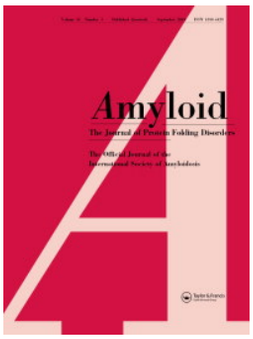

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RESEARCH ARTICLE

Prognostic value of CMR-derived extracellular volume in AL amyloidosis: a multicenter study

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ABSTRACT

Background: This study aimed to assess the prognostic value of cardiac magnetic resonance (CMR) variables and compare them with biological and echocardiographic markers in patients with AL cardiac amyloidosis (CA).

Methods: We conducted a prospective study across three tertiary centres, where patients underwent clinical examination, blood tests, echocardiography, and CMR. The primary endpoint was all-cause mortality.

Results: A total of 176 patients with AL CA were included, with a median age of 68 years (IQR 58-75). According to the 2004 Mayo Clinic staging, 121 patients (69%) were in stage 3. During a median follow-up of 22 months (IQR 8–48), 45 patients died, and 55 were hospitalized for heart failure. Patients who died had higher NT-proBNP and troponin levels, and lower LVEF, cardiac output, and longitudinal strain. Among CMR variables, extracellular volume (ECV) was most strongly associated with all-cause mortality. In multivariate Cox models, including Mayo Clinic staging, ECV ≥ 0.45 was independently associated with mortality (HR 2.36, CI 95% 1.47–5.60) and also with heart failure hospitalizations (HR 4.10, 95%CI 2.15–8.8).

Conclusion: ECV is a powerful predictor of outcomes in AL CA, providing additional prognostic value on top of Mayo Clinic staging.

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KEYWORDS
AL amyloidosis; prognosis; cardiac MRI; myocardial extracellular volume; cardiac amyloidosis

Introduction

In systemic amyloidosis, early diagnosis and accurate prognostic stratification are critical. Effective prognostic stratification is essential for selecting the appropriate chemotherapy regimen. Cardiac involvement is the most severe prognostic factor in systemic amyloidosis (AL) [1, 2]. The Mayo Clinic staging system is the current gold standard for assessing the severity of AL amyloidosis, based on cardiac biomarkers such as NT-proBNP, cardiac troponins [3], and blood pressure [4]. However more and more of these patients are aged or have previous history of cardiac diseases, which can alter the predictive value of such biomarkers [5].

Besides cardiac biomarkers-based staging system, cardiac imaging can be particularly relevant for refining the stratification of these patients. As examples, the prognostic value of echography-derived longitudinal global strain (LGS) [6] as well as indexed stroke volume were validated in amyloidosis [7]. Cardiac magnetic resonance imaging (CMR) is the gold standard of cardiac imaging and provides more precise information on cardiac structure, function, and myocardial tissue composition than echographic examination [8]. Late gadolinium enhancement (LGE) in the subendocardial layer, along with abnormal gadolinium kinetics and simultaneous nulling of myocardium and blood, is often observed in cardiac amyloidosis [9]. Native T1 is a quantitative measure of myocardial T1 relaxation time, a non-invasive imaging technique that has garnered significant interest for early risk stratification. It represents a composite myocardial signal from both the interstitium and myocytes. The two most important biological determinants of increase in native T1 are edoema and the increase of interstitial space, the latter being due either to fibrosis or amyloid deposit [10,11]. Contrast-enhanced T1 mapping is used for mostly calculating the myocardial extracellular volume (ECV) fraction in combination with native T1 mapping. Myocardial ECV can quantify the cardiac amyloid burden because the interstitial compartment increases in cardiac amyloidosis (due to the extracellular nature of amyloid deposits) [12]. Indeed, an increase above a 40% threshold is strongly associated with cardiac involvement in amyloidosis, and changes over time serve as the earliest marker to track amyloid progression or regression [11]. Native T2, sensitive to edoema, is often present in AL cardiac amyloidosis and has been shown to correlate with prognosis [12]. Although several studies have

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highlighted the prognostic value of CMR-derived ECV and LGE, these studies were monocentric and did not compare these metrics with traditional prognosticators of AL amyloidosis, such as the Mayo Clinic staging system. Clerc et a have recently highlighted the prognostic value of GLS and ECV on top of Mayo Clinic staging in a small cohort of 80 patients [13].

Our objectives were to study the prognostic value of CMR variables, particularly ECV, in patients with systemic AL amyloidosis and cardiac involvement, to compare it with established biological and echocardiographic prognostic markers and to assess the prognostic value of ECV on top of Mayo clinic staging.

