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ORIGINAL ARTICLE

Graft intolerance syndrome requiring graft nephrectomy after late kidney graft failure: can it be predicted? A retrospective cohort study

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SUMMARY

Graft nephrectomy is recommended in case of early graft failure. When the graft fails more than 3–6 months after transplantation, it is current practice to follow a wait-and-see policy. A common indication for graft removal is the graft intolerance syndrome. We aimed to create a risk prediction model for the occurrence of graft intolerance resulting in graft nephrectomy. We collected data of kidney transplantations performed in our center between 1980 and 2010 that failed at least 6 months after transplantation. We evaluated the association between baseline characteristics and the occurrence of graft nephrectomy because of graft intolerance using a competing risk regression model. Prognostic factors were included in a multivariate prediction model. In- and exclusion criteria were met in 288 cases. In 48 patients, the graft was removed because of graft intolerance. Donor age, the number of rejections, and shorter graft survival were predictive factors for graft nephrectomy because of the graft intolerance syndrome. These factors were included in a prediction rule. Using donor age, graft survival, and the number of rejections, clinicians can predict the need for graft nephrectomy with a reasonable accuracy.

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Key words
graft intolerance syndrome, graft nephrectomy, kidney graft failure

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Introduction

The number of kidney transplantations and therefore the number of patients with a failed kidney graft, returning to dialysis therapy is increasing. Mortality after graft failure is high, with mortality rates more than three times higher compared to patients with a functioning graft [1]. The main causes of death after graft failure are cardiovascular events and infections. Dialysis patients with a failed graft commonly experience a chronic inflammatory state, which could contribute to cardiovascular morbidity and mortality [2].

After reinstitution of dialysis, the failed graft can be removed or left *in situ*. In the case of early graft failure, *that is*, within three to 6 months after transplantation, graft nephrectomy is universally recommended in order to avoid systemic and local effects of acute rejection. After late graft failure, the risk of acute rejection is presumably much smaller, and the graft is usually left *in situ*. Widely accepted indications for graft nephrectomy are as follows: (i) to create space for retransplantation, (ii) to enable immediate complete withdrawal of immunosuppression, (iii) graft malignancy, and (iv) graft intolerance.

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Graft intolerance is a clinical syndrome of pain or swelling of the graft, hematuria, fever, malaise, or refractory anemia with raised C-reactive protein [3]. It occurs in 30–50% of patients with graft failure, and mostly within the first year of dialysis initiation despite various immunosuppression withdrawal protocols. It reflects a chronic inflammatory state induced by the retained graft.

Various predictive factors for the need for graft nephrectomy have been identified in small observational studies. For example, early graft failure (<1 year after transplantation) is more likely to result in graft nephrectomy [4]. Moreover, Madore *et al.* [5] identified the history of multiple rejections as risk factor for graft intolerance and consecutively graft nephrectomy. Additionally, tapering of immunosuppressive medication was found to be associated with a higher rate of graft nephrectomy compared to maintenance on medication. Maintaining immunosuppression, however, can also be regarded as unfavorable because of a higher risk of infections [6].

Unfortunately, graft nephrectomy is associated with considerable morbidity and mortality, with bleeding being the leading cause of morbidity and infection the main cause of mortality [7,8]. It also increases the likelihood of developing antibodies to human leukocyte antigens (HLA) [4,9]. The effect of the formation of these antibodies on subsequent kidney transplantations is unclear, as several studies show conflicting results of retransplantation [10–20].

A decision on whether or not to remove a failed graft should be made by balancing the benefits and risks for the individual patient. Usually, a watchful waiting policy is adopted in patients who are reinstituted on dialysis treatment, and in whom there is no urgent reason for graft nephrectomy. Nevertheless, in a substantial proportion of these patients, a graft nephrectomy will be required at a later stage. The ability to predict future graft nephrectomy would help decision making and may improve outcome, as a preemptive, planned intervention may minimize the risk of peri-operative morbidity and mortality [7].

Therefore, we performed a retrospective study in patients with late graft failure (defined as >6 months since transplantation) in whom a watchful waiting policy was followed. The aim of the study was to create a risk prediction model for the occurrence of graft intolerance resulting in graft nephrectomy, to be used for timely identification of patients with late graft failure who may benefit from early, elective graft nephrectomy.

