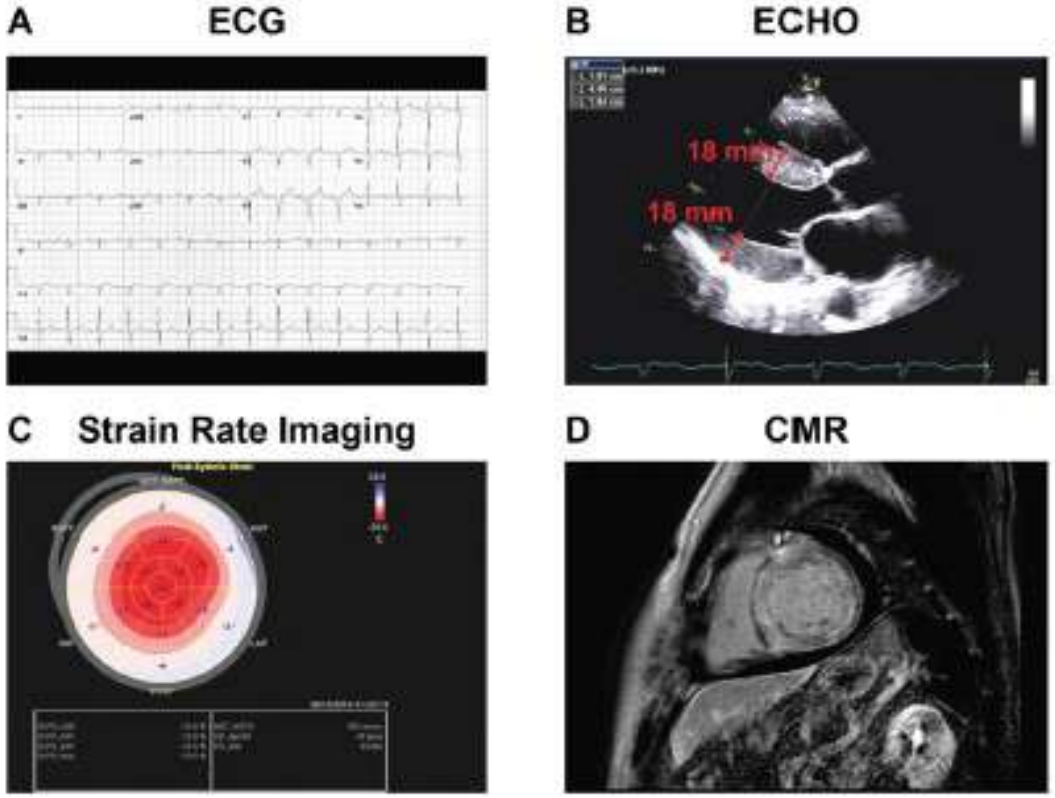
C Strain Rate Imaging



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

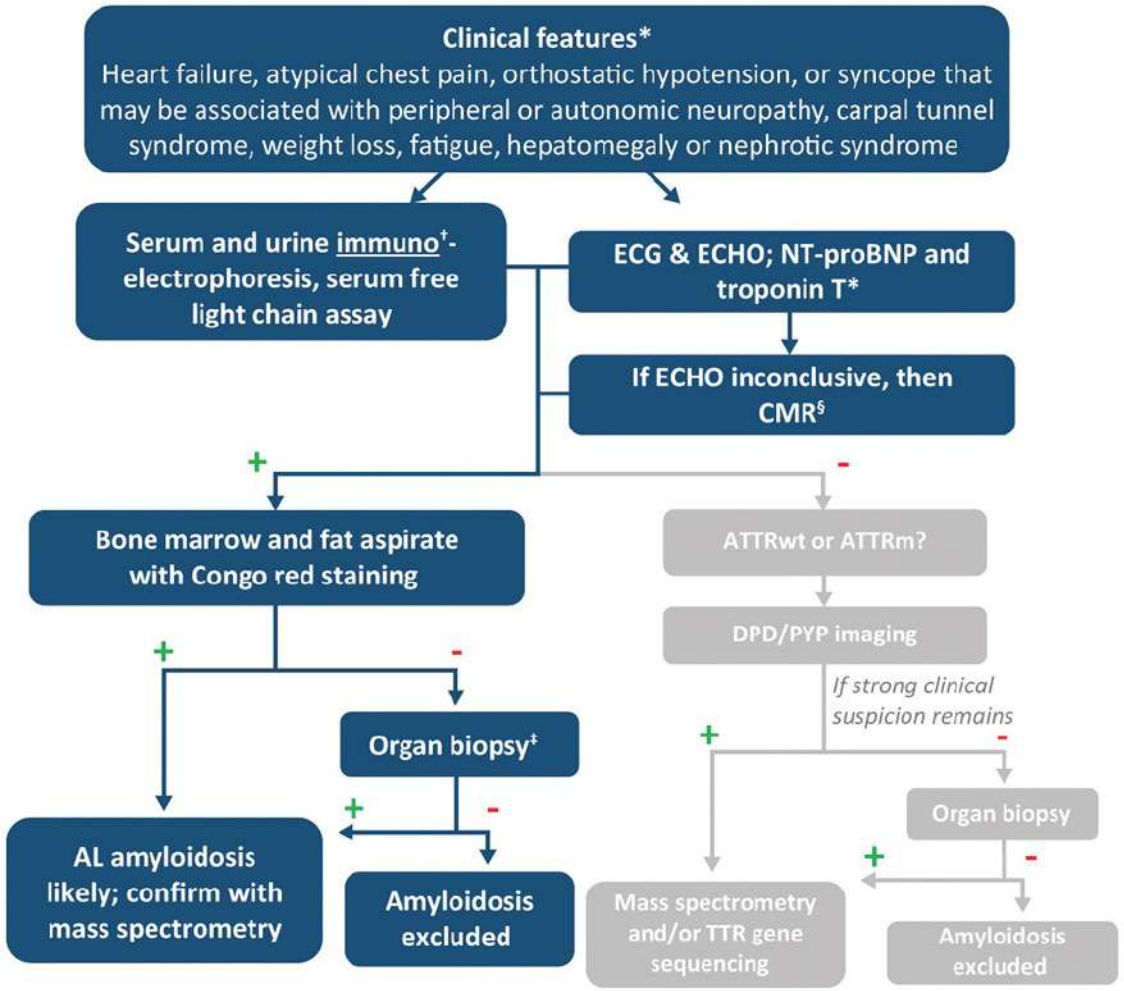
The gold standard for diagnosing cardiac amyloidosis is **endomyocardial biopsy**, but noninvasive cardiac imaging can replace the need for cardiac biopsy.

Cardiac MRI late gadolinium enhancement was shown to be highly sensitive (80–100%) with a negative predictive value of 85–100%, while the specificity and positive predictive values are 80–94 and 81–92%, respectively.
Cardiac MRI is unable to reliably differentiate between the various subtypes of cardiac amyloidosis.

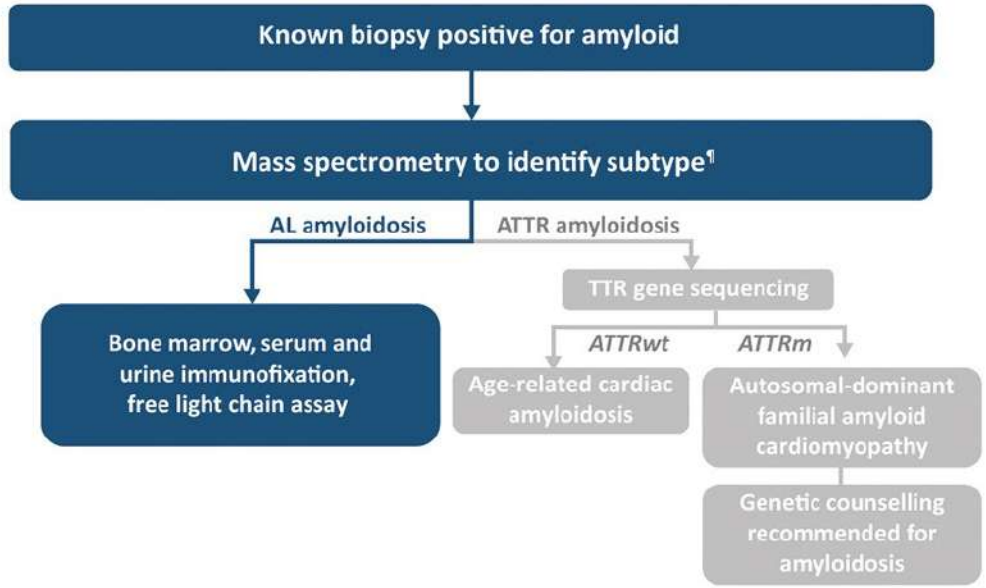
Scintigraphy with Tc-99m-pyrophosphate (99mTc-PYP) is a noninvasive and widely available method useful in identifying patients with the ATTR subtype

Amyloidosis AL -hearth

A Algorithm for diagnosis in patients with suspected cardiac amyloidosis*



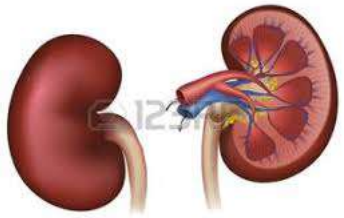
B Algorithm for diagnosis in patients with amyloidosis established by biopsy



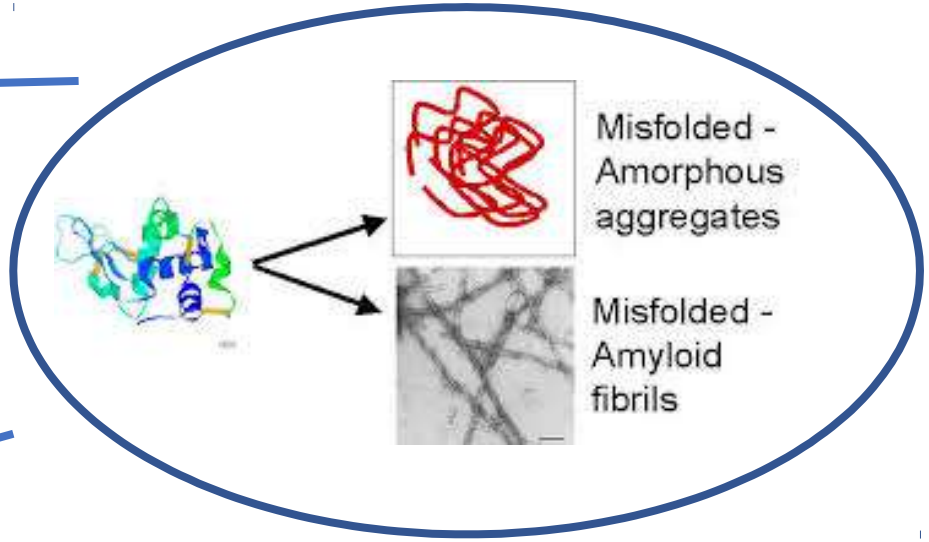
Grogan M et al. Heart 2017

AL Amyloidosis

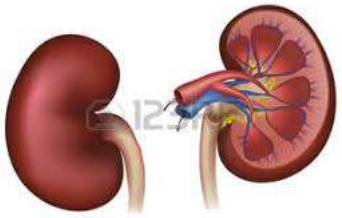
Hearth 71%



Kidney 58%



Amyloidosis AL -kidney



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

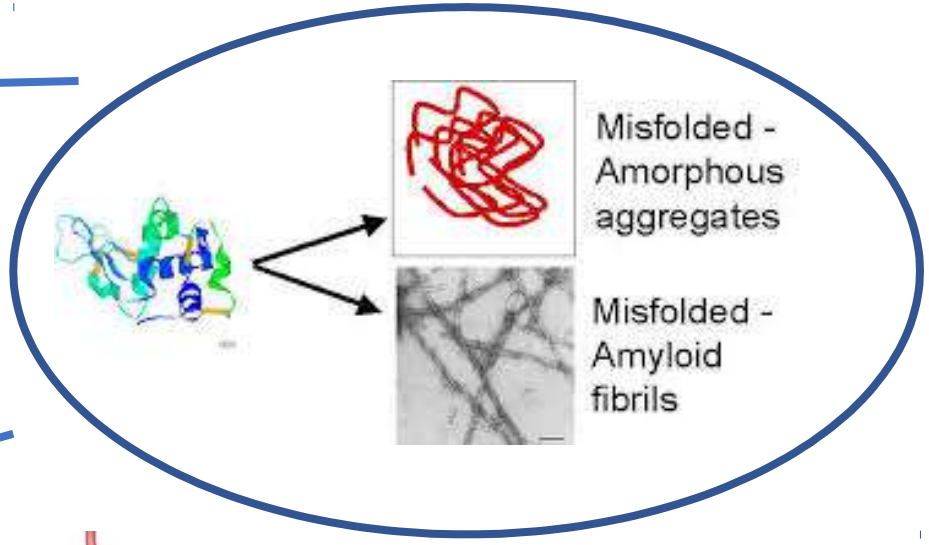
The patient may present with **peripheral edema, anasarca, foaming urine, or symptoms of uremia**.