Methods

Patients and AL amyloidosis assessment

Patients with systemic AL amyloidosis and cardiac involvement were included from three hospitals between 2016 and 2023. All patients underwent clinical examination, blood tests for high-sensitivity cardiac troponin T, N-terminal pro B-type natriuretic peptide (NT-proBNP), and free light chains, a 12-lead electrocardiogram, and a comprehensive echocardiographic examination following the American Society of Echocardiography guidelines [14]. Echocardiography was performed using the Vivid 9 (General Electric, Horten, Norway), assessing left ventricular (LV) dimensions, LV mass, and mass index using the Cube formula, as well as left ventricular ejection fraction (LVEF) by the biplane Simpson's method. LV diastolic function was estimated by measuring E/A, deceleration time, E/e', and left atrium volume. Global longitudinal strain (GLS) was analysed using General Electric AFI software. Ninety percent of patients underwent echocardiography within the same week as the cardiac CMR. For the remaining 10% of patients, the maximum interval between these two exams was 2 weeks.

Cardiac troponin T and NT-proBNP levels were measured using commercial assays (Roche Diagnostics). Serum-free light chains were determined using the Freelite assay (Binding Site, Birmingham, Meylan, France).

AL amyloidosis was diagnosed by the presence of monoclonal gammopathy or abnormal free light chain values in blood or urine, along with cardiac or non-cardiac biopsy evidence of amyloid deposition (apple-green birefringence under cross-polarized light at Congo red staining) and anti-light-chain antibodies. All patients were included in our study within two months of their initial diagnosis of AL amyloidosis. Cardiac involvement was diagnosed using echocardiography (ventricular pseudo-hypertrophy, decreased global longitudinal strain with apical sparing), elevated cardiac biomarkers, and typical abnormalities on cardiac magnetic resonance imaging [15, 16]. The Mayo 2004 classification with the European 2015 modification [3, 4] was used to stage each patient using NT-proBNP (cut-off 332 ng/L) and cardiac hypersensitive troponin T (Hs TnT) (cut-off 50 ng/L). Stage I was defined by all biomarkers at normal levels, stage II by one biomarker above normal levels, stage IIIa by NTproBNP between 332 and 8499 ng/L and stage IIIb was defined by NT-proBNP > 8500 ng/L and/or systolic blood pressure < 100 mmHg according to Dispenzieri and Wechalekar [3, 4].

Exclusion criteria included age < 18 years, pregnancy, breastfeeding, Randall's disease, and diagnosis of other forms of amyloidosis.

CMR

A 1.5-T clinical scanner (Magnetom Aera or Magnetom Altea, Siemens Healthcare, Germany) was used in all three centres. All CMR images were analysed using syngo.*via* software (Siemens Healthineers, France). Within a conventional clinical scan [localizers and cine imaging with a steady-state free precession (SSFP) sequence], LGE imaging was acquired using both magnitude inversion recovery and phase-sensitive inversion recovery (PSIR) sequence reconstructions with SSFP read-outs. T1 measurement was performed using the modified look-locker inversion recovery sequence. For native T1 mapping, basal and midventricular short-axis and 4-chamber long-axis sequences were acquired after regional shimming. After a bolus of gadoterate meglumine (0.1 mmol/kg, gadolinium-DOTA, Dotarem, Guerbet S.A., France) and LGE imaging, post-contrast T1 mapping was performed using the same sequence and slice positions. T1 mapping was repeated 15 min post-contrast using the same slice locations with the modified look-locker inversion recovery sequence, to produce automated inline ECV mapping reconstruction. For T2 mapping, a 4-chamber long-axis matching the T1 map was acquired.

All analyses were performed offline. LGE was graded as none, subendocardial, or transmural. T1 and T2 measurements were performed by drawing a region of interest in the basal to mid-septum of the 4-chamber map. For ECV measurement, a single region of interest was drawn in each of the four required areas: myocardial T1 estimates (basal to mid-septum in the 4-chamber map) and blood T1 estimates (LV cavity blood pool in the 4-chamber map, avoiding the papillary muscles) before and after contrast administration. Haematocrit was taken immediately before each CMR study. ECV was calculated as: myocardial ECV = (1 – haematocrit) x (ΔR1 myocardium/ΔR1 blood), where R1 = 1/T1 [17].

Outcome

The primary endpoint was all-cause mortality. Secondary outcomes included the first HF-related hospitalization and the composite mortality or HF hospitalization. Hematological relapse was defined by an increase in the free light chains ratio and/or an increase in organ amyloid burden leading to a new line of chemotherapy. The amyloid burden was defined by an increase in NT-proBNP > 30%, increase in cardiac troponins, decrease in longitudinal strain, and increase in left ventricular pseudo-hypertrophy; renal amyloid burden was defined by an increase in proteinuria > 30% and/or a decrease in creatinine clearance.

