


Prevalence and prognostic impact of left-sided valve thickening in systemic light-chain amyloidosis

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Abstract

Background Left heart valve thickening (LVT) was described in patients with light-chain amyloidosis (AL). This phenomenon reflects likely infiltration of the valve by amyloid proteins. However, the prevalence of LVT and its prognostic value have not been investigated in patients with AL.

Methods and results Comprehensive transthoracic echocardiography was performed at baseline in 150 patients [median age 68 (33–87) years; 59% male] with confirmed AL. The presence of abnormal mitral and/or aortic valve thickening (>3 mm) was assessed in all included patients. Overall, 42% had LVT at the time of diagnosis. Compared to patients without LVT, those with LVT were older and had a more advanced NYHA functional class (63% in patients with NYHA III-IV vs. 33% in

NYHA I-II, $p < 0.001$). They also had higher left ventricular (LV) wall thickness and mass, larger left atrium, higher mitral annulus E/E' ratio and systolic pulmonary artery pressures, and lower LV ejection fraction (all $p < 0.05$). Patients with more advanced Mayo Clinic stage had a higher incidence of LVT: 58% in stage III vs. 45% in stage II and 5% in stage I ($p < 0.001$). During a median follow-up of 2 years, 79 deaths occurred. The presence of LVT was significantly associated with reduced 5-year survival (32 ± 7 vs. $64 \pm 6\%$). In multivariate analysis, after adjusting for age, gender, NYHA functional class, and LV ejection fraction, LVT remained significantly associated with higher all-cause mortality (hazard ratio 1.90, 95% CI 1.10–3.34, $p = 0.02$).

Conclusion Left heart valve thickening is common in patients with AL and is associated with worse functional class, LV systolic and diastolic function, and more advanced stage of the disease. In addition, LVT appears to be a powerful marker of all-cause mortality.

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Keywords Amyloidosis · Light chains · Valve · Echocardiography · Survival · Prognosis

Introduction

Light-chain amyloidosis (AL) is an infiltrative systemic disease characterized by the extracellular deposition of fibrils in several organs. The accumulation of amyloid protein in the myocardial interstitial tissue is observed in more than 50% of AL patients [1] and this may gradually lead to a restrictive cardiomyopathy. Cardiac involvement in AL is associated with a poor prognosis, particularly in patients with heart failure symptoms, and in the setting of an advanced stage of the Mayo Clinic classification based

on cardiac biomarkers [2, 3]. When assessed by echocardiography, amyloid heart disease is associated with increased wall thickness involving both ventricles with normal or small left ventricular (LV) cavity size and either preserved or reduced LV ejection fraction (LVEF). LV systolic dysfunction is most often noted in advanced stages of the disease and is a marker of poor prognosis [4]. Bi-atrial enlargement associated with LV diastolic dysfunction and elevated filling pressures are common and adversely impact patient outcome [5, 6].

Left heart valve thickening (LVT) is known to occur in cardiac amyloidosis, probably as a result of valvular infiltration by amyloid fibrils. However, the prevalence and the prognostic significance of LVT at the time of diagnosis have not been investigated in large series of AL patients yet.

The aim of our study is: (1) to determine the prevalence of LVT+ at diagnosis using transthoracic echocardiography in patients diagnosed with AL; (2) to assess the impact of LVT on 1- and 5-year all-cause mortality. We hypothesized that the presence of LVT is associated with unfavorable outcome.

Methods

Baseline population

The study included 150 patients with confirmed AL, evaluated at our institution between June 1998 and September 2013. The diagnosis of AL was mainly established by peripheral tissue biopsy that demonstrated typical Congo red birefringence under polarized light. Myocardial biopsy was performed only when all other biopsies were non-diagnostic. The amyloid deposits were characterized as AL type by immunofluorescence on frozen tissues; borderline cases were confirmed by immune-electro-microscopy or proteomics. For patients with a compatible phenotype, DNA analyses were used to exclude familial amyloidosis. The presence of monoclonal proteins in the serum and/or a monoclonal population of plasma cells in the bone marrow were documented in all patients to confirm the type of AL [6]. The cardiac involvement and its severity were assessed using the Mayo Clinic staging beginning in 2004 [2, 3]. It includes two biological markers, NT-pro-BNP or BNP, using the different cut-off value: ≥ 332 ; ≥ 100 ng/L, respectively) and troponin (cut-off value: troponin I ≥ 0.1 $\mu\text{g/L}$; troponin T ≥ 0.035 $\mu\text{g/L}$; troponin Tc us ≥ 0.07 $\mu\text{g/L}$). In stage I, both biomarkers are below the cut-off values and patients are considered to have minor cardiac involvement. In stage II, one biomarker is above the cut-off value and cardiac involvement is considered to be moderate. In stage III, severe cardiac involvement is usually present and both biomarkers

are elevated beyond the cut-off values. Prior to 2004, patients were considered to have cardiac involvement on the basis of the clinical history, the traditional electrocardiographic findings (low QRS voltage, q-waves in the anterior leads) and echocardiographic features [LV wall thickness greater than 12 mm in the absence of other causes of LV hypertrophy, diastolic LV dysfunction, dilated left atrium (LA), pericardial effusion, and/or thickened right ventricular free-wall]. The involvement of any other organ was determined based on standard criteria for the evaluation of systemic amyloidosis [7].