Patients and methods

Patient selection and treatment

We included adult patients who received a kidney transplant in the Radboud university medical center between 1980 and 2010, and in whom the graft failed after at least 6 months since transplantation. Patients were excluded when there was a previous graft *in situ*, when graft nephrectomy was performed within 3 months after graft failure, or when duration of follow-up was less than 3 months. We excluded patients with a graft nephrectomy within 3 months after graft failure, as in these cases the indication for nephrectomy was apparently present at the time of failure, which precludes the need for prediction. In our center, graft nephrectomy after late graft failure is not a standard procedure, and in the past decades, it was our policy to perform graft nephrectomy only on indication. After graft failure, the immunosuppressive medication was stopped with immediate discontinuation of the antimetabolite, weaning of the calcineurin inhibitor in several weeks, and slow tapering of corticosteroids over a period of months.

Data collection

Patient characteristics (date of birth, gender, original kidney disease, cardiovascular co-morbidity, diabetes, and duration of dialysis previous to transplantation), donor characteristics (deceased or living and age), and data about the transplantation (HLA-mismatches, occurrence of delayed graft function, occurrence of acute rejections, graft survival, and immunosuppressive regime) were retrieved from a local transplant registry and patient records. The occurrence of rejection was determined through clinical assessment as reported in patient charts, preferably confirmed by histology results. Graft failure was defined as return to dialysis therapy. Reasons for graft nephrectomy were retrieved from patient's records as well. Graft intolerance was defined as the presence of one or more of the following clinical criteria in the absence of another plausible explanation after routine clinical examination: fever, malaise, hematuria, painful, or swollen allograft. We collected data on adverse events (bleeding, infection, and urine leakage), mortality and histopathologic findings after graft nephrectomy.

Statistical analysis

Baseline characteristics were presented as means and standard deviations, medians and interquartile ranges,

or frequencies and proportions where appropriate. The primary outcome measure was graft nephrectomy because of the graft intolerance syndrome. Graft nephrectomy for another indication (e.g. retransplantation) was handled as a competing risk. Patients with and without the need for graft nephrectomy because the graft intolerance syndrome were compared with a *t*-test or Mann–Whitney *U*-test for continuous variables, and chi-square test in case of dichotomous variables.

We used multiple imputation using chained regression equations (Stata's ice procedure) to impute missing values for all baseline covariates. Twenty imputed datasets were created. We visually checked the imputed values using scatter plots.

Next, we evaluated the association between baseline characteristics and the occurrence of graft nephrectomy because of the graft intolerance syndrome in a series of univariate survival models. As death, consecutive kidney transplantation and graft nephrectomy for another reason than graft intolerance were considered as competing events we used Fine and Gray regression [21,22]. Pooled parameter estimates were obtained using Rubin's rules (Stata's procedure). Prognostic factors that were associated ($P < 0.20$) with the outcome were included in a multivariate regression analysis. A backward selection procedure was used on each individual imputed data to create a parsimonious multivariate prediction model with P-value >0.10 for exclusion and $P < 0.05$ for re-inclusion. To adjust for overfitting, a bootstrap procedure was used during estimation with 100 repetitions per selection step. Models may differ between the imputed datasets after the backward selection procedure, making pooling using Rubin's rules impossible. Therefore, we chose to only select variables that were present in at least 18 of the 20 imputation models, analogous to $P > 0.10$ for exclusion. Subsequently, a Fine and Gray regression model including selected variables was then fitted on all the imputed datasets to obtain pooled parameter estimates. Bootstrapping (100 reps) was used again to obtain bias-adjusted parameter estimates.

The proportional hazards assumption for the prognostic factors in the final model was checked by plotting Schoenfeld's residuals by time. The linear predictor of the most parsimonious model was used to create a prognostic index score in the original, unimputed dataset [23]. The baseline cumulative hazard function was determined at population mean of this prognostic index. We used an ordinary least squares regression with fractional polynomials to describe the cumulative base hazard. To evaluate discriminative performance, we calculated the C-index at 6, 12, 24, 36, 48, 60, and 120 months of follow-up using the R package risk [24]. We created calibration plots at the same time points. Finally, we created four risk groups based on the 16th, 50th, and 84th percentiles of the prognostic index. These risk groups reflect very low (less than −1 standard deviation [SD]), low (between −1 SD and average), high (between average and +1 SD), and very high risk (greater than +1 SD). We plotted overlays of the observed and predicted cumulative incidence of graft nephrectomy by risk group to evaluate the predictive accuracy of the model. Analyses were performed using SPSS 22, STATA 11.2 and R version 3.2.0.

