A novel risk score to predict survival in advanced heart failure due to cardiac amyloidosis

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Abstract

Background Cardiac amyloidosis, caused by deposition of immunoglobulin light chains (AL) or transthyretin (ATTR), carries a poor prognosis. Established risk scores for amyloidosis may not predict outcomes in those patients who develop advanced heart failure and who are potential candidates for heart transplantation. Here, we aimed to identify predictive parameters for patients with severe heart failure due to amyloidosis.

Methods Out of > 1000 patients with cardiac amyloidosis (AL or ATTR) admitted to our centre between September 1998 and January 2016, a cohort of 120 patients with a complete cardiac assessment at diagnosis, including right heart catheterization, echocardiography and biomarkers, was analysed retrospectively in this study. Primary endpoint was all-cause mortality. We performed univariate and multivariate Cox regression analysis, generated risk scores to predict outcomes in AL and ATTR amyloidosis and compared those to established risk models for amyloidosis.

Results In the Cox multivariate model, high-sensitivity troponin T (hsTnT; hazard ratio (HR) 1.003; confidence interval (CI) 1.001–1.005; $p = 0.009$) and mean pulmonary artery pressure (HR 1.061; CI 1.024–1.100; $p = 0.001$) were found to significantly and independently predict outcomes for AL amyloidosis, whereas QRS duration (HR 1.021; CI 1.004–1.039; $p = 0.013$), hsTnT (HR 1.021; CI 1.006–1.036; $p = 0.006$) and N-terminal pro-brain natriuretic peptide (HR 1.0003; CI 1.0001–1.0004; $p = 0.002$) were the best predictors for ATTR amyloidosis. A simple risk score ("HeiRisk") including these parameters for AL and ATTR allowed a more precise risk stratification in our patient population compared to established risk models.

Conclusions Risk stratification for cardiac amyloidosis with the newly developed "HeiRisk" score may be superior to other staging systems for patients with advanced heart failure due to amyloid cardiomyopathy.

Introduction

Amyloidosis is a seldom disease characterized by extracellular deposition of pathological insoluble beta-fibrillar proteins in a number of different organs, including the heart [1]. Most common cardiac amyloidosis forms are light-chain (AL) and transthyretin (ATTR) amyloidosis [2]. Whereas AL amyloidosis is caused by plasma cell dyscrasia and monoclonal immunoglobulin light chains, ATTR amyloidosis is caused by wild-type or genetically mutated transthyretin protein [3–5]. Although amyloidosis is a rare disease, it has high clinical relevance due to common cardiac involvement presenting with advanced heart failure (more than 50% of patients) and its high morbidity and often fatal course [2, 6–8]. Despite emerging new therapies for ATTR amyloidosis [9, 10] and

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successful chemotherapy strategies for AL amyloidosis [11], medical treatment for cardiac amyloidosis in an advanced stage remains very limited. We and others have shown that in specialized centres, heart transplantation is a feasible treatment option for patients with symptomatic cardiac involvement, presuming careful patient selection and a multi-disciplinary approach [12–14]. However, while on the heart transplant waiting list, mortality among amyloidosis patients with advanced heart failure is very high [15, 16]. Risk scores established for amyloidosis in general as such as the Mayo score for AL [17] or the recently published score by Gillmore and colleagues for ATTR [18] may not be sufficient to predict outcomes in amyloid cardiomyopathy leading to advanced heart failure. Thus, a precise definition of "high-risk" or "high-urgency" for patients with advanced heart failure due to cardiac amyloidosis is pending and the current way of, e.g. patient selection for heart transplantation may not identify the most suitable patients and therefore should be questioned and re-evaluated. In the present study, we generated a simple risk stratification score ("HeiRisk" score) including clinical parameters and biomarkers to identify patients with cardiac AL or ATTR amyloidosis at exceptional high risk in order to facilitate clinical decisions as such as towards listing for heart transplantation and compared this score to established staging systems for amyloidosis.

Methods

The study conforms with the principles outlined in the *Declaration of Helsinki* [19]. The study protocol was approved by the local ethics committee.

Patient population

From January 1998 to April 2016, more than 2800 patients with amyloidosis presented at the interdisciplinary Amyloidosis Centre of the University of Heidelberg. Of these, 1034 patients had cardiac amyloidosis as per medical documentation: amyloidosis was either proven by biopsy in non-cardiac organs with immunochemistry of the amyloid and patients fulfilled echocardiographic or cardiac magnetic resonance imaging criteria [20, 21] for cardiac involvement; or cardiac amyloidosis was directly proven by endomyocardial biopsy. Organ involvement was determined following current guidelines. Successful heart transplantation for symptomatic cardiac amyloidosis was an exclusion criterion ($n=46$), as prognosis is determined by heart transplantation and not the natural course of the disease. As potential listing for heart transplantation in general requires invasive haemodynamic measurements, we only selected patients who were haemodynamically characterized with right heart catheterization. This resulted in 120 included patients with a complete cardiac assessment including cardiac biomarkers, echocardiography, and right heart catheterization (Fig. 1).

