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A nationwide evaluation of deceased donor kidney transplantation indicates detrimental consequences of early graft loss

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Early graft loss (EGL) is a feared outcome of kidney transplantation. Consequently, kidneys with an anticipated risk of EGL are declined for transplantation. In the most favorable scenario, with optimal use of available donor kidneys, the donor pool size is balanced by the risk of EGL, with a tradeoff dictated by the consequences of EGL. To gauge the consequence of EGL we systematically evaluated its impact in an observational study that included all 10,307 deceased-donor kidney transplantations performed in The Netherlands between 1990 and 2018. Incidence of EGL, defined as graft loss within 90 days, in primary transplantation was 8.2% (699/8,511). The main causes were graft rejection (30%), primary nonfunction (25%), and thrombosis or infarction (20%). EGL profoundly impacted short- and long-term patient survival (adjusted hazard ratio; 95% confidence interval: 8.2; 5.1-13.2 and 1.7; 1.3-2.1, respectively). Of the EGL recipients who survived 90 days after transplantation (617/699) only 440 of the 617 were relisted for re-transplantation. Of those relisted, only 298 were ultimately re-transplanted leading to an actual re-transplantation rate of 43%. Noticeably, re-transplantation was associated with a doubled incidence of EGL, but similar long-term graft survival (adjusted hazard ratio 1.1; 0.6-1.8). Thus, EGL after kidney transplantation is a medical catastrophe with high mortality rates, low relisting rates, and increased risk of recurrent EGL following re-transplantation. This implies that detrimental outcomes also involve convergence of risk factors in recipients with EGL. The 8.2% incidence of EGL minimally impacted population mortality, indicating this incidence is acceptable.

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KEYWORDS: deceased-donor kidney transplantation; early graft loss; graft survival; patient survival; primary nonfunction; re-transplantation

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Early graft loss (EGL), including primary nonfunction, is considered a catastrophic outcome of kidney transplantation. As a consequence, when donor kidneys are expected to have an increased risk of EGL, they are declined for transplantation. Although a permissive policy toward anticipated high-risk organs will result in an unacceptable high incidence of EGL, a more reticent attitude will compromise the donor use and, as such, contribute to increasing organ shortages and longer waiting-list times. Consequently, in a scenario with optimal use of available donor kidneys, the size of the donor pool is balanced by the risk of EGL, with the trade-off dictated by the impact of EGL.

To date, only 2 single-center studies have evaluated the consequences of EGL after kidney transplantation.[1,2] The authors concluded that EGL had a detrimental impact on short- and long-term patient survival. However, the low number of EGL cases did not allow an in-depth evaluation. [1,2]

Given the persistent donor organ shortage and the need to expand the donor pool without compromising outcomes, we considered a systematic, adequately powered evaluation of the

Table 1 | Descriptive characteristics of recipients with and without early graft loss after a first transplant procedure

