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Electrocardiographic left ventricular strain pattern, ST-segment depression and atrial fibrillation at the time of diagnosis of systemic light chain amyloidosis: Incidence and clinical significance

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ABSTRACT

Background: ST/T abnormalities recognized as electrocardiographic (ECG) left ventricular (LV) strain pattern are known as a marker of myocyte death and reduced survival. The purpose of this study was to determine whether ECG LV strain pattern, its components and atrial fibrillation (AF) predict lower survival at the time of diagnosis of systemic light chain (AL) amyloidosis.
Methods: 12-lead surface electrocardiogram (ECG), standard two-dimensional echocardiography, laboratory analyses were retrospectively evaluated within 2 months of diagnosis in 87 patients with biopsy-proven systemic AL amyloidosis from 2009 to 2017 in a single center. ECG strain pattern was defined as coexistence of ST-segment horizontal or downward sloping depression ≥0.05 mV at its most horizontal section and negative asymmetrical T-wave deeper than 0.1 mV in at least 1 of leads I,aVL,V1-V6. Patients with QRS >120 ms (BBB or major IVCD) were excluded from the analysis.
Results: Kaplan-Meier survival analysis revealed a 1.8-fold shorter overall survival (OS) at 2 years in the ECG strain (21% of participants) group ($p = 0.0078$), 2.0-fold shorter OS in the ST-segment depression (STd) (isolated and strain related as one group) (34% of participants) group ($p < 0.0001$), and 3.9-fold shorter OS in AF (23% of participants) group ($p < 0.0001$) compared with those without. Median survival of patients with STd and AF were and 13.0 (range 1–74) and 9.5 (range 1–74) months respectively. In univariate analysis STd and AF were stronger predictors of inferior OS than relative wall thickness, average E/e′ ratio, and LV ejection fraction, but weaker predictors of OS than B-type natriuretic peptide. In multivariate analysis STd and AF lost significance after adjustment for age, gender, number of organs involved and BNP.
Conclusions: ST-segment depression and AF were not significantly associated with reduced survival in AL amyloidosis at diagnosis.

Introduction

Light chain (AL) amyloidosis is a disorder of deposition of monoclonal immunoglobulin light chain-derived amyloid fibrils in various tissues [1]. Cardiac involvement in AL amyloidosis is common and ranges form 70% to 90% [1,2]. Degree of cardiac involvement is the most accurate determinant of prognosis in AL amyloidosis and is the major reason that limits treatment [2,3]. Electrocardiographic data on prognosis in AL amyloidosis are scarce [4]. From electrocardiographic point of view over the past 2 years several publications have confirmed that prolonged QTc interval is related to reduced survival in AL amyloidosis [5,6]. The abnormal repolarization variant defined as electrocardiographic (ECG) left ventricular (LV) strain pattern is prognostic in conditions of elevated LV mass [7,8]. ECG strain, defined as as coexistence of ST-segment horizontal or downward sloping depression with negative asymmetrical T-wave in either of leads V5-V6, predicts heart failure (HF) and all-cause mortality in patients with aortic stenosis, arterial hypertension and even subjects without past cardiovascular disease and is associated with myocardial fibrosis regardless of anatomic left ventricular hypertrophy (LVH) [7–9]. This variable was not analyzed in the setting of AL amyloidosis. In a research of Xin et al. (2011) ST-segment and T-wave changes were described as separate pathogenetic entities of ECG LV strain [10]. We aimed to assess prognostic significance of electrocardiographic LV strain pattern and its separate elements in subjects with AL amyloidosis (Fig. 1) as, to our

