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ORIGINAL ARTICLE

Early failure of kidney transplants in the current era—a national cohort study

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SUMMARY

Although short-term outcome after kidney transplantation has improved, a small proportion of grafts are lost during the first year. We characterize in detail all early graft losses in the current era in a nationwide cohort of kidney transplant recipients. Altogether 2447 kidney transplantations, performed between June 2004 and October 2016, were included. All graft losses (return to dialysis or patient death) occurring during the first post-transplant year were characterized. During the first post-tranplant year, altogether 109 grafts were lost, 67 grafts failed, and 42 patients died. Fifty-five per cent of the deaths were due to cardiovascular causes, and 29% due to infectious causes. Twenty-one per cent of the failed grafts were primary nonfunction of unknown reason, 34% were lost due to venous thrombosis and 9% due to arterial thrombosis, but only 10 (15%) patients lost a graft due to acute cellular or humoral rejection. Independent risk factors for death included diabetes, and longer duration of pretransplant dialysis treatment, whereas risk factors for graft failure included increased level of panel-reactive antibodies and increased cold ischaemia time. Kidney allografts are rarely lost due to immunological reasons during the first post-transplant year. The most common causes of early death after transplantation are cardiovascular and infectious causes.

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Introduction

The short-term outcome of kidney transplantation has improved substantially during the past decades, and most research emphasis has been on factors associated with the lack of improvement in the long-term results [1,2]. However, one-year graft survival is not 100%, and a small proportion of grafts are still lost during the first year after transplantation, either due to loss of graft function or due to premature death of the patient. With the increasing age and comorbidities of both the recipients and the donors in the current era, an increased risk of complications and early failure is to some amount acceptable to increase the number of transplantations. Ideally, however, the high-risk patients could be identified better to help organ allocation and risk stratification.

Only a few recent studies exist, which address the short-term survival of kidney transplants and factors leading to early graft loss in the current era, [3–5], and they mostly focus only on immediate loss of graft function during the first days or first month after transplantation.

The aim of our study was to analyse factors leading to graft loss during the first post-transplant year in our cohort of a single nationwide large renal transplant

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centre, to better identify already pretransplantation the patients at risk of early death or graft failure.

Patients and methods

All kidney transplantations performed in our institution, which is the only transplant centre in Finland, between June 2004 (the start date of the electronic patient record system) and October 2016 were included in this retrospective analysis of an inception cohort. No patients transplanted during the study period were excluded from the analyses, and no patients were lost to follow-up during the first post-transplant year. All transplantations were ABO compatible, and cytotoxic cross-match negative. The rate of living donation has been very low in our institution, and 95% of the grafts are from donation after brain death. Immunosuppression after kidney transplantation was a combination of cyclosporine or tacrolimus, mycophenolate and steroids. Induction with basiliximab or ATG was given to immunologically high-risk patients.

Patients and their pre- and post-transplant data were collected from the Kidney Transplant Registry, which is a national registry for the follow-up of kidney transplant patients obliged by law. Causes of graft loss were analysed from the patient files and pathology database. Primary nonfunction of unknown cause was defined as nonfunction of the graft without any apparent cause in the kidney biopsy (in addition to acute tubular necrosis), that is acute antibody-mediated or cellular rejection was ruled out as the cause of graft failure. Causes of death were evaluated and reported to the registry by the treating nephrologist, and in case of missing data, the causes of death were acquired based on the individual social security code from the official National Death Register at the Statistics Finland. There were no missing causes of graft loss or death. All patients with a graft loss or death during the first year after transplantation were analysed in detail from the electronic patient records. This study had the approval of the institutional review board of Helsinki University Hospital.