Results

Study population

Figure 1 shows the flowchart for our study population. Between 1980 and 2010, 2643 kidney transplantations in adults were performed at the Radboud university medical center. A total of 716 grafts failed. Graft survival was at least 6 months in 498 of these cases. In 68 patients, graft nephrectomy was performed within 3 months after graft failure. In 30 of these 68 cases, the graft was removed because of symptomatic (ongoing) rejection. Some other causes for graft nephrectomy in this group were suspicion of malignancy ($n = 3$), PTLD ($n = 2$), serious infections with the need to stop immunosuppression ($n = 7$) and Candida infection in the graft ($n = 2$). Another 116 patients were excluded because of a follow-up of less than 3 months (16 due to death, 13 due to retransplantation, and 87 patients were lost to follow-up), and 26 patients had a previous graft *in situ*. Late graft nephrectomy was performed in 74 patients of whom 48 had a graft intolerance syndrome. Other reasons for graft nephrectomy were infection ($n = 6$), hypertension ($n = 5$), malignancy ($n = 4$), to create space for retransplantation ($n = 4$), and kidney stones ($n = 2$). In five patients, the reason for graft nephrectomy was unknown. Consequently, we could include 288 patients for analysis, 214 with a graft *in situ* at latest follow-up and 74 with a graft nephrectomy, of which 48 because of graft intolerance. Median time to graft nephrectomy in our study cohort was 7.2 months (IQR: 4.3–10.0) after graft failure when graft nephrectomy was performed for the graft intolerance syndrome and 6.0 months (IQR: 3.9–21.5) when graft nephrectomy was performed for another reason. Median follow-up in the patients with a nonfunctioning graft remaining *in situ* was 21.0 months (IQR: 10.8–47.0) after graft

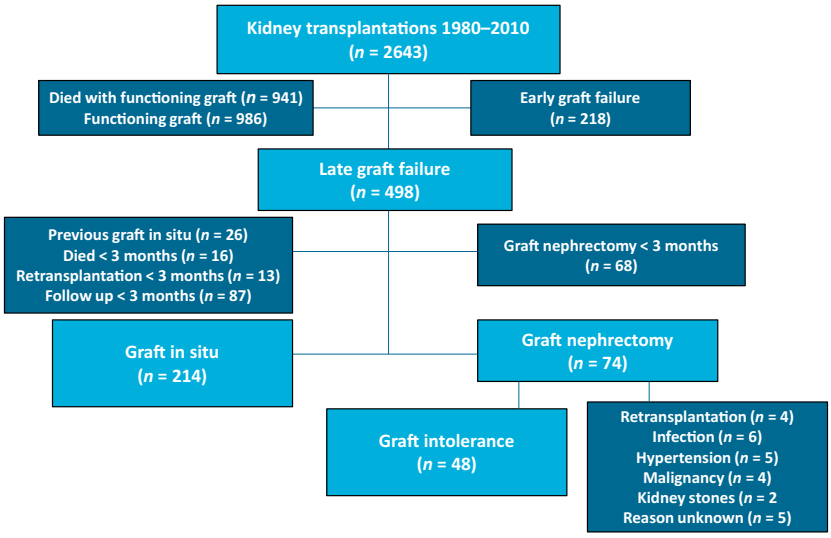

Figure 1 Flowchart for the in- and exclusion of patients.

failure. The cumulative incidence of graft nephrectomy after graft failure is shown in Fig. 2.

Patient and transplantation characteristics of patients with and without graft nephrectomy are shown in Table 1. Patients who underwent graft nephrectomy because of graft intolerance were younger on average compared to patients in the other groups. Furthermore, mean donor age and the proportion of patients with 2 or more HLA-mismatches were higher in the graft intolerance group. Finally, these patients were more likely to have suffered from acute rejection episodes (both early <3 months after transplantation and late) and had a shorter median graft survival time compared to patients without a graft nephrectomy.

