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ORIGINAL RESEARCH ARTICLE

Influence of renal insufficiency pre-heart transplantation on malignancy risk post-heart transplantation

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Abstract

Aims Recent reports demonstrated that patients with heart failure (HF) might have an increased risk to develop malignancies. This is also seen in patients with chronic kidney disease (CKD). Immunosuppression in heart transplantation (HT) recipients additionally increases the risk of malignancies. The aim of this study was to determine the relation between HF duration and CKD pre-HT and the risk of malignancy development post-HT.

Methods and results We included all adult HT recipients transplanted between January 2000 and November 2017 in our centre. Patients were excluded if they died or were retransplanted within 3 months post-HT. Clinical characteristics were retrospectively collected. Sixty out of 250 patients (24%) developed a malignancy after a median of 66 months [interquartile range 33–108] post-HT. In multivariable Cox regression analysis, HF duration was not a risk factor for all malignancies or solid organ malignancies post-HT [hazard ratio (HR) 1.033 (0.974–1.096), $P = 0.281$ and HR 1.036 (0.958–1.120), $P = 0.376$, respectively]. Age [HR 1.051 (1.016–1.086), $P = 0.004$] and CKD pre-HT [HR 2.173 (1.236–3.822), $P = 0.007$] were independent risk factors for all malignancies. CKD pre-HT [HR 2.542 (1.142–5.661), $P = 0.022$] increased the risk for solid organ malignancies. Exclusion of patients with durable mechanical circulatory support in the analysis did not alter the significance of these risk factors.

Conclusions Duration of HF pre-HT was not associated with malignancy risk post-HT. CKD was an independent risk factor for malignancies post-HT. More studies are needed to investigate this association.

Keywords Heart failure; Heart transplantation; Malignancies; Renal insufficiency

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Introduction

Chronic heart failure (HF) and cancer are diseases with high morbidity and mortality.[1,2] The association between (the treatment of) malignancies and HF has been studied thoroughly.[3] The inverse relationship, whether HF may be a risk factor for the development of malignancies, has been a topic of recent interest. Several epidemiologic studies have shown that patients with HF have an increased cancer risk compared with subjects without HF.[4,5] The association between HF and malignancies could be explained by lead-time bias[6] or shared risk factors such as smoking, hypertension, and obesity.[7] These comorbidities might lead to cardiovascular diseases first and, later in time, to the development of malignancies. In contrast to these results, a larger study with over 28 000 participants showed no association between HF and cancer risk.[8] Besides that, it is difficult in epidemiologic studies to show causality between HF and cancer due to bias and confounding factors.[9]

Nevertheless, a study performed in mice, aiming to investigate whether a causal relationship exists between HF and malignancies, has shown that HF stimulated tumour growth

by circulating factors.[10] Furthermore, the authors identified significantly elevated proteins in patients with HF responsible for tumour growth. Especially the protein serine proteinase inhibitor A3 (SerpinA3) was able to induce tumour growth in cell cultures in mice. In the same study, several other known cardiac markers (i.e. N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin T), neuroendocrine biomarker galectin-3, and inflammation markers (i.e. C-terminal proendothelin-1 and high-sensitivity C-reactive protein) were found as possible predictors for new-onset cancer in humans. Of note, patients with end-stage HF who undergo heart transplantation (HT) and use immunosuppressive treatment are even more at risk to develop malignancies. HF duration pre-HT could be associated with an increased malignancy risk post-HT, due to exposure to these circulating factors. This would imply that patients with a longer HF duration have an increased risk to develop malignancies post-HT compared with patients who have a shorter duration of HF pre-HT.

Chronic kidney disease (CKD) is the most prevalent comorbidity in patients with HF, ranging from 41% to 63%[11,12] and is the result of either reduced cardiac output and renal perfusion or volume retention and renal venous congestion.[13] Go *et al*. demonstrated that the prevalence of cardiovascular events increased when the estimated glomerular filtration rate (eGFR) declined.[14] The incidence of HF was almost two times increased in patients with reduced kidney function in comparison with individuals with a normal eGFR.[15] Renal insufficiency has also been linked to the development of malignancies.[16,17] This is most probably due to the reduced function of the immune system in combination with an increased inflammatory response increasing the risk for malignancy development.[17]

The aims of this study were to investigate the influence of HF duration and renal insufficiency pre-HT on malignancy incidence post-HT and to identify risk factors for the development of malignancies post-HT.

Methods

Study design and population

This is a retrospective cohort study including all adult (≥18 years) HT recipients transplanted between 1 January 2000 and 31 October 2017 in the Erasmus MC, Rotterdam, the Netherlands. Patients who died within 3 months post-HT were excluded. Patients who were retransplanted within 3 months post-HT were excluded. The remaining patients were followed until retransplantation, death, or end of follow-up (1 January 2019). The study conforms with the *Declaration of Helsinki*. The ethical board of the Erasmus MC approved this study (MEC-2017-421). Patients provided consent to have their data used for medical research. Clinical characteristics and malignancy risk factors were systematically collected from electronic patient records.