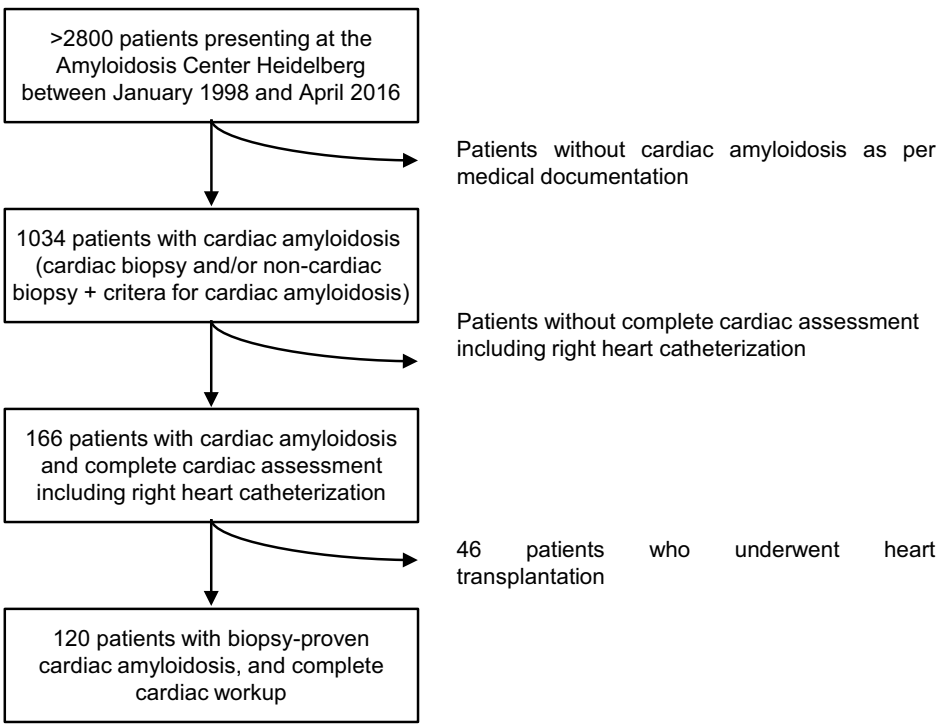

Fig. 1 Study protocol. Flowchart indicating patient selection for the present retrospective study. Only patients with biopsy-proven amyloidosis, when cardiac involvement was verified by cardiac biopsy or imaging criteria and criteria for cardiac amyloidosis were met according to current recommendations, were included. Furthermore, a complete cardiac assessment, including right heart catheterization, was required. Patients who were subsequently heart transplanted were excluded from the data analysis

Patients workup

This included the patient's medical history, careful clinical assessment and determining New York Heart Association (NYHA) class at time of diagnosis. Further, complete laboratory workup including cardiac biomarkers (high-sensitivity troponin T (hsTnT), N-terminal pro-brain natriuretic peptide (NT pro-BNP)), and serum creatinine, was done in all patients. Glomerular filtration rate (GFR) was calculated by using the MDRD (Modification of Diet in Renal Disease) formula. For hsTnT, cut-off values were as follows: reference < 14 pg/ml; 14–50 pg/ml observational zone; > 50 pg/ml elevated. In all patients with AL amyloidosis, immunofixation in serum and urine and free light chains in serum were measured. Echocardiography was performed according to current guidelines in clinical routine. Right heart catheterizations via a femoral venous approach were performed in all included patients in a stable and compensated condition to determine cardiac index, pulmonary artery (PA) pressures and pulmonary vascular resistance (PVR) and mixed-venous oxygen saturation (SvO_2) as described before [22]. Cardiac index was determined by saturation measurement according to the Fick principle. Pulmonary artery pressures, pulmonary capillary wedge (PCW) pressure, and right ventricular (RV) and right atrial (RA) pressures were measured during breath hold in baseline over at least three heart cycles. Mean PA pressure was calculated by Metek software (Metek GmbH, Roetgen, Germany). Pulmonary artery resistance was derived from PA resistance = (mean PA pressure − PCW pressure)/cardiac output.

Patient follow-up and endpoints

For the risk stratification analysis all-cause mortality was the primary endpoint. Follow-up was obtained by review of the patients' hospital chart or telephone interview with the patient or relatives.

Established risk scores

Besides the HeiRisk score that was developed in the present study (see "Results"), risk models previously established by others were applied to our patient cohort. These were all multivariate models for the prediction of all-cause mortality: (1) the Mayo staging system [17] that gives risk points for increased hsTnT (≥ 35 ng/l) and NT pro-BNP (≥ 332 ng/l) resulting in three stages (stage I: no risk point; stage II one risk point; stage III two risk points) and an additional stage IV that was recently introduced for AL when NT pro-BNP ≥ 8500 ng/l [7]; (2) an extended Mayo staging for AL [23] that gives risk points for high cardiac troponin T (≥ 25 ng/l), NT pro-BNP (≥ 1800 ng/l) and another additional risk point for elevated serum free kappa or lambda light chains (≥ 180 mg/l), resulting in four stages I–IV (stage IV three risk points); (3) a recently published staging system by Gillmore and colleagues [18] for ATTR amyloidosis, distributing risk points for elevated NT pro-BNP (> 3000 ng/l) and impaired renal function (GFR < 45 ml/min) resulting in three stages (stage I, no risk point; stage II one risk point; stage III, two risk points); and (4) haemodynamic criteria for high-urgency (HU) listing for heart transplantation [24]. High-urgency criteria are met when cardiac index < 2.2 ml/min/m^2 and SvO_2 < 55%, PCW pressure ≥ 10 mmHg and signs of secondary organ failure occur (sodium < 136 mmol/l, increase of creatinine, increase of transaminases, symptomatic of cerebral perfusion deficit).

Statistical methods

Continuous data are expressed as median and 25% and 75% percentile [Q_1; Q_3] or mean ± standard deviation of the mean. Categorical variables are expressed as absolute numbers and percentages and ordinal variables as mean ± standard deviation of the mean. Survival data were summarized by Kaplan–Meier survival curves and unadjusted survival rates were compared using the log rank test. Univariate Cox regression was performed to analyse the influence of relevant variables on overall all-cause mortality for AL and ATTR, respectively. Statistically significant parameters were tested in a multiple Cox regression model adjusting for NYHA class, number of organs involved by amyloidosis, age and sex. Variables remaining significant in multiple Cox regression where further analysed for optimal cut-off values. Optimal cut-off values for mean PA pressure and hsTnT were determined by using the highest Youden's index of the ROC (receiver operating characteristics) curve using the overall mortality 200 days after initial diagnosis for AL amyloidosis patients. Overall mortality 1000 days after diagnosis was used for ATTR amyloidosis patients, respectively, using hsTnT, QRS duration and NT pro-BNP as the dependent variables. Comparison between different risk stratification models was performed by comparing the odds ratios and significance levels of a binary logistic regression model predicting the 1-year overall mortality with each score as an independent variable. A $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS statistical software package (SPSS Inc., IBM Company, Chicago, IL) and GraphPad Prism (GraphPad Software, La Jolla, CA).

