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Clinical characteristics and outcomes of patients with adult congenital heart disease listed for heart and heart–lung transplantation in the Eurotransplant region

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BACKGROUND: The therapeutic success in patients with congenital heart disease (CHD) leads to a growing number of adults with CHD (adult CHD [ACHD]) who develop end-stage heart failure. We aimed to determine patient characteristics and outcomes of ACHD listed for heart transplantation.
METHODS: Using data from all the patients with ACHD in 20 transplant centers in the Eurotransplant region from 1999 to 2015, we analyzed patient characteristics, waiting list, and post-transplantation outcomes.
RESULTS: A total of 204 patients with ACHD were listed during the study period. The median age was 38 years, and 62.3% of the patients were listed in high urgency (HU), and 37.7% of the patients were in transplantable (T)-listing status. A total of 23.5% of the patients died or were delisted owing to clinical worsening, and 75% of the patients underwent transplantation. Median waiting time for patients with HU-listing status was 4.18 months and with T-listing status 9.07 months. There was no difference in crude mortality or delisting between patients who were HU status listed and T status listed ($p = 0.65$). In multivariable regression analysis, markers for respiratory failure (mechanical ventilation, hazard ratio [HR]: 1.41, 95% CI: 1.11−1.81, $p = 0.006$) and arrhythmias (anti-arrhythmic medication, HR: 1.42, 95% CI: 1.01−2.01, $p = 0.044$) were associated with a higher risk of death or delisting. In the overall cohort, post-transplantation mortality was 26.8% after 1 year and 33.4% after 5 years.
CONCLUSIONS: Listed patients are at high risk of death without differences in the urgency of listing. Respiratory failure requiring invasive ventilation and possibly arrhythmias requiring anti-arrhythmic medication indicate worse outcomes on waiting list.
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Advances in surgical and medical care have led to improved outcomes in patients with congenital heart disease (CHD).[1,2] As a consequence, the majority of patients nowadays survives to adulthood (adults with CHD, that is, adult CHD [ACHD]) with good quality of life.[3] Despite the surgical success, the morbidity and mortality of ACHD is higher than in the general population[4] and is linked to the development of heart failure (HF) in adulthood.[5]

HF occurs in approximately 25% of patients with ACHD, even in those patients in whom the congenital malformation has been corrected successfully in childhood.[6] The time course and presentation are heterogeneous owing to variable congenital malformation and limitation of treatment options.[7,8] ACHD with an anatomic right ventricle as the systemic ventricle (e.g., atrial switch operation in patients with transposition of the great arteries [TGAs]) and those with a functional single ventricle (e.g., Fontan circulation) appear to be at higher risk of developing HF.[9] Young age at initial corrective surgery—often in the first 2 years of life—and lack of specific medical therapies[8] can contribute to a high and early demand for heart transplantation in patients with ACHD.[10] The use of assist devices has been limited in patients with ACHD owing to anatomic or functional complexity.[11] Shortage of donor organs and competing demands from patients without ACHD could be aggravated by current criteria to determine high-urgency (HU) heart transplantation–listing status, which are derived from the overall HF population.[12] Allocation of resources to those in greatest need is currently hindered by lack of robust information on the number and characteristics of ACHD listed for transplantation.

The primary aim of this study was to provide comprehensive data on patients with ACHD listed for heart transplantation using data from the Eurotransplant Registry. A representative data set of patients with ACHD listed for transplantation was created and analyzed for (1) underlying heart condition and repair, (2) clinical characteristics, and (3) factors associated with adverse outcomes in patients with ACHD listed for heart transplantation.

Methods

Study population

The data of all consecutive patients with ACHD listed for solid organ transplantation between January 1, 1999, and December 31, 2015, from 20 of 52 Eurotransplant centers treating patients with ACHD were obtained. The Eurotransplant Registry gathers information on all patients listed for solid organ transplantation in the Eurotransplant region through reports from each transplant center (Figure 1a). Patients aged ≥18 years listed for the first orthotopic heart transplantation and heart transplantation combined with another organ transplantation were included in the dataset for this study (Figure 1b). Detailed information about the Eurotransplant Thoracic Allocation System is provided in the Supplementary Material available online at www.jhltonline.org.

Patients undergoing repeated transplantation as well as patients with arrhythmogenic right ventricular cardiomyopathy, non-compaction cardiomyopathy, or incomplete information regarding the underlying congenital heart defect were excluded from this analysis (Figure 1b).

End-points and definitions

The primary end-point of this study was a composite of 5-year waiting list mortality or delisting owing to worsening of clinical status on the waiting list (e.g., events that occurred after 5 years