Survival probabilities were estimated using the Kaplan–Meier method with death with a functioning graft, graft failure or the composite endpoint of death with a functioning graft or graft loss as the as the event. The association between patient survival after transplantation and patient characteristics was analysed using multivariable Cox proportional hazards models, with death, graft loss or the composite endpoint of death with a functioning graft or graft loss as the binary outcomes. Based on the recommendation, we did not include more than one variable per ten events in the multivariable models [6]. Those variables, which were available from the registry and which described patient characteristics before or at the time of transplantation, were included in univariable analyses, as the purpose of this study was to identify pretransplant risk factors for early graft loss. Variables that were significant risk factors in univariable analyses ($P < 0.10$) were selected to the multivariable models. All first-degree interactions between the variables were analysed, and no statistically significant interactions were found. All the analyses were also performed including only recipients of transplants from a deceased donor with similar results (data not shown), and therefore, all the patients in the cohort were selected to the final models. The calculations were performed using IBM SPSS Statistics (version 21, IBM Corporation, Somers, NY). Two-sided P-values < 0.05 were considered statistically significant. Data are expressed as mean $\pm$ 1 standard deviation in normally distributed variables and as median (interquartile rage) in variables that were not normally distributed.

Results

Altogether 2447 kidney transplantations were performed in our institution between June 2004 and October 2016. Patients are characterized in detail in Table 1. During the first post-transplant year, altogether 109 grafts were lost, of which 42 due to patient death and 67 due to loss of kidney function and return to dialysis. One-year graft survival was 95.5%, and one-year patient survival was 98.3%.

Early death after transplantation

Of the 42 deaths, six (14%) occurred during the first post-transplant month, and 16 (38%) during the first 3 months after transplantation. Causes of death during the first post-transplant year are depicted in Figure 1a. Of the deaths, 23 (55%) were due to cardiovascular causes, including 17 deaths due to coronary artery disease, three due to pulmonary embolism and three due to stroke. Infectious causes of death were identified in 12 (29%) patients, and included four deaths due to Influenza A (H1N1), four due to bacterial pneumonia, two due to invasive mucormycosis, one due to atypical mycobacterial infection and one due to *Staphylococcus Aureus* septicaemia. In addition, three deaths (7%) were due to malignancies, and four (9%) due to other causes.

Causes of graft failure

The reasons for graft failure during the first post-transplant year while the patient stayed alive are depicted in

Table 1. Patients transplanted between June 2004 and October 2016 in our institution (N = 2447).

Mean age	49 ± 16
Male/Female (%)	65/35%
Patients with retransplantation (%)	259 (11)
Cause of end-stage renal disease (%)	
Diabetic nephropathy	642 (26)
Glomerulonephritis	691 (28)
Polycystic kidney disease	428 (18)
Other	686 (28)
Deceased donor (vs. living donor) (%)	2321 (95)
Patients on cyclosporine (vs. tacrolimus) (%)	1813 (74)
Mean cold ischaemia time (h)	20 ± 6
HLA A and B mismatch	1.8 ± 0.9
HLA DR mismatch	0.7 ± 0.6
Number of patients with positive class I PRA before transplantation (%)*	1145 (47)
Mean maximal PRA I before transplantation in patients with detected PRA (%)	39 ± 37
Number of patients with positive class II PRA before transplantation (%)*	444 (18)
Mean maximal PRA II before transplantation in patients with detected PRA (%)	59 ± 33
Delayed graft function (%)	856 (35)
Mean donor age	51 ± 15
Median duration of dialysis before transplantation (months)	24 (interquartile range 29)

Mean ± SD unless otherwise indicated. PRA, panel-reactive antibodies.

*All patients had PRA class I and II % measured before transplantation.

Figure 1b. Of the failed grafts, 14 (21%) were primary nonfunction of unknown reason, 23 (34%) were lost due to venous thrombosis and six (9%) due to arterial thrombosis, 10 (15%) due to acute cellular or antibody-mediated rejection unresponsive to treatment, four (6%) due to recurrence of primary disease, two (3%) due to acute thrombotic microangiopathy and eight (12%) due to other reasons. In the whole population, the incidence of primary nonfunction of unknown reason was 0.6%, the incidence of venous thrombosis leading to graft loss was 0.9% and the incidence of arterial thrombosis was 0.2%. The risk of losing a graft due to acute rejection during the first year after transplantation was 0.4%.