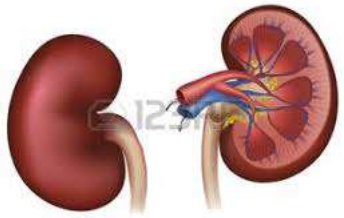
Laboratory tests may show elevated lipid levels, hypoalbuminemia, and nonselective proteinuria.

Ultrasound or CT may demonstrate enlarged kidneys.

AL Amyloidosis

Hearth 71%





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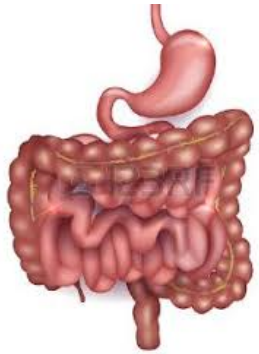
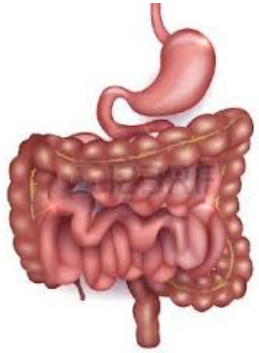


GI tract 22%

Amyloidosis AL –GI tract

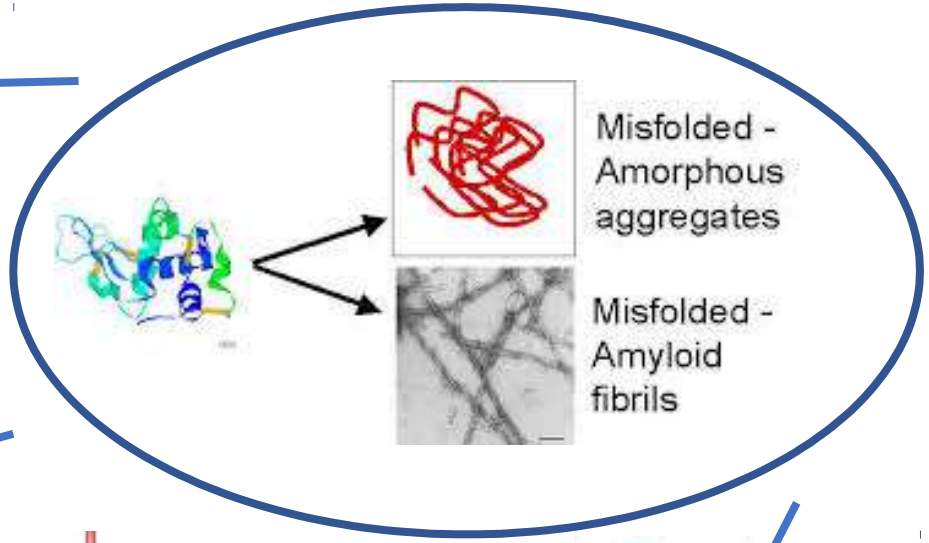


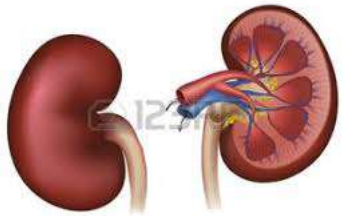
GI involvement manifests itself as **constipation, diarrhea, early satiety, GI bleeding, heartburn, nausea and vomiting due to gastroparesis, and weight loss**.

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.

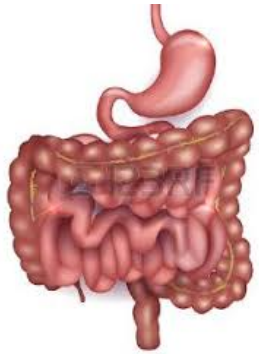
AL Amyloidosis

Hearth 71%





Kidney 58%



GI tract 22%

Nervous system 23%

Amyloidosis AL –nervous system

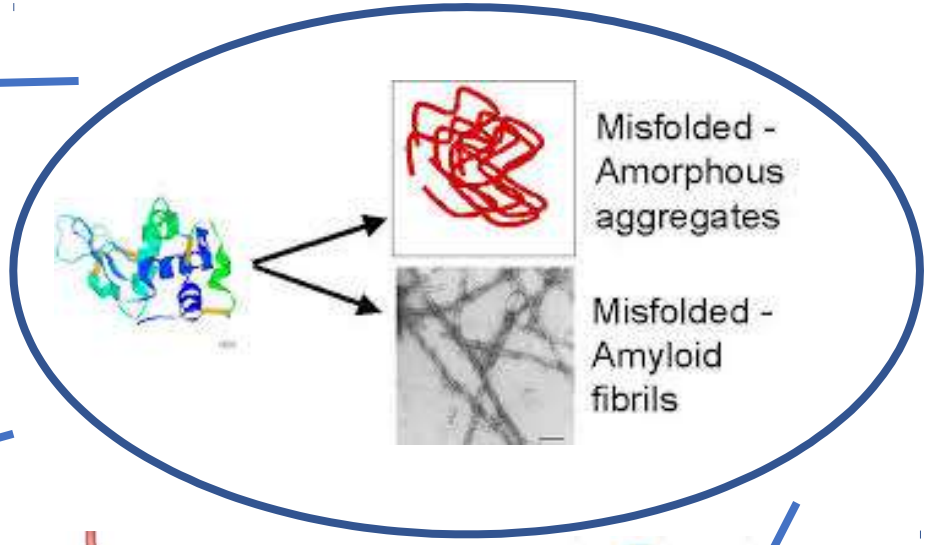
Mixed sensory and motor peripheral neuropathy (20%) and **autonomic neuropathy** (15%) are prominent features in AL amyloidosis.

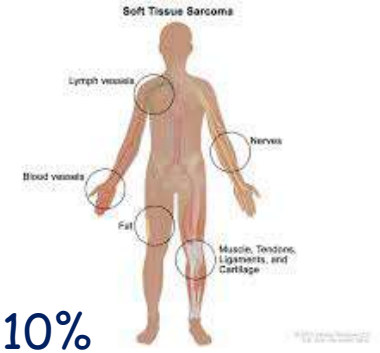
Symptoms of **numbness, paresthesia, and pain** are frequently noted resulting from the involvement of peripheral nerves, especially the median nerve within the carpal tunnel.
Symptoms of **bowel or bladder dysfunction** and **orthostatic hypotension** are caused by autonomic nervous system damage.

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.

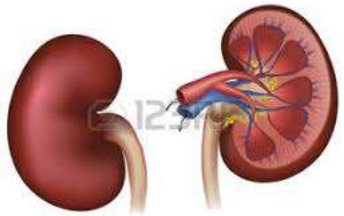
AL Amyloidosis

Hearth 71%

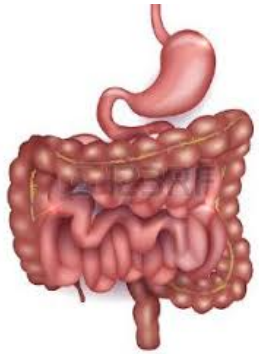




Soft tissue 10%



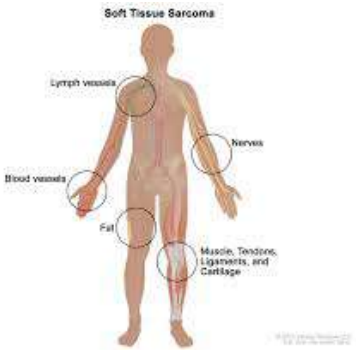
Kidney 58%



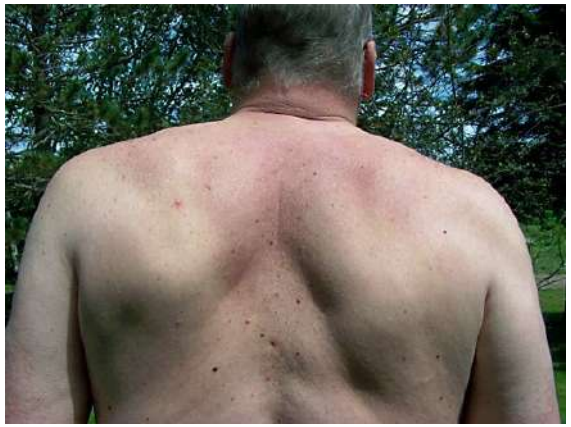
GI tract 22%

Nervous system 23%

Amyloidosis AL –soft tissue

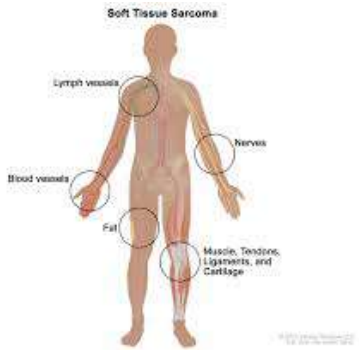


AL amyloidosis patients may present with **hoarseness, dysarthria, obstructive sleep apnea, periorbital purpura** often occurring after mild trauma or physical activity, **submandibular gland swelling, xerostomia**, and periarticular involvement causing the **shoulder pad sign** (enlargement of the anterior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

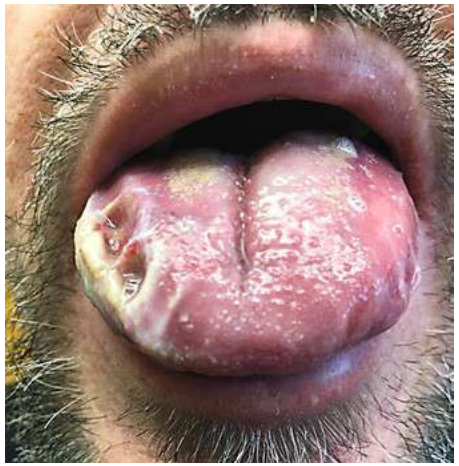


Shoulder pad sign

Amyloidosis AL –soft tissue

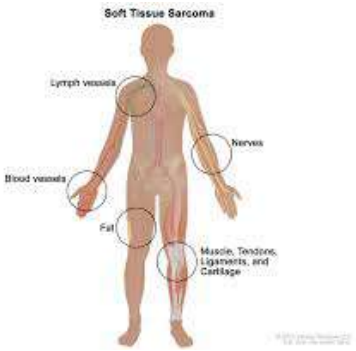


Macroglossia can cause significant morbidity due to problems with breathing, talking, and chewing, resulting in the need for feeding tubes and tracheostomy.