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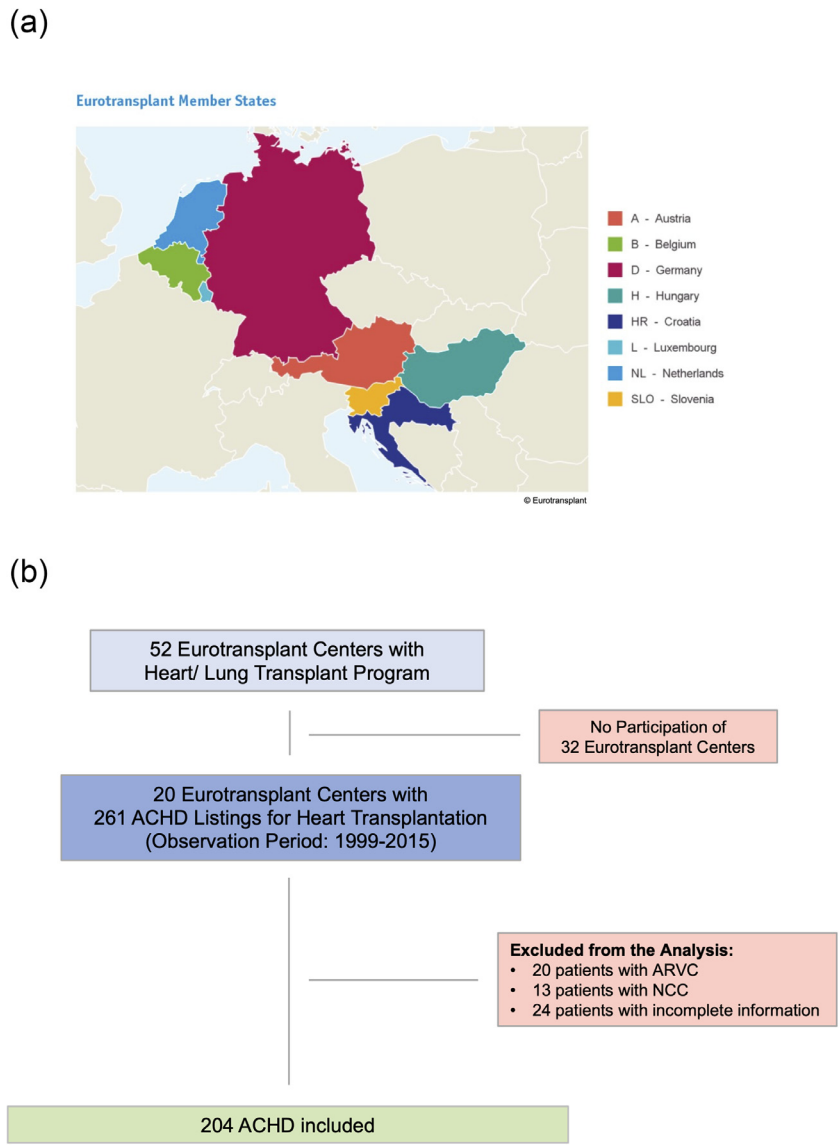

Figure 1 Study design and patient population. (a) Eurotransplant member states and (b) patients analyzed in the study (flow diagram). ACHD, adult CHD; ARVC, arrhythmogenic right ventricular cardiomyopathy; CHD, congenital heart disease; NCC, non-compaction cardiomyopathy.

were censored). The day of first listing for heart transplantation was considered as baseline.

For post-transplantation analysis, the occurrence of all-cause mortality within 18 years was examined with the day of transplantation as the baseline.

Statistical analyses

Summary statistics were reported for continuous variables as medians (25th percentile, 75th percentile) and for binary variables as absolute counts (frequencies). Population with ACHD was separated in time series and cohorts as follows: 1999–2003, 2004–2007, 2008–2011, and 2012–2015. A non-parametric Spearman test was conducted to examine a potential trend over the time intervals. The null hypothesis of no trend in data was tested for every group. p-Values > 0.05 indicated no trend.

Cumulative incidence analyses were estimated, wherein heart transplantation was considered a competing risk of the primary composite end-point death on waiting list or delisting within 5 years and was calculated by the Aalen−Johansen estimator for the 5-year follow-up period. The reverse Kaplan−Meier estimator was used to calculate the median waiting time to transplantation. All candidates were included in this analysis.

To evaluate the predictors of 5-year death/delisting, univariable and multivariable Cox regression models were fitted. For the multivariable Cox regression model, variables with less clinical relevance and missing in >20% of the sample were excluded. The Cox regression models were then weighted by the Fine and Gray estimator, which accounts for the competing risk (transplantation or death/delisting).[13] To assess the success of transplantation, 18-year post-transplantation all-cause mortality was analyzed. Survival probabilities were estimated using the Kaplan−Meier method.

For all regression models, change in continuous variables was modeled as a change per SD to enable the comparability of variables. A 2-sided p-value < 0.05 was considered statistically significant. All statistical methods were implemented in R statistical software, version 3.6.0 (The R Foundation, Vienna, Austria).

Results

Baseline characteristics on the waiting list

A total of 204 patients with ACHD were listed for heart transplantation during the study period (Table 1).

Table 1 Baseline Characteristics of All Patients With ACHD Listed in the Eurotransplant Region Between 1999 and 2015