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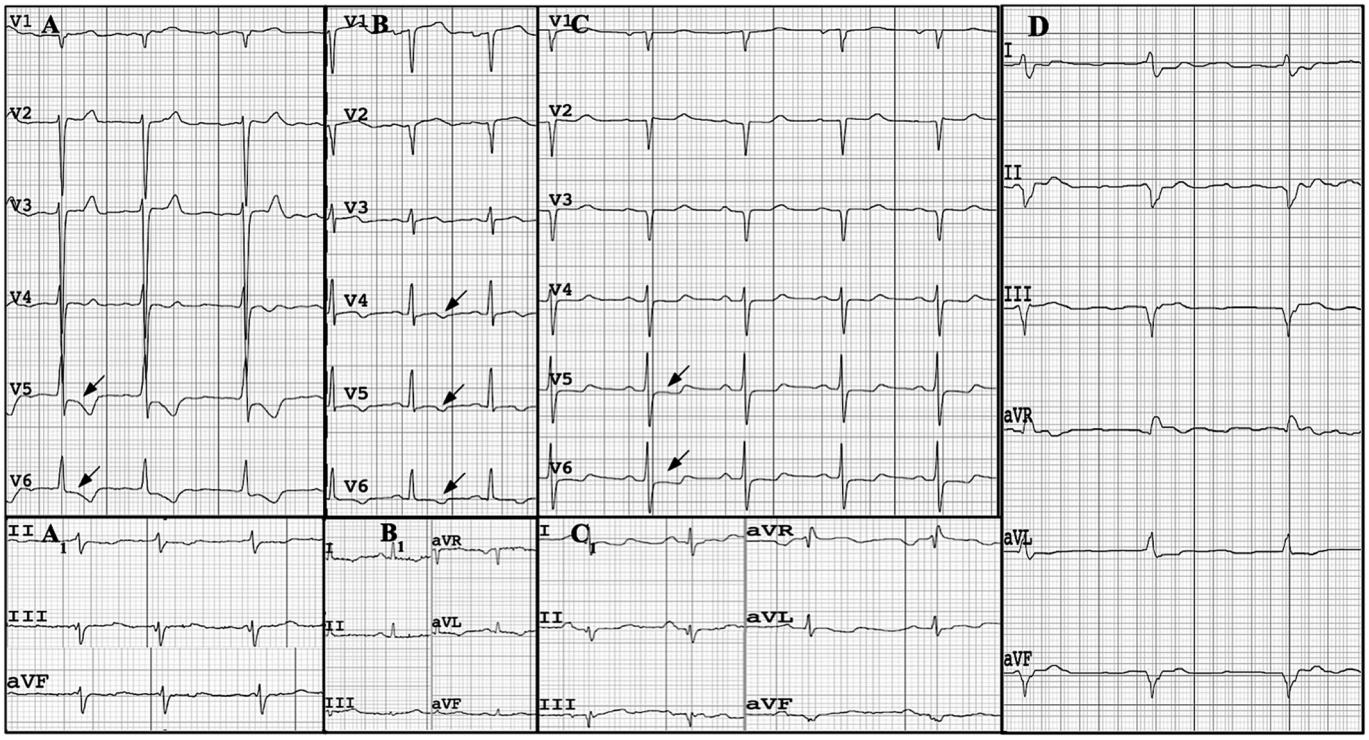

Fig. 1. Panels A, B, C: repolarization abnormalities in patients with newly diagnosed systemic light chain amyloidosis and heart rate 60–100 beats/min: electrocardiographic (ECG) left ventricular strain pattern (A, arrows, RWT – 0.69, IVSd – 1.7 cm, LVEDD – 4.6 cm, LV EF – 49%), negative T-wave (B, arrows, RWT – 0.59, IVSd – 1.3 cm, LVEDD – 4.2 cm, LV EF – 55%), isolated ST-segment depression (C, arrows, RWT – 0.7, IVSd – 1.8 cm, LVEDD – 4.8 cm, LV EF – 55%) which was proved to be a surrogate of ECG strain. The lower panel demonstrates the limb leads of respective electrocardiograms. Panel D demonstrates Frederick syndrome in patient A, which evolved 53 days after the diagnosis of light chain amyloidosis. In all ECGs speed – 25 mm/s, voltage – 10 mm/mV. RWT: relative wall thickness; IVSd: interventricular septum thickness at end-diastole; LVEDD: left ventricular end-diastolic diameter; LV EF: left ventricular ejection fraction.

knowledge, no studies examined this repolarization abnormality in this paraproteinemia before and did not specify individual value of ST-segment depression and negative T-wave in this plasma cell disorder, too.

Atrial arrhythmias are not uncommon in AL amyloidosis [11]. Larger studies, which analyzed the impact of AF on survival in AL amyloidosis patients, brought uncertainty to the field [12,13]. In a study of 123 AL amyloidosis patients atrial fibrillation (AF) was associated with prevalent and incident HF but not with reduced survival [12], yet another study of 239 patients with AL amyloidosis found 31% ($p < 0.001$) lower survival at 6 months after stem cell transplantation in patients with pretransplant AF on Holter in comparison to those without AF [13]. In a study of 1224 patients with systemic light chain amyloidosis atrial arrhythmias independently predicted reduced survival and even had incremental value to standard staging systems [14]. However, in the same year another study of 115 patients found no impact of atrial fibrillation on survival in people with cardiac AL amyloidosis [15]. Consequently, another goal of our study was to reassess prognostic implications of AF in AL amyloidosis and to describe its relation to repolarization indices and markers of myocardial structure and function.

Methods

Study population

A retrospective study of 87 biopsy-proven systemic AL amyloidosis patients diagnosed in Vilnius University Hospital Santaros Klinikos from September 2009 to December 2017 was conducted. Diagnosis of systemic AL amyloidosis was confirmed by Congo-red staining and apple-green birefringence under cross-polarized light in biopsy of periumbilical fat or target organ along with proof of clonal population of plasma cells in the bone marrow. Positive immunohistology for kappa or lambda light chain in biopsy was mandatory for diagnosis. All of the following: 12-lead surface ECG, echocardiography and laboratory analyses within 2 months of diagnosis, were mandatory for inclusion in the analysis.