Events were collected through an exhaustive review of medical records as well as phone calls to referring doctors and patients. The follow-up was conducted by physicians

blinded to the cardiac MRI results. In cases of hospitalization or death, careful review of medical records was undertaken to specify the causes.

Statistical analysis

Continuous data are expressed as medians and interquartile ranges (IQR), while categorical data are expressed as numbers and percentages. The unpaired t-test was used to assess differences in key continuous variables between subjects with and without events during the study. The Chi-square test assessed differences in categorical data between these subgroups. Receiver operating characteristic (ROC) curve analysis was used to establish cut-offs for relevant variables and their prognostic value, and to calculate their area under the curve (AUC).

Relationships between continuous variables were assessed with the Pearson correlation coefficient.

Survival was evaluated using Cox proportional hazards regression analysis, providing estimated hazard ratios (HR) and Kaplan–Meier curves. Variables were first explored using univariate Cox regression analysis. For multivariate regression, a forward conditional model was used with stepwise entry and removal criteria set at 0.05 and 0.10, respectively. Maximum iterations were set at 20. Given the relatively small number of clinical events, we limited the number of variables in the multivariate Cox models in accordance with the results of the univariate Cox analysis and the clinical relevance of the variables. These variables included systolic blood pressure, global longitudinal strain, indexed cardiac output, NT-proBNP, cardiac troponin, native T1, native T2, LGE, ECV, and the Mayo clinic score. Cut-off levels for troponin, NT-proBNP, and differential plasma free light chains were those involved in the 2004 Mayo clinic staging with the 2015 European modification, as described above [3]. The ECV cut-off was 45% [18–21]. For other variables, the cut-off threshold was defined using ROC analysis and Youden's index. Co-linearity of variables was tested in each model. In cases of co-linearity, separate models were used.

In order to specify further the added prognostic value of ECV on top of Mayo staging, net reclassification improvement (NRI) and likelihood ratio test (LRT) were assessed.

Inter- and intra-observer variability for CMR variables (native T1, native T2, LGE, and extracellular volume) was analysed in 40 randomly selected patients, using the intraclass correlation coefficient to assess consistency both within the same observer and between different observers. The results are presented in Supplementary Table 1. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Informed and written consent was obtained from all patients.

Results

Patients

We included 176 patients with a confirmed diagnosis of systemic AL amyloidosis and evidence of cardiac involvement. In addition to cardiac involvement, 104 patients also had renal involvement, and 54 had neurological involvement. The median age was 68 years (IQR 58–75), with 53% of the patients being male. Bortezomib was administered to 85% of the patients, and daratumumab was given to 22%. According to the 2004 Mayo staging system, 8 patients (5%) were in stage 1, 47 (27%) in stage 2, 86 (49%) in stage 3A, and 35 (20%) in stage 3B.

CMR was performed just before the initiation of chemotherapy in 150 patients (85%). In the remaining patients, CMR was conducted before the second injection of chemotherapy.

Outcome

The median follow-up duration was 22 months (IQR 8–48). The primary outcome occurred in 45 patients. Fifty-five patients were admitted for unplanned HF-related hospitalizations. Among the 45 deaths, 42% were directly attributable to cardiovascular causes (12 HF, 5 sudden deaths, 2 strokes). Other causes of death included 10 pulmonary infections, of which 8 were due to Sars-CoV-2, 6 renal failures, 5 from other infections, and 4 of unknown causes.

Table 1 shows the clinical characteristics of patients according to outcomes. Most variables were significantly different according to the occurrence or not of adverse events.

Data regarding haematologic relapse were available for a subset 90 patients. Haematologic remission was achieved in 78 of these patients, while 22 required retreatment with a new chemotherapy regimen during a median follow-up of 22 months.

Prognostic value of variables

Supplementary Table 2 shows the prognostic value of our variables for all-cause death using AUC and metrics such sensitivity and specificity are given for cut-off. Cut-offs for continuous variables were derived from both the literature and our ROC curves (Supplementary Figure 1). For blood biomarkers, we used cut-offs og the 2004 Mayo staging with the European 2015 modification: NT-proBNP 332 pg/mLor 8500 ng/L for the stage IIIB, and troponin T 50 ng/L. For CMR-derived variables, we used cut-offs that demonstrated good agreement between the literature and our own ROC curves: ECV 0.45, native T1 1120 msec, native T2 55 msec. For LGS, the cut-off of −15% was obtained from our ROC curve.