Baseline characteristics	All ($n = 204$)	Still on waiting list ($n = 3$)	Transplanted ($n = 153$)	Died or worsened ($n = 48$)
Age at listing	38.0 (26.0, 47.0)	45.0 (30.0, 51.7)	37.0 (25.0, 46.0)	39.5 (29.4, 50.0)
Age at listing (categorical): 18–29 years, *n* (%)	67 (32.8)	1 (33.3)	54 (35.3)	12 (25.0)
Age at listing (categorical): 30–39 years, *n* (%)	45 (22.1)	0 (0)	33 (21.6)	12 (25.0)
Age at listing (categorical): 40–49 years, *n* (%)	50 (24.5)	1 (33.3)	38 (24.8)	11 (22.9)
Age at listing (categorical): 50–59 years, *n* (%)	32 (15.7)	1 (33.3)	22 (14.4)	9 (18.8)
Age at listing (categorical): >59 years, *n* (%)	10 (4.9)	0 (0)	6 (3.9)	4 (8.3)
Male, *n* (%)	132 (64.7)	2 (66.7)	104 (68.0)	26 (54.2)
Listing status, *n* (%)				
Urgency status: HU	127 (62.3)	3 (100)	92 (60.1)	32 (66.7)
Urgency status: T	77 (37.7)	0 (0)	61 (39.9)	16 (33.3)
Organs listed: heart	105 (51.5)	2 (66.7)	83 (54.2)	20 (41.7)
Organs listed: heart and lung	76 (37.3)	1 (33.3)	54 (35.3)	21 (43.8)
Organs listed: heart and others	23 (11.3)	0 (0)	16 (10.5)	7 (14.6)
Comorbidities, *n* (%)				
Diabetes mellitus	8 (3.9)	1 (33.3)	4 (2.6)	3 (6.4)
Arterial hypertension	25 (12.4)	0 (0)	19 (12.6)	6 (12.5)
Renal failure (eGFR <60 ml/min/1.73 m^2)	60 (30.5)	0 (0)	41 (27.9)	19 (40.4)
Smoking status	7 (4.1)	0 (0)	6 (4.6)	1 (2.7)
History of coronary artery disease	8 (4.0)	0 (0)	5 (3.3)	3 (6.5)
Difficulties in everyday life	170 (86.7)	1 (33.3)	126 (86.3)	43 (91.5)
Need for anti-arrhytmic medication	109 (54.5)	1 (33.3)	77 (51.7)	31 (64.6)
ICD	50 (24.5)	1 (33.3)	35 (22.9)	14 (29.2)
Of the ICD cohort patients with CRT	20 (10.2)	0 (0)	15 (10.3)	5 (10.6)
Clinical status, *n* (%)				
Previous cardiac surgery	140 (69.3)	3 (100)	108 (71.1)	29 (61.7)
Cyanotic heart disease	134 (66.7)	3 (100)	108 (72.0)	23 (47.9)
Eisenmengerś syndrome	68 (34.0)	1 (33.3)	48 (32.0)	19 (40.4)
Previous palliative surgery	82 (54.3)	2 (66.7)	67 (57.8)	13 (40.6)
Medical conditions, *n* (%)				
VAD	12 (6.3)	0 (0)	8 (5.6)	4 (8.7)
Invasive mechanical ventilation	13 (6.6)	0 (0)	6 (4.1)	7 (15.2)
Non-invasive mechanical ventilation	6 (3.1)	0 (0)	5 (3.4)	1 (2.3)
Inotrope support	51 (25.8)	0 (0)	39 (26.5)	12 (25.0)
Intensive care unit	37 (18.7)	0 (0)	26 (17.7)	11 (22.9)
Intermediate care unit	51 (26.0)	0 (0)	44 (30.1)	7 (14.9)
Hemodynamics				
Pulmonary vascular resistance (WU)	3.8 (1.4, 8.9)	4.8 (1.0, 8.7)	3.0 (1.5, 7.9)	5.2 (1.4, 12.3)
Pulmonary capillary wedge pressure (mm Hg)	21.0 (14.6, 30.0)	16.5 (15.0, 18.0)	19.0 (14.0, 30.0)	23.0 (18.4, 29.7)
Cardiac index (liter/min/m^2)	2.2 (1.7, 2.9)	1.6 (1.5, 2.3)	2.1 (1.7, 2.9)	2.4 (1.9, 3.1)
Peak O_2 oxygen uptake (ml/kg/min)	12.0 (9.7, 13.8)	17.0 (17.0, 17.0)	12.0 (9.9, 14.1)	11.5 (9.0, 12.6)
Laboratory measures				
Hemoglobin (g/dl)	14.1 (12.0, 16.6)	15.2 (14.2, 16.2)	14.1 (12.0, 16.6)	14.1 (11.3, 16.8)
Serum creatinine (mg/dl)	1.1 (0.9, 1.4)	1.2 (1.1, 1.5)	1.1 (0.9, 1.4)	1.1 (0.9, 1.7)
Blood urea nitrogen (mg/dl)	41.5 (26.0, 57.1)	14.6 (12.7, 31.6)	42.0 (27.2, 56.0)	44.0 (25.5, 76.0)
Bilirubin (mg/dl)	1.2 (0.8, 1.9)	0.3 (0.3, 0.4)	1.2 (0.8, 1.9)	1.1 (0.7, 1.9)
Albumin (g/liter)	39.8 (35.7, 44.0)	44.4 (44.4, 44.4)	40.0 (36.7, 44.7)	36.0 (33.7, 40.1)
Prothrombin time (s)	44.7 (25.2, 74.0)	63.0 (31.0, 95.0)	45.8 (24.2, 74.0)	44.0 (32.2, 68.9)

Abbreviations: ACHD, adult CHD; CHD, congenital heart disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HU, high urgency; ICD, implantable cardioverter-defibrillator; O_2, oxygen; T, transplantable; VAD, ventricular assist device; WU, wood unit.