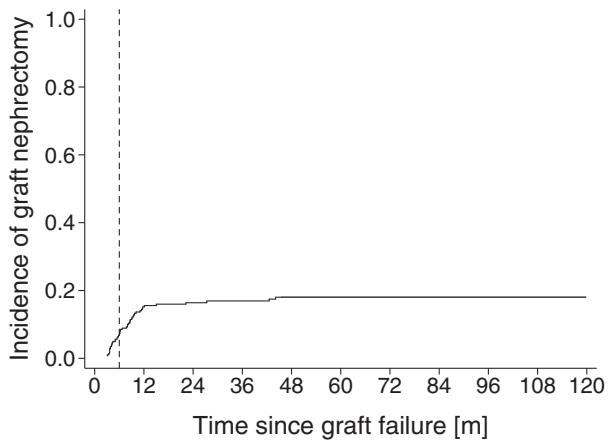

Figure 2 Cumulative incidence of graft nephrectomy. The cumulative incidence was estimated using a competing risk method. Death prior to graft nephrectomy, retransplantation, and graft nephrectomy for another reason than graft intolerance were considered competing events.

Predictive factors for graft nephrectomy

Results of our regression analyses are shown in Table 2. In multivariate analysis, donor age and the total number of rejections were predictive factors for graft nephrectomy because of graft intolerance. A better graft survival was inversely associated with graft nephrectomy.

We included these three variables in our prediction rule. We created a prognostic index (PI) with the parameter estimates of each of these three variables (i.e. the natural logarithm of the subhazard ratio). A baseline cumulative hazard was estimated at the population mean for the prognostic index. Using the PI and baseline cumulative hazard, we calculated predicted risk functions.

$$\textit{Log baseline cumulative hazard}:$$
$$\ln H_0(t) = -2.0252 - 32.3433t^{-2} + 0.0126t^{-0.5}$$

$$\begin{aligned}&\text{Prognostic index (PI)}:\\ \text{PI} = {}& 0.027 \times \text{donor age [in years]} - 0.011 \times\\ & \text{graft survival [in months]} + 0.336\times\\ & \text{total number of rejections}\end{aligned}$$

$$\text{Risk of graft nephrectomy at time } t:$$
$$R(t) = 1 - \exp[-\exp(\ln H_0(t))]^{\exp(\text{PI})}$$

The C-statistic for the final model was approximately 0.69 at all follow-up times considered. Figure 3 shows calibration plots by follow-up time. The green line is the line of identity denoting perfect calibration. The red line shows the predicted versus observed risk of graft nephrectomy in our population. The gray shaded area is the 95% confidence interval for the calibration. The

Table 1. Patient and transplantation characteristics at time of graft failure.