Information gathered included demographic, serologic, electrocardiographic (12-lead surface ECG) and standard two-dimensional transthoracic echocardiographic data. Study's end point was all cause mortality at maximum follow-up. Overall survival (OS) was calculated from the time of diagnosis to censor date (April 6th, 2018) for survivors and to the date of death for nonsurvivors.

Patients who died within two weeks from inclusion or were lost from follow-up within two weeks (among survivors) from inclusion were excluded from the analysis.

Echocardiography

All patients had a standard echocardiographic investigation performed according to the guidelines of American Society of Echocardiography and European Association of Cardiovascular Imaging [16,17] using Vivid 7 cardiovascular ultrasound system (GE Medical Systems) within 2 months of diagnosis. LV ejection fraction (EF), LV mass index, relative LV wall thickness, diastolic LV diameter, systolic LV diameter, left atrial (LA) volume index, early transmitral flow (E), average early mitral annular diastolic velocity (e′), the ratio of early transmitral flow to early average mitral annular diastolic velocity (E/e′), presence of pericardial effusion (>5 mm of pericardial separation in diastole) were used for analysis. Relative LV wall thickness was defined as 2 times posterior wall thickness divided by the LV diastolic diameter [16,18]. In atrial fibrillation velocity measurements from 10 consecutive cycles were averaged [17].

12-lead surface electrocardiography

All patients had at least one 12-lead surface electrocardiogram recorded at 10 mm/mV and 25 mm/s within 2 months of diagnosis. The 12-lead surface electrocardiogram closest to the time of diagnosis was independently analyzed by two investigators who were blinded to echocardiographic, serologic and clinical data. In case of incompatibility in ECG interpretation between two investigators, a third investigator independently evaluated the variable on ECG. For evaluation all ECGs were enlarged 4 times. ECG characteristics were evaluated in 3 consecutive beats. Segments with extrasystoles were not used. Patients with QRS >120 ms (BBB or major IVCD) were excluded from the analysis as repolarization abnormalities coexistent with QRS duration >120 ms may have different predictive values than primary repolarization abnormalities.

The 12-lead ECG was analyzed for the following characteristics: low voltage (defined by QRS amplitude ≤0.5 mV in each limb lead or ≤1 mV in each precordial lead [19]), pseudoinfarction pattern (defined by pathologic Q, QS or rS waves in at least two consecutive leads from V1 to V6 in the absence of myocardial infarction and left bundle branch block [5]), atrioventricular (AV) block (first degree AV block defined by PQ interval ≥ 220 ms [20]), intraventricular conduction delay (IVCD) (defined by QRS duration 90–120 ms in the presence of a supraventricular rhythm [21]), left ventricular (LV) hypertrophy pattern, repolarization abnormalities defined by ST-segment depression and/or flat/negative T-wave. ST-segment depression was defined by ST-segment horizontal or downward sloping depression ≥0.05 mV at its most horizontal section in at least 1 of leads I, aVL, V1-V6 [9]. The TP-segment was considered as the iso-electric line. T-wave was considered negative when it was deeper than 0.1 mV and flat when its peak amplitude was between 0.1 mV and −0.1 mV in at least 1 of leads I, aVL, V1-V6 [22]. ECG strain pattern was defined as coexistence of ST-segment horizontal or downward sloping depression ≥0.05 mV and negative asymmetrical T-wave in the same lead in at least 1 of leads I, aVL, V1-V6 [9]. LV hypertrophy was diagnosed on the basis of Cornell criteria (R-wave in aVL and S-wave or QS-complex in V3 > 2.8 mV in men and >2.0 mV in women), Sokolow-Lyons criteria (S-wave in V1 and R-wave in V5 or V6 ≥ 3.5 mV) or voltage criterion of R-wave in aVL >1.1 mV [23].

History of atrial fibrillation (AF) was verified if at the time of systemic AL amyloidosis diagnosis there was at least one ECG confirmed episode of AF in patients' history (Fig. 2). Status of AF (permanent vs. paroxysmal/persistent) was retrospectively identified from the medical records taken at the time of diagnosis of systemic AL amyloidosis. Patients with atrial flutter were considered as having atrial fibrillation and were analyzed in the same group with atrial fibrillation patients in statistical analysis.

Statistical analysis

Statistical analysis was performed using SPSS Statistics 20 software. Wilcoxon-Mann Whitney test and Independent samples *t*-test were used for continuous variables depending on their distributions. Shapiro-Wilk test was used to assess the normality of these variables. Comparison of the categorical variables was performed using Fisher's exact test. Continuous data were presented as median (range), categorical - as number of cases (percentage). To determine possible associations Spearman's correlation coefficient was used. The risk factors for OS were assessed by Cox regression analysis. *P* value of <0.05 was considered statistically significant.