Results

Patient population and outcomes

Of all 120 patients with cardiac amyloidosis analysed in the present study, 74 (62%) were AL and 46 (38%) were ATTR

patients (57% hereditary, 41% wild type, one patient undefined). Baseline characteristics of these patients are given in Table 1. Characterization of the two amyloidosis subtypes documents heart failure in both patient cohorts, AL and ATTR as indicated by NYHA class and haemodynamic parameters (Tables 2 and 3). Although a significant proportion of patients were only mildly symptomatic (NYHA class I or II in 31% of AL and in 46% of ATTR patients), we would like to term this an "advanced heart failure" population because of the very poor prognosis of this patient population [8, 15, 25, 26]. Likewise, in our cohort all-cause mortality was high with 31% and 54% at 1 year and 5 years after diagnosis, respectively. Whereas median survival in ATTR patients (1.015 days [616; 1461]) was superior compared to AL (726 days [105; 2600]; $p = 0.109$), 5-year survival proportion was low for both amyloidosis types, AL (38%) and ATTR (38%; Fig. 2).

Of 23 patients who died in the ATTR group, 13 (57%) died from cardiovascular reasons, whereas the cause of death for 7 (30%) patients was not documented or remained unclear. The remaining three patients died of complications after liver transplantation (two patients) and due to septic shock, respectively. In the AL cohort 55 patients died during follow-up. Of these, 50 (91%) died from cardiovascular reasons. In 4 patients (7%) cause of death was not documented, and one patient died due to progressive systemic AL amyloidosis.

Table 1 Patient characteristics

	AL	ATTR
Number of patients	74	46
Age	57 [53; 65]	69 [35; 86]
Sex		
Male	41 (55%)	34 (74%)
Female	33 (45%)	12 (26%)
Body mass index (kg/m^2)	25.0 (±5.1)	25.5 (±5.1)
Cardiac biopsy	52 (70%)	35 (76%)
LV	38 (73%)	28 (80%)
RV	14 (27%)	7 (20%)
Amyloidosis subtype	Lambda 54 (73%)	Hereditary 26 (57%)
	Kappa 17 (23%)	Senile 19 (41%)
	N/A 3 (4%)	N/A 1 (2%)
Organ involvement		
Heart	74 (100%)	46 (100%)
Kidney	29 (39%)	0
Nervous system	8 (11%)	7 (15%)
Liver	8 (11%)	1 (2%)
Lung	1 (1%)	0
Bone marrow	2 (3%)	0
Soft tissues	17 (23%)	2 (4%)
Gastrointestinal tract	20 (27%)	4 (9%)
NYHA class		
I	11 (15%)	6 (13%)
II	12 (16%)	15 (33%)
III	49 (66%)	23 (50%)
IV	2 (3%)	2 (4%)
1-year mortality	31 (42%)	6 (13%)
5-year mortality	45 (61%)	20 (43%)

Out of 1034 patients with cardiac amyloidosis presenting at the Amyloidosis Centre of the University of Heidelberg between 1998 and 2016, 120 patients with a complete cardiac assessment including cardiac biomarkers, echocardiography, and right heart catheterization were studied. *AL* light chain amyloidosis, *ATTR* transthyretin amyloidosis, *LV* left ventricle, *RV* right ventricle, *NYHA* New York Heart Association. Data are given as median [25–75 percentile], absolute number (%) or mean ± standard deviation of the mean

Risk stratification: univariate analysis

In order to identify risk factors for mortality, careful assessment of clinical parameters, standard echocardiographic parameters, right heart catheterization and lab workup was performed in all patients at time of diagnosis ($n = 120$). Univariate Cox regression was performed for clinical, echocardiographic and right heart catheterization parameters each separately for AL and ATTR (Tables 2, 3). For AL significant predictors for overall mortality were the biomarker hsTnT and parameters mirroring the severity of heart failure, assessed by right heart catheterization (SvO_2, RA pressure, mean PA pressure, PCW pressure) (Table 2). For ATTR only cardiac biomarkers (hsTnT and NT pro-BNP) and QRS duration, but not haemodynamic measures were significant predictors (Table 3).

Multivariate analysis of predictors of mortality

For AL amyloidosis the best predictors in the univariate analysis were the parameters obtained from right heart catheterization (SvO_2, RA pressure, mean PA pressure, and PCW pressure). However, to circumvent a potential bias caused by co-linearity of these parameters, we only selected the parameter with the highest significance among the invasively measured parameters, namely mean PA pressure, and combined it with the likewise highly significant biomarker hsTnT to test for independence in a multiple Cox regression model. For ATTR patients, all three predictors significant in the univariate analysis, NT pro-BNP, hsTnT and QRS duration were tested for independence. To identify parameters for risk prediction by using multivariate analysis we standardized for number of involved organs, NYHA class, age and sex. Multivariate analyses are essayed in Table 4. All parameters that were tested for independent predictive values remained significant in the multiple Cox regression model.

Table 2 Univariate analysis for light chain (AL) amyloidosis

	Total ($n=74$)	Hazard ratio (95% Cl)	p value
Clinical parameters			
Age (years)	57 [53; 65]	1.006 (0.967–0.036)	0.714
Organs affected	1.88 (±0.88)	0.807 (0.598–0.091)	0.163
NYHA class (I–IV)	2.60 (±0.78)	1.436 (0.972–0.120)	0.069
Heart rate (bpm)	81 [68; 92]	1.011 (0.998–0.024)	0.091
QRS duration (ms)	98 [89; 114]	1.008 (0.997–0.020)	0.157
Laboratory values			
hsTnT (pg/ml)	90 [4; 190]	1.003 (1.001–0.005)	**0.005**
NT pro-BNP (ng/l)	4549 [2053; 13,698]	1.000 (1.000–0.000)	0.380
GFR (ml/min)	71 [45; 96]	0.998 (0.990–0.006)	0.594
Echocardiography			
Left ventricular EF (%)	35 [25; 45]	0.993 (0.967–0.019)	0.606
Septum (mm)	16 [14; 20]	1.067 (0.987–0.154)	0.104
Posterior wall (mm)	15 [13; 18]	1.070 (0.992–0.155)	0.078
MAPSE (cm)	0.8 [0.6; 1.0]	0.646 (0.258–0.616)	0.350
TAPSE (cm)	1.2 [0.9; 1.8]	0.845 (0.478–0.493)	0.562
E/E'	16 [10; 20]	1.033 (0.990–0.077)	0.135
Right heart catheter			
Cardiac index (l/min/m^2)	2.4 [2.0; 2.8]	0.733 (0.509–0.053)	0.093
SvO_2 (%)	64 [56; 69]	0.963 (0.941–0.986)	**0.002**
RA pressure (mmHg)	10 [6; 16]	1.073 (1.025–0.122)	**0.002**
Mean PA pressure (mmHg)	25 [18; 32]	1.055 (1.025–0.086)	**< 0.001**
PCW pressure (mmHg)	18 [12; 25]	1.052 (1.019–0.086)	**0.002**
PVR (dyn s cm^{-5})	120 [82; 178]	1.004 (1.000–0.007)	0.053