Risk factors for graft failure after transplantation

The results of Cox regression models for early graft failure (censored for death) are expressed in Table 2. In univariable analyses, risk of early graft failure was associated with retransplantation, increased cold ischaemia time, increased donor age and increased level of panel-reactive antibodies (PRA, both class I and class II). In multivariable analysis, significant independent risk factors for graft failure included increased cold ischaemia time (hazard ratio, HR 1.08 per 1 h increase), and increased level of class I PRA (HR 1.27 per 10% increase) or class II PRA (HR 1.12 per 10% increase).

Risk factors for early death after transplantation

The results of Cox regression models for early death after transplantation are expressed in Table 3. In univariable analyses, increased recipient and donor age, number of HLA mismatches, duration of pretransplant dialysis treatment for more than 3 years and the presence of diabetes were associated with the risk of early death after transplantation. In multivariable analyses, only diabetes (HR 4.45) and dialysis duration of more than 3 years (HR 3.02) were independent predictors of early death after transplantation.

Risk factors for early composite graft loss

Risk factors for graft loss (composite endpoint including both death with a functioning graft and return to dialysis treatment) are presented in Table 4. In univariable Cox regression analyses, retransplantation, increased cold ischaemia time, increased panel-reactive antibodies (both class I and class II), increased donor age, diabetes and pretransplant dialysis duration of more than 3 years were associated with increased risk of graft loss. In multivariable analyses, increased PRA I% (HR 1.14 per 10% increase), PRA II% (HR 1.12 per 10% increase), increased donor age (HR 1.02 per one-year increase) and diabetes (OR 1.80) were independently associated with the risk of graft loss.

Discussion

Our current study demonstrates that in the modern era, the short-term prognosis of kidney transplantation is very good, with graft survival of 96% and patient survival of 98% at 1 year after transplantation. Graft failure (including primary nonfunction) was more common than early death with a functioning graft, and the most common causes of graft failure were venous thrombosis and primary nonfunction of unknown reasons, whereas the loss of kidney graft due to severe acute rejection was very rare, occurring only in 0.4% of patients after