	EGL n = 699 (8.2%)	Non-EGL n = 7812 (91.8%)	*P* value
Donor			
Donor type (% DCD)	222 (31.8)	2394 (30.6)	0.541
Age (yr)	49.8 ± 15.6	46.7 ± 16.3	<0.001
Sex (% male)	381 (54.5)	4228 (54.1)	0.845
Height (cm)	173.0 [166.8–180.0]	175.0 [168.0–180.0]	0.007
Weight (kg)	76.1 ± 17.6	75.5 ± 15.9	0.372
BMI (kg/m^2)	25.6 ± 5.0	24.8 ± 4.2	0.001
Last eGFR (CKD-EPI)	91.2 [69.6–106.1]	96.3 [75.6–111.1]	<0.001
Cause of death			<0.001
Trauma	150 (21.5)	2333 (29.9)	
Stroke	422 (60.4)	3886 (49.7)	
Cardiac arrest	30 (4.3)	446 (5.7)	
Other	97 (13.9)	1147 (14.7)	
Hypertension			0.002
Yes	157 (22.5)	1505 (19.3)	
No	321 (45.9)	4211 (53.9)	
Not registered[a]	221 (31.6)	2096 (26.8)	
Diabetes			<0.001
Yes	36 (5.1)	243 (3.1)	
No	273 (39.1)	4001 (51.2)	
Not registered[a]	390 (55.8)	3568 (45.7)	
Smoking			0.090
Yes	247 (35.3)	2870 (36.7)	
No	206 (29.5)	2826 (26.2)	
Not registered[a]	246 (35.2)	2116 (27.1)	
Cardiac arrest			0.768
Yes	176 (25.2)	1957 (25.1)	
No	379 (54.2)	4334 (55.5)	
Not registered[b]	144 (20.6)	1512 (19.5)	
Recipient			
Age (yr)	51.6 ± 14.2	51.6 ± 14.1	0.937
Sex (% male)	409 (58.5)	4698 (60.1)	0.400
Height (cm)	171.2 ± 10.5	171.4 ± 10.1	0.737
Weight (kg)	76.8 ± 15.9	74.5 ± 15.0	0.001
BMI (kg/m^2)	26.4 ± 4.8	25.3 ± 4.4	<0.001
Cause of renal failure			0.050
Diabetes	57 (8.5)	740 (9.9)	
Hypertension	80 (11.9)	881 (11.8)	
Glomerulonephritis	84 (12.5)	785 (10.5)	
(Poly)cystic kidney disease	101 (15.1)	1184 (15.9)	
Pyelonephritis	57 (8.5)	620 (8.3)	
IgA nephropathy	21 (3.1)	412 (5.5)	
Chronic renal failure, etiology unknown	100 (14.9)	1197 (16.0)	
Other	171 (25.5)	1651 (22.1)	
Preemptive			0.958
Yes	19 (2.7)	215 (2.8)	
No	679 (97.1)	7586 (97.1)	
Time on dialysis (yr)[a,c]	4.2 ± 2.4	3.8 ± 2.2	0.003
Panel reactive antibodies			0.002
<6%	601 (86.0)	7040 (90.1)	
≥6 and <85	89 (12.7)	707 (9.1)	
≥85	9 (1.3)	63 (0.8)	
Mismatches			
HLA-DR			
0	291 (41.8)	3468 (44.5)	0.242
1	368 (52.8)	3852 (49.5)	
2	38 (5.5)	465 (6.0)	
HLA-A			
0	209 (29.9)	2762 (35.4)	0.010
1	376 (53.9)	3947 (50.6)	
2	113 (16.2)	1087 (13.9)	
HLA-B			
0	127 (18.2)	2017 (25.9)	<0.001
1	413 (59.2)	4255 (54.6)	
2	158 (22.6)	1524 (19.5)	
Transplant			
First warm ischemic time in DCD grafts (min)	20.0 [16.0–27.0]	17.0 [14.0–21.0]	<0.001
Cold ischemic time (h)	22.0 [16.7–27.3]	19.1 [14.0–24.5]	<0.001
Graft anastomosis time (min)	35.0 [28.0–45.0]	33.0 [26.0–40.0]	<0.001

BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DCD, donation after circulatory death; eGFR, estimated glomerular filtration rate; EGL, early graft loss; HLA, human leukocyte antigen.

[a]The variables hypertension, smoking, and time on dialysis are consistently registered from 2000 onward.

[b]The variables diabetes and cardiac arrest are consistently registered from 2002 onward.

[c]Only applicable to non-preemptive recipients.

Data are presented as mean (±SD), median [interquartile range], or n (%).

clinical impact of EGL to be of importance. Therefore, we performed an in-depth, nationwide systematic analysis of the consequences of EGL in a cohort of 10,307 deceased donor kidney transplant procedures.

RESULTS

An evaluation of EGL was conducted in a cohort of 10,307 deceased donor kidney transplants that were performed between January 1, 1990 and January 1, 2018 in The Netherlands. Of these procedures, 8511 were primary transplant procedures. The observed incidence of EGL after a first kidney transplant was 8.2% (699 of 8511). Recipients with EGL received grafts from slightly older donors and had longer first warm ischemic, cold ischemic, as well as graft anastomosis times (Table 1). The main reported causes of EGL were rejection (30.2%), primary nonfunction (25.0%), and thrombosis or infarction (20.3%) (Table 2).