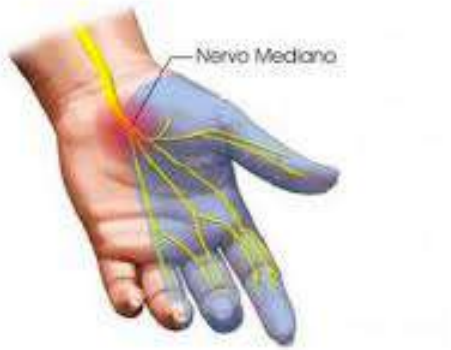
Macroglossia

Amyloidosis AL –soft tissue



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

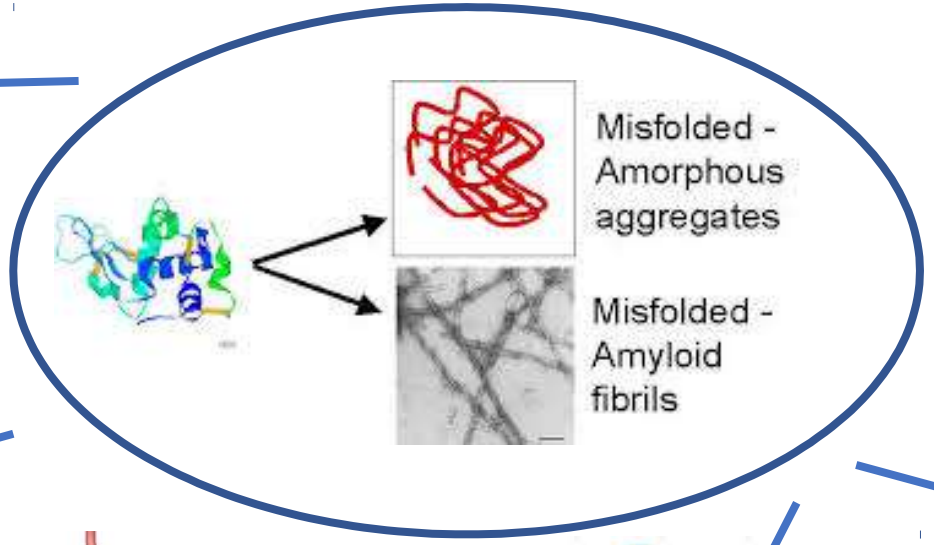
Carpal tunnel syndrome sometime precedes the tissue diagnosis of AL amyloidosis by years (range 1 month to 9.3 years).

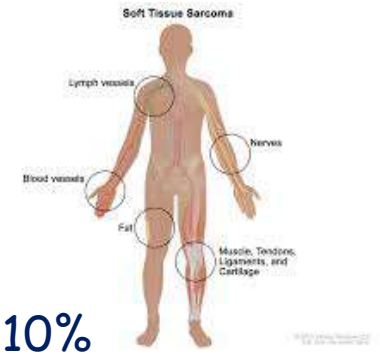


Carpal tunnel syndrome

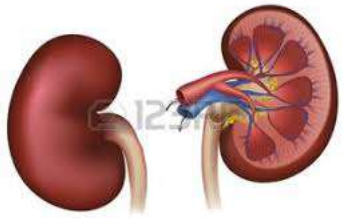
AL Amyloidosis

Hearth 71%

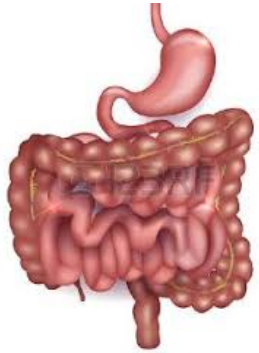




Soft tissue 10%

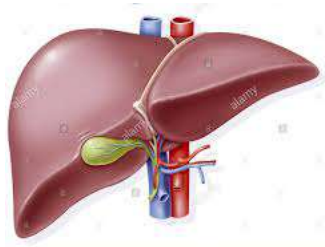


Kidney 58%



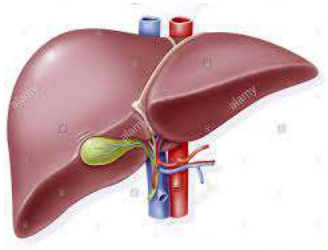
GI tract 22%

Nervous system 23%



Liver 16%

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

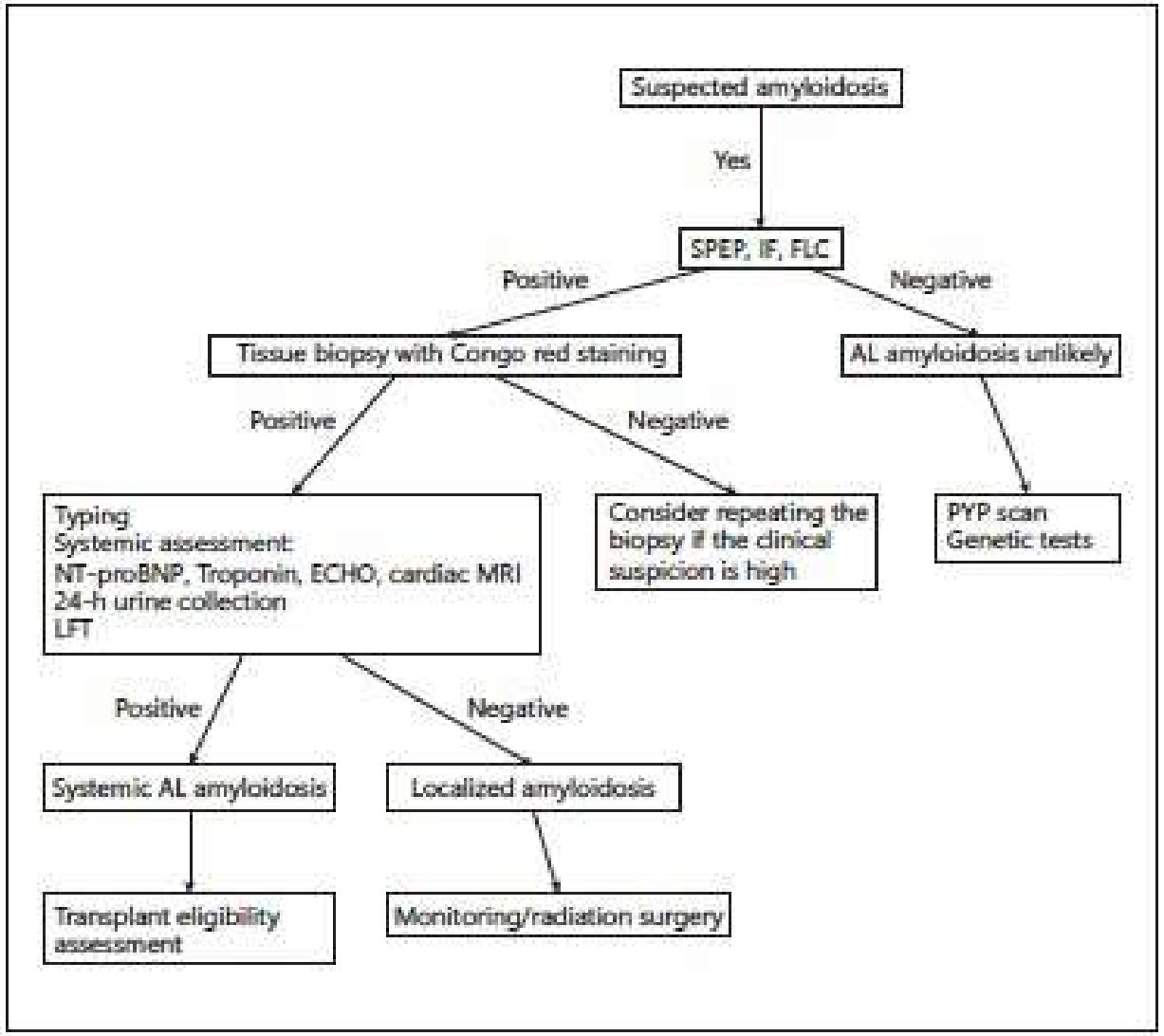
Amyloidosis AL -diagnosis

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 -diagnosis



The presence of a monoclonal gammopathy does not necessarily mean that the diagnosis is AL amyloidosis.

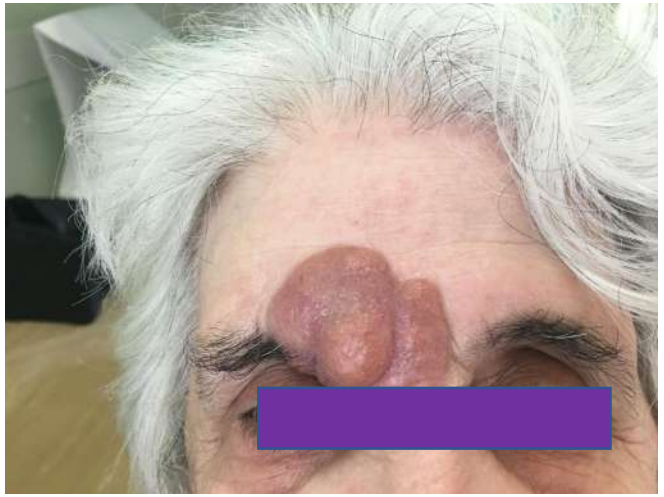
It should be noted that MGUS is very prevalent in patients over the age of 65 years, highlighting the need for amyloid typing to avoid misdiagnosis

Positive biomarker-based screening in patients at risk
(MGUS & abnormal FLC ratio)

- Elevated NT-proBNP
- Albuminuria

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.



Skin localized amyloidosis
Pre and post surgery

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.

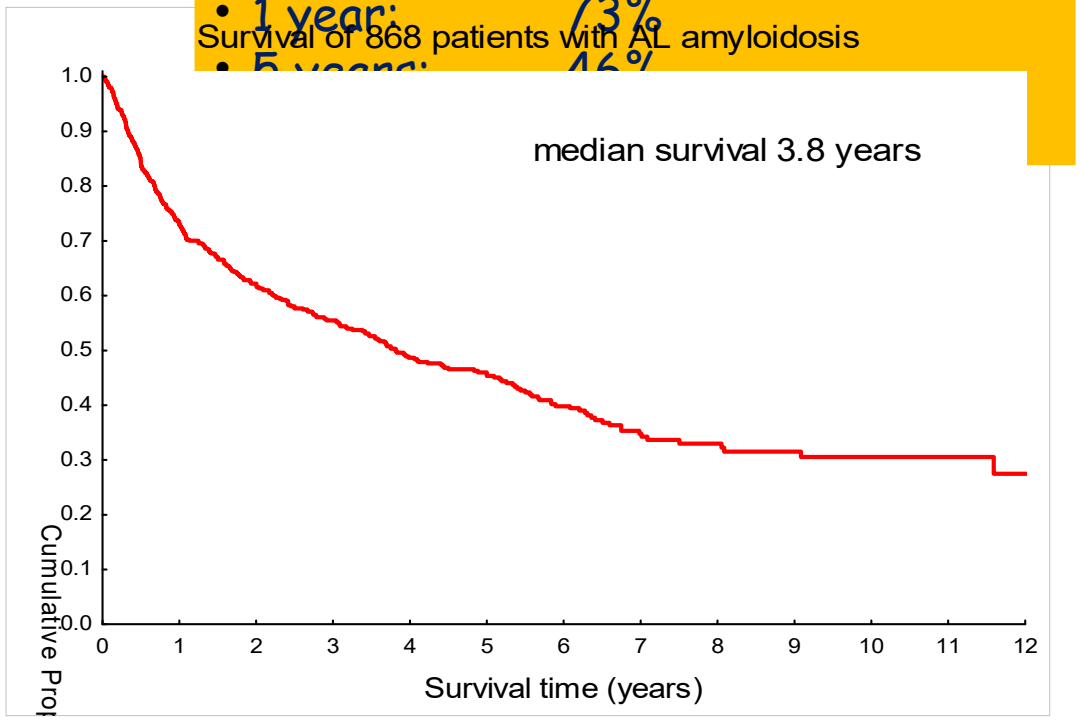
Gain of 1q21 is less frequent in AL amyloidosis than in MM, being found in less than 20% of patients. Gaining 1q21 conferred no adverse prognosis in patients treated with bortezomib.