	Allograft *in situ* $n = 214$	Graft nephrectomy		P*
		Graft intolerance $n = 48$	Other indication $n = 26$	
Patient characteristics				
Male (%)	140 (65.4)	33 (68.8)	14 (53.8)	0.66
Age at graft failure (median ± IQR)	46.0 (39–56)	39.5 (31–56)	41.0 (35–56)	0.17
Smoking (%)	93 (43.5)	14 (29.2)	12 (46.2)	0.05
Missing	28 (13.1)	6 (12.5)	0	
Cardiovascular co-morbidity (%)	67 (31.3)	9 (18.8)	6 (23.1)	0.08
Missing	16 (7.5)	4 (8.3)	0	
Dialysis before transplantation (%)	207 (96.7)	45 (93.8)	24 (92.3)	0.33
Dialysis duration (years) (median)	1.7 (1.0–3.6)	2.5 (1.2–4.6)	1.9 (0.9–3.1)	0.51
Transplantation characteristics				
Rank number of transplantation				
1	190 (88.8)	39 (81.3)	23 (88.5)	0.11
2	19 (8.9)	5 (10.4)	2 (7.7)	
3	4 (1.9)	4 (8.3)	1 (3.8)	
4	1 (0.5)	0	0	
Decade of transplantation				
1980–1990	79 (36.9)	12 (25.0)	10 (38.5)	0.20
1990–2000	103 (48.1)	25 (52.1)	14 (53.8)	
2000–2010	32 (15.0)	11 (22.9)	2 (7.7)	
Deceased donor (%)	173 (80.8)	39 (81.3)	21 (80.8)	0.95
Donor age (median)	42.2 (24–53)	51.0 (40–57)	35.2 (21–55)	<0.01
HLA-mismatches (%)				
0	30 (14.0)	4 (8.3)	3 (13.6)	0.26
1	41 (19.2)	4 (8.3)	5 (22.7)	
2	52 (24.3)	12 (25.0)	6 (27.3)	
3	63 (29.4)	20 (41.7)	7 (31.8)	
4	24 (11.2)	6 (12.5)	1 (4.5)	
5	4 (1.9)	2 (4.2)	0	
>2 HLA-mismatches	91 (42.5)	28 (58.3)	8 (36.4)	0.05
Cold ischemia time (h) (median)	26.1 (19.7–34.5)	22.6 (14.2–28.5)	26.3 (22.4–32.1)	0.08
Delayed graft function (%)	54 (25.2)	16 (33.3)	5 (19.2)	0.25
Acute rejection†				
<3 months (%)	83 (38.8)	25 (52.1)	18 (69.2)	0.09
>3 months (%)	78 (36.4)	26 (54.2)	13 (50)	0.02
Number of rejections				
0	85 (39.7)	7 (14.6)	3 (11.5)	0.02
1	92 (43.0)	29 (60.4)	14 (53.8)	
2	34 (15.9)	11 (22.9)	9 (34.6)	
>2	3 (1.4)	1 (2.1)	0	
Graft survival in months (median)	79.9 (45.0–136.9)	46.1 (22.0–85.7)	67 (30–117)	<0.01
Prednisolone dose at time of graft failure				
0	49 (23.0)	12 (25.0)	2 (7.7)	0.20
≤10 mg	136 (63.8)	25 (52.1)	21 (80.8)	
>10–20 mg	24 (11.3)	8 (16.7)	2 (7.7)	
>20 mg	4 (1.9)	3 (6.3)	1 (3.8)	
Use of calcineurin inhibitor at time of graft failure (%)	63 (29.4)	14 (29.2)	8 (57.1)	0.92
Missing	62 (29.0)	15 (31.3)	12 (46.1)	

*P-value for allograft *in situ* versus graft nephrectomy for graft intolerance.

†Occurrence of acute rejection is defined as antirejection therapy with or without biopsy proven rejection.

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Table 2. Hazard ratios (Fine & Gray regression) for graft nephrectomy because of graft intolerance syndrome. Hazard ratios with a p-value ≤ 0.10 are presented in bold.

	Univariate analysis Hazard ratio (95%-confidence interval)	*P*	Multivariate analysis Hazard ratio (95%-confidence interval)	*P*
Patient characteristics				
Male sex	0.83 (0.45–1.53)	0.55		
Age at graft failure (years)	**0.97 (0.94–1.00)**	**0.04**		
Smoking	0.72 (0.39–1.31)	0.28		
Cardiovascular co-morbidity	0.83 (0.49–1.42)	0.50		
Duration of dialysis (years)	**1.13 (1.02–1.25)**	**0.02**		
Transplantation characteristics				
Living donor	0.94 (0.46–1.92)	0.86		
Donor age (years)	**1.03 (1.01–1.04)**	**<0.01**	**1.03 (1.01–1.04)**	**<0.01**
HLA-mismatches				
0–2	**1**			
>2	**1.81 (1.02–3.21)**	**0.04**		
Delayed graft function	1.48 (0.81–2.68)	0.20		
Acute rejection <3 months	1.44 (0.82–2.54)	0.20		
Late acute rejection >3 months	**1.81 (1.03–3.18)**	**0.04**		
Total number of rejections (ref: 0)	**1.49 (1.10–2.00)**	**0.01**	**1.40 (0.94–2.08)**	**0.10**
Graft survival (months)	**0.99 (0.98–1.00)**	**<0.01**	**0.99 (0.98–1.00)**	**0.01**
Prednisolone dose at graft failure				
0	1			
≤10 mg	0.70 (0.35–1.40)	0.32		
>10 mg	1.42 (0.63–3.20)	0.40		
Calcineurin inhibitor at graft failure	1.03 (0.53–2.02)	0.92		

model tended to overestimate risk in the highest risk patients during early follow-up, and to underestimate the risk in these patients during later follow-up. Calibration was optimal over a time window of 36 months.

