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The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Outcomes in patients with cardiac amyloidosis undergoing heart transplantation: the eurotransplant experience

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BACKGROUND: When advanced heart failure occurs in cardiac amyloidosis, prognosis is poor. In this setting heart transplantation (HTX) is a treatment option for selected patients. We here present the results of post-transplantation outcomes in cardiac amyloidosis within the Eurotransplant area, investigating possible predictors of survival.

METHODS: Of 115 patients undergoing HTX due to cardiac amyloidosis in the Eurotransplant region between November 1987 and May 2020, detailed assessment prior to transplantation was available in 85 patients. The present study was conducted in a retrospective approach. Primary endpoint was

Abbreviations: AL, Immunoglobulin lightchain; ATTR, Transthyretin; HTX, Heart transplantation; HU, High urgency; ISHLT, The International Society for Heart and Lung Transplantation; NYHA, New York Heart Association; ASCT, Autologous stem cell transplantation; NTproBNP, N-terminal prohormone of brain natriuretic peptide; hsTnT, High-sensitivity troponin T; SvO_2, Mixed venous oxygen saturation; PCWP, Pulmonary capillary wedge pressure; PAP, Pulmonary artery pressure; CI, Cardiac index; CVP, Central venous pressure; PVR, Pulmonary vascular resistance; LVEF, Left ventricular ejection fraction; LVEDD, Left ventricular enddiastolic diameter; LVESD, Left ventricular endsystolic diameter

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1053-2498/$ - see front matter
https://doi.org/10.1016/j.healun.2023.01.001

mortality after HTX. Baseline variables were entered in a Cox proportional hazards model with the primary endpoint as a dependent variable.

RESULTS: Median overall survival following HTX was 6.3 years in the overall collective and the subgroup. Univariate Cox proportional hazards model revealed a significant relationship between overall survival and the transplantation period (2008 to 2020 vs 1987 to 2007; median survival 9.7 years vs 1.8 years, hazard ratio 0.45, $p = 0.01$). Further predictors were albumin concentration (hazard ratio 0.92, $p < 0.001$), and systolic blood pressure (hazard ratio 0.96, $p < 0.001$). The transplant period as well as albumin concentration remained significant independent predictors in the AL sub cohort in a multivariate Cox proportional hazards model.

CONCLUSIONS: HTX is a viable treatment option for patients at an advanced stage of cardiac amyloidosis as overall survival after transplantation has improved in the modern age. Patients at a very advanced stage of the disease, indicated by low serum albumin and blood pressure, show worse outcomes following HTX. Optimal timing and careful patient selection may therefore be particularly important to further improve post-HTX survival in amyloidosis patients.

J Heart Lung Transplant 2023;42:778−785

Amyloidosis is a systemic disease characterized by deposition of insoluble protein fibrils in diverse tissues.[1,2] Cardiac amyloidosis is most frequently caused by immunoglobulin light chains (AL) or transthyretin (ATTR) and commonly results in a severe, progressive restricted cardiomyopathy with often fatal outcome.[3−5] Regarding the underlying systemic disease chemotherapy regimens have shown to be a successful treatment option for AL amyloidosis[6] and new promising therapeutic approaches for ATTR stabilization were introduced in the past years.[7,8] However, due to the biventricular restrictive physiology treatment options for cardiac amyloidosis remain limited when advanced heart failure occurs. Namely, heart failure medication, implantable device therapy, or other "conventional" heart failure therapies are rather without effect.[9−12] For this group of patients heart transplantation (HTX) is an important treatment option and has been performed in specialized centres for many years. Whereas results for HTX in cardiac amyloidosis patients were disappointing in the early years,[13−16] outcome has significantly improved over the last decade. To date multiple specialized centres around the world have demonstrated promising results comparable to patients with non-amyloid cardiomyopathies following HTX.[14,15,17−19] Still, selecting candidates for HTX in this patient group remains challenging and predictors of post-transplantation survival have not been reported so far. This is reflected by the fact that clear guidelines handling HTX in amyloidosis patients are still lacking. Therefore, in the Eurotransplant region, high-urgency (HU) listing for cardiac amyloidosis is judged on a case-by-case basis.[20] The International Society for Heart and Lung Transplantation (ISHLT) recommends a comparable approach for HTX in amyloidosis patients.[21] In contrast the extremely poor prognosis for amyloidosis patients while on HTX waiting lists[16] underlines the urgent need for further data in this context. The present analysis shows post-transplantation outcomes of cardiac amyloidosis patients in a multi-centre cohort from the Eurotransplant region, while also focusing on possible pre-transplantation factors to predict survival.