Ethical considerations

The study was approved by Vilnius Regional Biomedical Research Ethics Committee (permission number 2020/1–1187-671) and was

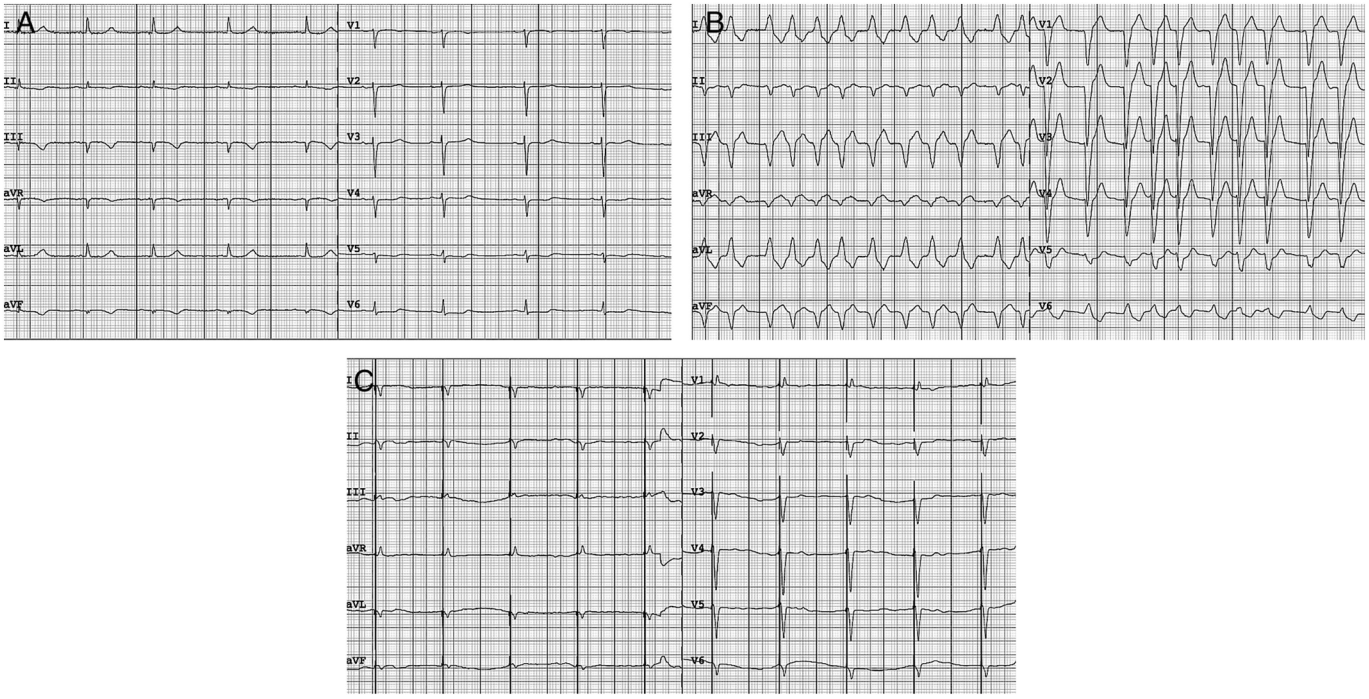

Fig. 2. Panels A and B: ECGs of a 76-year-old female newly diagnosed with systemic AL amyloidosis (RWT – 0.68, LVEDD – 3.84 cm, LV EF – 40%). Panel A: sinus rhythm, ST-segment depression without negative T-wave in leads V5-V6. Panel B (recorded 10 h after ECG A): atrial fibrillation, complete left bundle branch block, secondary ST segment depression and T-wave inversion (leads I, aVL, V6). Panel C: ECG of a 72-year-old male with permanent atrial fibrillation and newly diagnozed systemic AL amyloidosis (RWT – 0.61, LVEDD – 4.49 cm, LV EF – 35%). 2 years before the diagnosis of AL amyloidosis the patient was in sinus rhythm. Note ventricular pacing compatible with extensive conduction system disease. In all ECGs speed – 25 mm/s, voltage – 10 mm/mV. ECG – electrocardiogram, AL: light chain, RWT – relative wall thickness, LVEDD – left ventricular end-diastolic diameter, LV EF – left ventricular ejection fraction.

performed in accordance with the ethical standards expressed in the Declaration of Helsinki.

Availability of data

The datasets generated during the present study are available from the corresponding author on reasonable request.

Results

Baseline characteristics of the study group

The final study group consisted of 87 patients (median age – 61.2 years, 52% men). During the follow up 47 (54%) patients died. Median observation period of the study population was 579.5 days (range 28–3667 days, 858.5 days in survivors (30–3667), 517.0 days in nonsurvivors (28–3365)). Median time from diagnosis to ECG was 14 days (range 1–39 days).