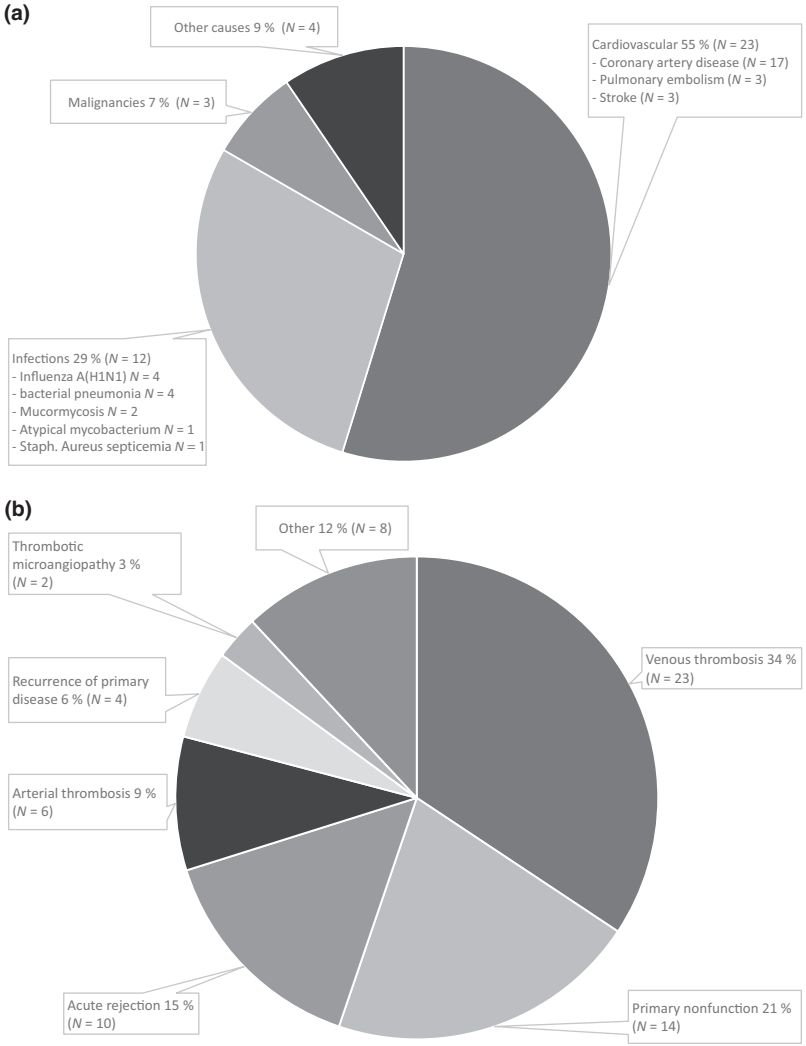

Figure 1 (a) Causes of death and (b) causes of allograft loss within the first post-transplant year.

kidney transplantation. The most common causes of death were cardiovascular causes, accounting for more than half of the early deaths. Interestingly, early death due to infectious causes was very rare, as only 12 patients (of the total 2447) died due to infections during the first post-transplant year.

A few recent studies have analysed the risk of early graft loss in the current era. In a study by Cruzado *et al.* [4], the rate of early graft loss (within 48 h of transplantation or primary nonfunction) was approximately 5%, and risk factors included first transplant, short period of dialysis and increased residual urine volume. Similarly in a study by Hamed *et al.* [5], the risk of early graft loss during the first 30 days after transplantation was 6.2%, with the most important risk factors being the use of donors after circulatory death (DCD) or extended criteria donors. The frequency of early graft loss in our current analysis seems somewhat lower compared to the previous reports, but may also be explained by the lack of DCD donors, and lower donor age in our material.

Acute rejection is a very rare cause of graft loss during the first year after transplantation, with only 0.4% of recipients losing a graft due to acute rejection within 1 year from transplantation in our current study. Despite the very low risk of graft loss due to acute rejection, higher PRA levels were associated with an increased risk of graft loss. Some evidence associates previous sensitization as a risk factor for delayed graft function [7–9], and this could similarly contribute to primary nonfunction, seen in 0.6% of patients in the current study. The data about the presence of donor-specific antibodies were unfortunately unavailable for this registry study, which limits our analyses. However, all the patients with primary nonfunction of unknown reason had multiple kidney graft biopsies performed after transplantation and had either donor-specific antibodies or flow cytometry cross-match analysed and

Table 2. Univariable and multivariable Cox regression of the risk factors for early graft failure after transplantation.

	Univariable HR (95% CI)	Multivariable HR (95% CI)
Retransplantation	3.00 (1.73–5.21), $P < 0.001$	0.67 (0.34–1.32), $P = 0.25$
Recipient age (years)	1.00 (0.98–1.01), $P = 0.89$	
Cold ischaemia time (h)	1.10 (1.05–1.16), $P < 0.001$	1.08 (1.03–1.13), $P = 0.004$
Recipient male sex	1.18 (0.71–1.99), $P = 0.52$	
Panel-reactive antibodies (PRA) II (per 10% unit increase)	1.28 (1.21–1.35), $P < 0.001$	1.12 (1.04–1.20), $P = 0.003$
PRA I (per 10% unit increase)	1.33 (1.25–1.41), $P < 0.001$	1.27 (1.17–1.37); $P < 0.001$
Number of HLA mismatches	1.03 (0.83–1.28), $P = 0.78$	
Deceased (vs. living) donor	21.77 (0.17–2720.3), $P = 0.21$	
Donor age (years)	1.02 (0.99–1.03), $P = 0.08$	1.02 (0.99–1.03), $P = 0.11$
Duration of pretransplant dialysis (reference less than year):	$P = 0.07$	$P = 0.97$
1–3 years	1.26 (0.59–2.67), $P = 0.55$	1.02 (0.47–2.23), $P = 0.95$
>3 years	2.06 (0.98–4.36), $P = 0.06$	0.99 (0.43–2.23), $P = 0.99$
Diabetes	0.62 (0.33–1.17), $P = 0.14$	

All first-degree interactions between the variables were analysed, and none were found.