Data collection

Our study was conducted in a retrospective manner with demographic, clinical, biological, and echocardiographic data were extracted from the echo reports (derived from the 1st baseline echocardiography performed at diagnosis of AL) collected using patients' charts.

Mortality data were obtained from death certificates, family physician questionnaire, or hospital records. To avoid misclassification of the cause of death, the primary outcome was all-cause mortality regardless of the underlying cause [8]. All cases were performed using harmonic imaging. Echo data were obtained following the available American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines [9]. These include: (1) LV end diastolic and systolic diameters in the parasternal long-axis view; (2) end-diastolic thickness of the inter ventricular septum and posterior wall; (3) 2D-LVEF using the Simpson method; (4) diastolic LV function using the trans mitral E/A ratio and E/e' ratio at the lateral mitral annulus; and (5) LA size using the systolic area in the 4-chamber view (LA considered as dilated when the area exceeds 20 cm^2) [9]. The 2D maximal LA volume was available in 46% of patients in the 2- and 4-chamber view according to the Simpson method and was considered as significantly dilated when >34 mL/m^2 [9]. The mitral and aortic valves were inspected and the presence of LVT (i.e., LVT+: leaflet thickening >3 mm [10, 11] in apical view for the mitral valve and in the long-axis parasternal view for the aortic valve) was reported at the time of echocardiography (Fig. 1). The presence of valve thickening related to leaflet localized nodular or calcification was not considered as LVT+. The presence of any valve regurgitation or stenosis was estimated semi-quantitatively from grade 1 (mild) to grade 4 (severe) according to published guidelines [12]. The systolic pulmonary artery pressure (PAP) was derived from the sum of the right ventricular-right atrial (RA) pressure gradient as estimated using the tricuspid regurgitation jet velocity added to the RA pressure as assessed using the inferior vena cava dimensions and collapsibility with inspiration.