Univariate Cox regression was performed to analyse the influence of relevant variables on overall all-cause mortality for 74 AL amyloidosis patients. Data are given as median [25–75 percentile] for continuous data and as mean ± standard deviation of the mean for ordinal variables. A p value of < 0.05 was considered statistically significant (bold numbers)

AL light chain amyloidosis, *CI* confidence interval, *NYHA* New York Heart Association, *hsTnT* high-sensitivity troponin T, *NT pro-BNP* N-terminal pro-brain natriuretic peptide, *GFR* glomerular filtration rate, *EF* ejection fraction, *MAPSE* mitral annular plane systolic excursion, *TAPSE* tricuspid annular plane systolic excursion, *SvO_2* mixed-venous oxygen saturation, *RA* right atrium, *PCW* pulmonary capillary wedge, *PVR* pulmonary vascular resistance

Finding cut-offs for risk-associated parameters

We further analysed the aforementioned parameters (mean PA pressure, hsTnT, QRS duration and NT pro-BNP) to generate cut-off values that could distinguish between high-risk and moderate-risk patients. For the two parameters used for risk stratification in AL amyloidosis the strategy was to find cut-offs for mean PA pressure and hsTnT with a high predictive value because patients at exceptional risk had either one or the other parameter elevated (or both). For the AL amyloidosis cohort, we found that the best cut-off value for mean PA pressure measured by right heart catheterization was 22.5 mmHg with a sensitivity of 76.0% and a specificity of 56.5% for death within 200 days. Median survival time was 2144 days [499; 3833] for AL amyloidosis patients with mean PA pressure of < 22.5 mmHg compared to 158 days [47; 1310] for patients with > 22.5 mmHg ($p < 0.001$). Best cut-off value for hsTnT was 58.5 pg/ml, resulting in a sensitivity of 82.6% and a specificity of 53.8% for death within 200 days. AL amyloidosis patients who had values for hsTnT above 58.5 pg/ml had a median survival time of 155 days [59; 1590], whereas patients who did not reach this cut-off survived for 1718 days [392; 3121] ($p = 0.006$).

As opposed to this strategy cut-off values for QRS duration, hsTnT and NT pro-BNP were calculated for the ATTR amyloidosis cohort in order to balance between sensitivity and specificity because all three parameters were elevated in many ATTR patients. We found that the best cut-off value for QRS duration was 104 ms with sensitivity of 68.2% and specificity of 50% for death within 1000 days. Patients with a QRS duration < 104 ms had a median survival time of 1240 days [742; 2203], patients with a QRS duration > 104 ms survived for 805 days [247; 1295], which resulted in 1-year survival of 94% in ATTR

Table 3 Univariate analysis for transthyretin (ATTR) amyloidosis

	Total ($n=46$)	Hazard ratio (95% Cl)	p value
Clinical parameters			
Age (years)	70 [61; 75]	1.002 (0.974–1.031)	0.885
Organs affected	1.27 (±0.48)	0.108 (0.439–1.198)	0.108
NYHA class (I–IV)	2.61 (±0.75)	1.055 (0.597–1.867)	0.853
Heart rate (bpm)	72 [63; 80]	0.972 (0.965–1.038)	0.972
QRS duration (ms)	115 [92; 144]	1.014 (1.001–1.027)	**0.038**
Laboratory values			
hsTnT (pg/ml)	40 [22; 59]	1.020 (1.006–1.034)	**0.004**
NT pro-BNP (ng/l)	2752 [647; 7102]	1.0002 (1.0001–1.0004)	**0.001**
GFR (ml/min)	69 [54; 85]	1.006 (0.994–1.019)	0.584
Echocardiography			
Left ventricular EF (%)	40 [32; 50]	0.996 (0.954–1.039)	0.840
Septum (mm)	16 [15; 20]	0.981 (0.856–1.125)	0.787
Posterior wall (mm)	14 [13; 17]	1.021 (0.898–1.161)	0.752
MAPSE (cm)	0.8 [0.6; 1.1]	0.484 (0.122–1.917)	0.302
TAPSE (cm)	1.3 [1.1; 1.7]	0.741 (0.318–1.727)	0.487
E/*E*′	15 [11; 18]	1.033 (0.999–1.079)	0.152
Right heart catheter			
Cardiac index (l/min/m^2)	2.3 [2.0; 3.2]	1.092 (0.714–1.669)	0.686
SvO_2 (%)	66 [57; 72]	0.956 (0.906–1.009)	0.100
RA pressure (mmHg)	10 [7; 15]	1.030 (0.957–1.108)	0.431
Mean PA pressure (mmHg)	25 [18; 31]	1.016 (0.974–1.060)	0.453
PCW pressure (mmHg)	17 [13; 24]	1.008 (0.956–1.062)	0.775
PVR (dyn s cm^{-5})	143 [91; 214]	1.002 (0.998–1.006)	0.260

Univariate Cox regression was performed to analyse the influence of relevant variables on overall all-cause mortality for 46 ATTR amyloidosis patients. Data are given as median [25–75 percentile] for continuous data and as mean ± standard deviation of the mean for ordinal variables. A p value of <0.05 was considered statistically significant (bold numbers)

ATTR transthyretin amyloidosis, *CI* confidence interval, *NYHA* New York Heart Association, *hsTnT* high-sensitivity troponin T, *NT pro-BNP* N-terminal pro-brain natriuretic peptide, *GFR* glomerular filtration rate, *EF* ejection fraction, *MAPSE* mitral annular plane systolic excursion, *TAPSE* tricuspid annular plane systolic excursion, *SvO_2* mixed-venous oxygen saturation, *RA* right atrium, *PCW* pulmonary capillary wedge, *PVR* pulmonary vascular resistance