Methods

The study conforms with the principles outlined in the *Declaration of Helsinki,* as well as the *ISHLT* statement on transplant ethics[22,23] and was conducted in a retrospective approach. Patient data was provided by Eurotransplant as collected in the Eurotransplant registry. The Eurotransplant registry gathers information on all patients listed for HTX in the Eurotransplant region through reports from each transplant centre.

Patient population and data acquisition

In the Eurotransplant registry 115 patients were reported undergoing HTX due to cardiac amyloidosis in the Eurotransplant region which includes Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia, between November 1987 and May 2020. Patients receiving HTX in combination with either liver or kidney transplantation were included in this study. For 85 patients more detailed pre-transplantation and follow-up data was provided by the HTX centres. Data from all transplant centres were provided pseudonymized by Eurotransplant. Cardiac amyloidosis in all patients was diagnosed according to current recommendations.[24]

Baseline characteristics prior to HTX

The baseline characterization of patients prior to HTX included age, sex, body mass index, New York Heart Association (NYHA) class, amyloidosis subtype, blood group as well as patients' history of autologous stem cell transplantation (ASCT). Furthermore, systolic blood pressure, heart rate, peak oxygen uptake in cardiopulmonary exercise testing, results of blood testing including N-terminal prohormone of brain natriuretic peptide (NTproBNP), high-sensitivity troponin T (hsTnT), creatinine, hemoglobin and albumin, echocardiographic parameters as well as invasive hemodynamics prior to transplantation were collected. Invasive hemodynamics included mixed venous oxygen saturation (SvO_2), pulmonary capillary wedge pressure (PCWP), pulmonary artery pressure (PAP), cardiac index (CI) and central venous pressure (CVP) as well as pulmonary vascular resistance (PVR). Echocardiographic parameters included left ventricular ejection fraction (LVEF) and left ventricular enddiastolic (LVEDD) as well as endsystolic diameter (LVESD).

Risk stratification

Risk stratification for each individual patient was calculated from pre HTX data as previously described.[25] In brief, the Mayo staging system for AL amyloidosis was calculated giving risk points for increased hsTnT (≥ 35 ng/l) and NTproBNP (≥ 332 ng/l) resulting in 3 stages (stage I: no risk point; stage II 1 risk point; stage III 2 risk points).[26] The staging system suggested by Grogan and colleagues for ATTR patients was calculated using thresholds for hsTnT (50 ng/l) and NTproBNP (3,000 ng/l) resulting in 3 stages.[27] Hemodynamic criteria for HU listing in the Eurotransplant area for HTX as recently updated[20] were calculated as follows: HU criteria were met when cardiac index ≤ 2.0 ml/min/m^2, SvO_2 < 50%, and PCWP ≥15 mm Hg were present. The Gillmore staging system for ATTR amyloidosis was calculated by giving risk points for high NTproBNP (≥ 3000 ng/l) and for low glomerular filtration rate (glomerular filtration rate < 45 ml/min) resulting in 3 stages.[28] The recently developed HeiRisk staging system defining "high risk" for AL when hsTnT (> 58.5 pg/ml) and mean PAP (> 22.5 mm Hg) are elevated and the HeiRisk staging for ATTR defining "high risk" when at least 2 of the following criteria are met: prolonged QRS duration (> 104 ms), elevated NTproBNP (>6330 ng/l) or elevated hsTnT > 55 pg/ml was calculated.[25] We and others could previously demonstrate that the outcome of patients suffering from cardiac amyloidosis undergoing HTX improved after the year 2007. This is mainly attributed to improved patient selection and new therapeutic strategies for AL patients including so-called "novel therapeutics", like proteasome inhibitors, which were introduced in 2008, as well as improvements in ASCT.[14] Furthermore, new definitions of organ involvement were suggested in 2005 and increasingly implemented in the years following.[29] We therefore added the time periods 1987-2007 and 2008-2020 to our risk stratification.

Patient follow up and endpoint

Primary endpoint was defined by death from any cause following HTX. The date of death was reported to Eurotransplant by HTX centres.