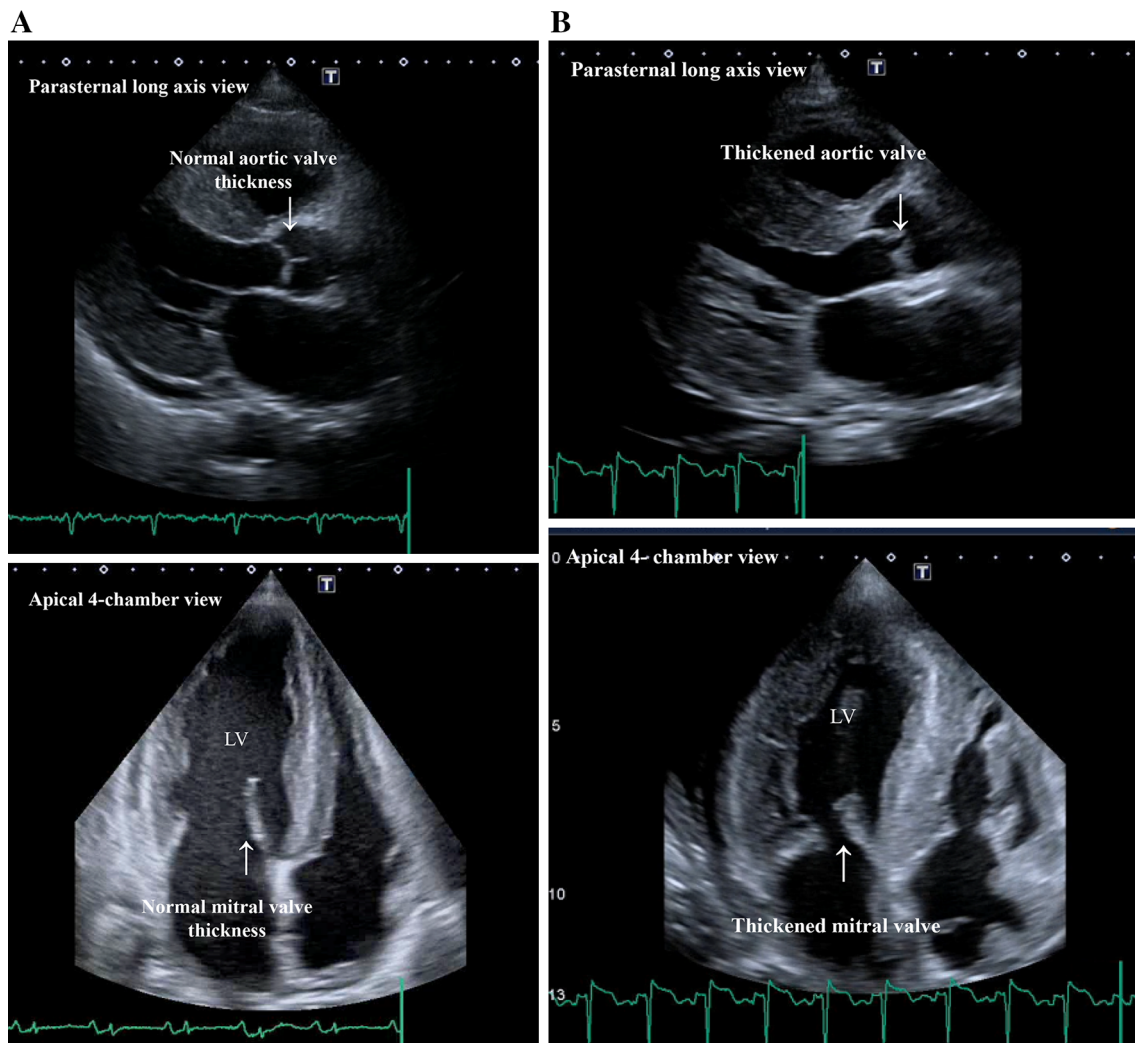


Fig. 1 Transthoracic echocardiogram in the parasternal long-axis and 4-chamber apical views of a patient with AL and normal aortic and mitral valve thickness (a) versus a patient with abnormal valvular thickening (b)

Statistical analysis

Patients were divided into two groups according to the presence or absence of LVT as reported by echocardiography. Continuous data were expressed as median (minimal; maximal) and were compared by Student's *t* test or Kruskal–Wallis test as appropriate. Categorical data were given as numbers and percentages and were compared using the Chi-square test. The primary outcome was the overall mortality calculated from the date of the initial echocardiographic study until the date of the last available follow-up or death. The cumulative probability of event was estimated using the Kaplan–Meier method and results are presented at 1 and 5 years. Log-rank test was used to test for significance in survival between the two groups. Univariate Cox proportional-hazard analysis was performed to assess the association between all-cause mortality and the most clinically

relevant variables, as well as the echocardiographic parameters known to affect survival in this population.

A multivariable analysis was then performed and included age, gender, and variables that were significantly associated with all-cause mortality in the univariate analysis. Results were reported as hazard ratios with corresponding 95% confidence intervals. A *p* value <0.05 was considered as statistically significant. Statistical analyses were performed using the JMP software version 10.0.0, 2012 (SAS Institute Inc., Cary, NC, USA).

Results

Our study population included 150 patients who were referred to the National Reference Centre for AL in the Department of Hematology at our institution with a 1st

available echocardiographic data obtained at baseline before the beginning of any treatment. The median follow-up was 2.0 (0–18) years for the whole cohort. The follow-up was completed by January 2014 in 99% of patients and only two patients were lost from FU during this period. The median interval between baseline diagnosis and echocardiography was 0 (–1; 2) days.

Baseline characteristics of the patient population

Among our patients, 89 (59%) were men and the median age was 68 (33–87) years. Median LVEF was 61% (25–84%) with a median interventricular septal thickness (IVST) of 14 mm (7–26 mm). Other echocardiographic characteristics are shown in Table 1.