Definitions

Comorbidities and clinical characteristics

The diagnosis of diabetes mellitus (DM) was based on the definition of the World Health Organization.[18] Hypertension and peripheral artery disease were defined according to the corresponding European Society of Cardiology guidelines.[19,20] Chronic obstructive pulmonary disease diagnosis was determined by using the Global Initiative for Chronic Obstructive Pulmonary Disease criteria.[21] CKD pre-HT diagnosis was based on the KDIGO criteria,[22] defined as an eGFR below 60 mL/min/1.73 m^2 for at least three consecutive months in the 6 months pre-HT. Post-HT, new onset of DM, hypertension, and CKD were noted only if present for >1 year to exclude post-operative influences and short episodes of illness.

The first reported date of HF, diagnosed by a cardiologist, was used as date of onset. If only the year of HF onset was available, the sixth month of the year was used as date of diagnosis. Cytomegalovirus and Epstein–Barr virus (EBV) serology was determined during the screening period before HT. Post-transplant, cytomegalovirus virus, and EBV titres were monitored by PCR on annual basis and extra when there was a clinical indication. Use of mechanical circulatory support as bridge to transplant included left ventricular assist device, biventricular assist device, extracorporeal membrane oxygenation, and intra-aortic balloon pump.

Immunosuppression and rejection

Immunosuppressive treatment post-HT consists of several regimes, depending on factors such as graft rejection, as previously described.[23] Induction therapy included anti-thymocyte globulin, basiliximab, or orthoclone OKT3. At 1 year post-transplantation, use of immunosuppressive drugs was noted. Diagnosis of rejection was based on the grading system adopted by the International Society for Heart and Lung Transplantation.[24]

Endpoints

The primary endpoints of this study were cumulative incidence of malignancies post-HT in relation to HF duration and renal insufficiency. HF duration was considered the period between HF diagnosis and date of HT. Any malignancies post-HT were documented and classified into skin malignancies and solid organ malignancies. All lymphomas (post-transplant lymphoproliferative disorder, Hodgkin's lymphoma, and non-Hodgkin's lymphoma) and leukaemia were seen as one group and included in the solid organ malignancies for analysis. All *in situ* malignancies or

precursors of malignancies (such as Morbus Bowen) were excluded. The date of malignancy diagnosis was used as date of onset.

Statistical analysis

Categorical variables were expressed as numbers and percentages and compared with the χ^2 or Fisher's exact test if appropriate. Continuous variables were examined for the distribution of normality using the Shapiro–Wilk test. Normally distributed variables were presented as means ± standard deviation. For normally distributed data, a two-sample *t*-test was used to compare means. If not normally distributed, data were presented as medians and interquartile range (IQR) and compared with the Mann–Whitney *U*-test.

Clinically relevant risk factors for the development of malignancies, based on current literature, were studied in univariate Cox proportional hazards regression analysis. Subsequently, significant variables in univariate analysis were tested in a multivariable Cox analysis using the enter method. 'Duration of HF' and 'CKD pre-HT' were added to the multivariable analysis as study determinants. Patients without malignancies post-HT were censored at death, retransplantation, or end of study.

One multiple imputation was performed on 'alcohol during HF' as 28% of data was missing. A total of five imputations were performed, and the pooled data were analysed. The imputed data of this variable were used in the univariate analysis. Other variables were mostly complete or maximum 10% missing.

Kaplan–Meier curves assessing survival post-HT and malignancy incidence post-HT stratified by groups (based on presence of risk factors to develop a malignancy) were computed and compared by log-rank test. For survival analysis, patients were censored at retransplantation or on 1 January 2019. For the cumulative incidence of malignancies, patients were censored at retransplantation, death, or on 1 January 2019.

$P < 0.05$ was considered as statistically significant for all tests. Data were analysed using IBM SPSS statistics 25 (IBM Corp., New Orchard Road, Armonk, NY 10504, USA) and GraphPad Prism version 5.0a (GraphPad Software, La Jolla, CA, USA).

Results

Study population

Between January 2000 and November 2017, 285 adult patients were transplanted. Within 3 months post-HT, 33 patients died (due to a non-malignancy-related cause) and 2 patients received a retransplantation. These patients were excluded. Of the 250 remaining patients, 60 (24%) developed a malignancy during a median follow-up period of 98 months ([IQR 55–149]; *Tables 1* and *2*). Patients with a malignancy post-HT had a significantly longer follow-up period compared with patients without a malignancy (126 [IQR 89–176] vs. 90 [IQR 48–139] months, $P < 0.001$).

Clinical characteristics pre-heart transplantation

Patients who developed a malignancy post-HT were more likely to be older at HF onset (47 [IQR 42–53] vs. 42 [IQR 35–48] years, $P = 0.001$). There was no difference in HF duration between patients with and without a malignancy post-HT (72.5 [IQR 47–124] vs. 71.0 [IQR 37–120] months, $P = 0.44$). Non-ischaemic cardiomyopathy was the most frequent aetiology of HF (69%). Pre-transplant, 41% of patients developed CKD. Median serum creatinine at HT was 118 [IQR 97–145] μmol/L. Patients with a malignancy post-HT were more likely to be EBV seronegative pre-HT (12% vs. 3%, $P = 0.017$).