Statistical methods

Continuous data are expressed as median and 25 and 75 percentiles (Q1; Q3). Categorical variables are expressed as absolute numbers and percentages. Survival data were summarized by Kaplan-Meier survival curves and unadjusted survival rates were compared using the log rank test. Pre-implantation variables were included in a univariate Cox proportional hazards model with the primary endpoint as a dependent variable. Significant predictors of post-transplantation outcomes were further analysed in a subcohort depending on amyloidosis type. These variables were separately entered in a multivariate Cox regression model adjusted for age at transplantation, the invasive HU criteria as defined by Eurotransplant as well as the Mayo staging system for AL patients or the Grogan staging system for TTR patients. Due to their broad use and known high reliability the Mayo staging system as well as hemodynamic criteria for HU listing were included for variable adjustment. For each covariate the corresponding set of scaled Schoenfeld residuals with time was correlated to test for independence between residuals and time. Additionally, it performs a global test for the model as a whole. Statistical analyses were conducted using R (R Core Team, 2014) as well as using the package ggplot 2 (Wickham, 2009). We did not perform data imputation because data was not missing at random and data imputation could not properly address this issue. The data that support the findings of this study are available on request from the corresponding author.

Results

Survival following HTX

Median overall survival following HTX for all patients (n = 115) was 2228 days (6.3 years), Figure 1) and also 6.3 years in the subgroup of 85 patients with more detailed information. Fifty-four patients (39%) died within the study period. Median survival was numerically longer in ATTR amyloidosis patients (4447 days, 12.2 years) than in AL amyloidosis patients (1631 days, 4.5 years). However, there was no statistically significant difference in survival between both amyloidosis subtypes (p = 0.79, Figure 2).

Patient population

Of the 85 patients with detailed patient information within the study period from November 1987 to May 2020, 46 (54%) were diagnosed with AL amyloidosis while 29 (34%) were suffering from ATTR amyloidosis. In ten cases amyloidosis subtype was not transmitted to Eurotransplant. From the remaining patients 9 were diagnosed with Val20Ile mutation, 2 with Ser50Arg mutation and in 2 patients no specific mutation was found. The remaining 6 patients showed Ala19Asp, Asp18Glu, Gly47Glu, Ile68-Leu, Ile84The and Thr79Lys mutations. Three patients underwent liver transplantation prior to HTX, 4 patients received combined liver/heart transplantation and 1 patient underwent liver transplantation following HTX. All patients undergoing liver transplantation were suffering from ATTR amyloidosis. One patient receiving combined transplantation survived for 15 days, 1 died after 6 months, 1 after 6.7 years and 1 was lost to follow-up after more than 11 years. Six patients were listed for re-transplantation due to recurrence of cardiac amyloidosis following HTX and 1 patient underwent liver transplantation following recurrence of ATTR amyloidosis. Sixteen AL amyloidosis

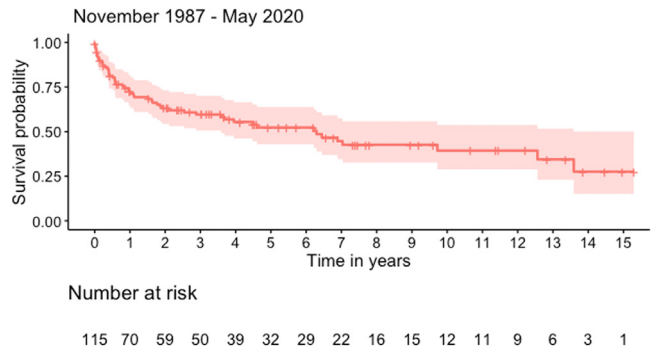

Figure 1 Overall survival curve for patients undergoing heart transplantation in the Eurotransplant region between November 1987 and May 2020. Vertical bars indicate censored events. Red area indicates confidence interval of Kaplan Meyer curve.

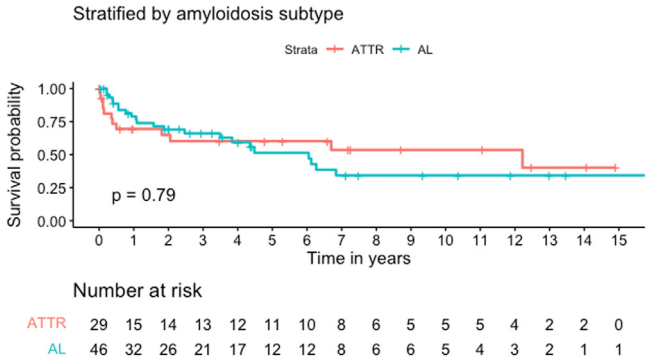

Figure 2 Overall survival curve for patients undergoing heart transplantation in the Eurotransplant region stratified by amyloidosis subtype. P-value is the result of a log-rank test. Vertical bars indicate censored events. AL, light chain amyloidosis; ATTR, transthyretin amyloidosis.

patients received ASCT following HTX and 2 patients prior to HTX. Patient characteristics are given in further detail in Table 1. Most patients (79%) were listed in status "high urgent" ("HU") at the time of transplantation.