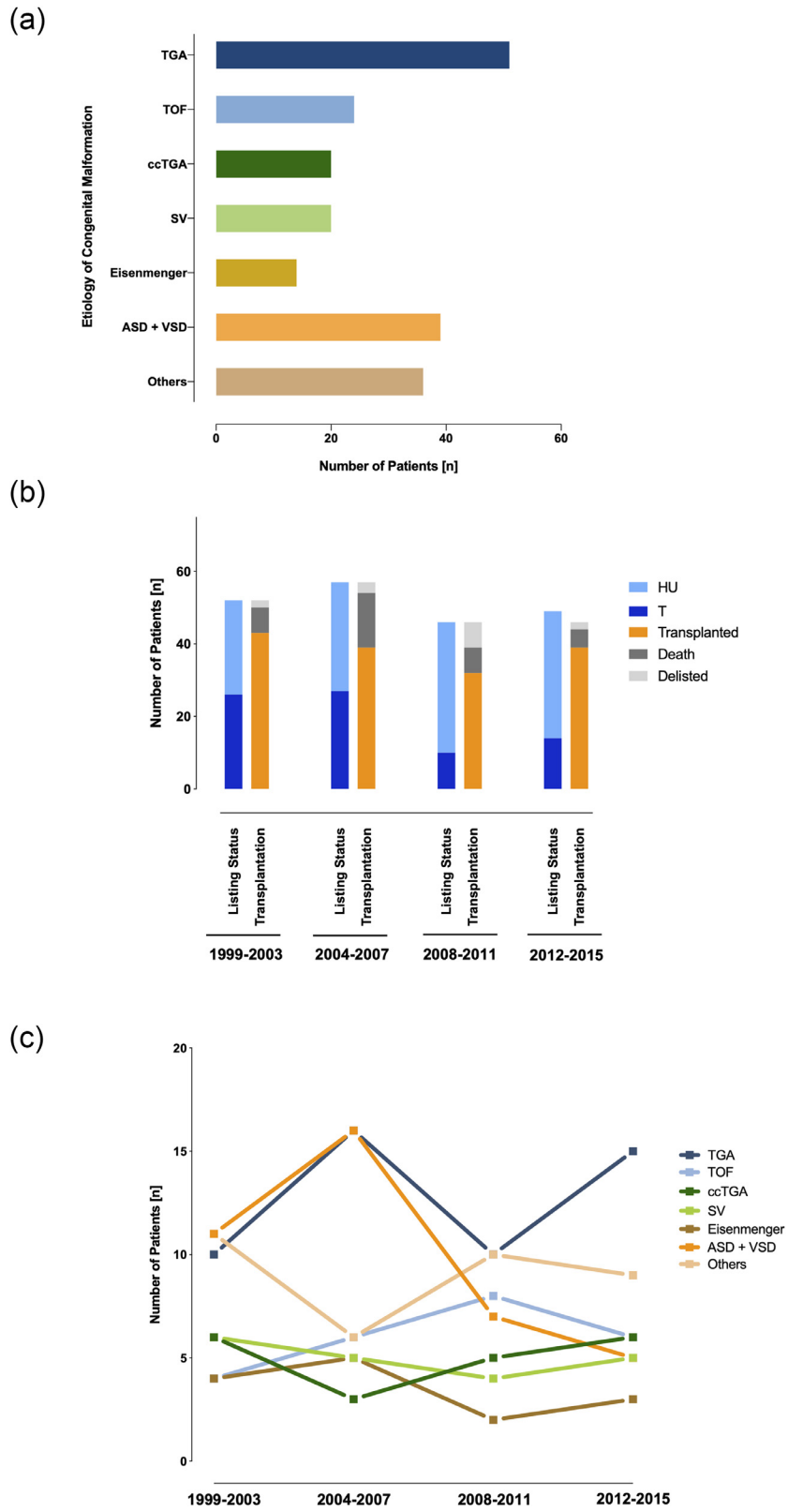

Figure 2 Etiology of the underlying congenital heart defect and trends over the time. (a) Etiology of the underlying congenital heart defect, (b) listing status and outcome over the time, and (c) etiology of the underlying congenital heart defect in trends over the time.

ASD, atrial septal defect; ccTGA, congenitally corrected TGA; HU, high urgency; SV, single ventricle; T, transplantable; TGA, transposition of the great artery; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Approximately 64.7% were male ($n = 132$). Listing occurred at a median age of 38 years. The most common congenital malformation was TGAs ($n = 51$, 25%, all after atrial switch surgery), followed by tetralogy of Fallot (TOF) ($n = 24$, 11.8%) and congenitally corrected TGA ($n = 20$, 9.8%) (Figure 2a). The totality of ventricular and atrial septal defects was found in 19.1% ($n = 39$). Other common causes were Eisenmenger and single ventricle.

A total of 105 patients (51.5%) were listed for isolated heart transplantation. A total of 76 patients (37.3%) were listed for a combined heart and lung transplantation, and 23 patients (11.3%) were listed for heart transplantation combined with another organ (e.g., kidney [Table 1]). A total of 127 patients (62.3%) were listed as HU status, and 77 patients (37.7%) were listed as transplantable (T) status (Figure 2b). The proportion of patients who were HU listed and T listed did not change over time (HU: p-value of trend test = 0.333, T: p-value of trend test = 0.417; Figure 2b).

At the time of listing, 51 patients (26%) required intermediate care, and 37 patients (19%) required intensive care, with 13 (6.6%) requiring mechanical ventilation. Inotropic medication was required in 51 patients (25.8%), and 12 patients (6.2%) received permanent ventricular assist device therapy. In addition, baseline characteristics with classification according to etiology are shown in Supplementary Table S1 online

Temporal trends

Type of listing did not change over time (Figure 2b). Temporal trends in etiology did not significantly differ over time (p-value of trend test for each etiology >0.05, Figure 2c).

Death or delisting owing to HF worsening while on waiting list

Cumulative incidence of the primary end-point of mortality or delisting on the waiting list was 11.3% after 1 year and 23.5% ($n = 48$) after 5 years. There was no significant difference in mortality or delisting for clinical worsening between patients listed in HU or T status ($p = 0.65$) (Figure 3a).

Patients with ACHD listed for isolated heart transplantation had a cumulative incidence of the primary end-point of 11.4% after 1 year and 18.1% after 5 years on the waiting list. Patients with ACHD listed for a combined heart and lung transplantation had a cumulative incidence of the primary end-point of 9.2% after 1 year and 23.7% after 5 years. In addition, patients listed for combined heart transplantation except lung had a mortality or delisting rate of 17.4% after 1 year and 26.1% after 5 years on the waiting list (Figure 3b). Cumulative incidence of the primary end-point of mortality or delisting did not differ between isolated heart transplantation, combined heart and lung transplantation, and/or heart and multiple organs transplantation ($p = 0.61$) (Figure 3b). A more detailed competing risk analysis for patients classified by the statuses is provided in Supplementary Figure S1 online.

Predictors of death or delisting owing to worsening on the waiting list

The predictors associated with death or delisting owing to worsening from the univariable Cox regression models are shown in Table 2. The univariable analysis indicated that the need for invasive mechanical ventilation (hazard ratio [HR]: 1.32, CI: 1.11−1.57, $p = 0.002$), increased blood urea nitrogen levels (HR: 1.39, CI: 1.10−1.76, $p = 0.006$), and decreased albumin levels (HR: 0.58, CI: 0.39−0.87, $p = 0.008$) were associated with a higher risk of death or delisting (Table 2).