Table 2 and Supplementary Table 3 show results of the univariate Cox analysis for mortality as well as HF-related hospitalizations. NTproBNP and troponin values, echographic-derived cardiac output and LGS, and ECV were significantly associated with adverse events whether as continuous and categorical variables. Among CMR variables, only ECV was significantly associated with both mortality and HF-hospitalizations. In multivariate Cox analyses involving most continuous variables (Supplementary Table 3), only ECV was significantly associated with both death and HF hospitalization.

Table 1. Characteristics of patients according to the occurrence or not of death.

	All patients $n=176$	Death $N=45$	No death $n=131$	p
Clinical parameters				
Age (years)	68 (58–75)	70 (61–76)	66 (57–73)	0.04
NYHA class 3 and 4	86 (49%)	27 (60%)	59 (45%)	0.05
Systolic BP (mmHg)	120 (108–131)	113 (105–125)	122 (110–136)	0.009
Heart rate	83 (72–95)	83 (75–95)	82 (71–95)	0.94
NT-proBNP (ng/L)	2169 (853–4744)	3400 (1980–7742)	1228 (559–3292)	0.001
hs Troponin T (ng/L)	51 (28–96)	65 (43–132)	44 (27–71)	0.003
eGFR (mL/min/1.73m^2)	54 (33–74)	52 (35–73)	55 (33–74)	0.86
DFLC (mg/L)	190 (69–544)	206 (61–862)	182 (71–478)	0.53
Mayo staging 3A and 3B	121(69%)	35 (78%)	86(66%)	0.04
Furosemide (mg/day)	40 (0–60)	40 (20–120)	20 (0–40)	0.001
Echocardiography				
Indexed LV mass (g/m^2)	130 (103–152)	135 (118–160)	125 (99–148)	0.21
LVEF (%)	60 (51–75)	56 (47–64)	60 (55–65)	0.02
Indexed CO (L/min/m^2)	2.7 (2.2–3.1)	2.4 (2.0–2.7)	2.9 (2.5–3.2)	0.001
LGS (-%)	14.6 (11–18)	12.1 (10–16)	15.8 (13–20)	0.001
E/Ea	14 (10–17)	14 (11–19)	12 (9–14)	0.03
IVS thickness (mm)	13 (12–14)	13 (12–15)	13 (12–14)	0.21
sPAP (mmHg)	35 (30–42)	40 (30–43)	33 (28–39)	0.005
TAPSE (mm)	18 (16–21)	17 (12–21)	19 (17–21)	0.02
CMR				
LVEF (%)	56 (50–64)	54 (42–61)	59 (53–65)	0.001
LVEDVi (mL/m^2)	75 (69–77)	72 (66–73)	74 (70–78)	0.32
Indexed LV mass (g/m^2)	82 (64–102)	93 (78–106)	74 (57–95)	0.001
ECV (%)	42 (36–50)	45 (41–53)	40 (34–46)	0.002
Native T1 (ms)	1127 (1058–1191)	1150 (1092–1185)	1110 (1050–1194)	0.39
Native T2 (ms)	55 (50–60)	56 (50–56)	54 (49–57)	0.52
Subendocardial LGE	17 (23%)	2 (4%)	15 (11%)	0.02
Transmural LGE	20 (11%)	7 (16%)	13 (10%)	0.67
Diffuse LGE	126 (72%)	40 (89%)	86 (67%)	0.02

BP: Blood pressure; CMR: cardiac magnetic resonance; CO: cardiac output; E/Ea: ratio of peak of pulsed Doppler E wave/average peak of annulus TDI e' wave; ECV: extracellular volume; DFLC: differential of free light chains; HR: heart rate; IVS: Interventricular septum thickness; LGE: late gadolinium enhancement; LGS: longitudinal global strain; LV: left ventricle; LVEDV: left ventricular end diastolic volume; LVEF: Left ventricular ejection fraction; RV: right ventricle; PAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular systolic excursion.

ECV and its prognostic value on top of Mayo staging

Correlations between ECV and other prognostic variables are depicted in Supplementary Table 4. There was no correlation with age and renal function and poor correlation with DFLC. In contrast, the Pearson coefficient was ≥0.50 with the two cardiac biomarkers -Troponin and NTproBNP- and with the echography-derived LGS.

Figure 1 displays survival curves according to ECV for A/all-cause mortality, B/HF-related hospitalizations and C/ all-cause mortality or HF hospitalization.

The prognostic value of ECV was also evaluated with multivariate Cox models including 2004 Mayo Clinic staging (Table 3) with ECV as categorial and continuous variable respectively). Besides the Mayo stage IIIB, ECV was significantly associated with the risk of all-cause death whatever ECV as a continuous or as a categorical variable: HR = 1.07 (95%CI 1.03–1.11) and 2.36 (95%CI 1.47–5.60), respectively. ECV was also significantly associated with the risk of HF hospitalization.