Factors associated with EGL were explored using a multivariate regression analysis. Considering the procedural and potential biological differences between organs donated after brain death (DBD) and organs donated after circulatory death (DCD), these donor types were analyzed separately. Common risk factors for the development of EGL in both DBD and DCD transplant procedures were donor age, stroke as donor's cause of death, and graft anastomosis time (Tables 3 and 4). Additional risk factors for the DCD transplant procedures were diabetes mellitus in the donor and the duration of first warm and cold ischemic time (Table 3). For

Table 2 | Causes of early graft loss after first transplant procedures

Causes of early graft loss	N = 699
Rejection	211 (30.2)
Primary nonfunction	175 (25.0)
Thrombosis or infarction	142 (20.3)
Technical or operative problems	96 (13.7)
Infection (graft- and nongraft-related)	12 (1.7)
Recurrent primary disease	10 (1.4)
Other	53 (7.6)

Data are presented as n (%).

the DBD grafts, donor's last serum creatinine, the number of years on dialysis before transplantation, and a panel reactive antibody (PRA) value ≥6% were found to further associate with EGL (Table 4). Donor characteristics, such as donor diabetes and cardiac arrest, are only registered from 2002 onward. As such, there is a high proportion of missing data (Supplementary Table S1). Additional sensitivity analyses of the multivariate models were performed for the 2002–2018 timeframe, which showed similar outcomes (Supplementary Tables 2A and B). Of note, formal significance was lost for the associations between *donor age* and *stroke as cause of death* and EGL in the DCD group ($P = 0.07$ and 0.09, respectively) (Supplementary Table S2A).

Table 3 | Multivariate analysis (odds ratio [95% confidence interval]): risk factors associated with early graft loss after a first DCD transplant procedure

	DCD
Donor	
Age (yr)	1.018 (1.003–034)[a]
Height (cm)	0.987 (0.969–1.006)
Body mass index (kg/m^2)	1.014 (0.978–1.050)
Last creatinine (μmol/l)	1.005 (0.999–1.011)
Hypertension	1.102 (0.715–1.698)
Diabetes	2.815 (1.537–5.155)[b]
Cause of death	
Trauma	Reference
Stroke	1.704 (1.051–2.764)[a]
Cardiac arrest	0.782 (0.380–1.609)
Other	1.930 (1.094–3.405)[a]
Recipient	
Cause of renal failure	
(Poly)cystic kidney disease	Reference
Diabetes	0.937 (0.464–1.894)
Hypertension	1.176 (0.602–2.297)
Glomerulonephritis	1.179 (0.543–2.563)
Pyelonephritis	0.979 (0.394–2.436)
IgA nephropathy	0.409 (0.117–1.435)
Chronic renal failure, etiology unknown	0.979 (0.518–1.849)
Other	1.238 (0.689–2.224)
Panel reactive antibodies ≥6%	1.538 (0.640–3.698)
Transplant	
First warm ischemic time (min)	1.049 (1.023–1.076)[b]
Cold ischemic time (h)	1.049 (1.014–1.085)[a]
Graft anastomosis time (min)	1.026 (1.014–1.038)[b]
Year of transplant procedure	0.962 (0.914–1.012)

DCD, donation after circulatory death.
[a]$P < 0.05$.
[b]$P < 0.005$.
Variables with $P < 0.1$ in the univariate analysis were entered.

Table 4 | Multivariate analysis (odds ratio [95% confidence interval]): risk factors associated with early graft loss after a first DBD transplant procedure