Clinical characteristics post-heart transplantation

There were no differences in donor characteristics between patients with and without a malignancy post-HT. Hypertension (77%) was the most common comorbidity post-HT, followed by CKD (66%) and DM (41%) (*Table 2*). Patients with a malignancy post-HT were more likely to have CKD post-HT compared with patients without a malignancy (78% vs. 62%, $P = 0.017$).

Malignancy incidence post-heart transplantation

The median time to malignancy was 66 months [IQR 33–108] (*Table 3*). The median age at malignancy diagnosis was 62 years [IQR 53–67]. The cumulative incidence of malignancies at 5, 10, and 15 years post-HT was 11.8%, 28.4%, and 40.3%, respectively (*Figure 1*). Sixty patients developed a total of 161 malignancies. Skin malignancies were the most frequent (81%), followed by lung/bronchus malignancies (5%) and lymphomas (post-transplant lymphoproliferative disorder) and leukaemia (3%). Other malignancies (8%) are specified in *Table 3*.

Risk factors for malignancies post-heart transplantation

In univariate Cox proportional hazards regression analysis, age at HF onset [hazard ratio (HR) 1.06 per year, 95% confidence interval (1.02–1.09), $P < 0.001$], CKD pre-HT [2.84 (1.68–4.78), $P < 0.001$], EBV-negative serostatus pre-HT [2.67 (1.21–5.90), $P = 0.015$], EBV primary infection post-HT

Table 1 Clinical characteristics of patients pre-heart transplantation

	All (*n* = 250)	Malignancies post-HT (*n* = 60)	No malignancy post-HT (*n* = 190)	*P*-value
Demographics				
Age at HF onset (years)	44 [36–49]	47 [42–53]	42 [35–48]	**0.001**
Female gender, *n* (%)	88 (35)	18 (30)	70 (37)	0.33
Caucasian race, *n* (%)	232 (93)	58 (97)	174 (92)	0.26
Indication for HT				0.15
Ischaemic cardiomyopathy, *n* (%)	77 (31)	23 (38)	54 (28)	—
Non-ischaemic cardiomyopathy, *n* (%)	173 (69)	37 (62)	136 (72)	—
Dilated cardiomyopathy, *n* (%)	99 (57)	23 (62)	76 (56)	—
Hypertrophic cardiomyopathy, *n* (%)	26 (15)	4 (11)	22 (16)	—
Myocarditis, *n* (%)	9 (5)	1 (3)	8 (6)	—
Valve disease, *n* (%)	7 (4)	1 (3)	6 (4)	—
Other, *n* (%)	32 (19)	8 (22)	24 (18)	—
Duration of heart failure (months)	71.0 [41–122]	72.5 [47–124]	71.0 [37–120]	0.44
Comorbidity before HT				
Diabetes, *n* (%)	31 (12)	7 (12)	24 (13)	0.84
Hypertension, *n* (%)	24 (10)	6 (10)	18 (10)	0.87
PAD, *n* (%)	2 (1)	0 (0)	2 (1)	1.00
COPD, *n* (%)	17 (7)	4 (7)	13 (7)	1.00
CKD, *n* (%)	103 (41)	34 (57)	69 (36)	**0.005**
Malignancy, *n* (%)	14 (6)	6 (10)	8 (4)	0.11
Virus serology at HT screening				
CMV seronegative, *n* (%)	111 (44)	28 (47)	83 (44)	0.69
EBV seronegative, *n* (%)	13 (5)	7 (12)	6 (3)	**0.017**
Intoxications				
Smoking before HT, *n* (%)	166 (66)	44 (73)	122 (64)	0.19
Alcohol during HF, *n* (%)	152 (61)	41 (68)	111 (58)	0.17
MCS, *n* (%)	59 (24)	9 (15)	50 (26)	0.07
LVAD, *n* (%)	38 (15)	6 (10)	32 (17)	—
BiVAD, *n* (%)	2 (1)	0 (0)	2 (1)	—
ECMO, *n* (%)	10 (4)	2 (3)	8 (4)	—
IABP, *n* (%)	30 (12)	6 (10)	24 (13)	—

BiVAD, biventricular assist device; CKD, chronic kidney disease; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disorder; EBV, Epstein–Barr virus; ECMO, extracorporeal membrane oxygenation; HF, heart failure; HT, heart transplantation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; MCS, mechanical circulatory support; *n*, number; PAD, peripheral artery disease.
Categorical variables are presented as %. Continuous values are expressed as median [interquartile range]. The bold *P*-values were used to demonstrate significant values ($P<0.05$).

[2.93 (1.06–8.16), *P* = 0.039], and the number of immunosuppressive drugs at 1 year [0.47 (0.28–0.79), *P* = 0.004] were significant risk factors for the development of malignancies post-HT (Supporting Information, *Table S1*). Because of a significant correlation between the variables 'EBV serostatus' and 'EBV primary infection' (Spearman's rho: 0.776), only EBV serostatus was selected for further analysis. In Supporting Information, *Table S1*, a list of the results of the univariate analysis is provided.