Cardiac parameters

The majority of patients (91%) were classified as either NYHA class III or IV at baseline. In accordance to the advanced NYHA class in this cohort invasive hemodynamics reflect advanced heart failure with a median cardiac index of 1.8 l/min/m^2 (1.6; 2.2) and elevated PCWP (22 mm Hg [18; 28]). Seventeen patients (20%) met all 3 invasive HU criteria, cardiac index $\leq$ 2.0 ml/min/m^2, SvO_2 < 50% and PCWP $\geq$ 15 mm Hg, as defined by Eurotransplant in 2020.[20] Systolic heart function as measured by echocardiography was decreased with a median left ventricular ejection fraction of 31% [22; 41]. Cardiac biomarkers hsTnT (75 pg/ml [50; 127]) and NTproBNP (7383 ng/l [4582; 13344]), as well as creatinine (1.1 mg/dl [0.9; 1.5]) were elevated and consequently a majority of patients were classified as "high risk" according to the Mayo staging system (n = 49, 58%). Detailed baseline cardiac parameters are given in Tables 1 and 2.

Univariate cox regression of predictors of post-transplantation survival

In order to identify risk factors for post-transplantation survival clinical parameters, standard echocardiographic parameters, right heart catheterization hemodynamics, cardiac biomarkers as well as information about urgency status and time on waiting list were entered separately in a univariate Cox proportional hazard model. The proportional hazard assumption was supported by a non-significant relationship between each residual and time. Therefore, we can assume the proportional hazards. In a first analysis of the overall cohort (n = 115) year of transplantation, the transplantation period, age at transplantation, time on waiting list, and urgency status at transplantation as well as sex were analysed. The year of transplantation showed to be a significant predictor of survival (Cox proportional hazard ratio 0.94, p = 0.01). Median survival in the time period before 2008 was 624 days (1.8 years) and 3441 days (9.7 years) in the period from 2008 to 2020. This difference reached statistical significance (Cox proportional hazard ratio 0.45 (0.26-0.79), log rank test p = 0.004, Figure 3A). In the subset of 85 patients with more detailed patient information further parameters were investigated. Light chain amyloidosis patients showed a significant difference in overall survival in the 2 different time periods (median survival first vs. second period 1.9 vs 6.8 years, p = 0.0071, Figure 3B) while there was no significant difference in ATTR patients (median survival in the first period 12.2 years, not reached in the second period, p = 0.85, Figure 3C). Low systolic blood pressure at baseline, as well as lower albumin concentration, were significantly associated with a higher mortality (hazard ratio 0.92 (0.88-0.97) and 0.96 (0.93-0.99) respectively, p < 0.001 in both). Neither age, urgency status, sex, time on waiting list nor any other invasive hemodynamic, echocardiographic parameter or cardiac biomarker was significantly related to the outcome in the overall cohort.

Multivariate analysis

In a second step all initially significant variables were entered separately in a multivariate Cox proportional hazards model divided into 2 subgroups depending on amyloidosis type. This multivariate model was adjusted for age at transplantation, the Mayo staging system and the invasively measured HU criteria as defined by Eurotransplant for AL patients. For ATTR patients the model was adjusted to age, HU criteria as well as the Grogan staging system. In the AL group (n = 46) the transplant period from 2008 to 2020 showed a significant decrease in overall mortality when compared to the period from 1987 to 2007 (hazard ratio 0.16 (0.04-0.81), p = 0.03). Further, higher albumin concentration (g/l) prior to transplantation was associated with an increase in post-transplantation survival (hazard ratios 0.89 (0.81-0.99), p = 0.02, Table 3). In the smaller ATTR patient group (n = 29) none of the initially relevant predictors reached statistical significance (Table 3).