AL Amyloidosis - prognosis

AL amyloidosis

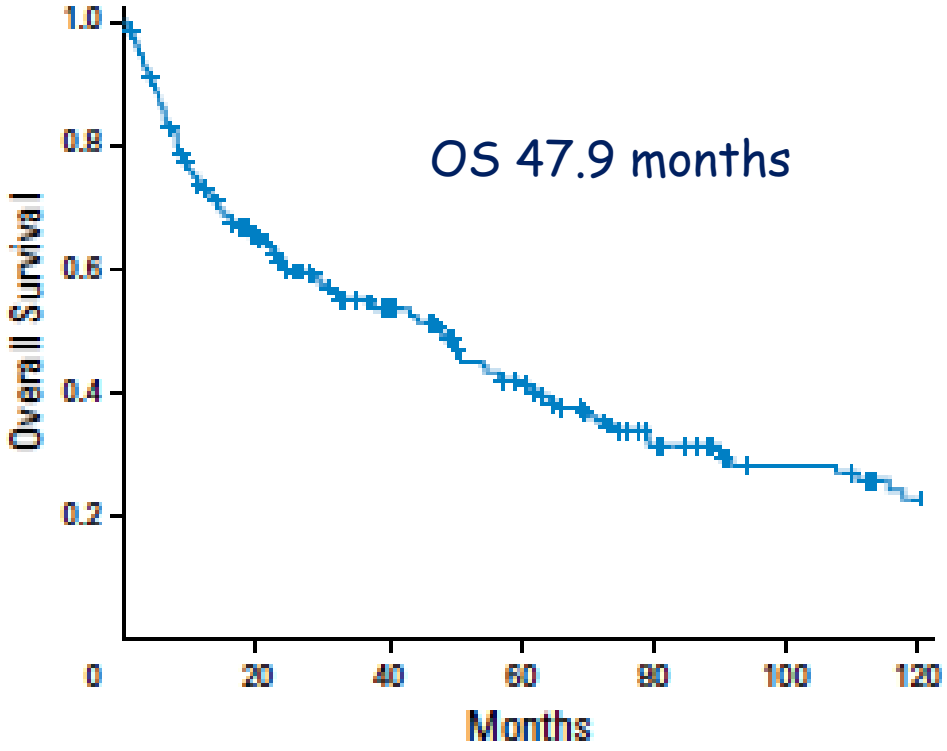
Cumulative proportion surviving:

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



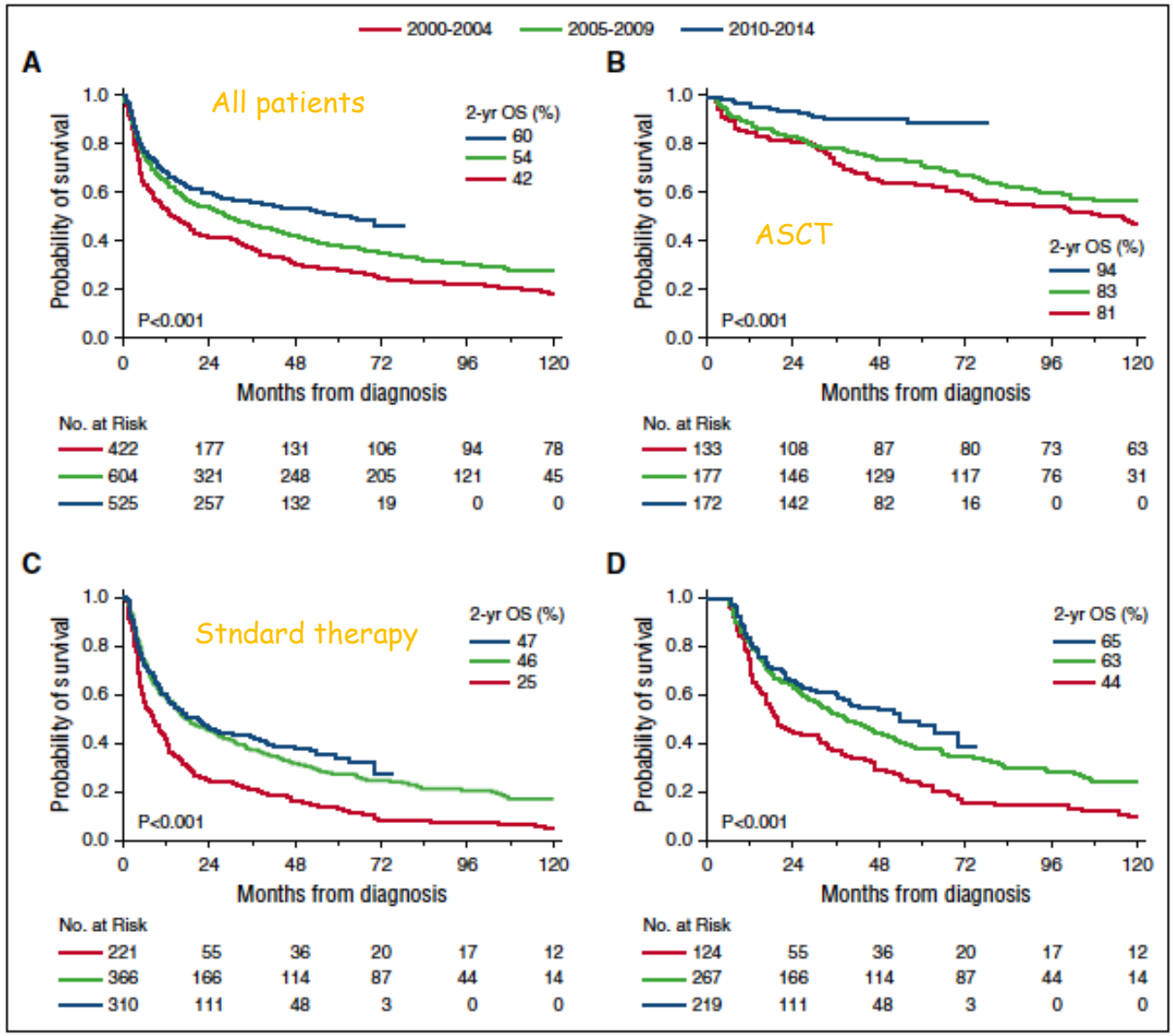
Merlini G, et al JCO 2011 (29) 14: 1924-1933

IgM –AL amyloidosis



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

AL Amyloidosis - prognosis



Therapy has translated into significant improvements of median survival that has nearly doubled over the past decade, with a significant proportion of patients **(30% to 40%) now surviving more than 10 years**

Muchtar e et al Blood. 2017;129(15):2111-2119.

AL Amyloidosis - risk stratification

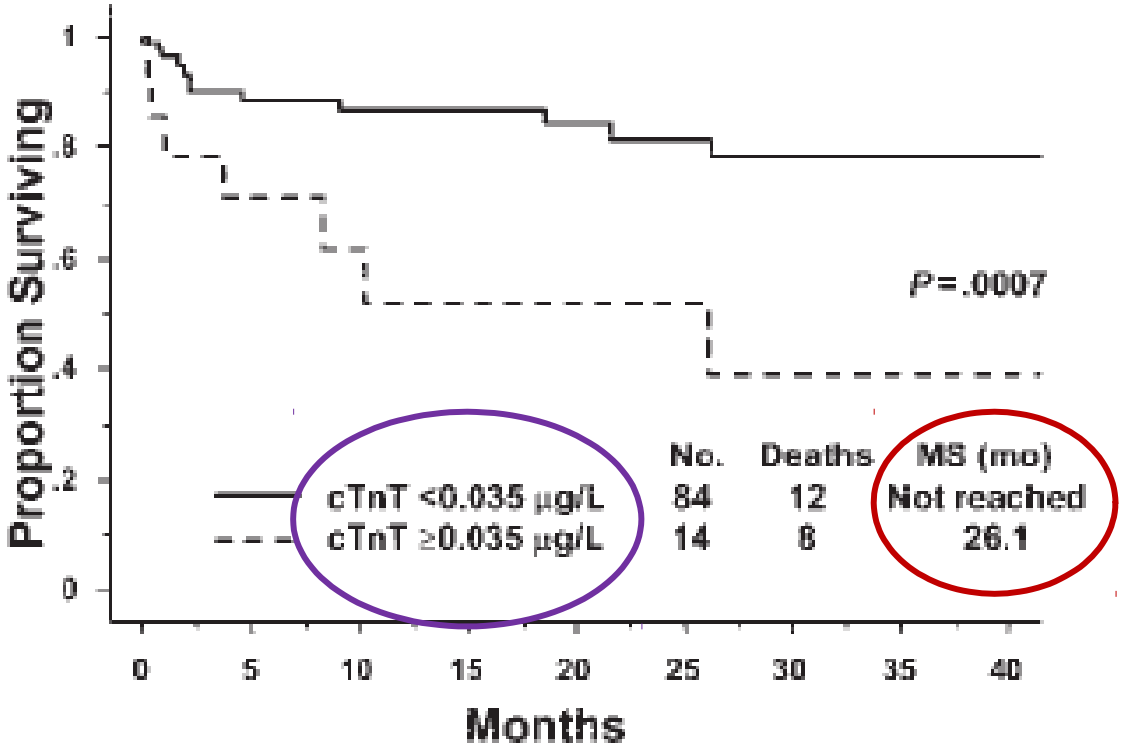
Cardiac involvement is the major prognostic factor for survival, and changes in cardiac function after therapy can be easily assessed by monitoring NT-proBNP and Troponin.

This has been validated in 98 patients undergoing ASCT (Mayo Clinic staging system).
Dispenzieri A et al. JCO 2004;22:3751-3757