Duration of HF was not significantly associated with malignancy risk post-HT in multivariable analysis [HR 1.03 per year (0.97–1.10), *P* = 0.28; *Table 4*]. However, the presence of CKD pre-HT increased malignancy risk post-HT more than twice [HR 2.17 (1.24–3.82), *P* = 0.007]. Furthermore, age was an independent risk factor for malignancies post-HT [HR 1.05 per year (1.02–1.09), *P* = 0.004]. EBV serostatus and the number of immunosuppressive drugs were not associated with malignancy risk post-HT [HR 1.50 (0.64–3.55), *P* = 0.35 and HR 0.60 (0.35–1.03), *P* = 0.06, respectively]. In Supporting Information, *Figure S1*, cumulative incidence of malignancies stratified by age (A) and CKD pre-HT (B) is shown.

Incidence of solid organ malignancies post-heart transplantation

Twenty-eight patients (11%) developed 31 solid organ malignancies post-HT. Cumulative incidence of solid organ malignancies was 4.4%, 12.0%, and 21.2% at 5, 10, and 15 years post-HT, respectively (*Figure 1*). Duration of HF was not significantly different between patients with and without a solid organ malignancy post-HT (83 [IQR 44–133] vs. 71 [IQR 41–119] months, *P* = 0.39; Supporting Information, *Table S2*).

In patients with a solid organ malignancy post-HT, CKD pre-HT and post-HT was more frequent (61% vs. 39%, *P* = 0.026 and 86% vs. 63%, *P* = 0.017, respectively). There was a significantly higher occurrence of primary EBV infections post-HT (11% vs. 2%, *P* = 0.048).

Risk factors for solid organ malignancies post-heart transplantation

In univariate Cox analysis, CKD pre-HT [HR 2.98, 95% confidence interval (1.39–6.41), *P* = 0.005] and malignancy pre-

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Table 2 Clinical characteristics of patients post-heart transplantation

	All (n = 250)	Malignancies post-HT (n = 60)	No malignancies post-HT (n = 190)	P-value
Donor characteristics				
Age (years)	45 [35–54]	43 [32–51]	46 [35–54]	0.08
Female gender, *n* (%)	148 (59)	40 (67)	108 (57)	0.18
BMI (kg/m^2)	24 [22–27]	23 [22–26]	24 [22–27]	0.50
Cause of death				0.65
Brain trauma, *n* (%)	69 (28)	20 (33)	49 (26)	—
Intracerebral haemorrhage, *n* (%)	160 (64)	36 (60)	124 (65)	—
Anoxia, *n* (%)	20 (8)	4 (7)	16 (8)	—
Other, *n* (%)	1 (0)	0 (0)	1 (1)	—
Clinical characteristics recipient				
Age at transplant (years)	50 [43–58]	56 [48–60]	49 [42–56]	**0.001**
BMI (kg/m^2)	24 [22–27]	24 [22–26]	24 [22–27]	0.27
Comorbidity post-HT				
Diabetes, *n* (%)	103 (41)	24 (40)	79 (42)	0.83
Hypertension, *n* (%)	192 (77)	49 (82)	143 (75)	0.31
PAD, *n* (%)	14 (6)	4 (7)	10 (5)	0.75
COPD, *n* (%)	18 (7)	5 (8)	13 (7)	0.78
CKD, *n* (%)	164 (66)	47 (78)	117 (62)	**0.017**
Intoxications				
Smoking post-HT, *n* (%)	20 (8)	7 (12)	13 (7)	0.28
Alcohol post-HT, *n* (%)	112 (45)	34 (57)	78 (41)	0.09
Induction therapy				
ATG, *n* (%)	233 (93)	55 (92)	178 (94)	0.57
Basiliximab, *n* (%)	2 (1)	0 (0)	2 (1)	1.00
OKT3, *n* (%)	1 (0)	0 (0)	1 (1)	1.00
Immunosuppression at 1 year	*N* = 244	*N* = 58	*N* = 186	
Cyclosporine, *n* (%)	48 (20)	16 (28)	32 (17)	0.08
Tacrolimus, *n* (%)	196 (80)	42 (72)	154 (83)	0.08
Steroids, *n* (%)	228 (93)	53 (91)	175 (94)	0.54
MMF, *n* (%)	144 (59)	31 (53)	113 (61)	0.32
Everolimus, *n* (%)	19 (8)	2 (3)	17 (9)	0.26
Sirolimus, *n* (%)	1 (4)	1 (2)	0 (0)	0.24
Number of immunosuppressants				
1 or 2, *n* (%)	95 (39)	29 (50)	66 (36)	**0.048**
3, *n* (%)	149 (61)	29 (50)	120 (65)	
Statin use				
Statin use 1 year	209 (84)	50 (83)	159 (84)	0.89
Pravastatin	207 (99)	49 (98)	158 (99)	—
Atorvastatin	2 (1)	1 (2)	1 (1)	—
Post-operative course				
Primary CMV infection, *n* (%)	54 (22)	13 (22)	41 (22)	0.99
Primary EBV infection, *n* (%)	8 (3)	4 (7)	4 (2)	0.10
Any rejection, *n* (%)	173 (69)	46 (77)	127 (67)	0.15
Kidney transplantation, *n* (%)	10 (4)	2 (3)	8 (4)	1.00
Endpoint				
Retransplantation, *n* (%)	1 (0)	0 (0)	1 (1)	—
Alive, *n* (%)	187 (75)	38 (63)	149 (78)	—
Death, *n* (%)	62 (25)	22 (37)	40 (21)	**0.015**
Cause of death				**<0.001**
Malignancy, *n* (%)	14 (22)	14 (64)	0 (0)	—
Kidney-related, *n* (%)	12 (19)	2 (9)	10 (25)	—
CAV-related, *n* (%)	12 (19)	3 (14)	9 (23)	—
Infection, *n* (%)	8 (13)	2 (9)	6 (15)	—
Rejection, *n* (%)	5 (8)	0 (0)	5 (13)	—
Other, *n* (%)	11 (18)	1 (5)	10 (25)	—
Duration of follow-up (months)	98 [55–149]	126 [89–176]	90 [48–139]	**<0.001**