Table 3. Univariable and multivariable Cox regression of the risk factors for early patient death after transplantation.

	Univariable HR (95% CI)	Multivariable HR (95% CI)
Retransplantation	1.16 (0.46–2.94), $P = 0.76$	
Recipient age (years)	1.03 (1.01–1.05), $P = 0.03$	1.02 (0.99–1.05), $P = 0.24$
Cold ischaemia time (h)	1.00 (0.96–1.05), $P = 0.94$	
Recipient male sex	0.79 (0.56–1.12), $P = 0.18$	
Panel-reactive antibodies (PRA) II (per 10% increase)	1.02 (0.91–1.14), $P = 0.74$	
PRA I (per 10% increase)	0.95 (0.86–1.07), $P = 0.43$	
Number of HLA mismatches	1.31 (1.01–1.69), $P = 0.04$	1.29 (0.98–1.71), $P = 0.07$
Deceased (vs. living) donor	2.33 (0.32–16.9), $P = 0.40$	
Donor age (years)	1.03 (1.01–1.05), $P = 0.02$	1.02 (0.99–1.05), $P = 0.14$
Duration of pretransplant dialysis (reference less than year):	$P = 0.001$	$P = 0.002$
1–3 years	1.36 (0.45–4.18), $P = 0.59$	0.99 (0.32–3.13), $P = 0.99$
>3 years	4.06 (1.41–11.7), $P = 0.009$	3.02 (1.03–8.28), $P = 0.04$
Diabetes	4.33 (2.35–7.98), $P < 0.001$	4.45 (2.40–8.28), $P < 0.001$

All first-degree interactions between the variables were analysed, and none were found.

found negative, ruling out acute antibody-mediated or cellular rejection as the cause of nonfunction. Similarly, no cases of hyperacute rejection were detected.

Venous thrombosis was the single most common reason for early graft loss in our current study with an incidence of 0.9%, which is in accordance with the previous literature reporting the rate of venous thrombosis being between 0.9% and 3.4% [10–13]. The incidence of arterial thrombosis in our current study was 0.2%, which is also similar to the range of 0.4–0.9% reported previously [10–12].

Death with a functioning graft occurred in 1.7% of patients in our material during the first year after transplantation, which is somewhat lower compared to previous reports [14,15]. Interestingly, the most common causes of death during the first year after transplantation were cardiovascular, and not infectious causes, and the risk of infectious death during the first post-transplant year in our current study was only 0.5%. This may be related to the high frequency of cyclosporine use in our cohort, and the policy of using induction therapy only in immunologically high-risk patients. Of note, three of the four patients who died due to Influenza A(H1N1) have been included in our previous description of an outbreak in our kidney transplant unit [16], showing a protective effect of pretransplant seasonal Influenza vaccination. In

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Table 4. Univariable and multivariable Cox regression of the risk factors for early graft loss (including death with a functioning graft and graft failure) after transplantation.

	Univariable HR (95% CI)	Multivariable HR (95% CI)
Retransplantation	2.21 (1.38–3.52), $P = 0.001$	0.64 (0.36–1.13), $P = 0.13$
Recipient age (years)	1.00 (0.99–1.02), $P = 0.71$	
Cold ischaemia time (h)	1.06 (1.02–1.09), $P = 0.003$	1.02 (0.98–1.07), $P = 0.34$
Recipient male sex	1.31 (0.87–1.98), $P = 0.20$	
Panel-reactive antibodies (PRA) II (per 10% increase)	1.20 (1.14–1.25), $P < 0.001$	1.12 (1.05–1.19), $P = 0.001$
PRA I (per 10% increase)	1.20 (1.14–1.25), $P < 0.001$	1.14 (1.07–1.21), $P < 0.001$
Number of HLA mismatches	1.13 (0.96–1.34), $P = 0.14$	
Deceased (vs. living) donor	5.94 (0.83–42.5), $P = 0.08$	1.89 (0.22–16.58), $P = 0.56$
Donor age (years)	1.02 (1.01–1.04), $P = 0.004$	1.02 (1.01–1.03), $P = 0.009$
Duration of pretransplant dialysis (reference less than year):	$P < 0.001$	$P = 0.04$
1–3 years	1.29 (0.69–2.41), $P = 0.43$	1.09 (0.57–2.07), $P = 0.80$
>3 years	2.68 (1.46–4.90), $P = 0.001$	1.80 (0.94–3.46), $P = 0.08$
Diabetes	1.51 (1.02–2.24), $P = 0.04$	1.80 (1.20–2.70), $P = 0.005$