In the multivariable Cox regression analysis, the need for invasive mechanical ventilation and anti-arrhythmic medication were the only variables associated with a higher risk of death or delisting owing to clinical worsening (HR: 1.41, CI 1.11−1.81, $p = 0.006$; HR: 1.42, CI: 1.01−2.01, $p = 0.044$) (Table 3).

Transplantation

A total of 153 patients with ACHD were transplanted after a median waiting time of 7.4 (5.5−9.6) months. Waiting time for HU-listing status was 4.2 (median, [3.4−9.4]) months. Waiting time for patients with T-listing status was 9.1 (7.4, 13.1) months.

Of those transplanted, 60.1% ($n = 92$) of patients with ACHD were listed in HU status, and 39.9% ($n = 61$) of patients with ACHD were listed in T status; of those who died or were delisted owing to clinical worsening, 66.7% ($n = 32$) of patients with ACHD were listed in HU status, and 33.3% ($n = 16$) of patients with ACHD were listed in T status.

Patients listed for isolated heart transplantation had the shortest waiting time to transplantation (HU: 3.75 [2.86, 9.37] months; T: 8.71 [6.02, 12.43] months) in comparison with patients listed for combined heart and lung transplantation (HU: 5.62 [2.7, 14.86] months; T: 8.05 [5.46, not applicable] months).

Waiting time for patients with HU-listing status listed for combined heart and lung transplantation was 5.62 (2.7, 14.86) months and 8.71 (6.0, 12.43) months for patients with T-listing status.

Outcome after transplantation

Cumulative incidence of the secondary end-point of mortality after transplantation was 26.8% after 1 year, 33.4% after 5 years, and 37.4% after 10 years. There was no significant difference in mortality between all patients and those listed in HU-listing or T-listing statuses ($p = 0.82$) (Figure 4a).

Kaplan−Meier curves of the secondary end-point of mortality did significantly differ between isolated heart transplantation, combined heart and lung transplantation, and/or heart and multiple organs transplantation ($p = 0.018$) (Figure 4b).

Discussion

To the best of our knowledge, this is a comprehensive report of patients with ACHD listed for heart

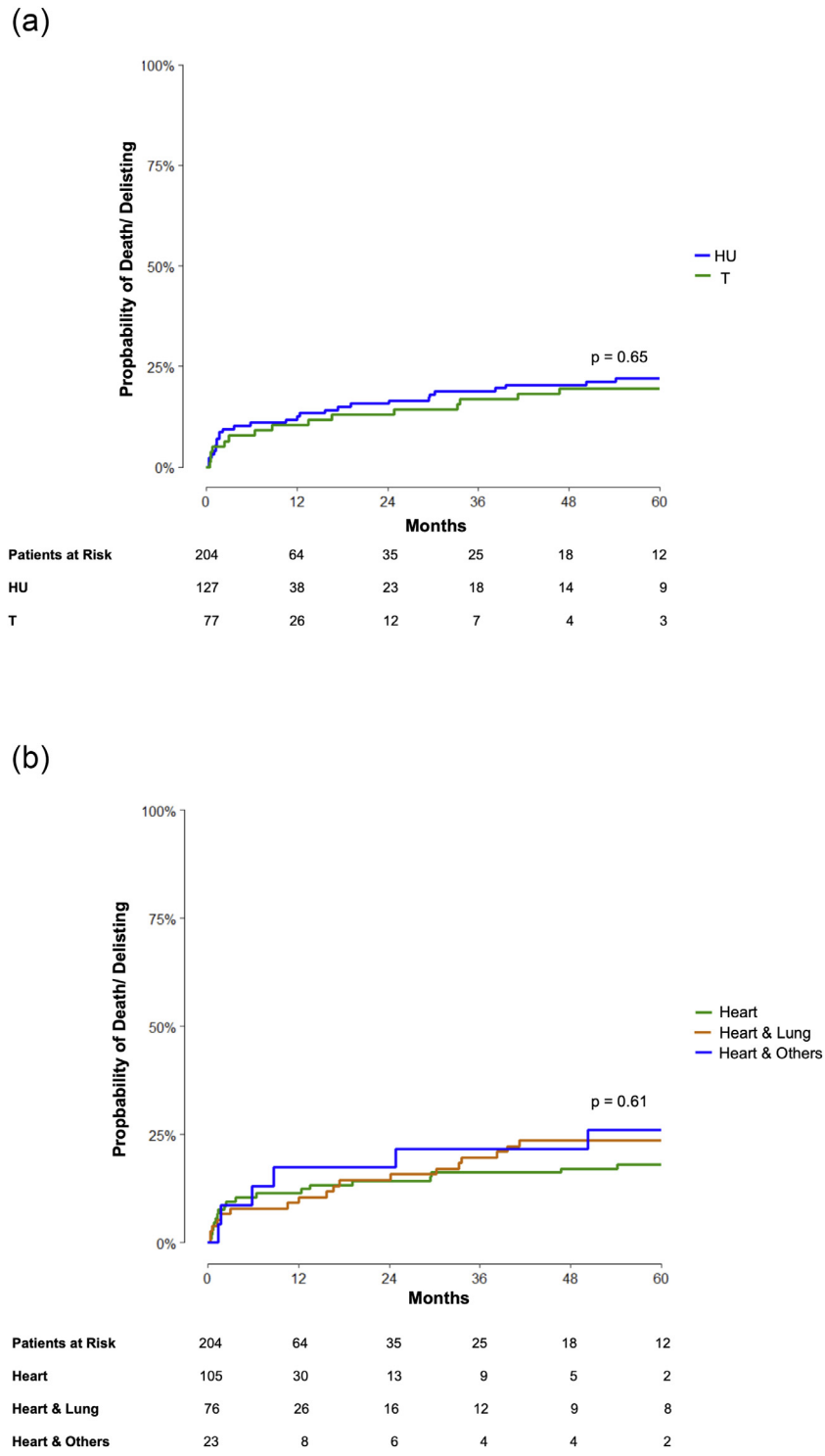

Figure 3 Probability of death or delisting owing to worsening clinical status in ACHD. Competing risk curves for all observations depending on (a) listing status and (b) specific listing by organ. ACHD, adult CHD; CHD, congenital heart disease; HU, high urgency; T, transplantable.

