Beyond ATTR in Japan: Accurate diagnosis of cardiac AL in the TTR stabilizer era

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Recognizing cardiac AL beyond ATTR patterns

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Key red flags that should raise suspicion for cardiac AL vs more typical ATTR presentations



Rapidly progressive HF symptoms[1,2]



Nephrotic syndrome[2]



Hypotension or orthostatic hypotension[2–5]



Refractory pleural and/or pericardial effusions[1,2,4,5]



Periorbital purpura or macroglossia[1–6]



Unintentional weight loss[4]

AL, amyloid light-chain; ATTR, transthyretin amyloidosis; HF, heart failure.

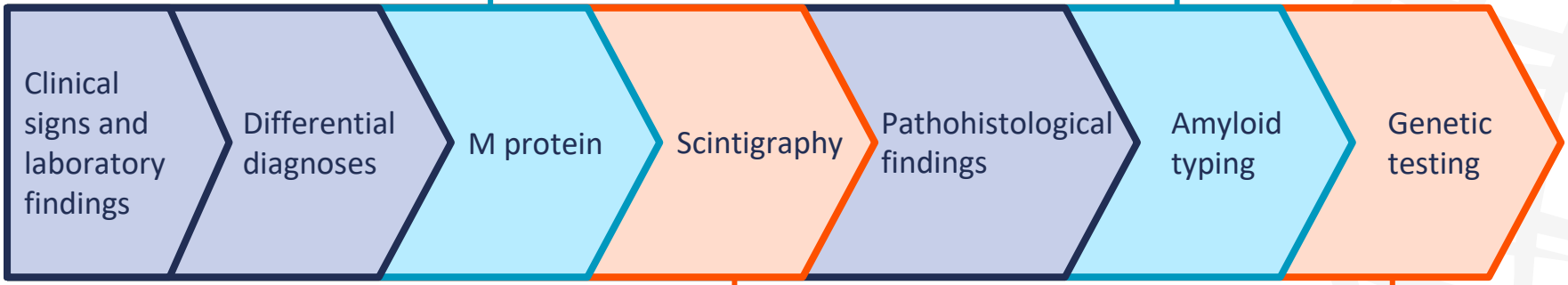
1. Aus dem Siepen F, Hansen T. *J Clin Med*. 2024;13:5873; 2. Marchionni G, et al. *J Clin Med*. 2025;14:8458; 3. Kitaoka H, et al. *Circ J*. 2020;84:1610–71; 4. Dima D, et al. *JCO Oncol Pract*. 2023;19:265–75; 5. Alashqar R, et al. *J Clin Med*. 2025;14:6668; 6. Chopra N. *J Pract Cardiovasc Sci*. 2024;10:1–8.

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JCS diagnostic algorithm for CA*

- Typically present in AL amyloidosis
- Not expected in isolated ATTRwt†

Positive for immunoglobulin light chains or TTR



- Bone scintigraphy has a sensitivity of 58–99% and a specificity of 79–100% for detecting ATTR
- Most false positives occur in cardiac AL

Identification of TTR pathogenic variants

***Investigations may occur in parallel; a non-biopsy ATTR diagnosis relies on bone scintigraphy plus absence of monoclonal protein.**
†If detected, further evaluation is required because ATTRwt and MGUS may coexist.
AL, amyloid light-chain; ATTR, TTR amyloidosis; CA, cardiac amyloidosis; JCS, Japanese Circulation Society; M protein, monoclonal protein; MGUS, monoclonal gammopathy of undetermined significance; TTR, transthyretin; wt, wild type.
Kitaoka H, et al. *Circ J*. 2020;84:1610–71.

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Applying the JCS algorithm before TTR stabilizers

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Applying the JCS pathway to diagnose cardiac AL

M protein screen[1]

SPEP/IFE alone are insufficiently sensitive for M protein screening in suspected AL

Serum FLC should also be obtained

Biopsy strategy[2]

Tissue confirmation of amyloid deposition is **required for diagnosis** of AL amyloidosis

Use less-invasive sites first, where appropriate; biopsy from another site or repeat as needed

Amyloid typing[2]

Essential for determining the treatment plan

Tissue specimens can be referred to the MHLW-supported amyloidosis typing consultation service for expert pathological evaluation

IHC usually recommended, but mass spectrometry may be used if higher sensitivity is required

Integration with imaging[2–5]

Echocardiography, CMR and scintigraphy support suspicion, urgency, and overall interpretation

Imaging supports diagnosis but does not replace biopsy and definitive AL typing

AL, amyloid light-chain; CMR, cardiac magnetic resonance imaging; FLC, free light chains; IEF, immunofixation electrophoresis; IHC, immunohistochemistry; JCS, Japanese Circulation Society; M protein, monoclonal protein; MHLW, Ministry of Health, Labour and Welfare; SPEP, serum protein electrophoresis.

1. Rubinstein SM, Stockerl-Goldstein K, et al. *JAAC CardioOncol*. 2021;3:590–3; 2. Kitaoka H, et al. *Circ J*. 2020;84:1610–71; 3. Dima D, et al. *JCO Oncol Pract*. 2023;19:265–75; 4. Chaudhari M, Ashwath ML. *J Clin Med*. 2025;15:163; 5. Jimenez-Zepeda V, et al. *Clin Lymphoma Myeloma Leuk*. 2023;23:194–202.

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Why does correct amyloid subtyping matter?

	AL[1–3]	ATTR[1–3]
Disease course	**Rapidly progressive** disease, with worsening of symptoms within months	**Slowly progressive** disease
Prognosis	High mortality rate; prognosis with advanced HF may be as short as 4–6 **months***	ATTRv: 3–12 **years**† ATTRwt: 2–7 **years** without treatment*
Therapeutic target	Clonal light chain production	TTR misfolding and synthesis
Approved therapies	Include **plasma cell-directed therapy**	Include **TTR stabilizers and silencers**

Determining the CA subtype is critical because AL and ATTR require different treatment approaches[4]

*Prognosis depends on stage; †Prognosis depends on stage and degree of cardiac involvement.
AL, amyloid light chain; ATTR, TTR amyloidosis; CA, cardiac amyloidosis; HF, heart failure; TTR, transthyretin; v, variant; wt, wild type.
1. Aus dem Siepen F, Hansen T. *J Clin Med*. 2024;13:5873; 2. Bloom MW, et al. *J Card Fail*. 2025;31:456–63; 3. Alashqar R, et al. *J Clin Med*. 2025;14:6668;
4. Rubinstein SM, Stockerl-Goldstein K, et al. *JAAC CardioOncol*. 2021;3:590–3.

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Avoiding misdiagnosis in the TTR stabilizer era

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Practical tips to prevent TTR stabilizer misuse

- Exclude AL before confirming ATTR
- Do not diagnose ATTR on bone scintigraphy alone; always exclude AL first
- If MGUS is detected, complete AL workup; don’t assume MGUS alone explains the findings
- Look for discrepancies between imaging findings and clinical presentation
- Check for extra-cardiac organ involvement

AL, amyloid light chain; ATTR, transthyretin amyloidosis; MGUS, monoclonal gammopathy of undetermined significance.
Kubo T. Expert opinion. June 25, 2026.

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