AL Amyloidosis - risk stratification

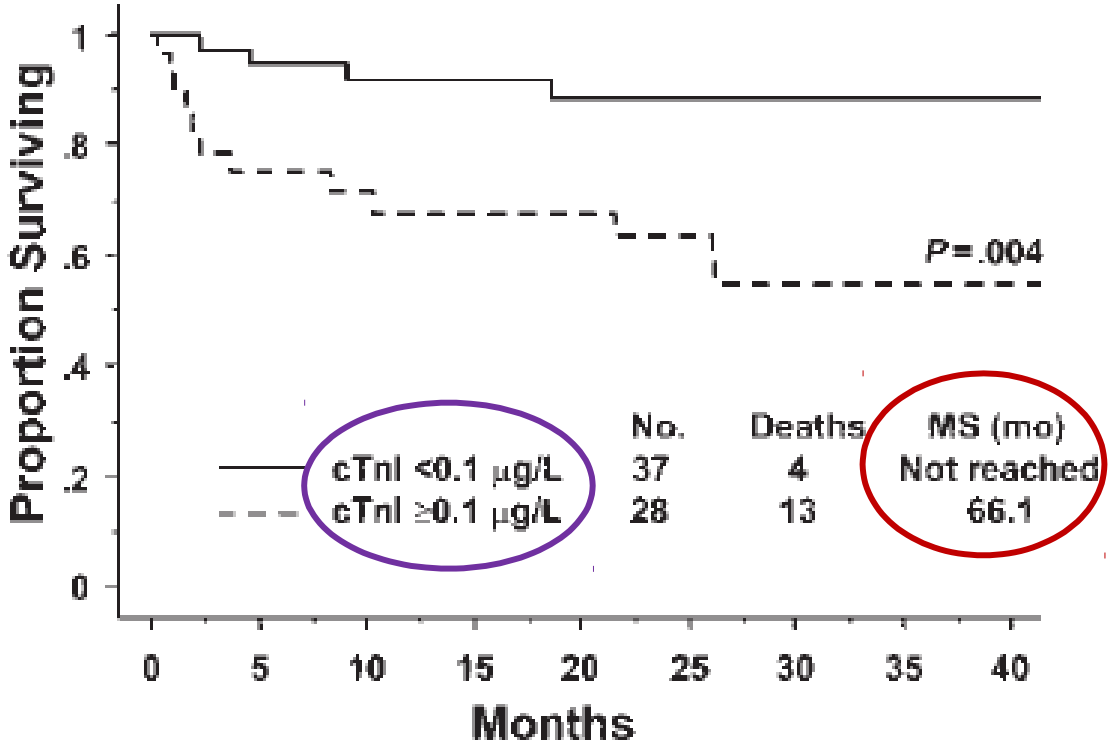
Troponin T

14% of patients



Troponin I

43% of patients

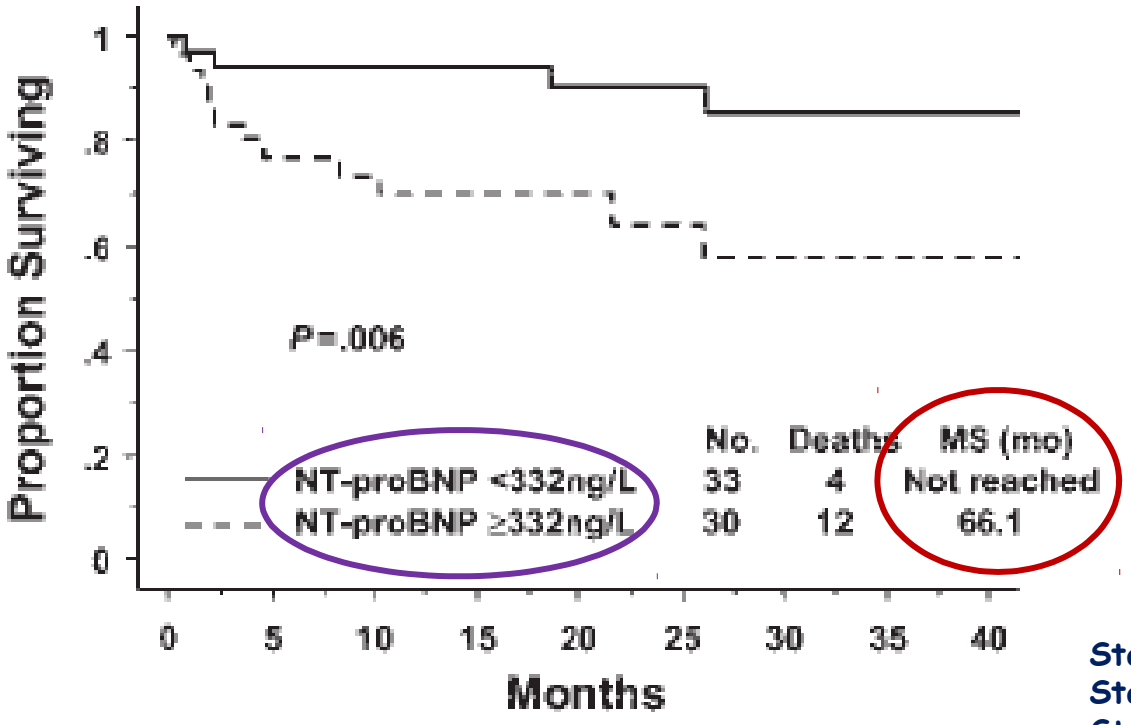


Dispenzieri A et al. JCO 2004;22:3751-3757

AL Amyloidosis - risk stratification

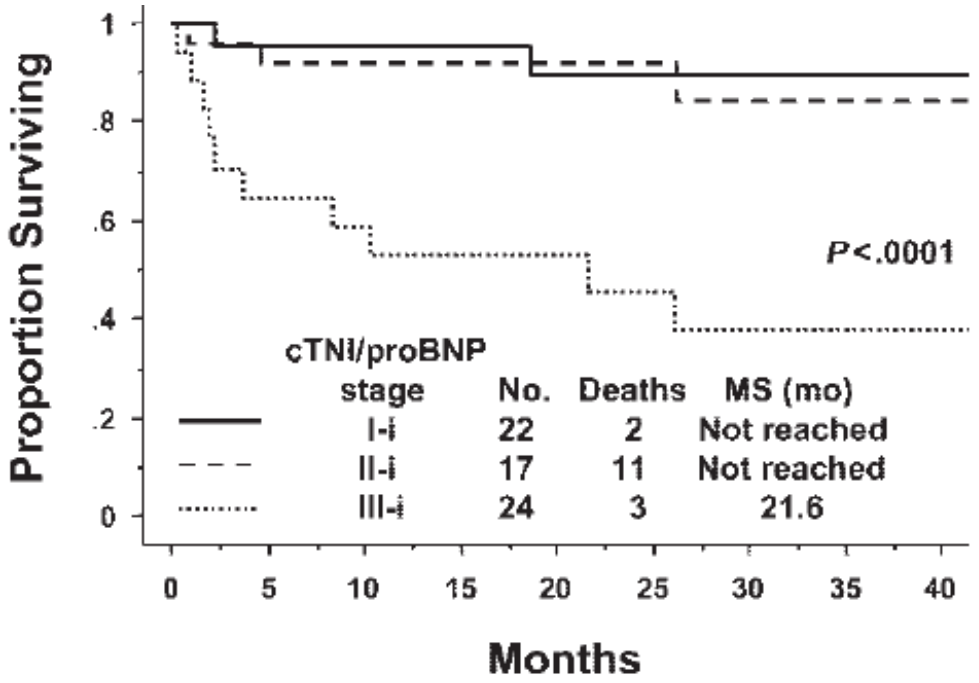
NTproBNP

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

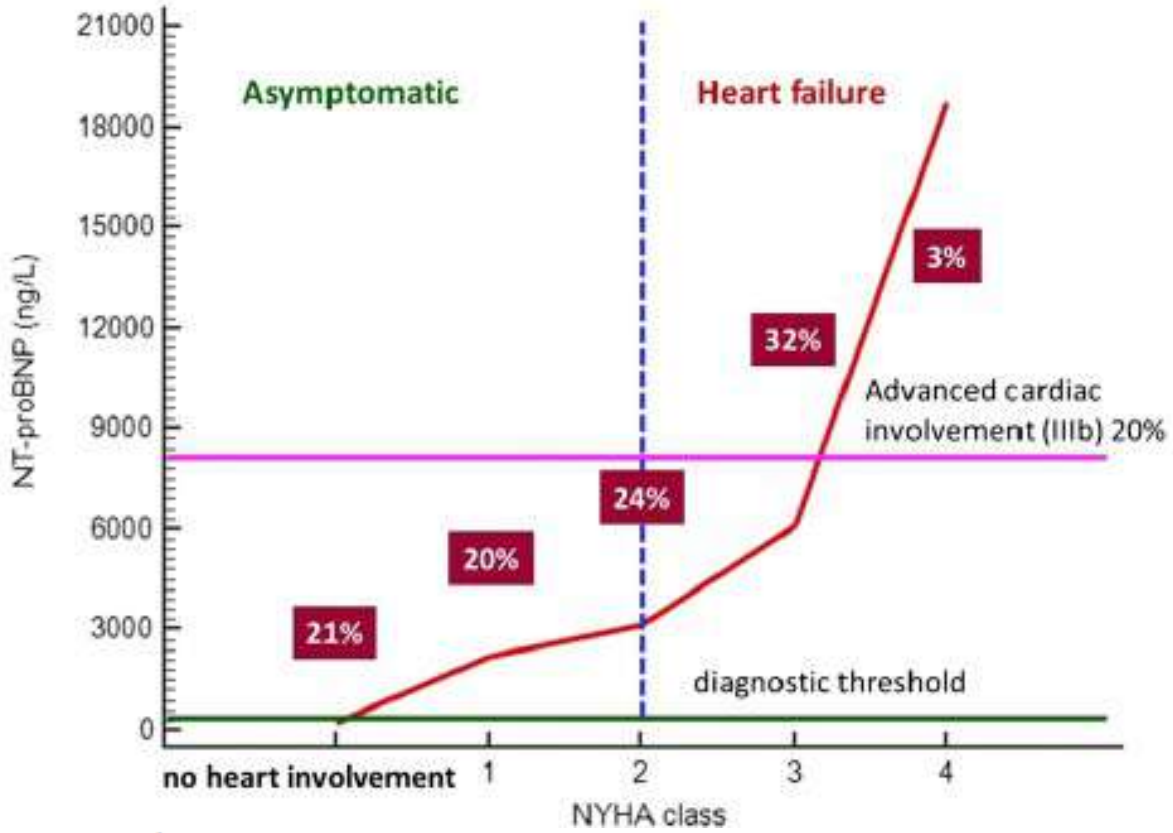
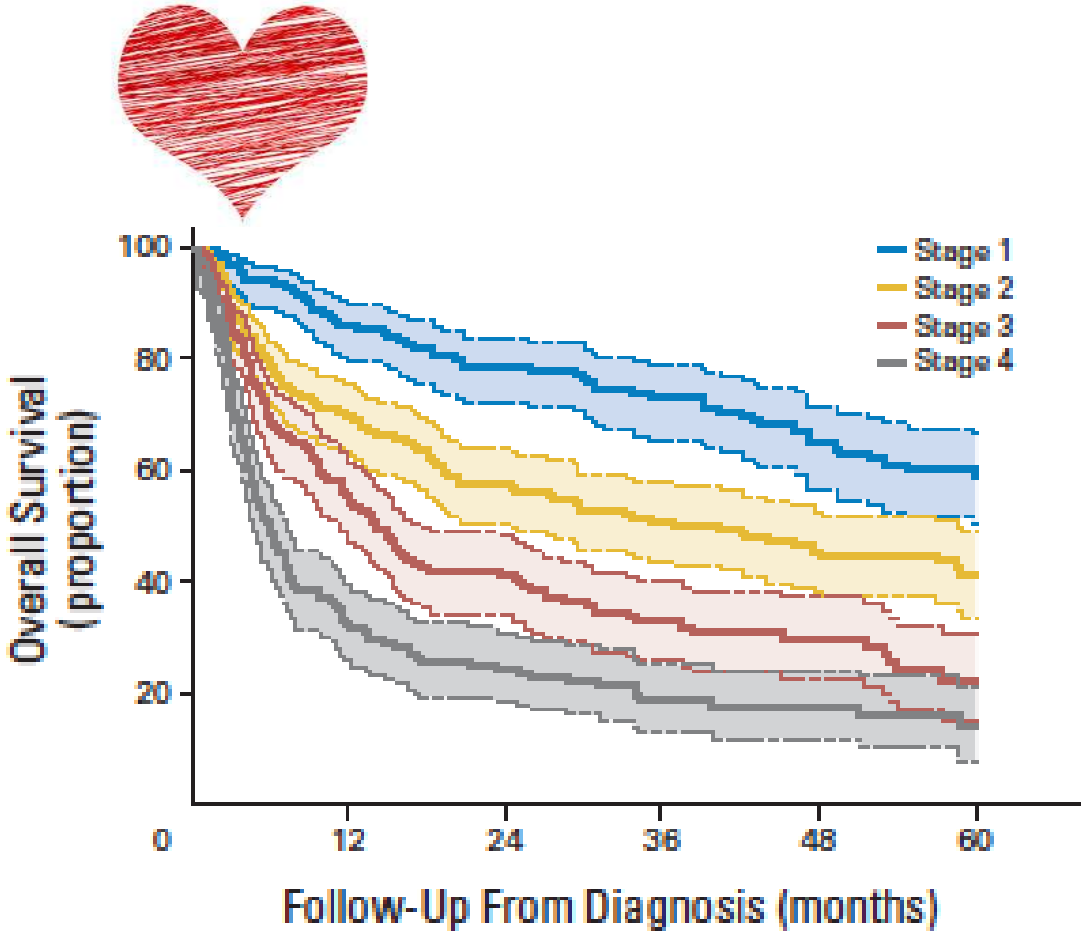


Figure 2. NT-proBNP increase above the threshold of 332 ng/L anticipates symptomatic cardiac failure. NT-proBNP concentration at diagnosis in 1065 patients is plotted versus cardiac symptoms (New York Heart Association [NYHA] class). The cardiac biomarker NT-proBNP can detect cardiac involvement before 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



Revised Prognostic Staging System for Light Chain Amyloidosis Incorporating Cardiac Biomarkers and Serum Free Light Chain Measurements