ATG, anti-thymocyte globulin; BMI, body mass index; CAV, cardiac allograft vasculopathy; CKD, chronic kidney disease; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disorder; EBV, Epstein–Barr virus; HT, heart transplantation; MMF, mycophenolate mofetil; *n*, number; OKT3, orthoclone OKT3; PAD, peripheral artery disease.
Categorical variables are presented as %. Continuous values are expressed as median [interquartile range]. The bold P-values were used to demonstrate significant values ($P<0.05$).

HT [3.10 (1.07–8.96), P = 0.04] were significantly associated with increased risk for solid organ malignancies post-HT (Supporting Information, *Table S3*).

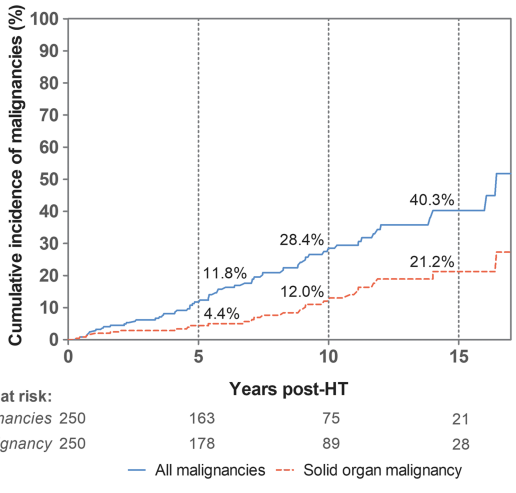
In the multivariable analysis, HF duration was not a significant risk factor for solid organ malignancies post-HT [HR 1.04 per year (0.96–1.12), P = 0.38]. CKD pre-HT was an

Table 3 Characteristics of malignancies post-heart transplantation (in 60 patients with a malignancy)

Age at first malignancy (years)	62 [53–67]
Time to malignancy (months)	66 [33–108]
Type of malignancy	
• Skin malignancies	130 (81)
○ *Basal cell carcinoma*	86 (53)
○ *Squamous cell carcinoma*	38 (24)
○ *Malignant melanoma*	4 (3)
○ *Merkel-cell carcinoma*	1 (1)
○ *Sebaceous carcinoma*	1 (1)
• Lung/bronchus	8 (5)
• PTLD/lymphoma/leukaemia	5 (3)
• Gastrointestinal	5 (3)
• Other	13 (8)
○ *Kidney/bladder*	3 (2)
○ *Breast*	2 (1)
○ *Prostate*	2 (1)
○ *Sarcoma (Kaposi and myxofibro)*	2 (1)
○ *Brain*	1 (1)
○ *Carcinoid*	1 (1)
○ *Oropharyngeal carcinoma*	1 (1)
○ *Salivary gland carcinoma*	1 (1)
Total	161 (100)

PTLD, post-transplant lymphoproliferative disorder.
Continuous values are expressed as median [interquartile range]. Number of tumours given as a number with proportion of all malignancies in %.

Figure 1 Cumulative incidence of malignancies and solid organ malignancies post-HT. HT, heart transplantation.



independent risk factor for the development of solid organ malignancies post-HT [2.54 (1.14–5.66), P = 0.02] (Supporting Information, *Table S4*). Malignancy pre-HT was not associated with an increased risk for a solid organ malignancy post-HT [2.13 (0.72–6.31), P = 0.17]. In Supporting Information, *Figure S2*, the incidence of solid organ malignancies stratified by CKD pre-HT is shown.

Risk factors excluding durable assist devices

In patients with a durable assist device, such as a left ventricular assist device or biventricular assist device, the circulation is restored and multi-organ function can recover. This is why a subgroup analysis was performed to determine risk factors for malignancies and solid organ malignancies excluding patients with durable assist devices pre-HT. The risk factors for both all malignancies as well as solid organ malignancies did not change compared with the analysis of the whole population (Supporting Information, *Tables S5–S8*).