Table 1 Baseline characteristics according to LVT

Variables	Total, <i>n</i> = 150	LVT–, <i>n</i> = 87 (58%)	LVT+, <i>n</i> = 63 (42%)	<i>p</i> value
Demographic and clinical data				
Age, years	68 (33; 87)	66 (33; 87)	72 (47; 86)	0.009
Male, %	59	60	59	0.9
BSA, m ²	1.8 (1.3; 2.3)	1.8 (1.3; 2.1)	1.8 (1.3; 2.3)	0.6
NYHA ≥III, %	56	33	63	<0.001
Smoking, %	24	19	30	0.1
Hypertension, %	33	31	35	0.7
Dyslipidemia, %	15	16	15	0.9
Diabetes, %	5	4	7	0.3
Coronary artery disease, %	7	7	7	0.9
Atrial fibrillation, %	9	2	18	0.001
Biological data				
NT-proBNP/BNP increased, %	80	68	96	<0.001
Troponin increased, %	48	38	61	0.02
Creatinine, μmol/L	96 (34; 423)	87 (34; 204)	113 (42; 423)	0.07
GFR, mL/min/1.73 m ²	65 (3; 173)	76 (3; 173)	55 (7; 156)	<0.001
DFLC mg/L	243 (2; 74,920)	225 (2; 74,920)	323 (4; 7178)	0.5
Echocardiographic data				
LV septum wall thickness, mm	14 (7; 26)	14 (7; 23)	15 (8; 26)	0.01
LV post. wall thickness, mm	13 (8; 28)	12 (8; 23)	13 (8; 28)	0.03
LV ED diameter, mm	43 (30; 73)	42 (31; 73)	43 (30; 58)	0.6
LV ES diameter, mm	28 (16; 47)	27 (16; 41)	30 (18; 47)	0.1
Indexed LV mass, g/m ²	93 (29; 321)	80 (29; 199)	110 (29; 321)	0.02
LVEF, %	61 (13; 84)	65 (40; 84)	58 (13; 84)	<0.001
S' wave mitral annular, cm/s	6 (2; 15)	8 (2; 15)	5 (3; 14)	0.01
<i>E/A</i> ratio	1.2 (0.1; 8.9)	0.9 (0.1; 4.1)	1.9 (0.5; 8.9)	<0.001
Deceleration time, ms	188 (83; 418)	199 (83; 418)	164 (88; 373)	0.04
<i>E/e'</i> ratio	13.6 (4.0; 40)	11.2 (4.0; 40)	17.1 (5; 40)	<0.001
LA diameter, mm	40 (23; 60)	38 (23; 60)	41 (26; 60)	0.04
Index LA volume, mL/m ²	32 (10; 66)	25 (10; 49)	38 (12; 66)	<0.001
LA area, cm ²	21 (11; 37)	18 (11; 37)	23 (11; 34)	<0.001
Maximal LA volume, mL	54 (14; 120)	44 (14; 90)	67 (20; 120)	<0.001
S' wave Tric. annular, cm/s	12 (4; 26)	13 (4; 26)	10 (5; 18)	<0.001
Systolic PAP, mmHg	31 (3; 80)	30 (3; 59)	39 (24; 80)	<0.001
Dilated vena cava, %	34	25	45	0.03
Pericardial effusion, %	38	29	49	0.03

BSA body surface area, GFR glomerular filtration rate, DFLC delta free light chains, ED end diastolic, ES end systolic, LA left atrial, LV left ventricular, LVEF left ventricular ejection fraction, NYHA New York heart association, PAP pulmonary arterial pressures

Overall, 63 patients (42%) showed LVT+, of whom 30 (48%) had isolated mitral LVT, 11 (17%) had isolated aortic LVT, and 22 (35%) had both mitral and aortic LVT. No patient had more than grade 2 aortic or mitral regurgitation, and 75 (50%) and 20 (13%) patients had grade 1 and grade 2 mitral regurgitation, respectively. In addition, 38 (25%) patients had grade 1 aortic regurgitation and 1% had grade 2 aortic regurgitation. No significant aortic stenosis or mitral stenosis was found in this cohort.

The Mayo Clinic staging started to be performed after 2004 [2, 3], and thus was available in 113 (75%) patients. However, no significant difference was found between the 113 patients with a Mayo Clinic staging and those without, in terms of age, gender, prevalence of LVT, number or type of organs involvement, NYHA functional class, LVEF, and all other echocardiographic variables.

Twenty (18%), forty (35%), and fifty-three (47%) patients were in Mayo Clinic stages I, II, and III, respectively. Based on standard criteria for the evaluation of affected organs by AL, 88 (59%) had renal involvement.

Comparison of patients according to LVT

The comparison of the two groups is reported in Table 1. Patients with LVT were significantly older [72 (47–86) vs. 66 (33–87) years; $p = 0.009$]. However, no significant difference was noted between both groups in terms of gender, presence of hypertension, type of monoclonal free light chain involved, and renal or other solid organ involvement (all $p > 0.05$, Table 1). However, mean baseline LVEF was lower (Fig. 2) and the IVST was higher in patients with LVT. Moreover, almost all diastolic parameters were more altered in the group with LVT as compared to those without ($p < 0.05$, Table 1).

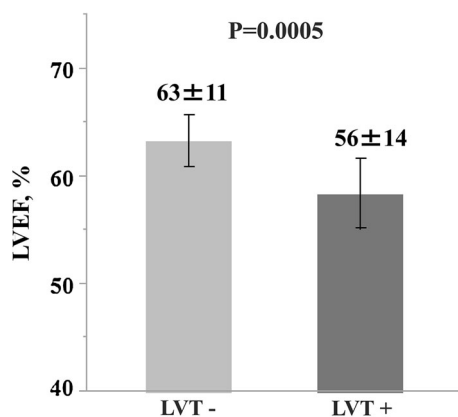


Fig. 2 Left ventricular ejection fraction according to the absence or presence of LVT. The number reported above each histogram is the mean \pm standard deviation

There was no significant difference in terms of baseline demographic, clinical, biologic, and echocardiographic data between patients with isolated mitral LVT, isolated aortic LVT, or LVT affecting both valves, except for age. Indeed, patients with isolated aortic LVT were significantly older than those with isolated mitral LVT or bi-valvular LVT (respectively, 78 ± 7 vs. 67 ± 9 vs. 71 ± 11 years, $p = 0.004$).