Figure 4 shows the predicted (dotted lines) and observed (solid lines) cumulative incidence of graft nephrectomy by four risk groups. In the high-risk group, our model seems to underestimate the risk of graft nephrectomy because the graft intolerance syndrome. In the intermediate risk groups, both discrimination and calibration were good as indicated by curves for observed cumulative incidence of graft nephrectomy, and only one patient in the lowest risk group needed graft nephrectomy.

In Table 3, we provide an example for the clinical application of the model by presenting the calculated risk of graft nephrectomy in three imaginary patients. An Excel sheet to calculate predicted risk is provided in the Appendix S1.

Adverse events after graft nephrectomy for graft intolerance

The total number of patients with one or more complications after graft nephrectomy because of graft intolerance was fifteen. There were local infections in four patients (three requiring surgical intervention). Postoperative bleeding occurred in 10 patients (four requiring surgical intervention). Other complications were an occlusive lesion of the external iliac artery with need for a vascular bypass ($n = 1$), lymphocele ($n = 1$), and occlusion of the arteriovenous dialysis fistula ($n = 1$). In the group with graft nephrectomy because of the graft intolerance syndrome, none of the patients died (within 30 days) after graft removal. In the group of 26 patients with a graft nephrectomy for another indication two patients died within 30 days of the graft removal, one of them due to a severe sepsis with multiple organ failure and the other patient probably due to a cardiac event.

Histopathology of grafts

Histopathology reports were available for 45 of 48 removed grafts that were removed because of graft intolerance. There were signs of rejection (acute or chronic) in all assessable grafts. In three grafts, the presence of rejection could not be determined because of necrosis. Other relevant reported findings were as

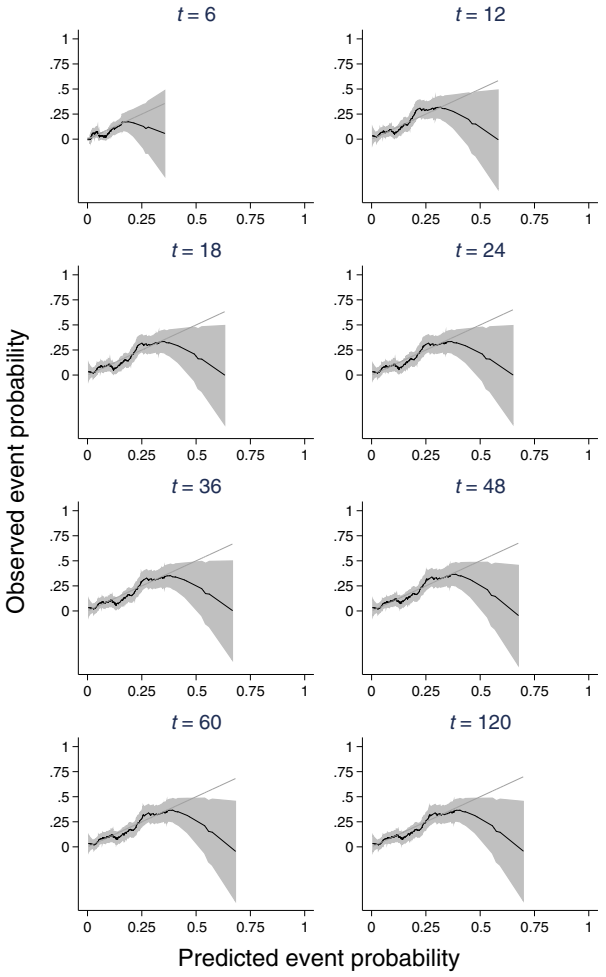

Figure 3 Calibration by follow-up time. The solid line illustrates the predicted versus the observed event probability with the 95% confidence interval in gray. The diagonal line is the line of identity denoting perfect calibration. In the very high-risk range, data were sparse, and no events were observed. Therefore, the predicted risk overestimates the actual risk in this range.