transplantation from the Eurotransplant Registry covering a large part of the population in central Europe. The main findings are that (1) a failing systemic right ventricle is the most common cause of HF leading to transplant listing in patients with ACHD, (2) patients with ACHD are at a high risk while waiting for transplantation (mortality or delisting was 11.3% after 1 year and 23.5% after 5 years) without differences between listing statuses, (3) patients with isolated heart transplantation or combined heart and lung transplantation had no different outcome on waiting list for transplantation, (4) approximately 75% of listed patients are transplanted after a median of 7 months on the waiting list, (5) concomitant respiratory failure and arrhythmias requiring therapy could be markers for urgent transplantation in patients with ACHD, and (6) patients with ACHD showed good outcome with low mortality rates of 26.8%

Table 2 Univariate Predictors of Death or Delisting Owing to Worsening

Univariate predictors	HR per SD (95% CI)	*p*-value
Demographics		
Male sex	0.80 (0.62, 1.05)	0.11
Age at listing	1.18 (0.89, 1.57)	0.25
Comorbidities		
Renal failure (eGFR < 60 ml/min/1.73 m^2)	1.28 (0.99, 1.67)	0.063
Need for anti-arrhythmic medication	1.26 (0.94, 1.69)	0.12
Previous cardiac surgery	0.85 (0.65, 1.12)	0.24
Difficulties in everyday life	1.22 (0.88, 1.70)	0.24
Diabetes mellitus	1.11 (0.90, 1.36)	0.32
History of coronary artery disease	1.12 (0.90, 1.39)	0.32
Smoking status	0.89 (0.59, 1.35)	0.59
Hypertension	0.98 (0.74, 1.29)	0.87
Medical conditions		
Invasive mechanical ventilation	1.32 (1.11, 1.57)	0.0021
Intermediate care unit	0.71 (0.50, 1.03)	0.069
Intensive care unit	1.17 (0.90, 1.51)	0.25
VAD	1.10 (0.87, 1.39)	0.44
Non-invasive mechanical ventilation	0.95 (0.68, 1.33)	0.77
Inotrope support	1.01 (0.76, 1.35)	0.95
Hemodynamics		
Peak O_2 oxygen uptake (ml/kg/min)	0.72 (0.43, 1.20)	0.20
Pulmonary capillary wedge pressure (mm Hg)	1.22 (0.85, 1.74)	0.28
Pulmonary vascular resistance (WU)	1.21 (0.85, 1.72)	0.29
Cardiac index (ml/kg/min)	1.11 (0.73, 1.69)	0.63
Listing		
Year of listing	0.94 (0.70, 1.25)	0.67
Organs listed		
Heart	1 (reference)	
Heart and lung	1.20 (0.89, 1.61)	0.22
Heart and others	1.16 (0.89, 1.51)	0.26
Laboratory measures		
Blood urea nitrogen	1.39 (1.10, 1.76)	0.006
Albumin	0.58 (0.39, 0.87)	0.008

Abbreviations: eGFR, estimated glomerular filtration rate; HR, hazard ratio; O_2, oxygen; VAD, ventricular assist device; WU, wood unit.

Table 3 Multivariable Predictors of Death or Delisting Owing to Worsening

Multivariable predictor	HR per SD (95% CI)	*p*-value
Demographics		
Male sex	0.80 (0.58, 1.10)	0.17
Age at listing	0.98 (0.69, 1.38)	0.90
Comorbidities		
Need for anti-arrhythmic medication	1.42 (1.01, 2.01)	0.044
Renal failure (eGFR < 60 ml/min/1.73 m^2)	1.35 (0.99, 1.84)	0.059
Previous cardiac surgery	0.94 (0.69, 1.28)	0.69
Medical conditions Listing		
Inotrope support	0.75 (0.50, 1.11)	0.15
Invasive mechanical ventilation	1.41 (1.11, 1.81)	0.0057
VAD	1.07 (0.79, 1.45)	0.67
Listing		
Year of listing	1.03 (0.72, 1.46)	0.87
Organs listed		
Heart	1 (reference)	
Heart and lung	1.13 (0.79, 1.62)	0.51
Heart and others	1.12 (0.84, 1.49)	0.46

Abbreviations: eGFR, estimated glomerular filtration rate; HR, hazard ratio; VAD, ventricular assist device.

after 1 year and 33.4% after 5 years, whereas patients with ACHD undergoing isolated heart transplantation showed the lowest mortality rates.

Characteristics and the failing systemic right ventricle

Improved treatment of CHD has led to a growing population of patients with ACHD. These patients have a high risk of developing HF,[5] with an increasing number of patients with ACHD being referred for heart transplantation.[14] This study shows systemic right ventricular failure (e.g., the systemic right ventricle is unable to manage the constant demands regarding the pressure of the systemic circulation) as the most frequent underlying pathology of listing for heart transplantation among patients with ACHD, consistent with published disease courses in patients with a systemic right ventricle.[15] In this study, common causes of a systemic right ventricle in patients with ACHD is TGA repaired by an atrial switch technique (Mustard or Senning) or congenitally corrected TGA. Regarding this cohort, patients suffering from TGA are without exception patients after atrial switch correction (Senning and Mustard) with a systemic right ventricle.[16] The atrial switch operation by Mustard and Senning was the preferred surgical correction procedure until the early 1990s.[17] Nowadays, anatomic correction by arterial switch procedure[18] is the preferred procedure in patients with TGA. Consequently, it can be speculated that this will reduce the risk of HF for patients with TGA[19] and will obviate the need for heart transplantation in the future. Similarly, patients with TOF have a high risk of developing HF, which mainly depends on the prevalence/absence of pulmonary valve insufficiency.[20] In the future, continued improvement of early surgical treatment (e.g., decreasing the likelihood of relevant pulmonary valve insufficiency in adulthood) might reduce the number of patients with TOF listed for heart transplantation.[21]