All first-degree interactions between the variables were analysed, and none were found.

a recent study analysing deaths occurring during the first year after transplantation in a large cohort from United Kingdom [14], death within the first year after transplantation was reported in 3% of patients, most commonly from infectious or cardiovascular causes. Risk factors for early death included the use of deceased donors, higher recipient age, the presence of comorbidities pretransplantation and residence in a socio-economically deprived area [14]. Our study is limited by the lack of information about socio-economical status and pretransplant comorbidities. On the other hand, we identified additional risk factors for the risk of early death after transplantation, such as diabetes and increased duration of pretransplant dialysis duration. Several studies have reported the detrimental effect of pretransplant dialysis duration on patient survival after transplantation [17,18]. In our own recent analysis, increased dialysis duration was associated with increased risk of cardiovascular deaths after transplantation also in the current era [19].

Cardiovascular causes were the most common causes of death in our study, despite routine pretransplant cardiological screening. Our findings are in accordance with the previous literature, suggesting that acute coronary events are the most common causes of death, especially in the early post-transplant period [15,20–22]. In our study, diabetes was a risk factor for early death after transplantation, and similarly, previous studies have shown that the risk of cardiovascular events and death after transplantation is increased especially in patients with diabetes [15,23,24].

Our study has some limitations of note. This study is based on a patient cohort from a single centre, and the results may not be applicable to other cohorts. Although this is a single centre study, our centre is the only transplant centre in Finland, and our cohort is a nationwide complete cohort representing the whole kidney transplant population of Finland. In addition, although the treatment protocol in our institution regarding immunosuppression and surgical techniques has remained largely the same since 2004, some changes have occurred in the past few years. Most importantly, the increased number of kidney transplantations (166 transplantations in 2005 compared to 262 transplantations in 2016) performed in our institution has probably lead to acceptance of patients with more comorbidities to the waiting list, possibly associated with worse outcomes during the last years of the study cohort. On the other hand, in the current study, we describe a large single centre cohort with complete follow-up data with no missing causes of death or graft losses. Despite the large cohort, the number of events (deaths or graft losses) remains relatively low, but still large enough to adjust for multiple confounding factors in multivariable models. Our study was focused on the risk of early graft loss after transplantation, and therefore, no conclusion can be made about the association of the identified risk factors with long-term outcome. In addition, the associations seen in this registry study do not prove causality. Other, unidentified confounding factors may exist that could create a bias in the results. Most importantly, data about cardiovascular comorbidities

were not available, which may explain in part the risk associated with patients with diabetes. Data about post-transplant events (such as acute rejections, changes in immunosuppression, cardiovascular events) were not available, but on the other hand, the purpose of this registry study was to identify pretransplant risk factors to help in kidney allocation and patient selection.

In conclusion, a small proportion of grafts are still lost during the early post-transplant period, and the most common reasons for graft loss were death due to cardiovascular causes and venous thrombosis. Grafts are lost very rarely due to immunological reasons in the current era. Most important risk factors for early graft loss were the presence of diabetes, increased donor age, previous sensitization and increased duration of pretransplant dialysis.

Authorship

IH: designed the study, analysed the data and wrote the manuscript. JR: analysed the data and wrote the manuscript, PF: designed the study, contributed to statistics, analysed the data and wrote the manuscript. ML: designed the study and was the head of the registry.

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Conflicts of interest

The authors have declared no conflicts of interest.

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