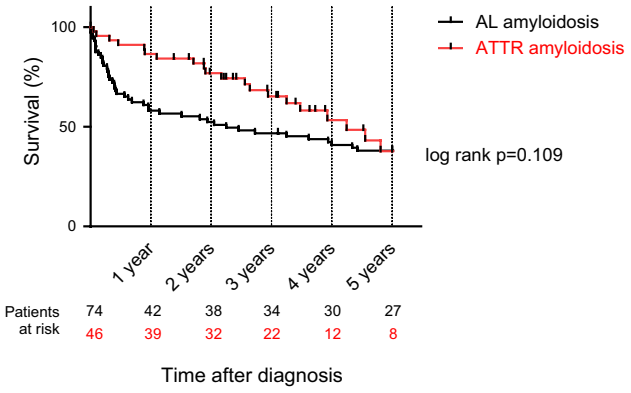

Fig. 2 Survival after diagnosis of cardiac amyloidosis. Kaplan–Meier survival curve for patients included in this study. All patients were diagnosed at the Amyloidosis Centre of the University of Heidelberg between January 1998 and April 2016 with cardiac involvement in light chain (AL; $n=74$; black line) and transthyretin (ATTR; $n=46$; red line) amyloidosis. Vertical bars represent censored events

amyloidosis patients with a QRS duration of < 104 ms versus 78% survival for patients with > 104 ms. Best cut-off value for NT pro-BNP was 6330 ng/l with a sensitivity of 43.5% and a specificity of 89.5% for death within 1000 days. ATTR amyloidosis patients who had values for NT pro-BNP above this cut-off had a 1000-day survival of only 38%, whereas in patients who did not reach this cut-off survival after 1000 days was 74%. We found that the best cut-off value for hsTnT in ATTR patients was > 55 pg/ml with a sensitivity of 100% and a specificity of 81% for death within 1000 days. Patients with hsTnT < 55 pg/ml had a median survival time of 1128 days [692; 1476], patients with hsTnT > 55 pg/ml survived for 685 days [114; 1314].

Table 4 Multivariate proportional variate hazard models for AL and ATTR amyloidosis

	Hazard ratio	95% CI	*p* value
Model for AL amyloidosis			
hsTnT	1.003	1.001–1.005	**0.009**
SvO_2	0.965	0.938–0.992	**0.012**
RA pressure	1.087	1.030–1.148	**0.003**
Mean PA pressure	1.061	1.024–1.100	**0.001**
PCW pressure	1.056	1.016–1.100	**0.006**
Model for ATTR amyloidosis			
QRS duration	1.021	1.004–1.039	**0.013**
hsTnT	1.021	1.006–1.036	**0.006**
NT pro-BNP	1.0003	1.0001–1.0004	**0.002**

Statistically significant parameters in the univariate model were tested in a multiple Cox regression model separately for AL (light chain) and ATTR (transthyretin) amyloidosis adjusting for New York Heart Failure Association (NYHA) class, number of organs involved in cardiac amyloidosis, age and sex. Hazard ratios, confidence intervals (CI) and *p* values are given. A *p* value of < 0.05 was considered statistically significant (bold numbers)

A novel stratification score ("HeiRisk") to predict mortality

We applied these cut-off values to create a simple risk stratification system termed "HeiRisk" (Heidelberg risk stratification model) for patients with AL and ATTR amyloidosis, respectively. Based on the calculated cut-off values, risk groups were defined as follows. AL patients at high risk: mean PA pressure > 22.5 mmHg and hsTnT > 58.5 pg/ml. ATTR patients at high risk when at least two criteria were met: QRS > 104 ms or NT pro-BNP > 6330 ng/l or hsTnT > 55 pg/ml. All other patients were defined as "moderate risk". Due to high mortality in the patient cohort we did not define a "low risk" group. Kaplan–Meier survival curves are given for this risk stratification in Figs. 3 and 4. One-year survival proportion for AL patients at high risk was 17% compared to 79% for patients at moderate risk (log rank test: $p < 0.0001$; Fig. 3). For death before day 200, specificity and sensitivity of the HeiRisk score for AL were 82% and 74%, respectively, whereas positive and negative predictive values were 71% and 84%. For ATTR patients at high risk 1-year survival was 65%, but 5-year survival proportion was 0% versus 55% in the moderate-risk group ($p < 0.0001$; Fig. 4). For death before day 1000 specificity and sensitivity of the HeiRisk score for ATTR were 64% and 91%, respectively, whereas positive and negative predictive values were 78% and 83%.

Comparison of different staging systems

To test whether the HeiRisk models yield additional predictive power we compared the HeiRisk scores to previously published staging systems for AL and ATTR; the Mayo staging system [17], the extended Mayo staging for AL [23], the Gillmore staging for ATTR [18], and haemodynamic criteria for HU listing for heart transplantation [24]. Figures 3 and 4 present Kaplan–Meier survival curves for the staging systems for AL and ATTR, respectively. Statistical comparison of the risk stratification models by comparing the predictive ability using binary logistic regression are given in Table 5 demonstrating that the novel HeiRisk risk scores were superior compared to the established risk scores in our patient cohort.

Discussion

The present study aims to establish a novel risk prediction score termed "HeiRisk" explicitly for patients with cardiac amyloidosis and severe heart failure. This score system is, at least when adapted to patients with advanced cardiac amyloidosis from our centre, superior to previously published predictive scores as, e.g. the Mayo score for AL amyloidosis or a recently published score by Gillmore and colleagues for ATTR amyloidosis. Furthermore, we could demonstrate that the "HeiRisk" score is more accurate in identifying the patients who carry the worst prognosis than the criteria that are demanded by the Eurotransplant Foundation for high-urgency (HU) listing for heart transplantation. We believe that there is an urgent need for a specific and clear definition of the "high-risk" or "high-urgency" patient with advanced heart failure due to cardiac amyloidosis. In particular appropriate heart transplantation HU criteria for these patients yet need to be defined.