Table 2. Prognostic value of clinical, biological, echocardiographic and CMR variables for all-cause death and for HF hospitalizations (univariate Cox analysis and categorical variables).

	All-cause death		HF hospitalization	
	HR (CI 95%)	p	HR (CI 95%)	p
DFLC > 180 mg/L	1.19 (0.73–1.89)	0.51	1.63 (0.95–2.80)	0.07
NTproBNP > 1800 ng/L	3.23 (1.81–5.73)	0.001	3.71 (1.97–6.99)	0.001
NTproBNP > 332 ng/L	1.72 (0.54–5.47)	0.36	1.28 (0.18–9.1)	0.62
hs TnT > 50 ng/L	2.28 (1.39–3.74)	0.001	2.88 (1.37–6.10)	0.005
Syst BP < 100 mmHg	1.37 (0.54–2.36)	0.34	1.03 (0.50–2.13)	0.93
CO < 2.5 ml/min/m2	3.32 (1.89–5.83)	0.001	2.40 (1.33–4.45)	0.004
LGS >–15%	3.45 (1.92–5.89)	0.001	4.19 (1.52–11.3)	0.001
ECV ≥ 0.45	4.04 (2.19–7.50)	0.001	4.32 (2.11–8.84)	0.001
Native T1 > 1120 ms	1.35 (0.97–3.82)	0.06	2.89 (1.37–6.09)	0.005
Native T2 > 55 ms	0.59 (0.21–1.63)	0.31	1.50 (0.66–3.40)	0.33
Diffuse LGE	1.68 (0.93–3.02)	0.08	1.88 (0.89–4.00)	0.07

BP: Blood pressure; CO: cardiac output; ECV: extracelullar volume; DFLC: differential of free light chains; LGE: late gadolinium enhancement; LGS: longitudinal global strain; TnT: T troponin T.

Figure 2 shows survival curves for all-cause death according to ECV ≥ or < 0.45 in subgroups of patients A/Mayo 1 or 2 stage, B/Mayo stage IIIA and C/Mayo stage IIIB. Patients with ECV ≥ 0.45 had the worst prognosis regardless of Mayo stage.

Supplementary Table 5 details the number of patients classified as dead or alive with ECV ≥ 0.45 or < 0.45 in each Mayo staging in order to assess NRI. If we considered Mayo I–II stage as low-risk and Mayo IIIa–IIIb stages as high risk, ECV on top of Mayo staging resulted in an NRI of 0.53. If only I–II (low-risk) and IIIb stages (high risk) were considered, NRI was 0.18. In addition, LRT was 3.87 for all-cause death.

In contrast, ECV was not predictive of haematologic relapse (HR 0.33, 95% CI 0.09–1.28, $p=0.13$), even in the subgroup of patients with long follow-up > 6 months ($p=0.60$).

Discussion

In this study, we have demonstrated that ECV, assessed by CMR, is a powerful prognostic marker in AL cardiac amyloidosis, independent of the Mayo staging system, which has been the gold standard for prognostic staging for two decades. To the best of our knowledge, our study is the first multicenter study with the highest number of patients that analyse and compare the prognostic value of comprehensive CMR with echographic variables and biomarkers and Mayo staging, using a hard primary endpoint (all-cause death) and relevant secondary endpoints (HF hospitalizations; all-cause death and/or HF hospitalizations). Besides Mayo staging and cardiac biomarkers, we show that among CMR and echocardiographic variables, ECV is the strongest predictor of death as well as HF hospitalization and that the increase in ECV worsens the prognosis irrespectively of Mayo clinic staging.