	DBD
Donor	
Age (yr)	1.030 (1.011–1.051)[a]
Height (cm)	0.978 (0.956–1.001)
BMI (kg/m^2)	0.968 (0.917–1.021)
Last creatinine (μmol/l)	1.008 (1.004–1.013)[a]
Hypertension	0.985 (0.634–1.531)
Cause of death	
Trauma	Reference
Stroke	1.982 (1.065–3.688)[b]
Cardiac arrest	1.413 (0.428–4.665)
Other	1.017 (0.365–2.832)
Recipient	
Weight (kg)	1.002 (0.979–1.026)
BMI (kg/m^2)	1.020 (0.943–1.104)
Cause of renal failure	
(Poly)cystic kidney disease	Reference
Diabetes	0.568 (0.249–1.297)
Hypertension	0.564 (0.265–1.198)
Glomerulonephritis	0.461 (0.150–1.421)
Pyelonephritis	0.861 (0.348–2.130)
IgA nephropathy	0.335 (0.075–1.492)
Chronic renal failure, etiology unknown	0.808 (0.417–1.566)
Other	1.034 (0.560–1.909)
Time on dialysis (yr)	1.127 (1.042–1.218)[a]
Panel reactive antibodies ≥6%	2.502 (1.346–4.652)[a]
Transplant	
Mismatch HLA-DR	
0	
1	1.218 (0.747–1.985)
2	1.346 (0.639–2.832)
Mismatch HLA-A	
0	
1	1.108 (0.671–1.828)
2	1.784 (0.966–3.294)
Mismatch HLA-B	
0	
1	1.409 (0.756–2.627)
2	1.392 (0.685–2.831)
Cold ischemic time (h)	1.019 (0.989–1.049)
Graft anastomosis time (min)	1.027 (1.014–1.040)[a]
Year of transplant procedure	1.012 (0.967–1.060)

BMI, body mass index; DBD, donation after brain death; HLA, human leukocyte antigen.
[a]$P < 0.005$.
[b]$P < 0.05$.
Variables with $P < 0.1$ in the univariate analysis were entered.

The consequences of EGL on mortality, relisting, re-transplantation, and outcomes of re-transplantation are summarized in Figure 1. EGL was associated with a significant increase in short-term mortality and compromised long-term patient survival. In fact, 30-day and 90-day mortality rates of the recipients with EGL were 5.2% and 11.7%, respectively (Figure 1), compared with 0.8% and 1.7% in the reference population (i.e., recipients without EGL after their first kidney transplant procedure). This survival disadvantage persisted in the long term, with a