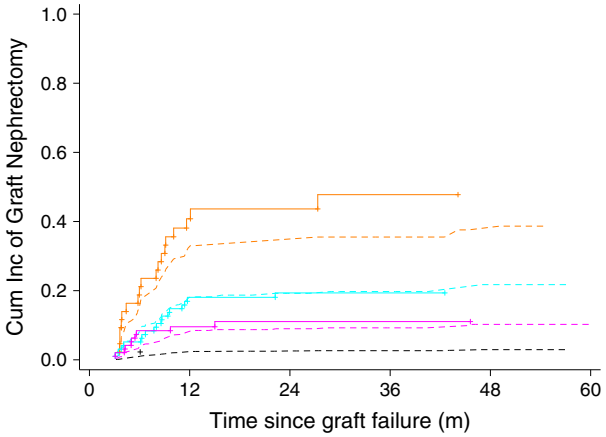

Figure 4 Predicted and observed cumulative incidence of graft nephrectomy by four risk groups based on the prognostic index. Black line: very low risk (<1 SD under mean risk). Purple line: low risk (−1 SD to mean risk). Green line: high risk (mean risk to +1 SD). Orange line: very high risk (>1 SD above mean risk). The solid lines are the Kaplan–Meier estimates and the dotted lines the predicted survival according to the prognostic model. "+" indicates a graft nephrectomy event.

Table 3. Risks for graft intolerance requiring graft nephrectomy for three imaginary patients.

	Patient 1	Patient 2	Patient 3
Donor age (years)	30	40	50
Graft survival (months)	60	48	24
Number of rejections	0	1	2
Risk of graft nephrectomy			
6 months	9.4%	18.6%	38.7%
1 year	17.5%	33.2%	61.8%
5 years	21.2%	39.3%	69.7%

follows: a renal cell carcinoma ($n = 1$), membranous nephropathy ($n = 1$), CMV localization ($n = 1$), and signs of diabetic nephropathy ($n = 1$).

Discussion

Prediction model

We created a model to predict risk of graft nephrectomy in patients with graft failure beyond 6 months after transplantation. To the best of our knowledge, the present study is the first to provide a prediction model for graft nephrectomy after late graft failure. The model includes donor age, number of rejections, and graft survival as prognostic factors. The strongest predictor of graft intolerance and consecutive graft nephrectomy in our cohort was the number of acute rejections. The total incidence of acute rejection was relatively high in both groups (70%), which is not unexpected in a cohort of patients with graft failure. In addition, this reflects the inclusion of patients who underwent transplantation in an era with higher rates of rejection. Graft survival was shorter in the group with graft nephrectomy (46 months) compared to the group with the graft remaining *in situ* after graft failure (80 months). The shorter graft survival reflects a more devastating course of transplantation. This is consistent with different studies in which allograft nephrectomy was more frequent in patients with early (<1 year) compared to late graft failure [4,7,12,13]. Apart from rejection and graft survival, older age of the donor was associated with graft intolerance in our multivariate analysis. This

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factor has been associated with an increased alloimmune response against the graft resulting in higher rates of acute rejection [25]. The total incidence of graft nephrectomy after late graft failure (graft survival >6 months) in our center was 28.5% during the study period. The incidence in various other studies varies from 4.5% to 84.4% [7,9]. These studies were heterogeneous with varying policies regarding the removal of failed grafts. In a large USRDS cohort (1995–2003), nephrectomy was performed in 27% of 15 400 patients with late graft failure (graft survival >1 year) [4,7,26–30]. In our cohort, most graft nephrectomies were performed shortly after graft failure (88% within 1 year), which is in agreement with findings in other studies [4,7].

Complications of graft nephrectomy

Importantly, one in three patients who underwent graft nephrectomy had a complication highlighting the risks associated with the procedure. In our cohort two patients died, while mortality rates in previous studies were between 1.3% and 9.5% and in the past mortality rates were even higher [4]. Taking into account all 142 graft nephrectomies (including early graft removals), the mortality rate in our center was 2.8%; four patients died within 30 days after graft nephrectomy. Two of them had an active infection at the time of surgery and two needed urgent graft nephrectomy shortly after graft failure, respectively due to thrombosis of the renal artery and suspicion of graft intolerance (fever, pancytopenia) which turned out to be caused by an aggressive lymphoma with a hemophagocytic syndrome.