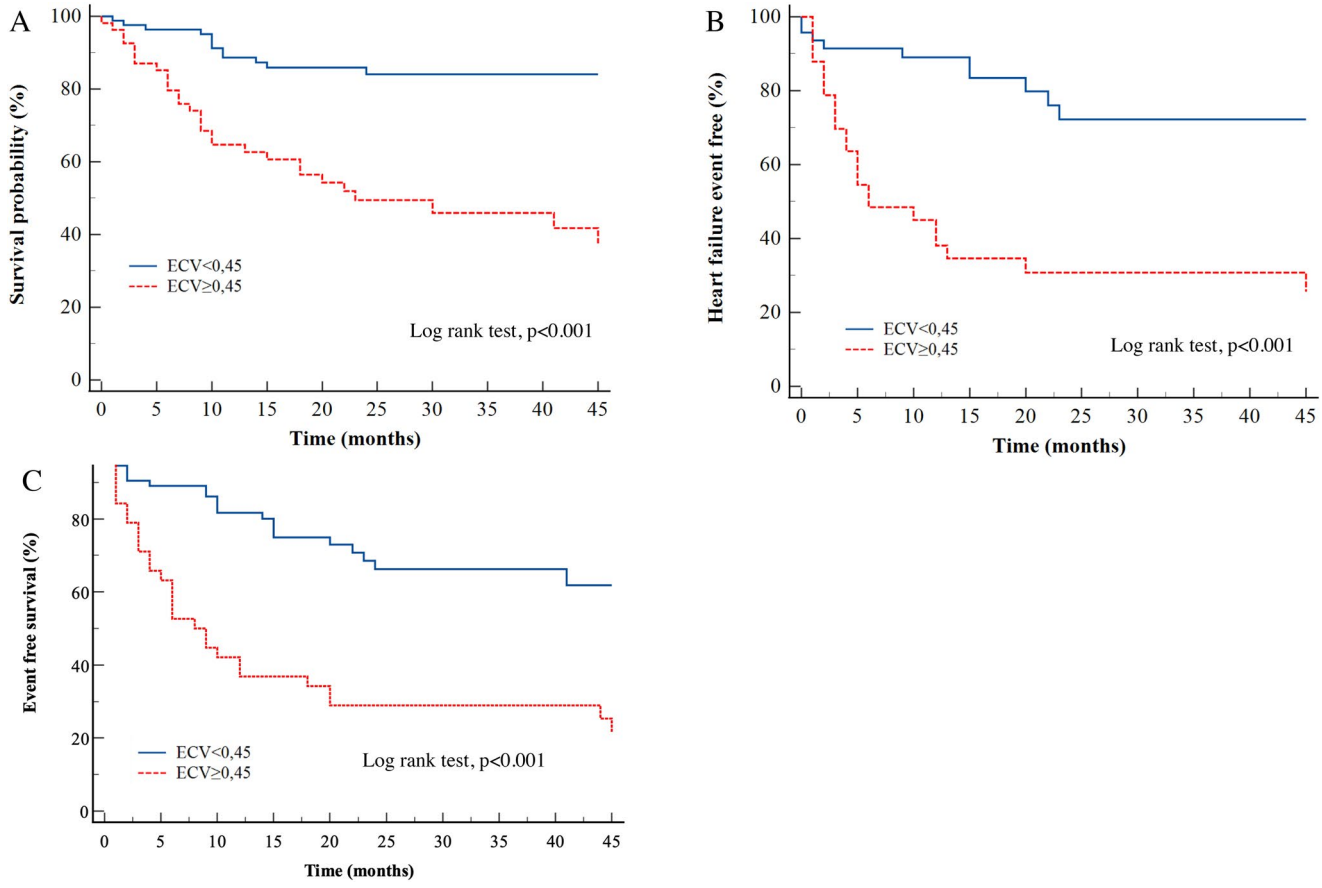

Figure 1. Survival curves according to ECV and 0.45 as cut-off for a/all-cause death, B/HF-related hospitalization, C/all-cause death or HF hospitalization.

Table 3. Multivariate Cox models with ECV and Mayo staging for predicting all-cause death, HF hospitalizations and the composite death or HF hospitalizations. ECV was included in the first model as categorical variable with 0.45 as cut-off and then as continuous variable.

	All-cause death HR (CI 95%)	HF hospitalization HR (CI 95%)	Death or HF hospitalization HR (CI 95%)
ECV ≥ 45%	2.36 (1.47–5.60)	4.10 (2.15–8.8)	2.48 (1.41–4.40)
Mayo I and II	0.90 (0.48–1.71)	0.62 (0.39–1.88)	0.43 (0.19–1.02)
Mayo IIIA	1.25 (0.75–2.51)	0.93 (0.89–1.98)	1.27 (0.66–2.46)
Mayo IIIB	1.80 (1.36–2.89)	1.74 (1.10–2.59)	1.79 (1.24–3.56)
	All-cause death HR (CI 95%)	HF hospitalization HR (CI 95%)	Death or HF hospitalization HR (CI 95%)
ECV (by 1% increase)	1.07 (1.03–1.11)	1.09 (1.07–1.14)	1.08 (1.05–1.12)
Mayo I and II	1.04 (0.49–2.20)	0.64 (0.39–1.88)	0.63 (0.19–1.02)
Mayo IIIA	1.12 (0.77–2.51)	0.94 (0.90–2.04)	1.22 (0.58–2.17)
Mayo IIIB	1.61 (1.03–3.50)	1.22 (1.02–1.98)	1.43 (1.11–2.64)