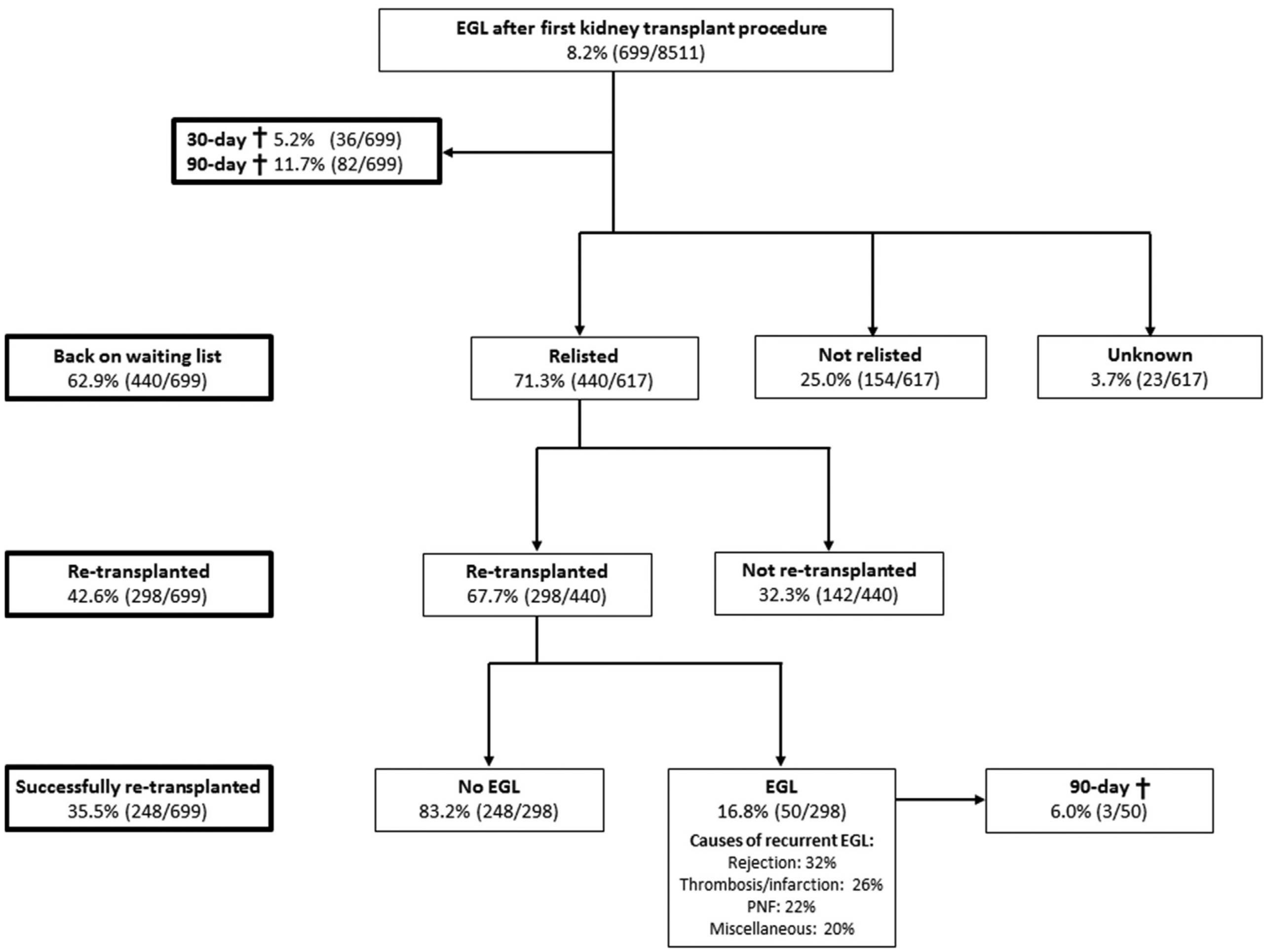


Figure 1 | The consequences of early graft loss on mortality, relisting, re-transplantation, and outcomes of re-transplantation. EGL, early graft loss; PNF, primary nonfunction.

significantly higher 10-year mortality risk (early-death censored) among the EGL recipients (adjusted hazard ratio [aHR]. 1.68; 95% confidence interval [CI], 1.33–2.13); $P < 0.001$] (Figure 2). Short-term and long-term patient survival after rejection-related or nonrejection-related EGL was similar (Supplementary Figure S1). Short-term and long-term causes of death are summarized in Table 5. The main causes of death were cardiovascular- and infection-related. The profound impact of EGL on patients experiencing EGL is clearly illustrated by a time of benefit of 5 years when compared with the estimated outcomes for patients on the waiting list (Figure 3).

Nearly three-quarters of the EGL recipients who survived 90 days after transplantation were relisted for re-transplantation, one-quarter did not return to the waiting list (Figure 1). The non-relisted recipients were approximately 10 years older than the relisted patients (Table 6). There were no indications that non-relisted patients were longer on dialysis before the initial transplant procedure (Table 6). Of the relisted patients, two-thirds were subsequently re-transplanted, resulting in an actual re-transplantation rate of 42.6% (Figure 1). The re-transplanted recipients were slightly younger compared with relisted not–re-transplanted recipients (mean age, 46.6 vs. 50.6 years, respectively) (Table 6). The proportion of immunized (45%) and highly immunized (24%) patients was equal in both groups (Table 6).

The analysis for re-transplantation showed a clear compromised outcome, with a doubled EGL incidence (16.8% vs. 8.2%, Figure 1). Among the re-transplanted patients, 83.2% were successfully re-transplanted (i.e., recipients without EGL after re-transplantation), resulting in an overall successful re-transplantation rate of 35.5% (Figure 1). For those successfully re-transplanted, 3-month and 1-year graft function (estimated glomerular filtration rate [eGFR]) was equal compared with the reference group ($P = 0.33$ and $P = 0.26$, respectively). Although long-term graft survival after re-transplantation was inferior (crude hazard ratio [HR], 1.47; 95% CI, 1.11–1.94), significance was lost after adjustment for potential confounders (aHR, 1.06; 95% CI, 0.62–1.81) (Figure 4). Subgroup analysis of long-term graft survival after rejection-related EGL showed a similar pattern: crude HR, 2.42; 95% CI, 1.59–3.70; and aHR, 1.71; 95% CI, 0.67–4.33 (Supplementary Figure S2).