Other patients with CHDs frequently listed for heart transplantation in this study were patients with single ventricle physiology, for example, Fontan circulation. Neonatal palliation and staged reconstruction toward Fontan circulation are feasible in most of the patients with ACHD with single ventricle physiology (such as hypoplastic left heart syndrome).[22] Whereas these complex surgeries enable survival until

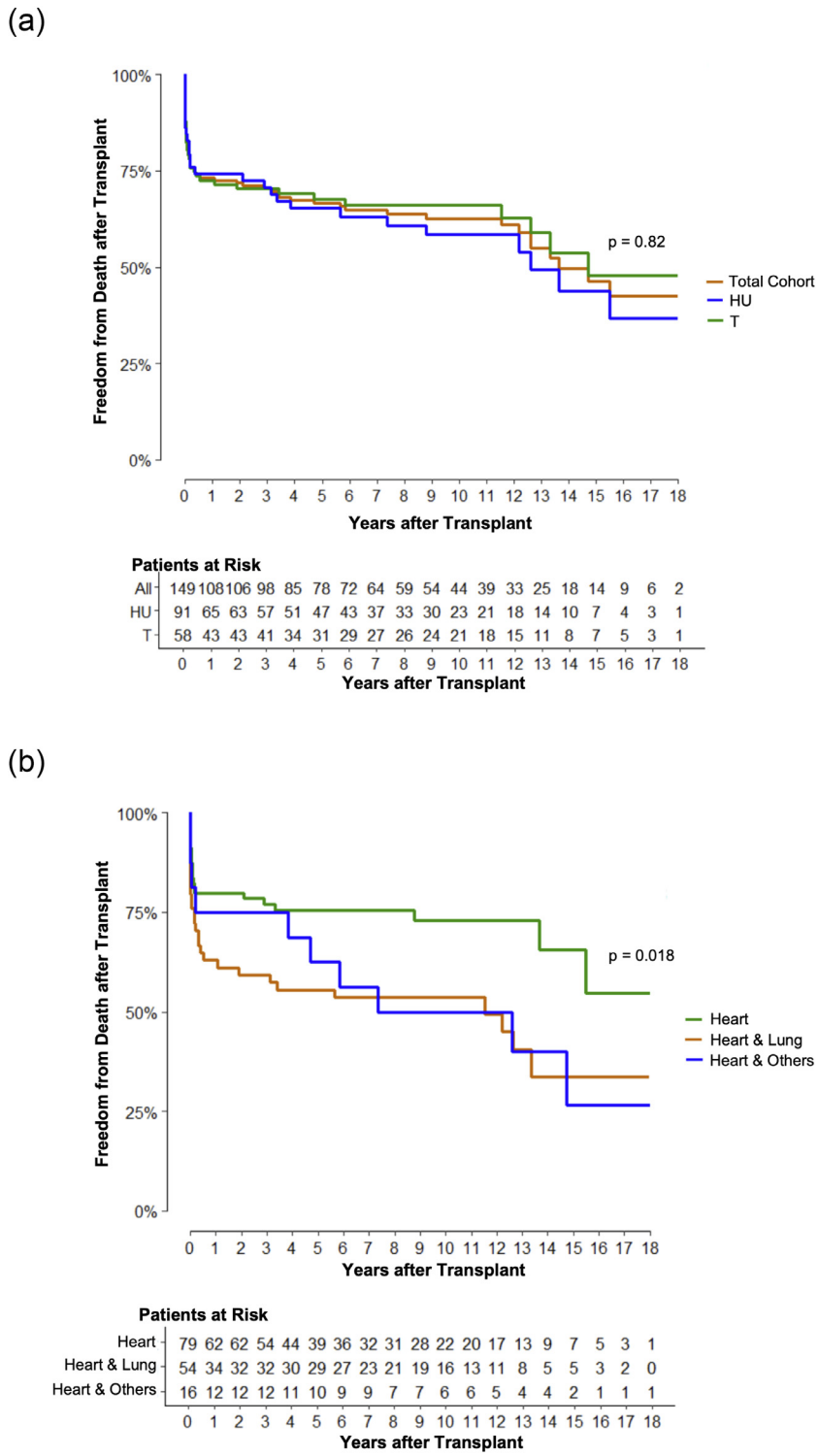

Figure 4 Freedom from death after transplantation by (a) listing status and (b) specific listing by organ. HU, high urgency; T, transplantable.

adulthood, HF is commonly found in the second to fifth decade of life.[23] Unlike TGA, this population is likely to still be in the need for advanced HF therapies (including transplantation) in the foreseeable future because the anatomic correction is not possible in these patients. It seems desirable to consider ventricular assist devices and transplantation early in the treatment process[22] because delayed listing can lead to worse outcomes.[24] This could potentially reduce the risk of death while waiting for heart transplantation.

Listing and transplantation

Timing of heart transplantation in patients with ACHD remains a clinical challenge even in the best multidisciplinary centers: HF prediction scores do not provide robust prognostic information,[25] urgent listing status for heart transplantation may be withheld from patients with ACHD,[26] waiting list times are longer than the waiting list time for patients with ACHD,[27] and transplant centers have

historically been reluctant to list patients with ACHD for heart transplantation owing to the complex transplant surgery.[28] These data demonstrate good outcomes (75% successful in getting to transplantation) in a large, unselected cohort of patients with ACHD listed for transplantation.

The HU-listing status was originally designed to rescue patients at the highest risk (e.g., allow for heart transplantation within few days)[29]; however, the median waiting time for HU-listed patients with ACHD was more than 4 months in this study.