ECV: extracellular volume DFLC: difference of free light chains; LGE: late gadolinium enhancement; LGS: longitudinal global strain, SBP: systolic blood pressure

The prognosis of AL amyloidosis has significantly improved with new therapies [2, 22], notably the combination of daratumumab with bortezomib, dexamethasone, and cyclophosphamide [23]. The haematologic response is based on free light chain measurements; the goal is to achieve a complete haematologic response defined by a normal Kappa/Lambda ratio. However, organ response is also crucial and challenging. Cardiac involvement is the main prognostic factor for AL amyloidosis patients [4]. The Mayo staging system involves two biomarkers – NT-proBNP and cardiac troponin T – with validated thresholds for each. We chose the 2004 Mayo Clinic staging [4, 24] rather than the 2012 Mayo Clinic staging [25] for two main reasons: first this the most used in clinical practice and second because the European modification was more discriminatory for poorer outcome as highlighted in the study of Khwaja et al. [26]. One point is given when the biomarker level is above its threshold, resulting in three stages (1 to 3 points). In elderly patients, those with renal failure, or those with a history of cardiac disease, cardiac biomarkers (NT-proBNP and troponin T) are often elevated and less specific for cardiac damage due to amyloidosis deposits. The specific cardiac response to treatment is currently based on two parameters: NYHA stage and NT-proBNP level. A favourable cardiac response is defined by a one-point improvement in NYHA and a 30% reduction in NT-proBNP [27]. Structural and functional echocardiographic variables often do not change significantly during follow-up, except for LV global longitudinal strain [6].

ECV is a parameter that assesses the cardiac amyloid load in vivo, allowing for a more accurate assessment of cardiac tissue composition. Additionally, ECV is a non-invasive,