Relationship between LVT, Mayo clinic stage, and functional class

Patients with LVT were more often in Mayo Clinic stage II and III as compared to those without: 18 (45%) and 31 (58%) vs. 1 (5%) in stage I ($p < 0.0001$). Moreover, the prevalence of NYHA functional class III–IV was significantly higher in patients with LVT ($p < 0.0008$).

Comparison according to LVT and stratified for IVST

Table 2 reports baseline demographic, clinical, biological, and echocardiographic data according to the presence of LVT stratified for IVST (i.e. <12 vs. ≥ 12 mm).

Patients LVT+ and IVST ≥ 12 mm had more frequently atrial fibrillation and more severe cardiac involvement with significantly more frequent Mayo Clinic stage III (68 vs. 54% in LVT– IVST ≥ 12 mm group, vs. 33% in LVT+ IVST < 12 mm group and vs. 4.5% in LVT– IVST < 12 mm group, $p < 0.0001$). Consistently, patients in LVT+ and IVST ≥ 12 mm group had higher rate of NYHA functional class $\geq III$ and had significantly higher indexed LV mass and diastolic impairment, lower LV ejection fraction and LV and right ventricular longitudinal function, and higher LA dimensions and systolic PAP, than those in LVT– and IVST < 12 mm group. Of note, patients in LVT+ and IVST < 12 mm group had significant lower LV ejection fraction, right ventricular longitudinal function, and higher E/A ratio than those in the LVT– and IVST < 12 mm group.

Long-term outcome of AL patients according to LVT

During the follow-up period, 79 (53%) patients died. The overall 1- and 5-year survival rates were 69 ± 4 and $51 \pm 5\%$, respectively. In patients with LVT+, the survival rates at 1 and 5 years were, respectively, at 51 ± 4 and $32 \pm 7\%$, which was significantly lower than in those without (70 ± 4 and $64 \pm 6\%$; $p = 0.0002$, Fig. 3).

Table 2 Baseline characteristics stratify according to LVT and interventricular septum (≥ 12 vs. <12 mm)

Variables	IVS <12 mm		IVS ≥ 12 mm		p value
	LVT-, n = 36, 24%	LVT+, n = 16.11%	LVT-, n = 48, 33%	LVT+, n = 47, 32%	
Demographic and clinical data					
Age, years	66 (45; 87)	70 (48; 86)	65 (33; 80)	70 (47; 85)	0.072
Male, %	53	50	65	62	0.599
BSA, m ²	1.7 (1.3; 2.0)	1.7 (1.5; 1.9)	1.8 (1.3; 2.1)	1.8 (1.3; 2.3)	0.355
NYHA \geq III, %	6	57	39	50	<0.0001
Smoking, %	11	25	25	28	0.287
Hypertension, %	25	31	33	30	0.874
Dyslipidemia, %	14	12.5	19	13	0.855
Diabetes, %	0	12	6	4	0.247
Coronary artery disease, %	0	6	12.5	6.5	0.167
Atrial fibrillation, %	0	12.5	4	17	0.02
Biological data					
Creatininemia, μ mol/L	130 (42; 1058)	168 (48; 618)	114 (18; 458)	164 (42; 746)	0.318
GFR, mL/min/1.73 m ²	86 (3; 182)	60 (8; 156)	82 (8; 520)	58 (7; 150)	0.051
DFLC mg/L	2750 (2; 7492)	607 (8; 2617)	617 (25; 3923)	729 (4; 7178)	0.457
Echocardiographic data					
LV septum wall thickness, mm	10 (7; 11)	11 (8; 11)	16 (13; 23)	16 (13; 26)	<0.0001
LV post. wall thickness, mm	10 (8; 14)	11 (8; 16)	14 (10; 23)	15 (10; 28)	<0.0001
LV ED diameter, mm	46 (34; 59)	44 (36; 58)	42 (31; 73)	43 (30; 56)	0.054
LV ES diameter, mm	27 (18; 35)	28 (20; 47)	27 (16; 41)	29 (18; 38)	0.436
Indexed LV mass, g/m ²	60 (29; 91)	74 (30; 140)	106 (45; 199)	130 (57; 321)	<0.0001
LVEF, %	66 (47; 82)	56 (13; 84)	61 (40; 84)	56 (25; 77)	0.002
S' wave mitral annular, cm/s	8.8 (3; 15)	7.7 (4; 13)	6.7 (2; 11)	5.5 (3; 14)	0.001
E/A ratio	1.1 (1; 2.5)	2.4 (1; 8)	1.6 (0.5; 4.1)	2.4 (0.5; 8.9)	<0.0001
Deceleration time, ms	236 (100; 418)	188 (115; 305)	196 (83; 384)	183 (88; 373)	0.037
E/e' ratio	11 (4; 33.5)	19 (8; 35)	16 (7; 40)	20 (5.4; 40)	0.022
LA diameter, mm	36 (23; 47)	38 (27; 56)	40 (27; 60)	42 (26; 60)	0.006
Index LA volume, mL/m ²	22 (10; 35)	34 (12; 63)	30 (14; 49)	39 (14; 66)	<0.0001
LA area, cm ²	16 (11; 23)	22 (12; 33)	20 (12; 37)	23 (11; 34)	0.001
Maximal LA volume, mL	38 (16; 60)	60 (20; 120)	53 (14; 90)	70 (22; 115)	<0.0001
S' wave tricuspid annular, cm/s	15 (8; 26)	9 (7; 12)	12 (4; 21)	10 (5; 18)	0.001
Systolic PAP, mmHg	31 (19; 50)	39 (27; 80)	34 (30; 59)	41 (24; 66)	0.001
Dilated vena cava, %	6	25	31	47	0.003
Pericardial effusion, %	11	37	37	51	0.016