Low voltage (69%) and pseudoinfarction pattern (43%) were the commonest findings on ECG. ECG strain pattern appeared in 18 (21%) patients. ST depression (with and without negative T wave as one group) in at least 1 lead was present in 30 (34%) patients. ST-segment depression was most commonly seen in leads V5 and/or V6 (77%). The vast majority (97%) of ST-segment depression cases were not associated with tachycardia, defined as heart rate > 100 beats per minute.

The prevalence of history of atrial fibrillation was 23% (3% permanent, 20% paroxysmal or persistent). Baseline ECGs of patients with a history of atrial fibrillation showed sinus rhythm in 94% and atrial fibrillation in 6%. Median heart rate in baseline ECGs with sinus rhythm of patients with a history of atrial fibrillation was 63 beats per minute in comparison to 72 beats per minute in patients without a history of AF ($p = 0.17$).

Baseline characteristics of the study population are shown in Table 1.

Thalidomide and bortezomib in the same or different treatment lines were administered for 68 (78%) patients. The majority (39%) of patients received thalidomide based chemotherapy, usually CTD (cyclophosphamide, thalidomide and dexamethasone). 15 (17%) patients received glucocorticoids/alkylators based therapy. Minority of included patients were treated with bortezomib-dexamethasone chemotherapy (11%) and some did not receive any chemotherapy (5%), mainly due to death prior to the start of the treatment. 25 patients (29%) received autologous stem cell transplantation.

Univariate analysis for overall survival

In univariate analysis (Tables 2 and 3) B-type natriuretic peptide (BNP) predicted reduced overall survival most accurately (HR: 1.001, $p < 0.000001$), followed by atrial fibrillation in the second position (HR: 6.698, $p = 0.000002$) and ST-segment depression (isolated and strain related as one group) in the third position (HR: 2.750, $p = 0.00007$). ST-segment depression predicted lower survival more accurately than ECG strain (HR: 1.929, $p = 0.005$), therefore, only ST-segment depression was involved in multivariate analysis.

Echocardiographic variables, that predicted overall survival in univariate analysis, were LA volume index, e′, E/e′, LV EF and presence of pericardial effusion.

Kaplan-Meier curves that reflect survival differences between patients with and without ST-segment depression and atrial fibrillation are shown in Fig. 3.

Table 1
Baseline characteristics: demographic, clinic, echocardiographic and electrocardiographic parameters.

Demographic and clinic parameters	All patients $N = 87$	ST-segment depression (−) $N = 57$	ST-segment depression (+) $N = 30$	P value
Age, years	61.2 (39.0–85.7)	57.2 (39.0–79.8)	65.0 (40.0–85.7)	0.075
Male (%)	46 (52)	24 (42)	22 (55) 16 (53)	0.145
Number of organs involved	2 (1–3)	2 (1–3)	2 (1–3)	0.398
Cardiac involvement present (%)[†]	54 (62)	28 (49)	26 (87)	0.015
History of atrial fibrillation (%)	20 (23)	8 (14)	12 (40)	0.014
BNP, ng/l	216.7 (46.8–4108.0)	122.6 (46.8–1196.6)	1084.1 (90.5–4108.0)	<0.001
BNP > 400 ng/l (%)	26 (30)	4 (7)	22 (73)	<0.001
BNP > 800 ng/l (%)	21 (24)	2 (4)	19 (63)	<0.001
eGFR (CKD-EPI), ml/min/1.73m^2	62.3 (2.0–116.5)	59.0 (2.0–114.7)	65.7 (4.5–116.5)	0.850
ALP, U/l	73.7 (35.5–767.5)	70.5 (35.5–620.5)	78.0 (44.5–767.5)	0.276
Free light chain difference, mg/l[‡]	149.1 (0.5–5706.9)	65.5 (0.5–5706.9)	209.4 (5.9–1980.0)	0.034
Echocardiographic parameters				
Diastolic LV diameter, cm	4.67 (2.69–5.53)	4.83 (4.13–5.43)	4.48 (2.69–5.53)	0.018
Systolic LV diameter, cm	2.89 (1.77–3.83)	2.91 (2.40–3.53)	3.25 (1.77–3.83)	0.024
Relative wall thickness	0.48 (0.32–0.86)	0.45 (0.32–0.71)	0.51 (0.35–0.86)	0.010
LV mass index, g/m^2	105.9 (52.4–292.0)	91.0 (52.4–206.0)	139.0 (68.0–292.0)	0.008
LA volume index, ml/m^2	46.5 (20.4–107.0)	32.1 (20.4–100.0)	52.1 (38.0–107.0)	0.001
Average e′ velocity, cm/s	6.7 (2.5–12.8)	7.2 (4.0–11.6)	5.9 (2.5–12.8)	0.058
Average E/e′ ratio	11.8 (4.1–42.0)	9.5 (5.4–18.5)	14.2 (4.1–42.0)	0.008
LV ejection fraction (%)	55.0 (10.0–55.0)	55.0 (50.0–55.0)	55.0 (10.0–55.0)	0.015
Pericardial effusion present (%)	30 (34)	18 (32)	12 (40)	0.197
Electrocardiographic parameters				
Low voltage (%)	60 (69)	39 (68)	21 (70)	0.777
Pseudoinfarction pattern (%)	37 (43)	18 (32)	19 (63)	0.045
AV block: first degree (%)	8 (9)	4 (7)	4 (13)	0.769
AV block: third degree (%)	4 (5)	1 (2)	3 (10)	0.218
AV block (%)	12 (14)	5 (9)	7 (23)	0.095
IVCD (%)	26 (30)	10 (18)	16 (53)	0.002
ECG strain pattern (%)	18 (21)			
ST-segment depression (%)	30 (34)			
Negative T-wave (%)	36 (41)	13 (23)	23 (77)	0.007
LV hypertrophy pattern (%)	10 (11)	3 (5)	7 (23)	0.045