Prognosis

On 1 January 2019, 37% of patients with any malignancy post-HT had died, compared with 21% of patients without a malignancy (P = 0.015; *Table 2*). The median survival of patients conditional on surviving the first 3 months post-HT was 16.5 years (Supporting Information, *Figure S3*). Patients with solid organ malignancy had a median survival after diagnosis of 1.4 years.

Discussion

To our best knowledge, this is the first study investigating the influence of HF duration and renal insufficiency on malignancy risk post-HT. No association was found between HF duration and the development of any malignancy post-HT or solid organ malignancies post-HT. However, age at HF onset (HR 1.05 per year) and CKD pre-HT (HR 2.17) were independent risk factors for malignancies post-HT. For solid organ malignancies post-HT, CKD pre-HT (HR 2.54) increased the risk significantly.

Heart failure and malignancy risk

Many studies have been performed to identify pre-transplant and post-transplant risk factors for malignancies post-HT.[25–27] Few studies have been performed on malignancy risk in patients with HF compared with the general population.[4,5,8] Meijers *et al.*[10] concluded that HF stimulates tumour growth by the release of proteins such as SerpinA3. Therefore, we assumed that a longer exposure to these factors would increase the malignancy risk post-HT even more. However, we were unable to detect this association. The association between HF and increased tumour growth might be more prominent in ischaemic HF. Others reported that patients with HF (without a history of cancer) had an increased risk to develop malignancies during follow-up compared with patients without HF.[4] Patients with an ischaemic cardiomyopathy had an additional increased risk (HR 1.23, P = 0.022).[4] Hasin *et al.*

Table 4 Risk factors for malignancies post-heart transplantation

	Univariate analysis		Multivariable analysis	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Duration of HF in years	1.04 (0.99–1.09)	0.12	1.03 (0.97–1.10)	0.28
Age at HF onset in years	1.06 (1.02–1.09)	**<0.001**	1.05 (1.02–1.09)	**0.004**
CKD pre-HT	2.84 (1.68–4.78)	**<0.001**	2.17 (1.24–3.82)	**0.007**
EBV-negative serostatus pre-HT	2.67 (1.21–5.90)	**0.015**	1.50 (0.64–3.55)	0.35
Number of immunosuppressants (3 vs. 1 or 2)	0.47 (0.28–0.79)	**0.004**	0.60 (0.35–1.03)	0.06

CI, confidence interval; CKD, chronic kidney disease; EBV, Epstein–Barr virus; HF, heart failure; HR, hazard ratio; HT, heart transplantation. Univariate and multivariable Cox analyses are shown with hazard ratios (confidence intervals). The bold *P*-values were used to demonstrate significant values ($P<0.05$).

investigated myocardial infarction survivors and compared patients who developed HF with patients who did not.[5] In patients who developed HF, the incidence of malignancies was significantly higher.[5] Although all patients had an ischaemic event, the combination of ischaemia and the development of HF seems to lead to a higher cancer risk. In our population, only 31% of patients had ischaemic cardiomyopathy. Therefore, we were unable to perform a specific analysis on ischaemic HF and malignancy risk.

Another study investigating the risk of malignancies post-HT was performed by Fröhlich *et al*.[28] In this single-centre study including patients between 1985 and 2007, it was found that the use of statins decreased the cancer risk by 67%.[28] In our study, this observation was not duplicated. This could be due to the fact that in our population most patients (80%) used tacrolimus and 84% of patients used statins. The small group of patients who do not use statins in combination with the use of a newer immunosuppressive regimen could explain this disparity.

Renal insufficiency and malignancy risk

Chronic kidney disease pre-HT was found to be an important independent risk factor for malignancies post-HT and especially for solid organ malignancies post-HT (HR 2.17 and HR 2.54, respectively). To our knowledge, this has not been reported in HT recipients before. However, the relationship between CKD and cancer has been described before. Wong *et al*. showed that with every 10 mL decrease in eGFR in men, cancer risk increased with 17%. The patients most at risk for cancer were patients with an eGFR below 40 mL/min/1.73 m^2.[16] In our study, we already found a relationship between CKD and malignancies post-HT when the eGFR was below 60 mL/min/1.73 m^2. Due to small groups, further analysis of subgroups was not possible.