BSA body surface area, GFR glomerular filtration rate, DFLC delta free light chains, ED end diastolic, ES end systolic, LA left atrial, LV left ventricular, LVEF left ventricular ejection fraction, NYHA New York heart association, PAP pulmonary arterial pressures

Predictors of all-cause mortality

In univariate analyses (Table 3), male gender, NYHA functional class \geq III, Mayo Clinic stage III, IVS thickness, LV ESV, LV indexed mass, LA diameter, LA area, LA volume indexed, E/A ratio, lateral E/e', systolic PAP, and pericardial effusion, as well as LVT+ were all associated with increased all-cause mortality. Factors associated with reduction in all-cause mortality were

increase in higher glomerular filtration rates, LVEF, E-wave deceleration time, and tricuspid annular S-wave velocity.

A very good hematologic response to chemotherapeutic treatment or better was associated with increased survival (at 5 years: 78 ± 10 vs. $46 \pm 7\%$, $p = 0.022$).

In multivariate analysis (Table 4), after adjusting for age and gender, the presence of LVT remained associated with all-cause mortality. Further adjustments for NYHA

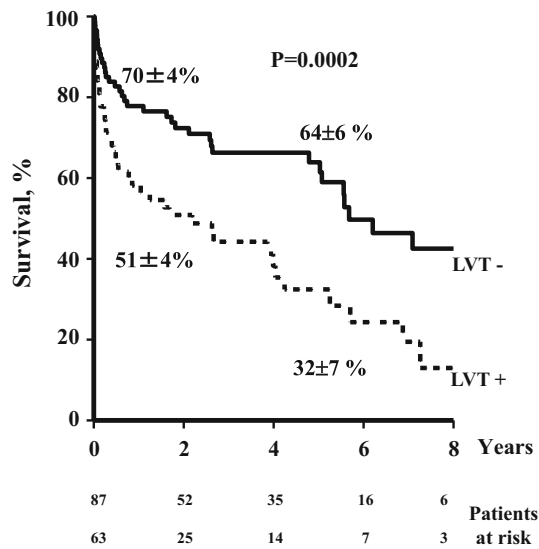


Fig. 3 Kaplan–Meier survival curves of AL patients with and without LVT

functional class, LVEF, and glomerular filtration rates (Model #1) did not modify the independent association between LVT and all-cause mortality. In addition, LVT + remains associated with reduced survival even after adding Nt-pro BNP for adjustment into the Model #1 (Table 4). When adding the troponin level in the Model #1, there was a definite trend for independent relationship between LVT+ and survival (Table 4).

In the subset of patients with available Mayo Clinic staging ($n = 113$), LVT+ remained associated with all-cause mortality after adjustment for age, gender, and Mayo Clinic staging (hazard ratio 1.83, 95% of confidence of interval 1.00–3.35, $p = 0.049$).

However, further adjustments for the LV diastolic parameters, systolic pulmonary artery pressure, IVST, and pericardial effusion weakened the statistical significance of the association between LVT+ and overall mortality (Table 4).

After adjustment for the hematologic response, LVT+ remains significantly associated with reduced survival (HR 2.65, 95% CI 1.4–5.1, $p = 0.003$).