Cardiac amyloidosis in a modern age of therapies

For patients with advanced heart failure the last decade brought tremendous developments and improvements in terms of medical therapy [27–32], interventional heart failure therapies and devices [33–39], heart failure-centred in- and outpatient care [40–43] and mechanical circulatory support [44–47]. However, many of these improvements have not been evaluated for patients with cardiac amyloidosis or had not been successfully translated to these patients [48–51]. More specific therapies for AL and ATTR amyloidosis have been established in recent years: for AL amyloidosis these include proteasome inhibitors [52] and immunomodulators [53, 54], as well as high-dose melphalan combined with autologous stem cell transplantation afterwards as a curative approach [55, 56]. However, in patients

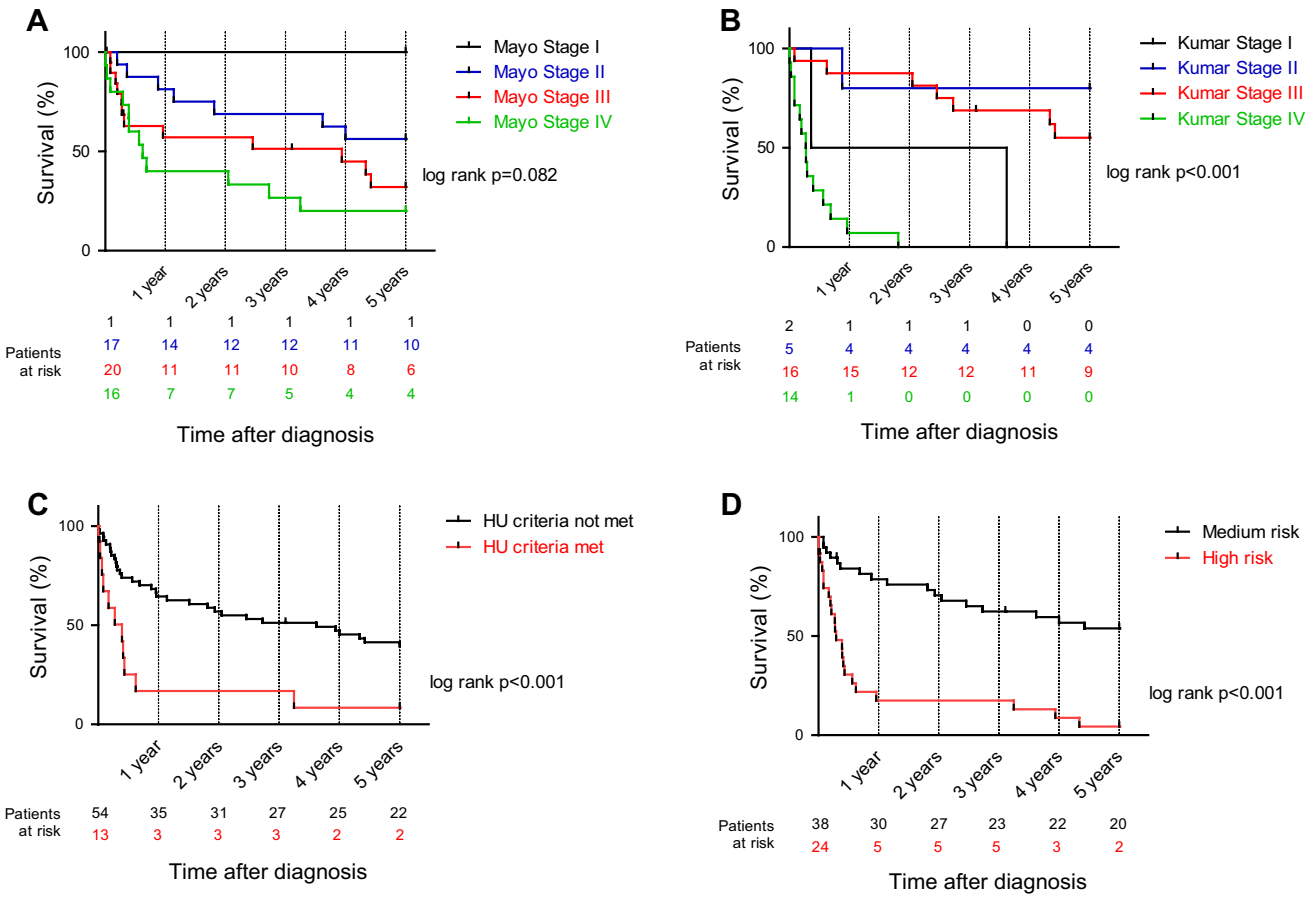

Fig. 3 Classification systems used for risk stratification in light chain (AL) amyloidosis. Four different multivariate classification systems were applied. All-cause mortality is given according to the respective risk classification. **a** The Mayo staging system stratifies patients by giving risk points for elevated cardiac troponin T (≥35 ng/l) and N-terminal pro-brain natriuretic peptide (NT pro-BNP) (≥332 ng/l) and an additional point when NT pro-BNP further increased to≥8500 ng/l, resulting in four stages (stage I: no risk point, black line; stage II: one risk point, blue line; stage III: two risk points, red line, stage IV: three risk points, green line). **b** An extended Mayo staging published by Kumar et al. stratifies patients by giving risk points for high cardiac troponin T (≥25 ng/l), N-terminal pro-brain natriuretic peptide (≥1800 ng/l) and another additional risk point for elevated serum free kappa or lambda light chains (≥180 mg/l), resulting in four stages I–IV (stage IV three risk points, green line). **c** High-urgency (HU) listing for heart transplantation is generally considered when haemodynamic criteria are met and signs of secondary organ failure occur (red line). **d** Newly developed HeiRisk staging for AL, defining "high risk"(red line) when high-sensitivity troponin T (>58.5 pg/ml) and mean pulmonary artery pressure (>22.5 mmHg) are elevated. Vertical bars represent censored events

with severe symptomatic cardiac amyloidosis mortality under this therapeutic regimen is high due to cardiotoxicity of the agents [56, 57]. Likewise, for ATTR amyloidosis novel medical therapies emerge and have recently been published in randomized studies: tafamidis, a stabilizer of ATTR proteins, has been evaluated in patients with cardiac amyloidosis [9, 58], with positive effects on mortality, hospitalizations and quality of life. Other novel agents are the small interfering ribonucleic acid patisiran [10] and the antisense oligonucleotide inotersen [59], inhibitors of the production of transthyretin in the liver and tested for treatment of amyloid polyneuropathy. However, the effects on cardiac involvement are yet to be investigated and all these novel therapies for amyloidosis are only effective in early stages of the disease [9, 60], whereas patients are often already in advanced stages when admitted to centres specialized in the treatment of amyloidosis patients.