A relevant proportion of patients with ACHD develop irreversible pulmonary arterial hypertension. These patients, 37% of all listed patients in this study, need combined heart and lung transplantation.[30]

Factors affecting waiting list mortality

Risk of death or delisting owing to clinical worsening on the waiting list was high (11.3% at 1 year and 23.5% at 5 years), without differences between patients listed as HU and those listed as T. This illustrates the need for new markers identifying patients at risk of death/delisting owing to clinical worsening on the waiting list to better prioritize transplantations to those with the highest benefit. Our dataset was sufficiently large to determine the risk factors for death in patients with ACHD on the waiting list. We found that respiratory failure requiring invasive mechanical ventilation and the need for anti-arrhythmic medication was independently associated with a higher risk of death or delisting. This is in line with a previous study from the United States, which also described invasive mechanical ventilation as an independent predictor of outcome in patients with ACHD.[14] Mechanical ventilation is often needed when severe hemodynamic worsening leads to low oxygen saturation and is associated with poor prognosis in patients without ACHD with advanced HF.[31]

The development of arrhythmias requiring therapy has been proposed as a sign for worsening HF.[32] In addition, anti-arrhythmic medications have negative inotropic effects and might, therefore, worsen outcomes in patients with ACHD listed for transplantation.[33,34] Although anti-arrhythmic therapy was associated with mortality in this cohort, this observation will require external validation.

Ultimately, both factors (the need for anti-arrhythmic medication as an early sign or a cause of worsening HF) and respiratory failure call for a careful evaluation of affected patients (either for heart transplantation listing or to increase heart transplantation urgency).

Patients with ACHD who are listed for transplantation are a particularly heterogeneous population and represent a small proportion of adults listed for transplantation. In the United States and the Eurotransplant region, waiting list mortality is disproportionately common for patients with ACHD, even for patients listed with the highest priority status.

The current allocation policies may be disadvantageous for the patients in the ACHD group because of the competition with other patients listed in HU status (i.e., infected mechanical circulatory support device and cardiomyopathy on inotropes). In addition, no specific listing scores are available that account for ACHD diagnoses. An allocation system that takes into account the distinctive diagnoses of ACHD may improve the outcome for this challenging population.

Post-transplantation outcome

Consistent with previous studies of post-transplantation outcomes, the diagnosis of ACHD is accompanied with an additional risk for increased post-transplantation mortality compared with adults with other diagnoses.[35,36] Furthermore, it has been reported that outcome in patients with ACHD after transplantation has significantly improved in the recent era.[37] In line with data from the United States, our study revealed similar results of post-transplantation outcome.[37]

In addition, our results showed that patients with ACHD with isolated heart transplantation had the most favorable long-term outcome after transplantation. In this regard, results from previous studies are in line with our findings for post-transplantation outcome.[38]

Limitations

The strength of this study is its inclusion of a large, representative, and contemporary cohort of patients with ACHD listed for heart transplantation with complete ascertainment of vital status from the largest institution for organ transplantation in Europe. The dataset was sufficient to identify temporal trends and predictors of death.

However, we acknowledge several study limitations. There was a proportion of missing data for certain variables, which could lead to bias. Delisting owing to clinical worsening was included in the primary outcome despite its subjective nature and unknown eventual outcome. External validation, ideally in population-based prospective cohort studies, is desirable. Patients with ACHD remain a heterogeneous group with various mechanisms of HF and indications for heart transplantation. Regional variations in patient populations and heart transplantation practices might limit the generalizability of our results. In addition, the time period of the study was from 1999 to 2015, spanning the time frame of the data listing of the Eurotransplant Registry. Thus, cases of the most recent past are not included, and treatment has changed over time, and this might as well have been affecting the outcome. Finally, a limitation of this study is the lack of a control group. However, our ACHD sample showed comparable mortality rates on the waiting list with the mortality rates of all the listed patients for transplantation in the Eurotransplant region.

Conclusions

In summary, the majority of patients with ACHD listed for heart transplantation in the Eurotransplant region were

successfully transplanted. Patients had a high risk of mortality or delisting owing to clinical worsening on the waiting list. A failing systemic right ventricle was the most frequent underlying pathology of listing, and 33% of patients with ACHD were listed for combined heart and lung transplantation. Patients with ACHD showed a good outcome with low mortality rates after transplantation, whereas patients with ACHD undergoing isolated heart transplantation showed the lowest mortality rates. Respiratory failure and arrhythmias requiring therapy emerge as independent risk factors, which could be used to identify patients with ACHD in need for urgent therapy while on the waiting list for organ transplantation.

Data availability statement

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

Disclosure statement

A.M.B. has received speakers fee from Abbott, Abiomed, BerlinHeart, Medtronic, Novartis.

B.S. has received speakers fee from AstraZeneca. C.M. has received speakers fee from Novartis, AstraZeneca, Loewenstein Medical Technology. C.S. has received speakers fee from AstraZeneca and Johnson & Johnson. D.W. has received speakers fee from AstraZeneca, Bayer, Novartis. E.Z. has received speakers fee from AstraZeneca and Johnson & Johnson. P.K. receives research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (United Kingdom), and German Centre for Cardiovascular Research and from several drug and device companies active in atrial fibrillation and has received honoraria from several of such companies in the past but not in the last 3 years. P.K. is listed as an inventor on 2 patents held by the University of Birmingham (Atrial Fibrillation Therapy WO 2015140571 and Markers for Atrial Fibrillation WO 2016012783). P.S. has received speakers fee from Novartis, Astellas, Neovia. S.B. has received speakers fee from Medtronic, Pfizer, Roche, Novartis, Siemens Diagnostics. B.S. is currently funded by the German Research Foundation. The remaining authors have no conflicts of interest to disclose.

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The Eurotransplant Thoracic Advisory Committee approved the study protocol for this study in accordance with the Declaration of Helsinki. All data were anonymized for country and transplant center.

Supplementary data

Supplementary data associated with this article can be found in the online version at www.jhltonline.org/.

Supplementary materials

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