Values are median (range) or n (%). ALP: alkaline phosphatase; AV: atrioventricular; BNP: B-type natriuretic peptide; ECG: electrocardiographic; eGFR: estimated glomerular filtration rate; IVCD: intraventricular conduction delay; LA: left atrial; LV: left ventricular.

[†] Cardiac involvement defined by mean LV wall thickness in end-ventricular diastole >12 mm in the absence of other known cardiac cause [37] or BNP > 100 ng/l in the absence of other known cardiac cause.

[‡] Difference between involved and uninvolved free light chains.

Table 2
Univariate analysis for overall survival: clinic and echocardiographic parameters.

Variable	HR	95% CI	P value
Age, years	**1.057**	**1.029–1.085**	**0.007**
Male gender	1.154	0.697–1.400	0.690
Number of organs involved	0.655	0.435–1.156	0.245
eGFR (CKD-EPI), ml/min/1.73m^2	1.001	0.095–1.097	0.875
BNP, ng/l	**1.001**	**1.0007–1.0015**	**<0.0001**
Diastolic LV diameter, cm	0.759	0.497–1.427	0.077
Systolic LV diameter, cm	1.059	0.865–2.675	0.158
LA volume index, ml/m^2	**1.055**	**1.017–1.079**	**0.049**
Relative wall thickness	5.004	0.989–12.889	0.067
Average e′ velocity, cm/s	**0.720**	**0.602–0.945**	**0.045**
Average E/e′ ratio	**1.115**	**1.037–1.174**	**0.011**
LV ejection fraction (%)	0.967	0.927–0.986	0.004
LV mass index, g/m^2	1.010	0.998–1.018	0.125
Pericardial effusion present (%)	**1.889**	**1.180–3.930**	**0.027**

BNP: B-type natriuretic peptide; eGFR: estimated glomerular filtration rate; LA: left atrial; LV: left ventricular.
Bold values shows statistically significant results p ≤ 0.05.

Table 3
Univariate analysis for overall survival: electrocardiographic parameters.

Variable	HR	95% CI	P value
Low voltage	1.453	0.637–2.569	0.757
Pseudoinfarction pattern	1.785	0.798–2.955	0.070
AV block: first degree	1.567	0.497–4.511	0.801
AV block: third degree	1.234	0.107–6.458	0.889
AV block	1.397	0.448–3.160	0.677
IVCD	1.504	0.889–2.775	0.087
LV hypertrophy pattern	1.345	0.675–2.786	0.109
ST-segment depression	**2.750**	**1.435–3.767**	**<0.0001**
ECG strain pattern	**1.929**	**1.485–3.115**	**0.005**
Negative T-wave	1.453	0.654–2.611	0.115
History of atrial fibrillation	**6.698**	**2.198–9.846**	**<0.0001**

AV: atrioventricular; ECG: electrocardiographic; IVCD: intraventricular conduction delay; LV: left ventricular.
Bold values shows statistically significant results p ≤ 0.05.

Multivariate analysis for overall survival

A separate multivariate model that included age at baseline and only echocardiographic variables, which were significant for overall survival in univariate analysis, was created. Neither of variables were significantly prognostic ($p > 0.05$) for overall survival in this model. In the final multivariate model only BNP (HR: 1.001, $p = 0.006$) retained its prognostic significance (Table 4).

Correlations

In correlation analysis the association of BNP with ST-segment depression (cc = 0.696, $p < 0.00001$) and the relation of relative wall thickness with E/e′ (cc = 0.678, $p = 0.00002$) were the most statistically significant correlations.

Correlation analysis of patients with systemic light chain amyloidosis is demonstrated in Supplemental Table 1.