Discussion

We here present one of the largest cohorts of patients with heart transplantations due to cardiac amyloidosis.[14,15,18,19] Moreover, our study is the first multinational one demonstrating that HTX for cardiac amyloidosis is a feasible treatment option. Besides, the relatively high number of patients allows for the first time the identification of potential factors in this patient group that can be correlated with patient survival after HTX. Thus, we do not only present HTX as a feasible treatment option but also add important information on how to select candidates for HTX in these particular vulnerable patients. According to the recent ISHLT report a total number of 108.034 patients received HTX between

Table 1 Baseline Characteristics Stratified by Amyloidosis Subtype and Transplant Era

Value (n)[a]	Overall (*n* = 85)	AL *n* = 46	ATTR *n* = 29	Era 1 (1987-2007) *n* = 30	Era 2 (2008-2020) *n* = 55
Age (years)	55 (50; 60)	56 (48; 57)	85 (76; 93)	54 (46; 57)	56 (52; 63)
Male sex	50 (59%)	24 (52%)	18 (62%)	16 (53%)	34 (62%)
BMI	24 (21; 27)	24 (22; 28)	24 (21; 26)	23 (21; 26)	24 (22; 27)
NYHA class					
II	2 (2%)	1 (2%)	0	2 (7%)	0
III	47 (55%)	27 (59%)	15 (52%)	19 (63%)	28 (51%)
IV	31 (37%)	17 (37%)	11 (38%)	6 (20%)	25 (45%)
Missing	5 (6%)	1 (2%)	3 (10%)	3 (10%)	2 (4%)
Blood group					
0	32 (38%)	23 (50%)	6 (21%)	14 (47%)	18 (33%)
A	39 (46%)	21 (46%)	14 (48%)	12 (40%)	27 (49%)
B	12 (14%)	2 (4%)	7 (24%)	3 (10%)	9 (16%)
AB	2 (2%)	0	2 (7%)	1 (3%)	1 (2%)
Urgency at transplantation					
HU	65 (76%)	41 (89%)	19 (66%)	21 (70%)	44 (80%)
Elective waiting list	19 (23%)	5 (11%)	10 (34%)	8 (27%)	11 (20%)
missing	1 (1%)	0	0	1 (3%)	
Right heart catheter hemodynamics					
CI (l/min/m^2) *(79)*	1.8 (1.6; 2.2)	1.8 (1.5; 2.1)	1.8 (1.7; 2.2)	2.0 (1.7; 2.2)	1.8 (1.5; 2.11)
SvO2 (%) *(71)*	53 (49; 61)	51 (48; 55)	57 (53; 62)	59 (54; 66)	52 (49; 58)
CVP (mm Hg) *(72)*	14 (11; 17)	15 (12; 18)	14 (8; 16)	13 (8; 15)	15 (11; 18)
Mean PAP (mm Hg) *(74)*	30 (25; 35	32 (27; 35)	29 (24; 35)	28 (24; 34)	32 (27; 35)
PCWP (mm Hg) *(78)*	22 (18; 28)	23 (19; 27)	22 (16; 25)	19 (15; 26)	23 (20; 27)
PVR (dyn*sec*cm-5) *(74)*	174 (119; 227)	160 (118; 208)	192 (110; 228)	165(127; 215)	176 (115; 229)
HU criteria fulfilled	17 (20%)	15 (38%)	2 (7%)	3 (10%)	14 (25%)
HU criteria not fulfilled	47 (56%)	25 (63%)	19 (65%)	21 (70%)	26 (44%)
Missing	21 (25%)	6 (13%)	8 (28%)	6 (20%)	15 (27%)
Echocardiography					
LVEF (%) *(80)*	31 (22; 41)	32 (21; 40)	30 (22; 41)	35 (25; 45)	30 (20; 40)
LVEDD (mm) *(61)*	41 (39; 46)	40 (39; 45)	42 (35; 48)	45 (40; 51)	41 (38; 45)
LVSED (mm) *(61)*	32 (29; 37)	32 (29; 35)	31 (25; 39)	34 (30; 41)	31 (28; 34)
Laboratory results					
Albumin (g/l) *(73)*	40 (37; 44)	40(37; 43)	41 (39; 45)	40 (37; 44)	41 (38; 43)
Creatinine (mg/dl) *(80)*	1.1 (0;9; 1.5)	1.1 (0.8; 1.4)	1.1 (1.0; 1.7)	1.0 (0.8; 1.5)	1.2 (1.0; 1.5)
NTproBNP (ng/l) *(52)*	7387 (4582; 13344)	7391 (4749; 17502)	7453 (4764; 11712)	6434 (4397; 9530)	7985 (4893; 16909)
hsTnT (pg/ml) *(62)*	75 (50; 127)	90 (53; 173)	76 (50; 105)	70 (49; 110)	85 (50; 147)
Hemoglobin (g/dl) *(80)*	12.2 (11.2; 13.4)	12.1 (11.2; 13.3)	12.7 (11.2; 14;1)	12 (11.2; 14.0)	12.3 (11.2; 13.3)
VO2max (ml/min/kg) *(56)*	11.4 (8.9; 14.0)	11.5 (8.0; 13.2)	10,7 (10; 14)	12.5 (10.9; 15.2)	10.2 (7.9; 12.6)
Systolic blood pressure '(mm Hg) *(79)*	100 (93; 110)	100 (90; 110)	108 (100; 110)	95 (84; 110)	100 (100; 110)
Heart rate (/min) *(79)*	81 (68; 92)	85 (76; 93)	76 (65; 87)	86 (72; 101)	80 (68; 88)

AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; BMI, body mass index; CI, cardiac index; CVP, central venous pressure; HU, high urgency; hsTnT, high sensitivity Troponin T; LVEDD, left ventricular enddiastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular endsystolic diameter; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; NTproBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SvO2, mixed venous oxygen saturation; VO2max, peak oxygen uptake in cardiopulmonary exercise testing.

[a]If no number of cases in the model is listed, data was complete. In ten cases no information about amyloidosis subtype was available. Values are given as median and 25% and 75% quartile or as absolute number and percent.

1992 and 2018.[30] Eurotransplant reports a total of 21.220 HTX within the study period between November 1987 and May 2020. Cardiac amyloidosis patients therefore account for only 0,5% of all organ recipients. However, we would assume a large variance in this percentage between transplant centers all over the world depending on e.g. local transplant regulations, experience with amyloidosis patients and many other factors. But due to the rising awareness of cardiac amyloidosis as well as the improved treatment options in recent years the number of cardiac amyloidosis patients undergoing HTX is likely to grow further in the future. It is noteworthy that at the transplant center at the University of Heidelberg, Germany, which serves as 1 national center for amyloidosis, 58 out of 258 (22%) patients receiving HTX between January 2008 and May 2020 were diagnosed with cardiac amyloidosis.

Outcomes after HTX are comparable to non-amyloid patients

The ISHLT reports a 3-year survival rate of 73% following HTX in Europe for patients between 50-64 years of age

Table 2 Risk Stratification Using Amyloidosis Risk Scores

	AL n = 46	ATTR n = 29
Mayo staging system		
I	0	
II	4 (9%)	
II	31 (67%)	
Missing	11 (24%)	
Grogan staging system		
I		1 (3%)
II		6 (21%)
III		13 (45%)
Missing		9 (31%)
HeiRisk staging for each Amyloidosis subtype		
Low risk	13 (28%)	3 (10%)
High risk	23 (50%)	17 (59%)
Missing	10 (22%)	9 (31%)
Gilmore staging system		
I		3 (10.32%)
II		16 (55.2%)
III		5 (17.24%)
Missing		5 (17.24%)

AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; VO2max, peak oxygen uptake in cardiopulmonary exercise testing.
Values are given as absolute number and percent.

within the period from 2013-2016[31] and of 80% for the age group 35-49 years. Our data now adds to previous studies that demonstrate an overall survival of amyloidosis patients comparable to the survival of non-amyloidosis patients undergoing HTX in recent years[17,18]: our colleagues from Los Angeles, for instance, who investigated a period from 2010 to 2018, report 3-year survival rates for HTX in cardiac amyloidosis between 76% and 81%.[17,19] Likewise, the present study including patients from over 3 decades cannot be interpreted without looking at different time periods: median survival improved drastically from 1.8 years to 9.2 years in the time period after 2007 and 3-year survival improved from 42% to 74% ($p = 0.0043$, Figure 3A). Taking this into account outcomes in the Eurotransplant area

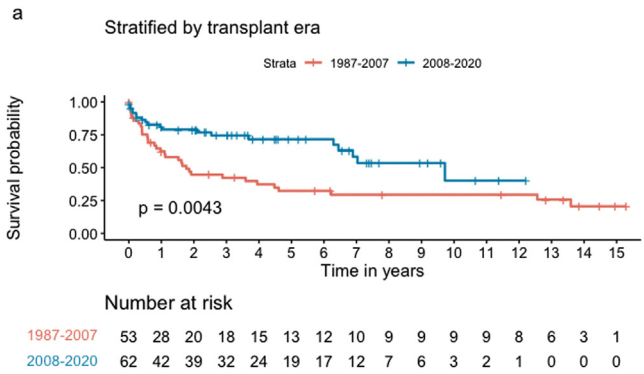

Figure 3A Overall survival curve for patients undergoing heart transplantation in the Eurotransplant region stratified by the time period of transplantation. P-value is the result of a log-rank test. Vertical bars indicate censored events.