Discussion

Our study includes a large cohort of patients with AL who underwent a baseline comprehensive echocardiographic study prior to the initiation of therapy. Our main findings indicate that LVT+ is common in patients with AL at the time of diagnosis, present in almost one half of patients, irrespective of the presence of significant valve regurgitation or stenosis. In addition, patients with LVT+ demonstrate a more advanced

Table 3 Univariate analyses of factors associated with all-cause mortality

Variables	Univariate analysis		
	HR	95% CI	<i>p</i> value
Age, per years	1.01	0.99–1.04	0.12
Male gender	1.58	1.00–2.54	0.049
NYHA \geq III	3.54	2.07–6.13	<0.0001
Involved organs \geq 2	1.15	0.68–2.03	0.6
DFLC	1.00	0.99–1.00	0.3
Nt-pro BNP, per ng/L	1.00	1.00–1.00	<0.0001
Troponin, per μ g/L	3.71	1.5–9.2	0.004
Mayo Clinic stage I	1	(Ref.)	–
Mayo Clinic stage II	2.35	0.73–10.4	0.16
Mayo Clinic stage III	9.50	3.37–39	<0.0001
GFR, per 1 mL/m ² decrease	0.99	0.99–0.99	0.01
LV IVS thickness, per 1 mm increase	1.14	1.06–1.22	0.0001
LV ED volume, per 1 mm increase	1.02	0.99–1.06	0.2
LV ES volume, per 1 mL increase	1.07	1.03–1.12	0.001
LVEF, per 1% increase	0.97	0.95–0.98	0.0002
LV indexed mass, per 1 g/m ² increase	1.01	1.00–1.01	<0.0001
LA diameter, per 1 mm increase	1.05	1.02–1.09	0.008
LA area, per 1 cm ² increase	1.09	1.04–1.15	0.0002
LA indexed volume, per 1 mL/m ²	1.02	1.04–1.03	0.01
Deceleration time, per 1 ms	0.99	0.98–0.99	<0.0001
<i>E/A</i>	1.36	1.16–1.58	0.0004
Mitral lateral annulus <i>E/e'</i>	1.05	1.02–1.08	0.0004
S' wave tricuspid annular, per 1 cm/s	0.87	0.79–0.96	0.004
Systolic PAP, per 1 mmHg increase	1.03	1.01–1.05	0.001
Pericardial effusion	1.90	1.19–3.02	0.0008
LVT	2.29	1.46–3.60	0.003

DFLC delta free light chains, *ED* end diastolic, *ES* end systolic, *GFR* glomerular filtration rate, *IVS* interventricular septum, *LA* left atrial, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *LVT* left valvular thickness in AL amyloidosis, *NYHA* New York heart association, *PAP* pulmonary arterial pressures

stage of the disease illustrated by higher rates of NYHA functional class, a higher proportion at Mayo Clinic stage II–III, and higher rates of other echocardiographic abnormalities related to cardiac AL involvement, including altered LV systolic and diastolic function and increased wall thickness.

Furthermore, patients with LVT+ have a poorer outcome as compared to those without LVT.

To the best of our knowledge, our report represents the first study to investigate the prognostic value of LVT in patients with AL at the time of diagnosis. Our population was relatively homogeneous, since it did not include patients with other types of amyloidosis (i.e., wild-type senile transthyretin or hereditary amyloidosis) who have a

Table 4 Impact of LVT+ on all-cause mortality in multivariate analysis

Model 1	LVT+		
	Hazard ratio	95% CI	<i>p</i> value
Left valve thickening + adjusted for age and gender	2.36	1.48–3.79	0.0003
+ NYHA class \geq III	1.94	1.12–3.39	0.01
+ GFR	1.98	1.13–3.49	0.01
+ LVEF	1.90	1.10–3.34	0.02
Model 1 + Nt-pro BNP	1.77	1.00–3.13	0.048
Model 1 + troponin	1.74	0.99–3.05	0.053
Model 1 + LA dilatation	1.74	0.96–3.19	0.06
Model 1 + <i>E/e'</i>	1.74	0.93–3.36	0.08
Model 1 + <i>E/A</i>	1.71	0.92–3.18	0.08
Model 1 + deceleration time	1.64	0.90–3.04	0.1
Model 1 + pericardial effusion	1.63	0.92–2.93	0.09
Model 1 + systolic PAP	1.60	0.89–2.90	0.11
Model 1 + IVS thickness	1.57	0.90–2.79	0.11

GFR glomerular filtration rate, *IVS* interventricular septum, *LA* left atrial, *LVEF* left ventricular ejection fraction, *LVT* left valvular thickness in AL amyloidosis, *NYHA* New York heart association, *PAP* pulmonary arterial pressures

distinct clinical presentation, natural history, prognosis, and management.