Discussion

AL amyloidosis has a characteristic appearance on cardiac MRI due to subendocardial late gadolinium enhancement (LGE) – a finding attributed to subendocardial amyloid infiltration [1,7]. LGE is a marker of myocardial replacement fibrosis and is also observed in scar related cardiomyopathy and other cardiac pathology associated with myocyte replacement [7,29]. In AL amyloidosis LGE, in addition to amyloid infiltration, potentially may be caused by myocyte necrosis due to toxic effect of amyloid fibrils or circulating amyloidogenic light chain or myocyte necrosis due to subendocardial ischaemia which results from small cardiac vessel amyloidosis. There are few pathomorphologic studies with AL amyloidosis patients, as a result the importance of replacement fibrosis in light chain amyloidosis is still unclear [29].

Amyloid cardiomyopathy is a condition of elevated LV mass [1]. To our knowledge, previous studies did not address the prognostic value of electrocardiographic LV strain pattern, also known as LV hypertrophy (LVH) associated ST-T abnormalities, in AL amyloidosis [5,8,24,25]. LV strain pattern is defined as downsloping ST-segment depression and asymmetrically inverted T-wave with polarity opposite the main QRS deflection in leads V5 and V6 and is a marker of anatomic LVH [8,26]. The pathogenetic mechanism of ECG strain is not clearly understood. Classically it is perceived as a result of different action potential duration in the presence of ischemia, situated in subendocardium or midwall [7,9,27,28]. The probable ischaemia was denied to have significant bond to epicardial coronary artery disease although may be associated with small cardiac vessel impairment [8,9,27,29].

Myocardial replacement fibrosis – a finding consistent with myocyte death – is quantified by late gadolinium enhancement (LGE) on MRI [7]. Currently ECG LV strain is considered to be a specific marker of replacement fibrosis [7,9,27]. Interestingly, patients who have LGE but do not have ECG strain show about 40% less replacement fibrosis in comparison to patients who have both LGE and ECG strain in aortic stenosis [7]. Its sensitivity reaches 66%, whereas its specificity is up to 100% [7], with an exception of apparently healthy individuals in whom the

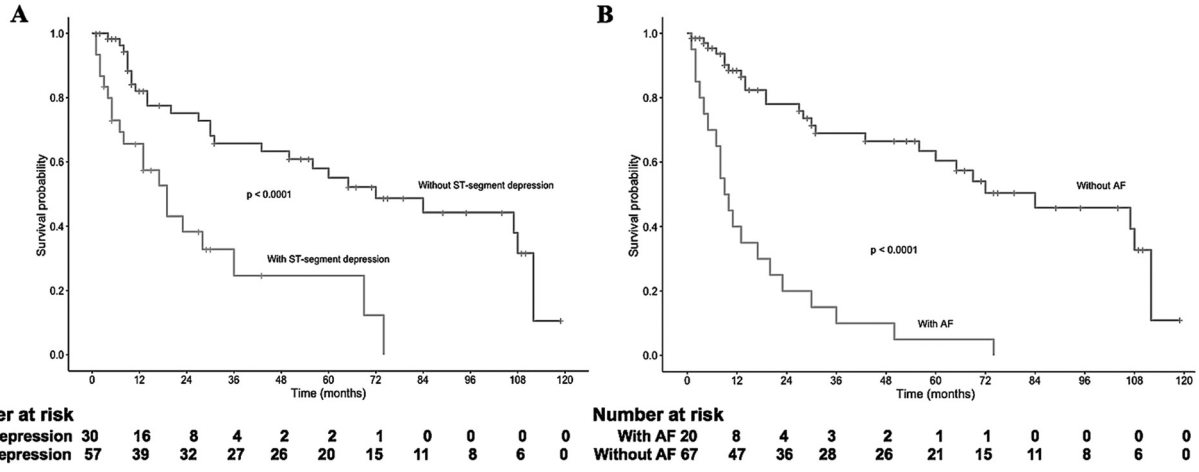

Fig. 3. Influence of ST-segment depression (A) and atrial fibrillation (AF, B) on survival of patients with newly diagnosed systemic light chain amyloidosis by Kaplan-Meier curves. AF had stonger stratification power than ST-segment depression.

Table 4
Multivariate Cox regression model.

Variable	HR	95% CI	P value
Age, years	1.089	0.846–1.108	0.152
Male gender	2.205	0.657–4.158	0.501
Number of organs involved	1.047	0.996–1.087	0.711
BNP, ng/l	**1.001**	**1.0007–1.0014**	**0.006**
ST-segment depression	1.366	0.991–3.159	0.105
History of atrial fibrillation	2.171	0.896–2.944	0.090

BNP: B-type natriuretic peptide.
Bold values shows statistically significant results p ≤ 0.05.

specificity of ECG strain to detect replacement fibrosis is 30% [9]. Myocardial interstitial fibrosis was also observed to be more outspread in patients with ECG strain in comparison to those without [7]. In severe aortic stenosis ECG strain pattern may be present without anatomic LVH [27].

Among 30 ECGs with ST-segment depression high-rate (>100 beats per minute) rhythm was observed in 1 ECG, whereas all other ECGs with ST-segment depression showed normosystolic sinus rhythm or normosystolic AF. Consequently, in our study ST-segment depression should be regarded as distinct phenomenon from tachysystolic AF or tachysystolic sinus rhythm.