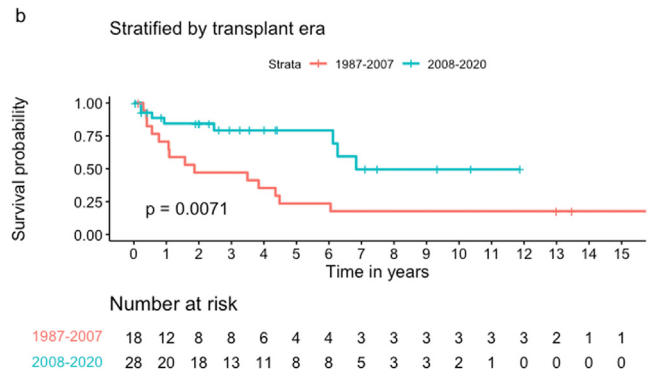

Figure 3B Overall survival curve for immunoglobulin light chain amyloidosis patients undergoing heart transplantation in the Eurotransplant region stratified by the time period of transplantation. P-value is the result of a log-rank test. Vertical bars indicate censored events.

are comparable to other single centre results from recent years and – and this is of particular interest – comparable to outcomes of non-amyloidosis patients undergoing HTX. This finding is particularly impressive when we look at the AL patient sub cohort, which showed a drastic decrease in mortality of 84% in the modern period (Table 3, Figure 3B). In addition, and in accordance with previous studies, there was no significant difference between AL and ATTR patients ($p = 0.79$ Figure 2).[18] There was no significant improvement in survival in ATTR sub cohort (Figure 3C). However, we and others demonstrate that HTX is a good and feasible treatment option for advanced stages of both types of amyloidosis, AL and ATTR, which improved significantly in recent years, if careful patient selection and modern treatment options are applied.

Predictors of post HTX survival using established scores

This importance of patient selection is in great contrast to the lack of data on predictors of outcomes after HTX in amyloidosis patients. The latter may be owed to rather small patient cohorts published so far, making statistical calculations difficult. Therefore, one aim of the present study was to take

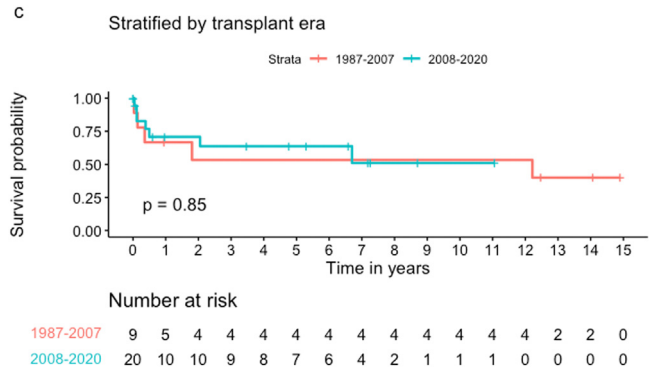

Figure 3C Overall survival curve for transthyretin amyloidosis patients undergoing heart transplantation in the Eurotransplant region stratified by the time period of transplantation. P-value is the result of a log-rank test. Vertical bars indicate censored events.

Table 3 Post-transplant mortality risk, adjusted for age, the High Urgency criteria and the Majo/Grogan staging system

Variable	Hazard rate (95% CI)	*p*-value
ATTR amyloidosis (adjusted for age, HU criteria and the Grogan staging system)		
Year of transplantation	1.13 (0.89-1.46)	0.32
Transplant period (> 2008 vs < 2008)	2.31 (0.28-19.31)	0.77
Albumin (g/l)	0.83 (0.64-1.07)	0.15
Systolic blood pressure (mm Hg)	0.97 (0.91-1.03)	0.29
AL Amyloidosis (adjusted for age, HU criteria and the Mayo staging system)		
Year of transplantation	0.76 (0.56-1.01)	0.06
Transplant period (> 2008 vs < 2008)	0.16 (0.04-0.81)	0.03
Albumin (g/l)	0.89 (0.81-0.99)	0.02
Systolic blood pressure (mm Hg)	0.96 (0.92-1.00)	0.07

AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; HU criteria, invasive high urgency criteria as defined by Eurotransplant. Hazard ratio refers to the exponential regression coefficients. Hazard ratio and p-values are the results of a multiple cox proportional hazard model with overall survival after heart transplantation as a dependent variable including age, the HU criteria as well as the Mayo staging system in AL patients and the Grogan staging system in ATTR patients. Each listed variable was entered separately into the model.

advantage of a relatively large number of patients to elaborate on possible predictors of post HTX outcome. In non-HTX patients with cardiac amyloidosis, several reliable scores for risk estimation can be used with a good predictive value for overall survival.[17–19,25] One central and particularly surprising finding of the present study is that neither of these established risk scores nor invasive HU criteria were useful to predict outcome post HTX in patients with amyloid cardiomyopathy. All established risk models showed not even a trend towards significance and therefore an error due to a potentially too small sample size is rather unlikely. But what are potential predictors and how can patient selection be facilitated? We could at least demonstrate a significant relationship between pre-transplantation blood pressure, albumin concentration and overall survival. It has previously been described that a loss of albumin through albuminuria is related to a worse outcome in AL amyloidosis patients.[32] However, both parameters systolic blood pressure and albumin concentration, reflect the overall patient condition and nutrition status.[33–35] A decrease in both parameters indicates a further progress of the underlying disease. Heart transplantation at this point may just come too late and therefore the right timing for HTX is of particular importance. Unfortunately HTX in cardiac amyloidosis is still decided on a case-by-case basis. We believe that our data should urge us to develop more reliable predictors to facilitate transplant candidate selection and chose the right timing for HTX in this particular vulnerable patient group.

Limitations

This study was conducted in a retrospective approach. This is why data sets from some transplant centres were not entirely complete and in particular details of the amyloidosis subtype are partially missing. Even though we here present the results of a comparably large cohort of cardiac amyloidosis patients undergoing HTX these limitations must be considered. The fact that not all transplant centres provided detailed patient data can be interpreted as a potential selection bias. Furthermore, the regression results of the sub cohorts must be interpreted with caution due to the small sample size. Further studies might potentially reveal additional statistically significant relationships. In addition, not all factors that presumably determine post HTX outcomes could be incorporated in the analysis. Data on chemotherapeutic regimens, for instance, was not included in this study. Also, due to the low number of events, adjustment in multivariate models was limited. Further, information about extracardiac organ involvement and details about patient selection were not available. However, advances in therapeutic approaches like broader use of proteasome inhibitors for AL amyloidosis as well as a more restrictive patient selection may be reflected by the increase in overall survival in the modern era.

Conclusion

When amyloid cardiomyopathy turns into advanced heart failure, treatment options are very limited. Heart transplantation is safe, feasible and can approach survival seen in non-amyloid patients. This needs to be taken into special consideration in view of the great advancements in the treatment of advanced heart failure in recent years – knowing that these new therapeutic options showed little effect on amyloidosis patients. Yet, careful patient selection and contemporary therapy strategies for AL and ATTR patients must be considered as well. However, patients at a very advanced stage of the disease characterized by compromised blood pressure and low albumin levels show worse outcomes following HTX.

Authors' Contribution

Martin J. Kraus: Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Writing, Visualization, Supervision. Jacqueline M. Smits: Supervision, Investigation, Resources, Methodology, Validation. Anna L. Meyer: Investigation, Review. Agita Strelniece: Resources, Investigation. Arne van Kins: Resources, Investigation. Udo Boeken: Investigation, Review. Alexander Reinecke:

Investigation, Review. Zdenek Provaznik: Investigation, Review. Oliver Van Caenegem: Investigation. Arnaud Ancion: Investigation, Review. Michael Berchtold-Herz: Investigation, Review. Johan J.A. Van Cleemput: Investigation, Review. Axel Haverich: Investigation, Review. Guenther Laufer: Investigation, Review. Jan Gummert: Investigation, Review. Matthias Karck: Investigation, Review. Gregor Warnecke: Investigation, Review, Supervision. Philip W. Raake: Investigation, Review. Norbert Frey: Investigation, Review. Michael M. Kreusser: Conceptualization, Methodology, Validation, Writing, Review, Supervision, Project administration.

Disclosure statement

The authors have no conflicts of interest to disclose. This manuscript received no funding.

Acknowledgments

We would like to thank Myriam Wittek and André Hochgesand for assistance with data acquisition and analysis.

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