Heart transplantation for cardiac amyloidosis

For patients with terminal heart failure due to cardiac amyloidosis, heart transplantation has become an available therapeutic option [12–14, 61]: at Eurotransplant Foundation in such cases an exceptional high-urgency (HU) status for critically ill patients who have very limited life expectancy if they do not receive heart transplantation may be requested [24]. However, general HU criteria are not specifically adjusted to amyloidosis patients. For instance,

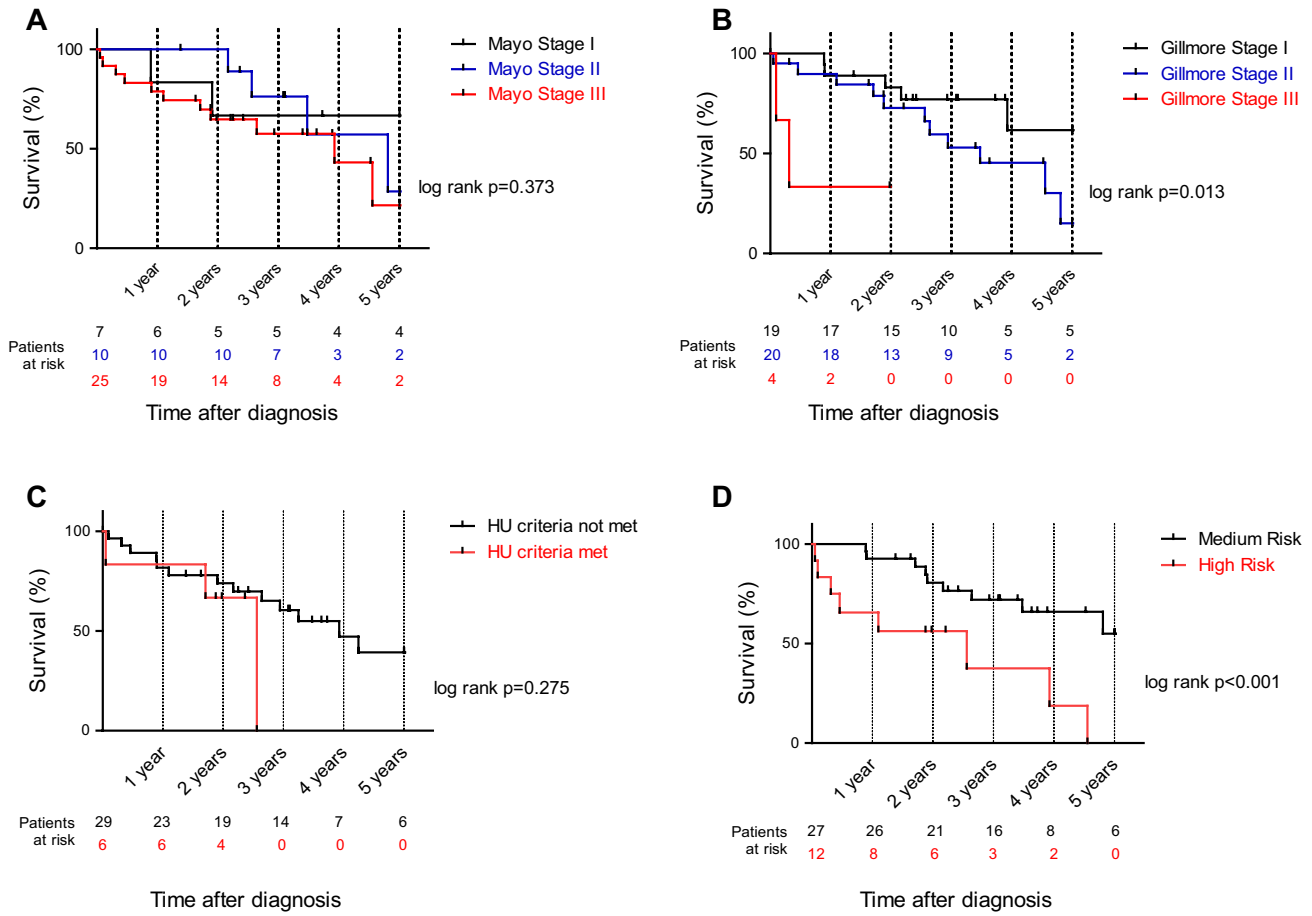

Fig. 4 Classification systems used for risk stratification in transthyretin (ATTR) amyloidosis. Four different multivariate classification systems were applied. All-cause mortality is given according to the respective risk classification. **a** The Mayo staging system stratifies patients by giving risk points for elevated cardiac troponin T (≥35 ng/l) and N-terminal pro-brain natriuretic peptide (NT pro-BNP) (≥332 ng/l) and an additional point when NT pro-BNP further increased to ≥8500 ng/l, resulting in four stages (stage I: no risk point, black line; stage II: one risk point, blue line; stage III: two risk points, red line, stage IV: three risk points, green line). **b** The Gillmore staging system stratifies patients by giving risk points for high NT pro-BNP (≥3000 ng/l) and for low glomerular filtration rate (GFR < 45 ml/min), resulting in three stages (stage I: no risk point, black line; stage II: one risk point, blue line; stage III: two risk points, red line). **c** High-urgency (HU) listing for heart transplantation is generally considered when haemodynamic criteria are met and signs of secondary organ failure occur (red line). **d** Newly developed HeiRisk staging for ATTR, defining "high risk" (red line) when at least two of the following criteria are met: prolonged QRS duration (> 104 ms ng/), elevated NT pro-BNP (> 6330 ng/l) or elevated high-sensitivity troponin T > 55 pg/ml. Vertical bars represent censored events

the in the general HU criteria presupposed catecholamine therapy bears an excessive mortality for patients with cardiac amyloidosis [25]. In addition, it needs to be taken into account that, in times of organ shortage and increasing waiting time on transplantation lists [62], candidates with cardiac amyloidosis are particularly vulnerable because these patients have a particularly high mortality on waiting lists [15]. Therefore, we believe that these patients at exceptional high risk need to be identified and then, a prioritization for these patients needs at least to be discussed, potentially resulting in an exceptional HU allocation. But how can we identify amyloidosis patients in advanced stages of the disease in order to guide therapy, e.g. by applying for an exceptional HU status?