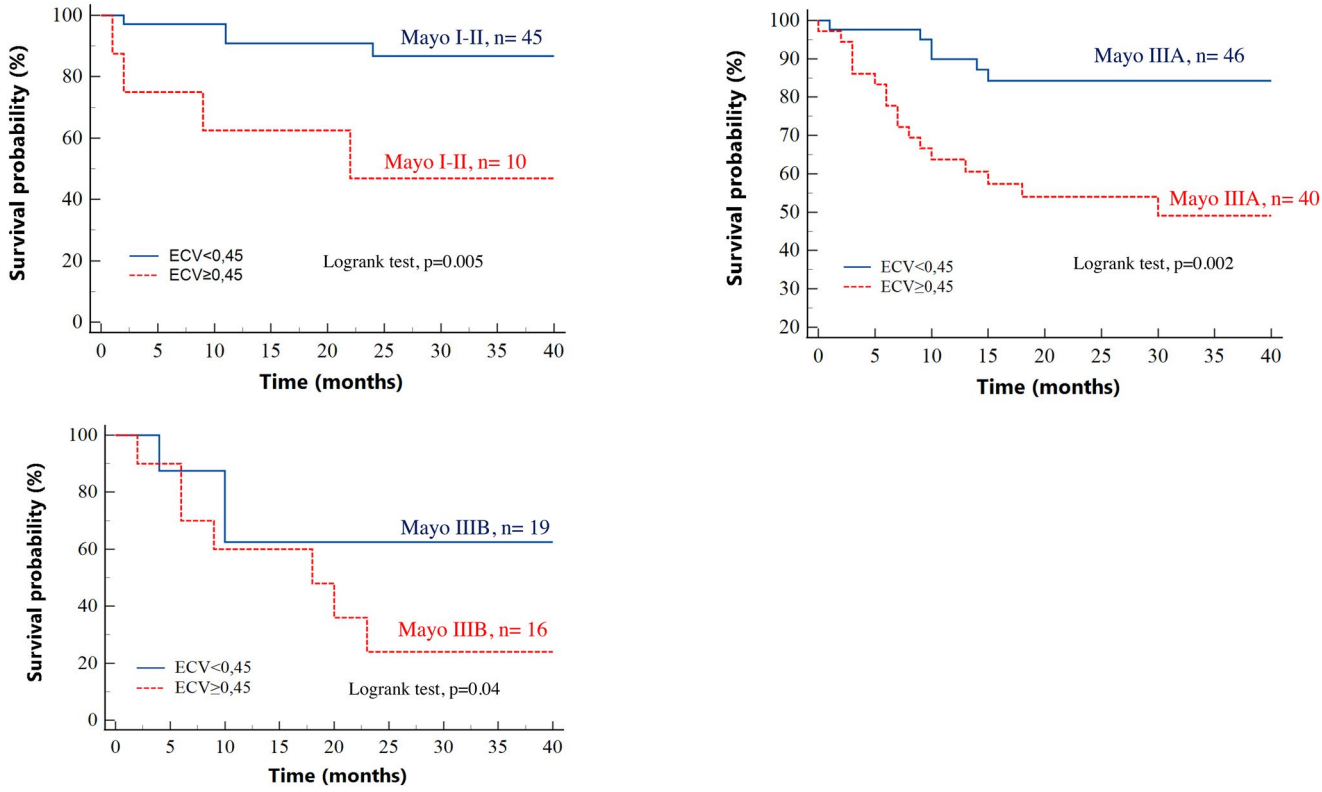

Figure 2. Survival curves for all-cause deaths according to ECV < or ≥ 0.45 and different 2004 Mayo Clinic stages: a/Mayo I and II, B/mato IIIA, C/Mayo IIIB.

quantitative, and reproducible tool. Previous studies in AL amyloidosis have shown that ECV is a superior prognostic marker compared to native T1 and LGE [18–21]. ECV has also been demonstrated to be independently associated with outcomes in multivariate analyses, including known echocardiographic prognosticators such as longitudinal global strain [6] and indexed cardiac output [7]. The significant increase in ECV in CA is attributed to amyloid deposits in the myocardial interstitial space and can be related to disease severity [28]. ECV could also be a relevant tool to monitor the response to chemotherapy in AL amyloidosis [11, 13, 29]. Interestingly, Martinez Naharro et al. [30] recently showed that a 5% decrease in ECV could predict death within 6 months. In their study, ECV was predictive of outcomes even after adjusting for hematological response, NT-proBNP, and LGS. Finally, ECV is less dependent on age and renal function compared to other prognostic variables. In our study, we used a categorical approach with a ECV cut-off of >0.45%, that is consistent with prior studies [20, 21, 31] and clinical practice. This 45% threshold has proven effective in stratifying patients with AL cardiac amyloidosis into high-risk and lower-risk categories, making it a valuable tool for clinical decision-making. The use of this cut-off provides a clear and actionable marker for clinicians, facilitating the identification of patients who may benefit from more intensive monitoring and therapeutic interventions. Furthermore, the 0.45 threshold reflects a biologically meaningful point where myocardial amyloid burden is significant enough to adversely impact cardiac function, justifying its use in prognostic models.

Native T1 and T2 are also CMR variables whose changes can be observed in cardiac amyloidosis. However, their prognostic value is not as strong as ECV. Native T1 is elevated early in cardiac amyloidosis and is associated with a high risk of heart failure and/or death. The increase in native T1 can be related to cardiac fibrosis, edoema, and infiltrative processes (amyloid deposits) and is influenced by both intracellular and extracellular factors. However, the prognostic value of native T1 was modest in our study, as previously described in the meta-analysis by Pan et al. [18]. Another limitation of native T1 is the lack of definitive norms and the variability in values with the magnetic field strength (1.5 Tesla versus 3 Tesla). In contrast, ECV is not dependent on the magnetic field. Native T2 and its increase are related to cardiac edoema, which is elevated in cardiac amyloidosis. Kotecha et al. [13] and Ridouani et al. [32] highlighted the presence of cardiac edoema at the time of the first diagnosis of cardiac amyloidosis [12], possibly due to the cardiac toxicity of light chains. In our study, native T2 had poor prognostic value.

Although access to CMR is still limited in many countries, the systematic use of CMR-derived ECV at the time of diagnosis of AL amyloidosis offers a robust prognostic tool that could be used throughout treatment to assess the cardiac response and potentially guide clinicians in choosing specific therapies [30].

Our study has several limitations. First, although it is a multicenter study, the number of patients remains insufficient to divide the population into derivation and validation groups. Additionally, patients were included and followed over a long period during which therapeutic strategies evolved with potential impact on outcomes. CMR with ECV mapping was performed before the second cycle of

chemotherapy in 15% of the population, which might have attenuated the prognostic impact of ECV. Hematological response was only analysed in a subset of 90 patients where we observed no relationship between hematological relapse and ECV, suggesting that ECV is mainly a marker of the severity of cardiac involvement, the latter being the key determinant of prognosis. Finally, the blood measurement of haematocrit is required at the time of the CMR examination to calculate ECV. In our study, haematocrit was obtained for all patients, but it is often missing in daily practice. However, recent studies suggest that ECV could be estimated without haematocrit [33].

In conclusion, a CMR-derived ECV ≥ 0.45 is a powerful predictor of death in AL cardiac amyloidosis irrespective of Mayo clinic staging. According our results and previous literature, comprehensive CMR including the measurement of ECV, should be systematically encouraged in the early stages of AL amyloidosis diagnosis to refine the assessment of cardiac involvement and to specify the prognosis of the disease.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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