94.1 months

40.3 months

14 months

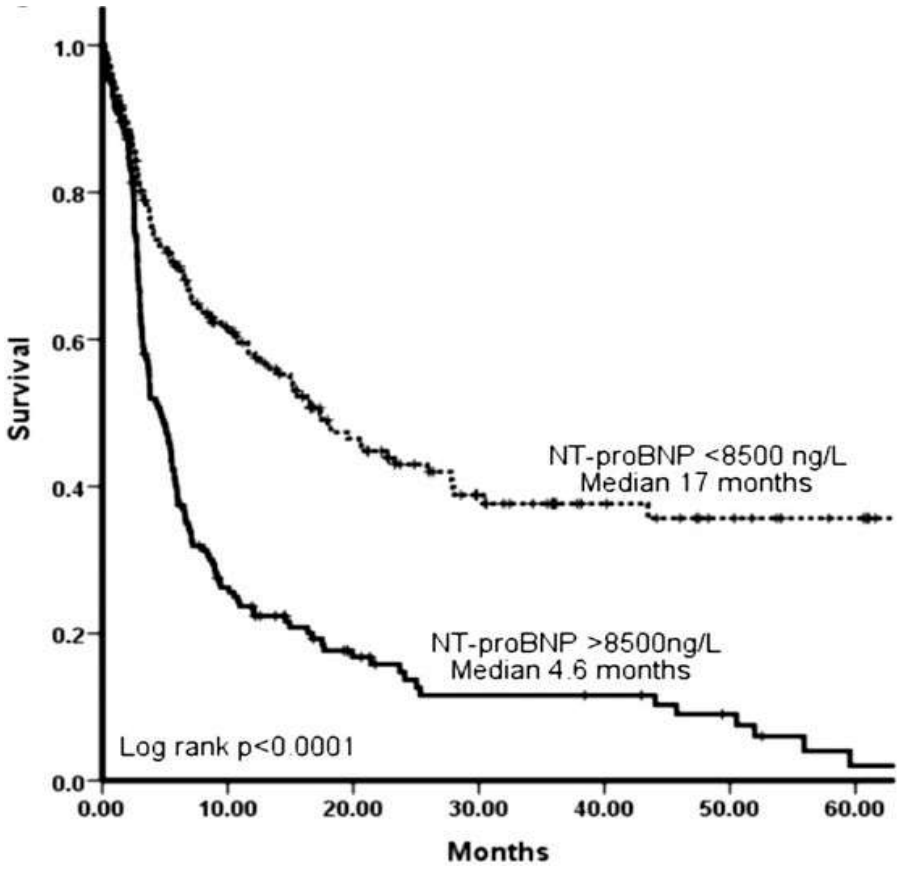
5.8 months

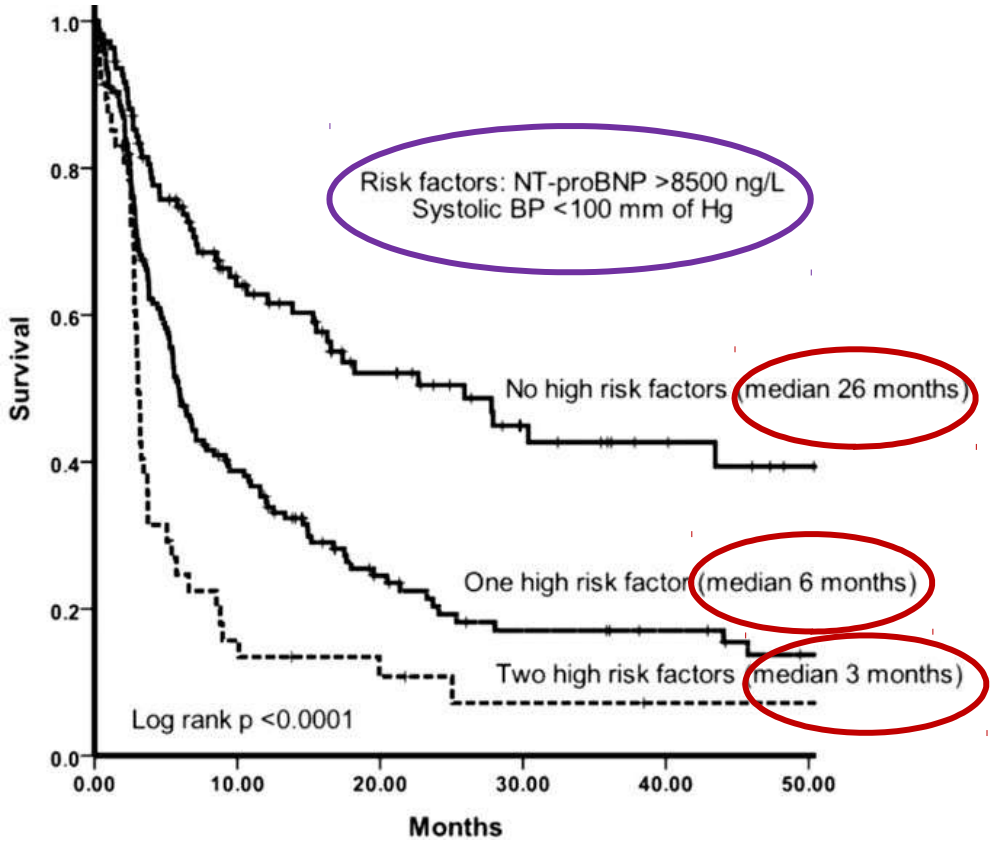
We assigned a score of 1 for each of the three prognostic variables (cTnT 0.025 ng/mL, NT-ProBNP 1,800 pg/mL, and FLC-diff 18 mg/dL); this was used to divide patients into four stages (I, II, III, and IV) with scores of 0, 1, 2, and 3, respectively

Kumar S et al. JCO 2012;30:989-994

AL Amyloidosis - risk stratification

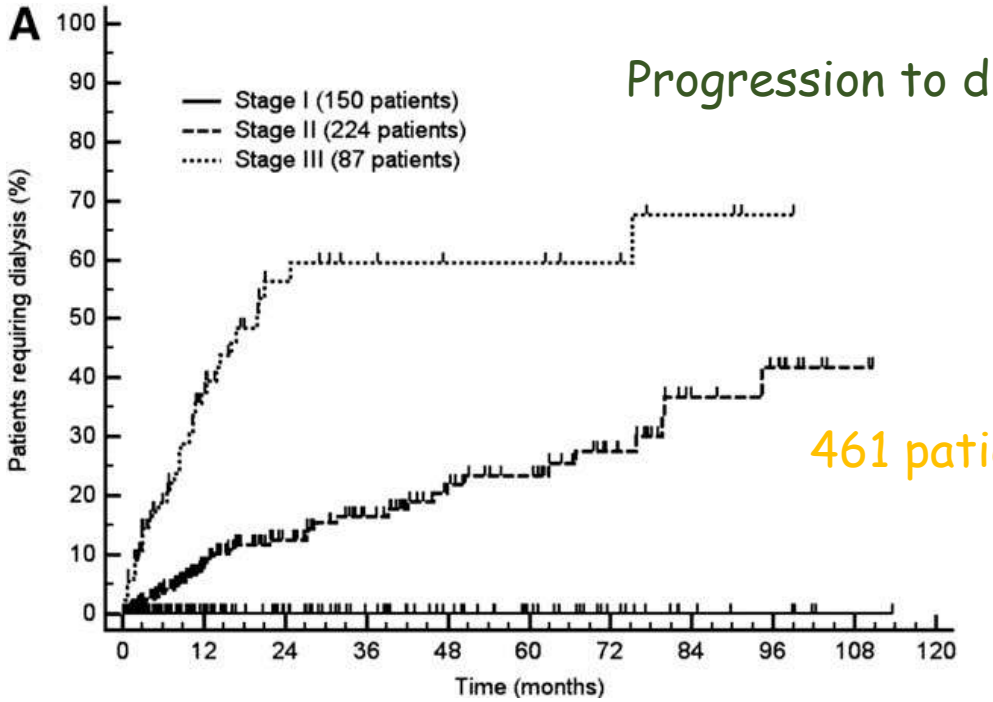
European study for stage III





Wechalekar AD et al. Blood 2013;131:3420-3427

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

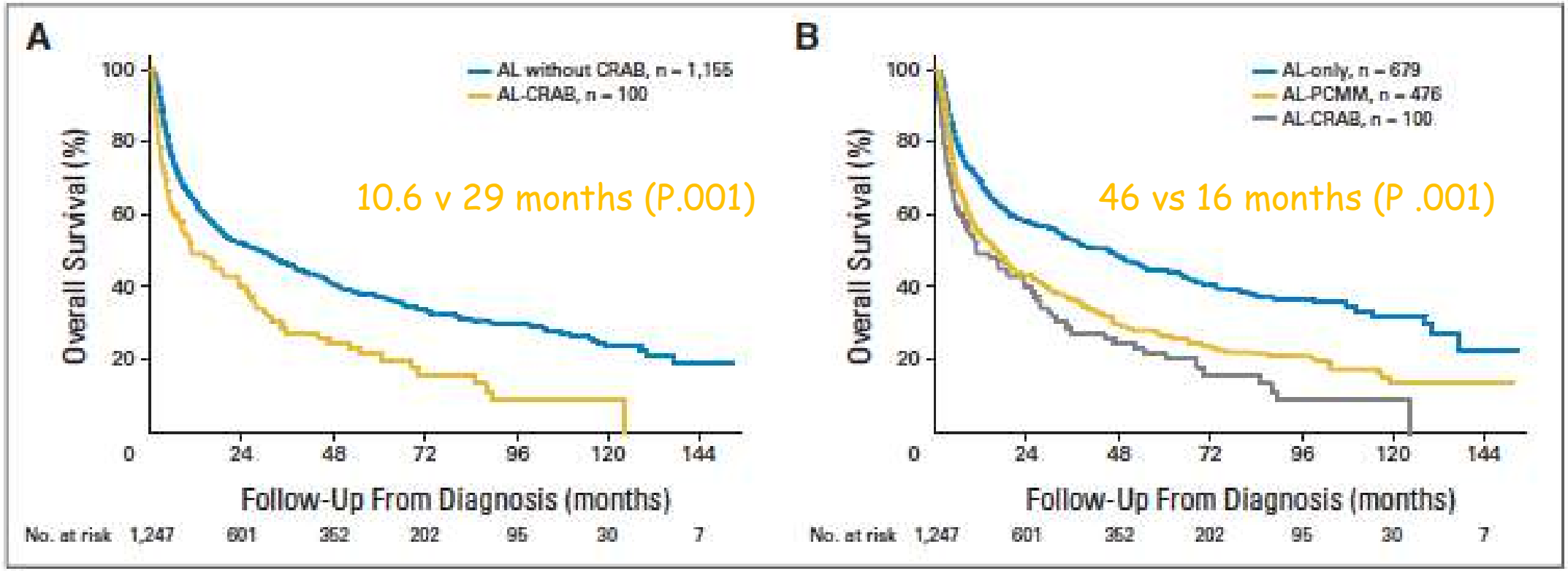


Fig 1. Kaplan-Meier curves for overall survival of patients with immunoglobulin light chain (AL) amyloidosis (A) with and without hypercalcemia, renal failure, anemia, and lytic bone lesions attributable to clonal expansion of plasma cells (CRAB criteria) and (B) according to percentage of bone marrow plasma cells (BMPCs). AL-CRAB, AL amyloidosis with CRAB; AL-only, AL amyloidosis with ≤ 10% BMPCs; AL-PCMM, AL amyloidosis with > 10% BMPCs.

Kourelis TV et al. *JCO*. 2013;31(34):4319-4324.

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.

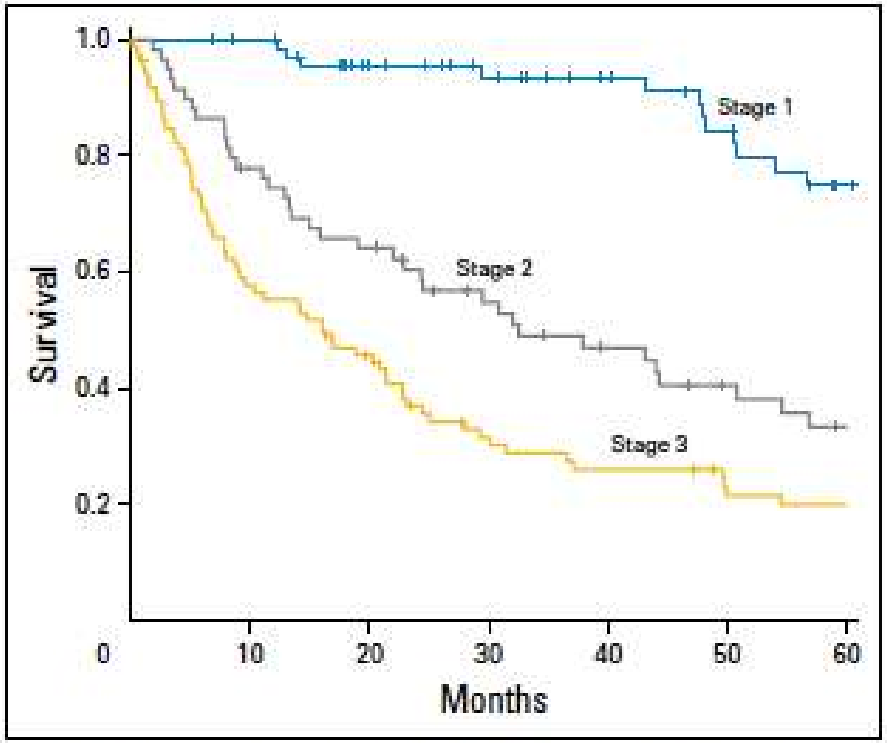


Fig A2. Shows survival curve for prognostic model with PNS involvement, abnormal BNP, abnormal Troponin T/Troponin I and liver involvement for patients with IgM-related AL amyloidosis. Stage 1, no abnormal features; stage 2, one abnormal feature; and stage 3, two or more abnormal features.