Strengths and limitations

The retrospective design of our study has several limitations. First, we cannot completely exclude that the clinical decision to perform a graft nephrectomy was actually based on factors found in our prediction model, which would imply that the model is the mere representation of a self-fulfilling prophecy. To avoid possible bias, we excluded all cases of graft nephrectomy performed within 3 months after graft failure as in these cases obvious reasons for graft nephrectomy were likely to be present at the time of graft failure. In the remaining cases, a wait-and-see policy was followed, and graft nephrectomy was performed because of a graft intolerance syndrome that was not present at the time of graft failure. Second, our model did not include the tapering schedule of immunosuppressive medication after graft failure, as detailed data on this subject were not available. In patients with a history of numerous rejections and thus a high risk of graft intolerance, a slower tapering might prevent the need for graft nephrectomy. There is limited data on the risk of maintaining or weaning of immunosuppressive therapy after graft failure. One study showed that continuation of a full immunosuppressive regime can prevent the need for graft nephrectomy, but maintenance on low-dose prednisone monotherapy does not [31]. Accordingly, another study showed no beneficial effect on the number of acute rejections or "graft intolerance" of low-dose maintenance immunosuppression (mainly corticosteroids). However, maintenance on low-dose immunosuppression was associated with more infections and cardiovascular morbidity [32].

Finally, we recognize that our study only included patients who received a kidney graft in our center, which may limit the applicability of our prediction model to other populations. As a next step, external validation of our findings in a different cohort is needed.

Clinical and research recommendations

Currently, it is common practice to delay graft nephrectomy in patients with late graft failure until symptoms of graft intolerance become manifest. However, the graft intolerance syndrome is frequently recognized in a relatively late stage, exposing the patient to the adverse effects of an inflammatory condition, which increases the risks of morbidity and mortality associated with surgery. Notably, graft nephrectomy is considered to be a procedure with high morbidity (17–60%) and mortality (1.5–14%) [9]. Moreover, it has been shown that urgent graft nephrectomy is associated with almost twice the incidence of complications and increased peri-operative mortality as compared to nonurgent graft nephrectomy [7]. Planning a preemptive graft nephrectomy could therefore be preferable in patients who are at high risk of experiencing graft intolerance syndrome.

In balancing the pro's and con's of an early, preemptive graft nephrectomy, the consequences of graft nephrectomy on the formation of anti-HLA antibodies and results of subsequent retransplantation should be considered as well. Earlier studies show conflicting results. Graft nephrectomy was shown to be followed by a rise in panel reactive antibodies, but the mechanism and the impact on outcomes are unclear. It is hypothesized that the allograft may serve as an antibody sponge and that graft nephrectomy may result in unleashing of donor-specific antibodies. However, a

rise of antibody titers has also been observed after (rapid) weaning of immunosuppression without graft nephrectomy [31].

Previous retrospective studies show a worse outcome of a subsequent transplantation after graft nephrectomy, but more recent studies, including our own data, show no significant effect of graft nephrectomy on the survival of a subsequent graft [10–18,20].

Our prediction model reaches a moderate C-statistic of 0.69. However, it is accurate in identifying high-risk patients (mean risk of 40%), and predicted risk may be a conservative estimate of the true risk in this group. For these patients, the model could potentially help in decision making.

Ultimately, a prospective clinical trial comparing preemptive graft nephrectomy versus a wait-and-see policy in patients with late graft failure and a moderate-to-high risk score for the occurrence of graft intolerance syndrome is warranted.

Conclusion

We have created a prognostic model to predict graft intolerance requiring graft nephrectomy in patients with kidney graft failure. Using donor age, the number of acute rejections and graft survival, three readily obtainable factors, clinicians can predict the need for graft nephrectomy with reasonable accuracy. The present model needs external validation before it can be implemented in clinical practice.

Authorship

KLWB: study design, data collection and interpretation, and manuscript preparation. CMV: study design, data collection and interpretation. JAJGB: statistical analyses and data interpretation. LBH: supervised all phases.

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Conflict of interest

The authors declare no conflict of interests.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1. Risk calculator for graft nephrectomy.

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