In this study ST-segment depression was examined and used as a surrogate of strain-like repolarization abnormalities as it comprises a part of ECG strain and showed stronger trend towards inferior survival than ECG strain. In the present investigation there was a strong association of ST-segment depression with markers of diastolic heart failure, i.g., elevated BNP ($cc = 0.696$, $p < 0.00001$) and increased LA volume index ($cc = 0.607$, $p < 0.001$). The association of ST-segment depression with LV EF was significant but weak ($cc = -0.397$, $p = 0.039$). In conclusion, authors speculate that changes in ST-segment may be associated with diastolic dysfunction and chronically elevated LV filling pressure. Although being widely investigated, diastolic dysfunction, however, is a result rather than a reason of ongoing processes in amyloidotic myocardium.

In our investigation the prevalence of AF in the study population was 23%. This percentage is considerably higher than in general population (1–4%) [30]. In our opinion, an important finding is that history of AF was more prevalent among patients with ST-segment depression in comparison to patients without ST-segment depression (40% vs. 14%, $p = 0.014$). Therefore, we theorize that ST-segment depression could appear earlier in the disease course and could predispose AF in AL amyloidosis. Further research could elucidate, if patients with ST-segment depression could benefit from being regularly examined for possible progression to AF.

Extensive areas of low voltage in LA, compatible with fibrosis, were demonstrated on electroanatomic mapping in patients with cardiac AL amyloidosis [10,31–33]. It is thought that oxidative stress due to amyloid infiltration, inflammation, atrial fibrosis, direct cardiotoxic effect of circulating amyloidogenic light chains play a role in promoting AF in AL amyloidosis [31,34]. Circulating monoclonal light chains increase BNP via activated protein kinase signaling, so may play a specific role in AF to emerge [35].

Although AL amyloidosis is a classical example of interstitial infiltrative heart disease [1], authors speculate that occurrence and extent of myocyte necrosis might be underevaluated in this paraproteinemia and more studies are needed to elucidate this process. Subendocardial LGE on MRI typical to AL amyloidosis is considered to reflect amyloid in cardiac interstitium, but also may be a sign of myocyte death as is proved in aortic stenosis [7,29,36]. We suggest that myocyte death related fibrosis along with diastolic dysfunction might be pathogenetic pathways that participate in genesis of ST-segment depression and AF. In our opinion, ST-segment depression and AF need to be examined systematically in prospective studies as potential markers of myocyte necrosis and unfavorable prognosis in AL amyloidosis.

In our study ST-segment depression and AF were statistically significant in univariate analysis. However, after adjustment of covariates in multivariate analysis they lost significance. Authors speculate this may be due to small population size. Another important reason for losing statistical significance is strong association of both variables with BNP.

Limitations

The main limitations of this study are retrospective nature, which may have resulted in selection bias, and small size of the study population. Due to small sample size study results should be interpreted cautiously. Mayo staging system uses troponin, BNP (or NT-proBNP) and difference between involved and uninvolved light chain (FLC-diff) [37]. Troponin was not included in our survival analysis as 57% (50 patients) were not feasible for troponin concentration. However, BNP and FLC-diff were analyzed in regression models. Long inclusion period may have resulted in slight variability of treatment of patients with AL amyloidosis, however, in the period between 2009 and 2017 the main treatment strategies (first-line chemotherapy, indications for stem cell transplantation) did not change. First-line treatment was triple therapy with immunomodulator (CTD – cyclophosphamide, thalidomide and dexamethasone) or proteasome inhibitor (VCD – bortezomib, cyclophosphamide and dexamethasone) and autologous stem cell transplantation. Indications for autologous stem cell transplantation in the period 2009–2017 did not change in Lithuania.

Conclusions

ST-segment depression and AF were not significantly associated with reduced survival in AL amyloidosis at diagnosis. However, the probable association of ST-segment depression and AF with the extent of myocyte death need to be clarified in future studies to extend the knowledge about the pathogenesis of AL amyloidosis.

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Author contributions

Rusnė Jakaitė: conception and design of the paper, collection, analysis and interpretation of the data, a major contributor in writing the manuscript, reviewing, editing. Valdas Pečeliūnas: conception and design of the paper, analysis and interpretation of the data, reviewing, editing. Sigita Aidietienė: conception and design of the paper, analysis and interpretation of the data, reviewing, editing. Agnė Bertašiūtė: collection of the data. Neringa Bileišienė: collection of the data. Orinta Mickevičiūtė: statistical analysis. Jūratė Barysienė: conception and design of the paper.

Ethical approval

The study was approved by Vilnius Regional Biomedical Research Ethics Committee (permission number 2020/1-1187-671) and was performed in accordance with the ethical standards expressed in the Declaration of Helsinki.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2021.08.011.

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