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.

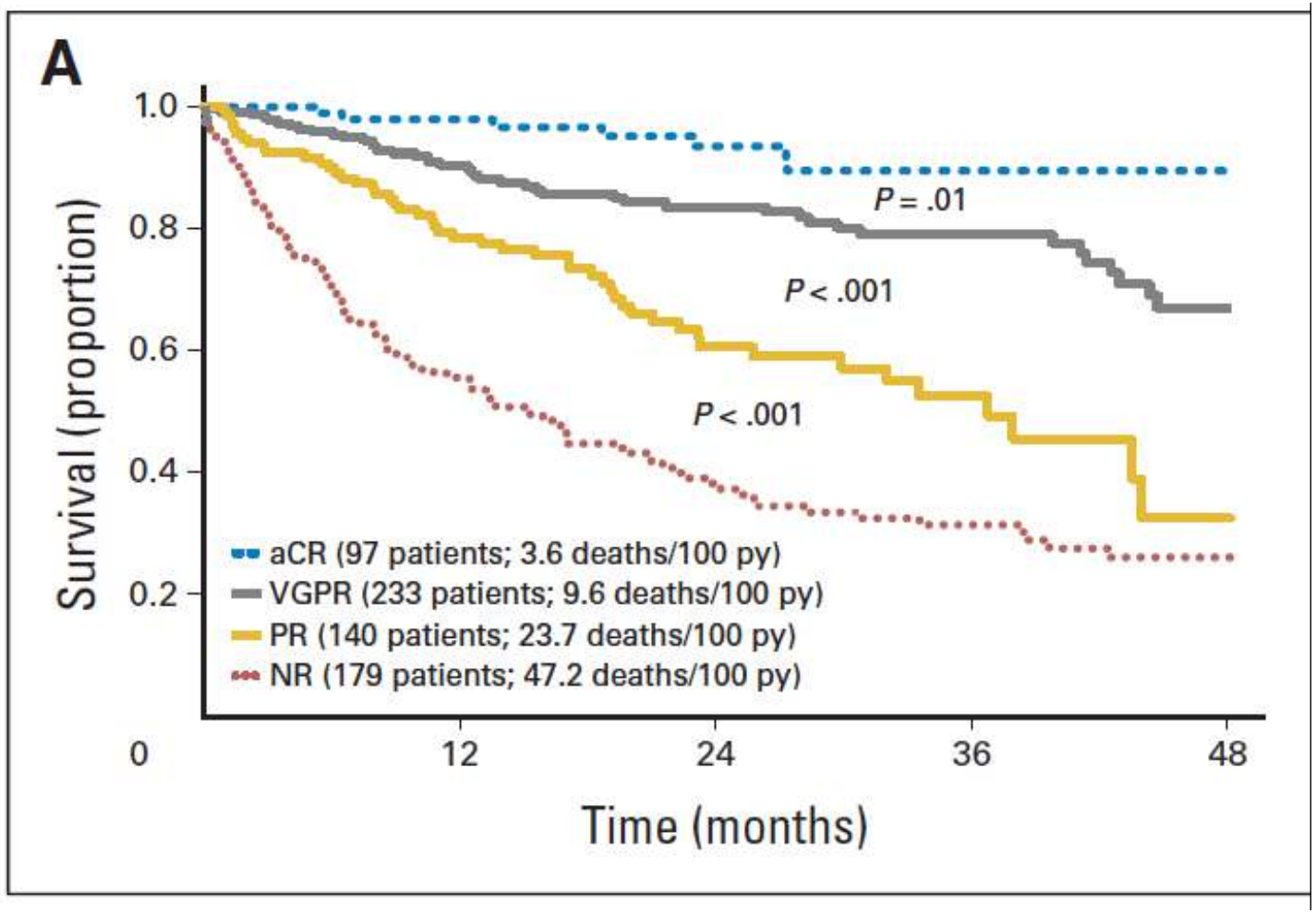
†For the model: $P < .001$; Harrel C = 0.72; Royston explained variation = 0.33.

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

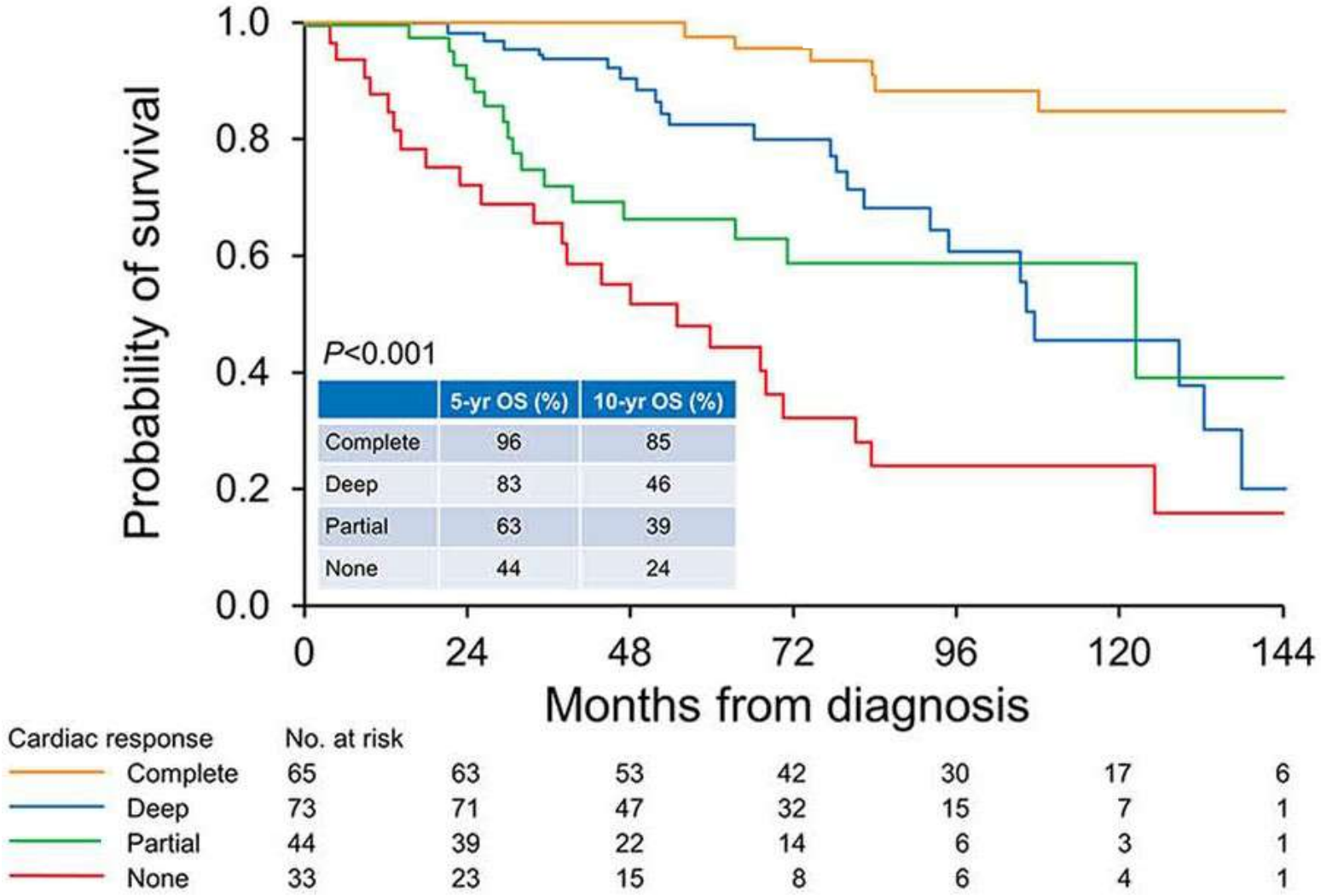
AL Amyloidosis – organ response

A study conducted at the Mayo Clinic evaluated **the organ response** of newly diagnosed AL amyloidosis patients to grade the depth of response.
The **median time to cardiac, renal, and hepatic response was** 9.4, 6, and 6.1 months, respectively. In all organs, the depth of organ response correlated with OS.

The authors defined four organ response criteria groups:
complete organ response (nadir NT-proBNP ≤400 pg/mL; nadir proteinuria ≤200 mg per 24 h; nadir alkaline phosphatase ≤2 the lower limit of normal);
very good partial organ response (> 60% reduction in the parameter not meeting the complete organ response definition);
partial organ response (31–60% reduction in the parameter),
nonresponders (≤30% reduction in the organ response parameter)

Kumar S et al. JCO 2012;30:989-994

AL Amyloidosis – organ response



	5-yr OS (%)	10-yr OS (%)
Complete	96	85
Deep	83	46
Partial	63	39
None	44	24

Muchtar E et al. Leukemia. 2018 Oct; 32(10): 2240–9.

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

The first issue in transplantation of AL amyloidosis patients is stem cell collection. The patients often accumulate fluids during filgrastim (granulocyte colony stimulating factor) mobilization and fluid balance should be meticulously followed and maintained.

The second issue is whether an induction before SCT improves outcomes.
A single-center, prospective randomized trial evaluated the role of induction (**two cycles of bortezomib and dexamethasone**) versus no induction in 56 AL amyloidosis patients. **OS at 24 months was 95% in the induction arm and 69% in the no induction arm**, with higher rates of CR in the induction arm

The **cardiac response** rates were higher in patients pretreated with bortezomib and **the 3-year PFS and OS were 66 and 73%**

Vaxman and Gertz Acta Haematol 2019;141:93–106

AL Amyloidosis – therapy

In a study from the MDACC the type of induction therapy and its impact on the outcome of autologous hematopoietic stem cell transplantation in AL was evaluated in 128 patients.

The patients were divided into 3 groups: no induction (20 patients), conventional chemotherapy-based induction (melphalan and steroids; 25 patients), and IMiD/proteasome inhibitor (PI)-based induction (83 patients).

Overall, the hematological response on day 100 was highest in the IMiD/PI group, and organ response at 1 year was highest in the conventional chemotherapy-based induction.

The 2-year PFS rates were 67, 56, and 73% in the no induction, CC, and IMiD/PI groups, respectively, and OS rates at 2 years were 73, 76, and 87%, respectively.

Mayo Clinic patients eligible for ASCT that have **bone marrow plasma cells lower that 10% aresent directly to ASCT**

Vaxman and Gertz Acta Haematol 2019;141:93–106

AL Amyloidosis – therapy

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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]	1536	After 2007 71 (37, —)	After 2007 K 32	NR	68% at 5 y
	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		
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
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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.

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

AL Amyloidosis – therapy

Considering the lower response rate to bortezomib-based regimens in the 40% to 60% of patients with **t(11;14)**, regimens **containing melphalan** at conventional dosage (MDex) or high dosage (ASCT) should be favored in such subjects.

Patients with **1q deletion are best treated with bortezomib-based** regimens.

Patients who are considered potential candidates **for ASCT** should be treated with **CyBorD** to preserve stem cells.

Patients with severe **neuropathy** should avoid bortezomib and are probably best treated with **MDex.**

Finally, patients who present with **high dFLC (>180 mg/L)** could benefit from **BMDex.**

Vaxman and Gertz Acta Haematol 2019;141:93–106

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

Between 259 patients who responded to upfront therapy, ninety-two patients (**35%**) needed second-line therapy after a median of 49 months

Cardiac and renal progression were observed in **22% and 12%** of patients, respectively. Patients who had **cardiac progression** had a median survival of 17 months compared with 62 months (P = .002) in those whose cardiac involvement did not progress, indicating that second-line treatment should start promptly at progression of FLC, before cardiac progression has occurred.

Time to next therapy was significantly reduced in patients retreated with the same therapy compared with that in patients treated with a different therapy (**22 months vs 32.3 months, respectively; P = .01**), but there was no impact on survival (30.8 months vs 51.1 months; P=.5).