Comparison to other risk scores for amyloidosis

Our data demonstrate that established risk scores for AL amyloidosis (Mayo staging [17], revised Mayo staging [23]) and ATTR amyloidosis (staging system published by Gillmore et al. [18]) are poor predictors of survival in advanced amyloid cardiomyopathy and therefore may not be ideal to identify those patients who need urgent heart transplantation. Whereas the Mayo criteria include troponin T and NT pro-BNP, the "HeiRisk" score combines only one of these cardiac biomarkers, hsTnT, with mean PA pressure, measured invasively. The latter has been shown to be predictive for outcomes in AL amyloidosis by others previously [63]. For ATTR amyloidosis, we found NT pro-BNP, hsTnT and

Table 5 Binary logistic regression of risk scores for AL and ATTR amyloidosis

	Odds ratio	*p* value
Risk scores for AL		
Mayo	7.22	**0.022**
Kumar	13.00	0.144
HU criteria	8.65	**0.008**
HeiRisk for AL	18.13	**< 0.001**
Risk scores for ATTR		
Mayo	4.17	0.215
Gillmore	16.00	0.054
HU criteria	0.88	0.915
HeiRisk for ATTR	7.14	**0.042**

Four different multivariate classification systems were applied for AL (light chain) and ATTR (transthyretin) amyloidosis. Odds ratio and *p* value for all-cause 1-year mortality calculated in a univariate binary logistic regression model are given according to the respective risk classification. For scores that include more than two parameters, the highest possible score value is compared to the lowest possible. For the Mayo staging system the highest possible score value is compared to Mayo Stage I and II combined, due to a low case number in stage I. A *p* value of < 0.05 was considered statistically significant (bold numbers)

QRS duration as predictive parameters, whereas Gillmore et al. incorporated NT pro-BNP and renal function [18]. These similarities demonstrate that (1) cardiac biomarkers, in particular hsTnT [64], are necessary for estimation of prognosis of patients with cardiac amyloidosis, and (2) that combination of biomarkers with distinct clinical parameters, QRS duration and PA pressure, may significantly improve the prognostic value [65, 66], at least in advanced amyloid cardiomyopathy patients. The fact that the combination of clinical parameters with cardiac biomarkers within the risk scores generates synergistic effects leading to an improved prognostic value is also documented by the superiority of the "HeiRisk" score compared to haemodynamic HU criteria, particularly in ATTR patients.

Risk stratification in cardiac amyloidosis: different from heart failure aetiologies

One surprising result of our study is that NYHA class, which is a well-established predictor in heart failure patients [67–69], is not clearly linked to prognosis in our study, neither in AL nor in ATTR amyloidosis. In addition to that, another well-established prognostic factor for heart failure, NT pro-BNP [70, 71], was only predictive in ATTR [72], but not in the AL group. The latter could be explained by the fact that in general, AL and ATTR amyloidosis have to be considered as two completely different entities and morphological and prognostic variances are mainly due to differences in the cardiotoxicity of the underlying misfolded proteins, whereas the free light chains have a direct toxic effect on cardiomyocytes [73]. However, this may not explain everything, and in line with the low predictive value of NYHA class and NT pro-BNP (at least for AL), the cut-off values for haemodynamic parameters determined in our study were significantly lower compared to patients with heart failure due to other aetiologies and close to the normal range. In summary, these observations demonstrate that patients with cardiac AL or ATTR amyloidosis require sophisticated risk stratification and different HU criteria than patients with heart failure due to other aetiologies.

Interestingly, echocardiographic parameters as E/E' were not predictive in our patient cohorts, neither in AL nor in ATTR amyloidosis. This observation is in concurrence with others [74, 75] and implies that echocardiography may be rather useful for the diagnosis of cardiac amyloidosis than for risk stratification in advanced stages of the disease. For three of the four parameters of prognostic value within our scores, we calculated cut-offs only slightly above the accepted normal range: mean PA pressure (normal range 10–20 mmHg; cut-off 22.5 mmHg), hsTnT [normal rage < 50 pg/ml; cut-offs 58.5 pg/ml (AL) and 55 pg/ml (ATTR)] and QRS duration (normal up to 100 ms; cutoff: 104 ms). An explanation for this may lie in the statistical approach that we used: the Youden's index balances between sensitivity and specificity yielding that in this case the cut-offs are rather low, but an optimal relation between specificity and sensitivity can be achieved. However, that the rather low cut-offs for these parameters may limit the value and clinical application of our risk score needs to be taken into account and calls for re-evaluation in a larger patient cohort. Nevertheless, the combination of these parameters, even with cut-offs close to normal range, showed to provide reasonable values for a good separation in low and high-risk patients in the log rank tests.

Limitations

This study was conducted as a single-centre, retrospective study. The patient population was relatively small and patients were only included when complete cardiac workup, including invasive haemodynamic measurements, was present. Patients who were finally heart transplanted and patients, e.g. too sick for right heart catheterization were excluded. Furthermore, the study comprises a relatively small number of patients in the two amyloid subtypes, potentially having negatively influenced the results of the Mayo score, modified Mayo score and Gilmore score in which the population was divided into three or four subgroups, whereas in the HeiRisk score it was divided into only two subgroups. Moreover, the fact that an only slightly over normal elevation of the parameters included in the HeiRisk score predicts a "high-urgency" situation may lower the true

specificity of the score and needs to be further evaluated in a larger population. Another limitation of our study in the view of many transplant surgeons and cardiologist may be that patients with cardiac amyloidosis only represent a small minority of cardiac transplantation candidates. For instance in our centre, which serves as one German centre for amyloidosis patients, among all heart transplanted patients, amyloidosis accounts for less than 10% of the underlying cardiac diseases. However, this can be seen as strength of our study, because it focuses on few patients who may, due to their poor prognosis on the waiting list, represent a cohort that needs exceptional attention and a higher prioritization within our heart transplant programmes. Finally, this study was performed in a dedicated patient cohort, and to produce more substantial data the "HeiRisk" score needs to be validated in an independent patient population.

Conclusions

Despite these limitations, our study demonstrates that currently available staging systems and scores for patients with cardiac amyloidosis are not sufficient, at least for patients with advanced stages of the disease who need to be considered for (high-urgency) heart transplantation. But for these particular patients, prioritization on heart transplantation waiting lists is urgently necessary because heart transplantation is a feasible treatment strategy, and mortality on the waiting list for these patients is unacceptable high and alternative therapies, e.g. mechanical circulatory support as "bridge to transplant", are not generally available. Thus, we observe an urgent need for a specific and clearly defined exceptional HU status for patients with terminal heart failure due to cardiac amyloidosis. We believe the herewith presented HeiRisk score system has to be re-evaluated in a larger patient population and then validated in a large, multicentre study.

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