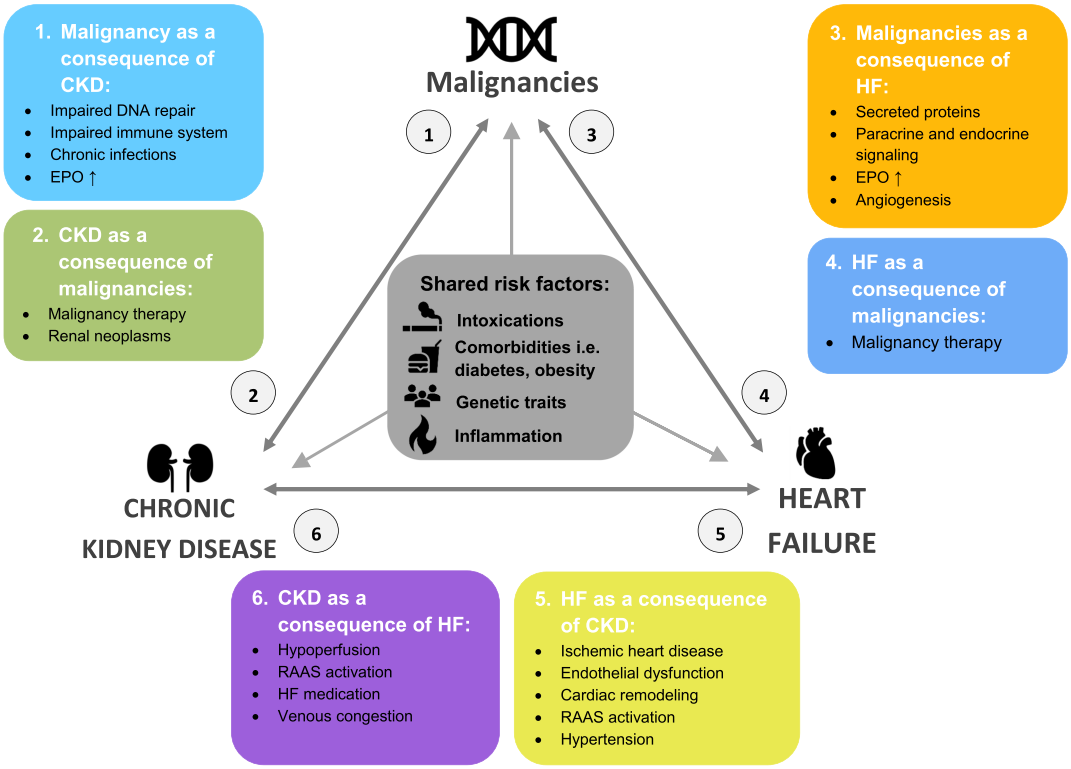
The way in which CKD might be associated with malignancies could be comparable with the way in which HF might be associated with tumour development. In *Figure 2*, the possible associations between HF, CKD, and malignancies are displayed. Hypertension, smoking, obesity, and DM are risk factors for both CKD and HF.[29] Furthermore, inflammation plays a role in the development of both conditions.[7,17] Vamvakas *et al*.[17] described several potential mechanisms of malignancy onset in patients with CKD. These include impaired function of the immune system, impaired DNA repair, chronic infections, and inflammation.[17]

The relation between CKD, HF, and malignancies is also demonstrated in patients with cardio-renal-anaemia syndrome (the combined presence of CKD, HF, and anaemia). Patients with cardio-renal-anaemia syndrome had an increased malignancy risk compared with patients with CKD and anaemia without HF.[30] The authors demonstrated that CKD on its own, when comparing with controls, was not a risk factor for the development of a malignancy in patients with CKD and anaemia.[30] However, current evidence is not sufficient to draw a definitive conclusion. The studies that have been performed on HF and malignancy risk did not all take CKD into consideration.[4,5,8] Similarly, studies examining the influence of CKD on malignancy risk did not report the incidence of HF.[16] That might be confounding the association found between either of these diseases and malignancies, as both diseases are associated with malignancy risk and with each other. More studies are needed to prove whether or not a (causal) association between HF and malignancies exists.

(Skin) malignancy incidence

Cumulative incidence of malignancies in our study was similar to the numbers presented in Jäämaa-Holmberg *et al*.[31], Van Keer *et al*.[27], and Higgins *et al*.[32] However, the proportion of skin malignancies in our population was higher compared with other studies investigating malignancy incidence post-HT.[25–27] This might be because our study had a longer follow-up period and patients were transplanted in a more recent era. The incidence of malignancies post-HT has been increasing temporally, mostly because of an increase in skin malignancy incidence.[33] Furthermore, our cohort was 93% Caucasian, which could explain the increased incidence of skin malignancies in our population. Another study found that skin cancer malignancies are significantly increased in HT patients increasing the risk for death especially in patients who develop melanomas.[34] As the risk is significantly increased and can be treated when detected in an early

Figure 2 The pathways in which HF, CKD, and malignancies might be related. CKD, chronic kidney disease; DNA, deoxyribonucleic acid; EPO, erythropoietin; HF, heart failure; RAAS, renin–angiotensin–aldosterone system.



stage, all HT patients should be regularly screened post-transplant and a pre-transplant screening is suggested to identify high-risk patients.[34]

Limitations

We were unable to collect data on malignancy risk factors such as physical activity and diet, which could have influenced our outcomes. Moreover, our number of patients with malignancies and especially patients with solid organ malignancies might have been too small to detect an association between HF duration and malignancy risk as with the association between malignancy pre-HT and malignancy risk post-HT. On the other hand, the compared groups (patients with and without malignancy post-HT) had similar clinical characteristics being all HT recipients. Therefore, the risk of screening or detection bias is smaller compared with studies on malignancy risk with healthy individuals as controls. If we compare our results with the International Society for Heart and Lung Transplantation registry, it has to be acknowledged that in our population, the use of induction therapy is significantly higher (94% vs. 53%).[35] We cannot exclude that the combination of induction therapy, renal insufficiency, and HF is the reason for the increased malignancy risk post-HT. Furthermore, it was not possible to further categorize renal insufficiency in all six CKD stadia due to the fact that the group sizes would become too small to perform adequate statistical analysis. Larger cohorts are needed to investigate whether the malignancy risk in this patient population increases with every CKD stage.