Vaxman and Gertz Acta Haematol 2019;141:93–106

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

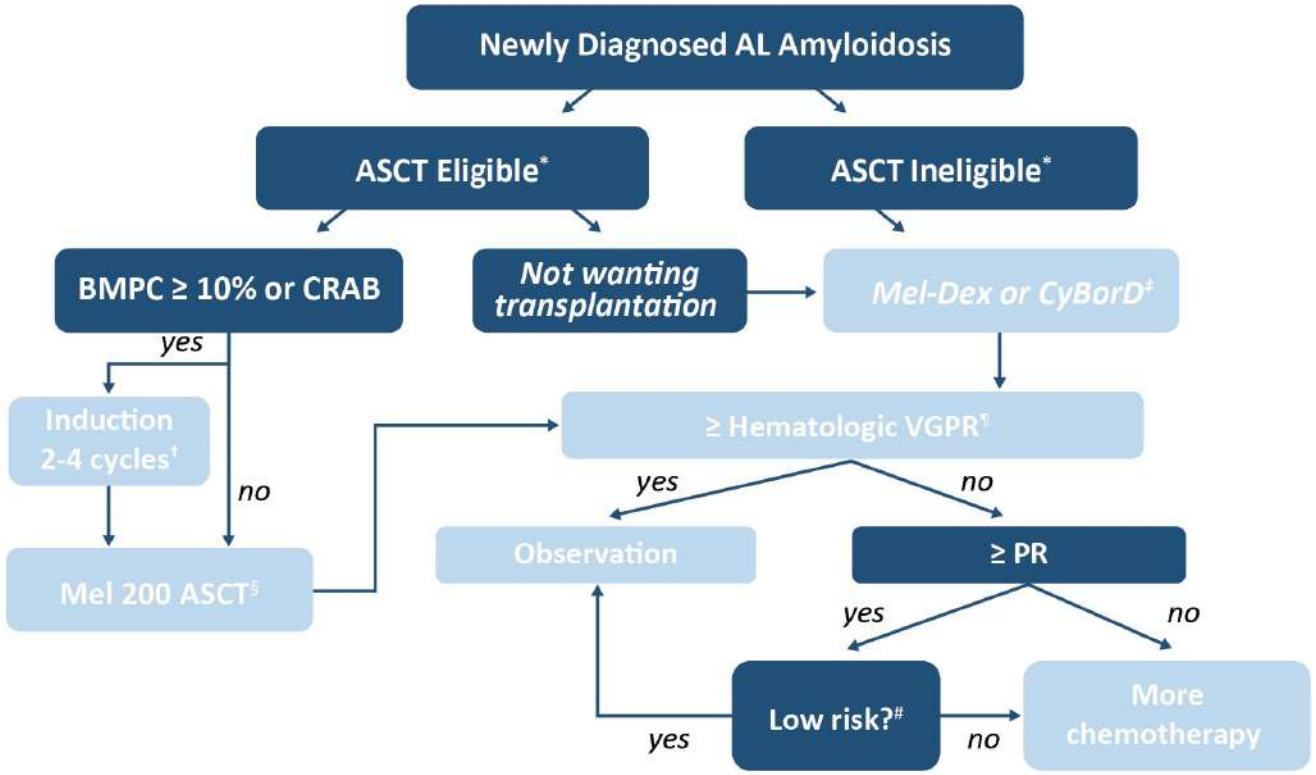
Table 2 Hematologic Response, Median OS, 2-Year Survival, and TTNT for Each Treatment Group

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

AL Amyloidosis – therapy



*Criteria for ASCT: Troponin T <0.06 and blood pressure ≥90 mmHg
†Induction also used if delay in proceeding to ASCT, or as clinically indicated
‡If < PR at 2 months, consider changing therapy
§For age >70 or creatine clearance <30 mg/mL, use Mel 140 mg/m^2
¶Day 100 ASCT or after 4-6 cycles of chemotherapy
#Mayo 2012 stage I or II

AL Amyloidosis – therapy

Lista 648 farmaco utilizzato per malattia rara(ultimo aggiornamento 16/01/19

Pomalidomide

Trattamento dell'amiloidosi a catene leggere (AL), in pazienti già trattati con terapia a base di bortezomib e di lenalidomide G.U. 04/06/2018 n. 127

Lista farmaci ad uso consolidato -Allegato 3 farmaci per oncoematologia aggiornamento 1/19

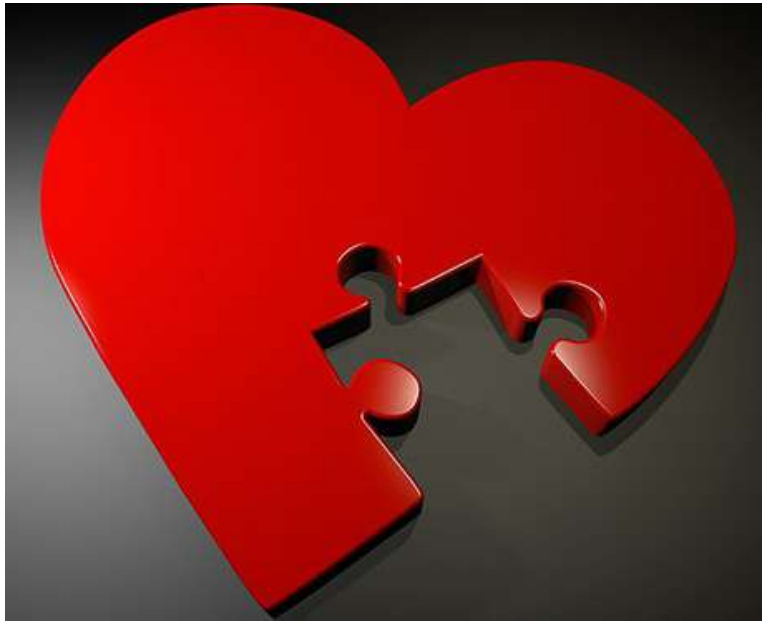
Bortezomib

Trattamento della prima linea con o senza desametasone

Lenalidomide

In paziente già trattati o non trattabili con bortezomib e/o melphalan

AL Amyloidosis – supportive care



Terapia di supporto (terapia delle scompenso cardiaco modificata) →

Mantenere adeguate pressioni di riempimento ventricolare.

Contrastare la ritenzione idrica e la congestione venosa bilanciando con precisione e continui adattamenti la ritenzione idrosalina e la terapia diuretica (educazione del pz e dei caregivers, supporto dietistico)

Attenzione all'assetto proteico (ipoalbuminemia)

Valutazione quotidiana del peso

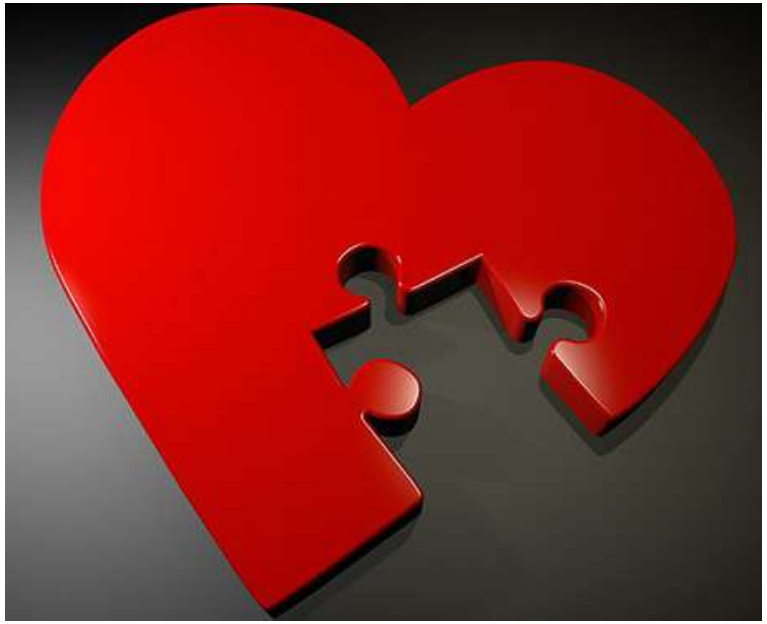
Valutazione settimanale diuresi 24h

Norme igienico-comportamentali per contrastare l'ipotensione ortostatica, postminzionale e da ipertono vagale (sovradistensione gastrica, shave..)

Calze elastiche classe I

Alfa.I agonisti (midodrina): il mantenimento PA adeguata può permettere dosi più alte di diuretico dell'ansa, spt nei pz con neuropatia autonomica.

AL Amyloidosis – supportive care



ACE-I: possono causare severa ipotensione (la PA dei pz con AL è dipendente dall'angiotensina)

Andrebbero riservati per trattare la proteinuria nei pz con s.nefrosica

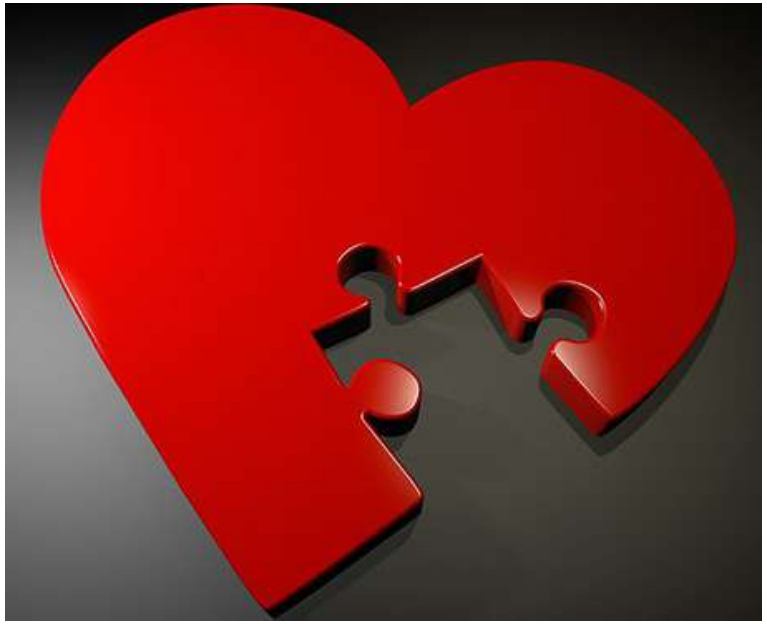
BETA-BLOCCANTI: nelle forme restrittive la GC dipende dalla FC (GC= GSxFC), per cui sono spesso mal tollerati.

Inoltre: beta-bloccante + talidomide (AL): bradicardia spiccata.

CALCIO-ANTAGONISTI (verapamil): abnorme legame con fibrille amiloidi, effetto intropo negativo

DIGITALE: aritmie pericolose anche a livelli di digossinemia apparentemente in range, per legame stretto e selettivo tra farmaco e fibrille. Non correlazione tra digossinemia e tossicità, che si esplica anche a dosaggi bassi.

AL Amyloidosis – supportive care



TAO: indipendentemente dalla presenza o meno del ritmo sinusale, l'infiltrazione degli atri porta a stasi e trombosi.

Valutare all'eco l'assenza o la spiccata riduzione di onda A.

I pz sono anche a rischio elevato di sanguinamento (alterazioni della coagulazione, fragilità vascolare….) e di traumi da sincope.

Mantenere mobilità ed evitare le cadute (deambulatori).

ATTENZIONE AI CORTICOSTEROIDI!!!

AMIODARONE 200 mg/die x 5 gg/sett se aritmie ventricolari sostenute all'Holter (valutare con attenzione!)

ICD → può non prevenire MCI perché spesso dovuta a dissociazione elettromeccanica.

Soglie elevate, benefici incerti.

PMD: sec guidelines, preferendo i PM bicamerali quando possibile

Trapianto cardiaco


COLLABORATION
TOGETHER
SUCCESS
KNOWLEDGE
LEARNING
SECTION
PRODUCTION
MANAGEMENT
GROUPS
WORK
PROJECT
COLLABORATIVE
LEADERSHIP
CORPORATION
PEOPLE
GROUP
SOFTWARE
DEVELOPMENT
INTERNET
TOOLS
HELP
IMPROVE
CITATIONS
ORGANIZATIONS
SOCIAL
COMMUNITIES
BETWEEN
INCLUDE
RELIABLE
ORGANIZATION
SOURCES
PEER
SKILLS
COMMUNICATION
INDUSTRY
BASED
UNITED
THEORY
PROJECTS
COMPLEX
POLITICAL
PRACTICE
TERM
WORKING
COMMUNITY
CHALLENGED
INCLUDING
SHARING
RESOURCES
INTEREST
TRADE
GOALS
SHARED
MEMBERS
EDUCATION


Together
Everyone
Achieves
More
TEAM