Prevalence of LVT in AL patients

We found that 42% of patients demonstrate abnormal mitral or aortic thickening (>3 mm) with 35% of patients showing thickening of both valves at the initial echocardiogram.

Cardiac involvement in AL patients is manifested by progressive infiltration of the left and right ventricular myocardium, inter atrial septum, and valvular endocardium with amyloid fibrils. The involvement of the valvular endocardium has been described in autopsy studies of AL patients [13]. Another post-mortem study of patients with familial hereditary transthyretin amyloidosis showed evidence of amyloid deposition in all cardiac valves [14]. Macroscopic analysis demonstrated mitral and tricuspid thickening in 50% and aortic valve involvement in 25% of patients. The prevalence of valvular involvement is similar in our patient population. Accordingly, the mitral valve thickening is more common than that of the aortic valve.

Prognostic impact of LVT in AL patients

This study is the first to analyze the prognostic value and impact of LVT+ on outcome in patients with AL. We have found that LVT, a fast and easy echocardiographic marker, was significantly associated with advanced NYHA functional class as well as cardiac involvement in AL. Patients with LVT are at a more advanced stage of the disease, a

finding that explains the higher rate of all-cause mortality at 5 years as compared to those without LVT. Despite adjustment for clinically relevant parameters associated with increased all-cause mortality, LVT remains an independent predictor of outcome. However, the adjustments for other hemodynamic echocardiographic parameters weakened the statistical significance of the association between LVT+ and overall mortality. These findings indicate a stronger impact of the hemodynamic alterations as compared to the morphological changes on the outcome of patients with AL. Importantly, the association between LVT+ and prognosis is not related to the severity of valve dysfunction, since LVT was not associated with any significant valve stenosis or regurgitation in this population. Studies in AL patients have shown that LV “hypertrophy” and valvular infiltration may persist for an extended period of time following organ and hematological remission in response to therapy [7]. This phenomenon is due to the delay (sometimes several years) necessary for the elimination of fibrils, whereas the direct toxicity of the light-chain immunoglobulin on the heart has already resolved with treatment [7]. This concept further supports our findings that the hemodynamic alterations have major prognostic implications as compared to the morphological abnormalities that may persist for many years following effective treatment.

Limitations

Our study has a retrospective design with potential limitations inherent to this type of study.

The exact cause of death in our patients was not always available, explaining why we opted to list the total mortality rather than cardiac mortality as outcome [8]. The Mayo clinic staging was not available in 25% of patients. However, we are unable to document any potential selection bias related to the change in the quantification of cardiac involvement in AL. No significant difference was found between baseline characteristics and prevalence of LVT of patients in whom the Mayo Clinic staging was performed and those without this staging system. The LVT is better assessed using transoesophageal echocardiography as it was previously described [10, 11]; but for ethical reasons, TEE could not be offered for our AL patients, because it was not clinically indicated. However, despite its lower sensitivity to detect abnormal thickening, TTE provided important prognostic information as demonstrated in our study.

The LVT may be caused by several other etiologies than amyloid infiltration; and it is difficult to define only by transthoracic echocardiography the exact cause of thickening, that is why, the clinical data are actually very helpful to address differential diagnosis. After reviewing patient's medical charts, we found no clinical data suggestive for active endocarditis. However, we cannot definitely exclude other causes of LVT (i.e., sclerosis), but the level of traditional risk factors was low, and we cannot consider a systematic bias favouring sclerosis in more advanced stages of the Mayo Clinic classification. In addition, although many efforts have been made to avoid to consider localized valve nodular thickening or calcification as LVT, we can not guarantee the absence of such assessment error. Nonetheless, in light of the low rate of cardiovascular risk factor of this population, these morphological features are very likely infrequent in our cohort.

Finally, assessment of thickening was limited to the left-sided heart valves and did not mention whether right heart valves were also involved in the process of amyloid infiltration. This lack of information regarding tricuspid and pulmonary valves is due to the retrospective design of our study and thus the absence of specific description of the right heart valves in the echocardiographic reports of included patients. Prospective studies are necessary to determine the prevalence and impact of right heart valves on outcome in AL patients.

Conclusion

Left valvular thickening is frequent, present in almost half of AL patients' naive of treatment, at the baseline echocardiographic study. It is associated with advanced NYHA functional class, Mayo clinic stage, systolic and diastolic dysfunction, as well as increased pulmonary

hypertension. Its presence is also associated with an increased risk of death at 5 years. We suggest that valve thickening should be systematically reported as a part of the echocardiographic study in patients with documented or suspected AL. Further prospective studies are required to confirm our findings and to determine whether LVT may be systematically used to detect degree of AL-related cardiac involvement or likelihood of progression/regression of disease after treatment.

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Compliance with ethical standards

Conflict of interest The authors deny any conflict of interest, financial, or otherwise, related to the submitted work.

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