Conclusions

In the current study, we identified CKD pre-HT and age at HF onset as risk factors that were associated with the malignancy risk post-HT. However, the duration of HF before the HT did not influence malignancy risk post-HT. Further investigation is needed to explore this association.

Conflict of interest

All authors declare no conflict of interest.

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No funding was obtained for this study.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Complete univariate Cox proportional hazards regression model for malignancies post-HT.
Univariate cox analyses are shown with hazard ratios (confidence intervals).
Abbreviations: ATG, anti-thymocyte globulin; BMI, body mass index; CKD, chronic kidney disease; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disorder; CRP, C-reactive protein; EBV, Epstein–Barr virus; HF, heart failure; HR, hazard ratio; HT, heart transplantation; LD, lactate dehydrogenase; MCS, mechanical circulatory support; MMF, mycophenolate mofetil; n, number; NYHA, New York Heart Association; PAD, peripheral artery disease; y, year.

Table S2. Clinical characteristics of patients with and without a solid organ malignancy post-HT.
Categorical variables are presented as %. Continuous values are expressed as medians and interquartile range (median, (IQR)).
Abbreviations: 1y, 1 year post-heart transplantation; CHD, congenital heart disease; CKD, chronic kidney disease; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disorder; EBV, Epstein–Barr virus; HF, heart failure; HT, heart transplantation; IQR, interquartile range; MMF, mycophenolate mofetil; n, number; PAD, peripheral artery disease.

Table S3. Complete univariate Cox proportional hazards regression model for solid organ malignancies post-HT.
Univariate cox analyses are shown with hazard ratios (confidence intervals).
Abbreviations: ATG, anti-thymocyte globulin; BMI, body mass index; CKD, chronic kidney disease; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disorder; CRP, C-reactive protein; EBV, Epstein–Barr virus; HF, heart failure; HR, hazard ratio; HT, heart transplantation; LD, lactate dehydrogenase; MCS, mechanical circulatory support; MMF, mycophenolate mofetil; n, number; NYHA, New York Heart Association; PAD, peripheral artery disease; y, year.

Table S4. Risk factors for solid organ malignancies post-HT.
Univariate and multivariable cox analyses are shown with hazard ratios (confidence intervals).
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HF, heart failure, HR, hazard ratio; HT, heart transplantation.

Table S5. Complete univariate Cox proportional hazards regression model for malignancies post-HT, excluding patients with durable mechanical circulatory support.
Univariate cox analyses are shown with hazard ratios (confidence intervals).
Abbreviations: ATG, anti-thymocyte globulin; BMI, body mass index; CKD, chronic kidney disease; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disorder; CRP, C-reactive protein; EBV, Epstein–Barr virus; HF, heart failure; HR, hazard ratio; HT, heart transplantation; LD, lactate dehydrogenase; MCS, mechanical circulatory support; MMF, mycophenolate mofetil; n, number; NYHA, New York Heart Association; PAD, peripheral artery disease; y, year.

Table S6. *Risk factors for malignancies post-HT, excluding patients with durable mechanical circulatory support.*
Univariate and multivariable cox analyses are shown with hazard ratios (confidence intervals).
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; EBV, Epstein–Barr virus; HF, heart failure, HR, hazard ratio; HT, heart transplantation.

Table S7. *Complete univariate Cox proportional hazards regression model for solid organ malignancies post-HT, excluding patients with durable mechanical circulatory support.*
Univariate cox analyses are shown with hazard ratios (confidence intervals).
Abbreviations: ATG, anti-thymocyte globulin; BMI, body mass index; CKD, chronic kidney disease; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disorder; CRP, C-reactive protein; EBV, Epstein–Barr virus; HF, heart failure; HR, hazard ratio; HT, heart transplantation; LD, lactate dehydrogenase; MCS, mechanical circulatory support; MMF, mycophenolate mofetil; n, number; NYHA, New York Heart Association; PAD, peripheral artery disease; y, year.

Table S8. Risk factors for solid organ malignancies post-HT, excluding patients with durable mechanical circulatory support.
Univariate and multivariable cox analyses are shown with hazard ratios (confidence intervals).
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HF, heart failure, HR, hazard ratio; HT, heart transplantation.

Figure S1. Cumulative incidence of malignancies post-HT according to age at HT (A) and presence of CKD pre-HT (B).
Abbreviations: CKD, chronic kidney disease; HT, heart transplantation.

Figure S2. Cumulative incidence of solid organ malignancies post-HT according to presence of CKD pre-HT.
Abbreviations: CKD, chronic kidney disease; EBV, Epstein Barr virus; HT, heart transplantation.

Figure S3. Cumulative survival post-HT conditional on surviving the first 3 months post-HT.
Abbreviations: HT, heart transplantation.

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