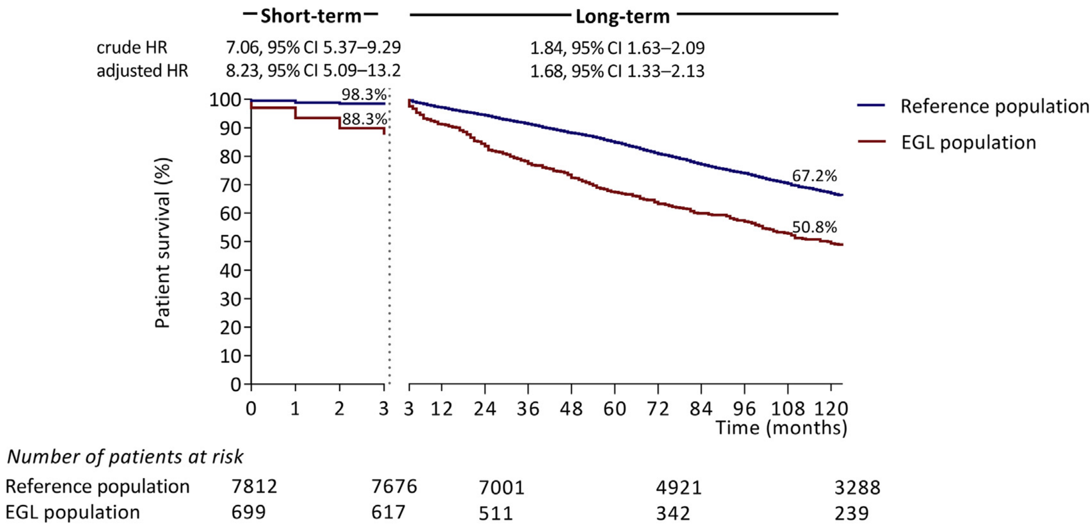


Figure 2 | Landmark analysis showing the short-term and long-term patient survival rates. Reference population: recipients without early graft loss after the first kidney transplant procedure. Early graft loss (EGL) population: recipients with early graft loss after the first kidney transplant procedure. The model adjusted for clinically relevant variables and variables with $P < 0.1$ in the univariate analysis. The short-term was adjusted for donor's cause of death, donor diabetes, recipient age, sex, height, body mass index (BMI), cause of renal failure, preemptive, time on dialysis, mismatch human leukocyte antigen (HLA)–DR, cold ischemic time, and year of transplant procedure. The long-term was adjusted for donor's cause of death, diabetes, hypertension, cardiac arrest, age, sex, height, BMI, last creatinine and recipient age, sex, weight, BMI, cause of renal failure, preemptive, time on dialysis, panel reactive antibodies, mismatch HLA-DR, HLA-A, and HLA-B; graft anastomosis time, and year of transplant procedure. CI, confidence interval; HR, hazard ratio.

Evaluation of a possible time effect showed a clear decrease in incidence of EGL over time ($P < 0.001$), yet the consequences of EGL were not influenced by time (Supplementary Table S3).

In the light of the profound impact of EGL, the question arises as to whether a more strict policy with regard to donor pool–quality by only accepting grafts with a minimal chance of EGL (and thus longer waiting lists) outweighs waiting list mortality. Data for the Dutch cohort studied herein allowed for the evaluation of the impact of the 8.2% *a priori* risk of EGL on recipient survival. Figure 5 shows that the 8.2% EGL risk for the Dutch donor pool minimally affects recipient survival (aHR [0% EGL is reference], 1.15; 95% CI, 0.99–1.34; $P = 0.07$) and that the consequences associated with a 8.2% EGL risk clearly outweighs simulated waiting-list mortality.

Table 5 | Causes of death among primary transplant recipients with early graft loss

	Short-term mortality		Long-term mortality
	≤ 30 d	> 30 and ≤ 90 d	> 90 d and ≤ 10 yr
Infections	10 (27.8)	13 (28.3)	56 (20.2)
Hemorrhage	2 (5.6)	5 (10.9)	8 (2.9)
Cardiovascular	13 (36.1)	5 (10.9)	43 (15.5)
Cerebrovascular	1 (2.8)	1 (2.2)	13 (4.7)
Dialysis-related[a]	–	–	27 (9.7)
Malignancy	–	1 (2.2)	14 (5.1)
Miscellaneous	8 (22.2)	8 (17.4)	12 (4.3)
Not determined	2 (5.6)	13 (28.3)	104 (37.5)
Total	36	46	277

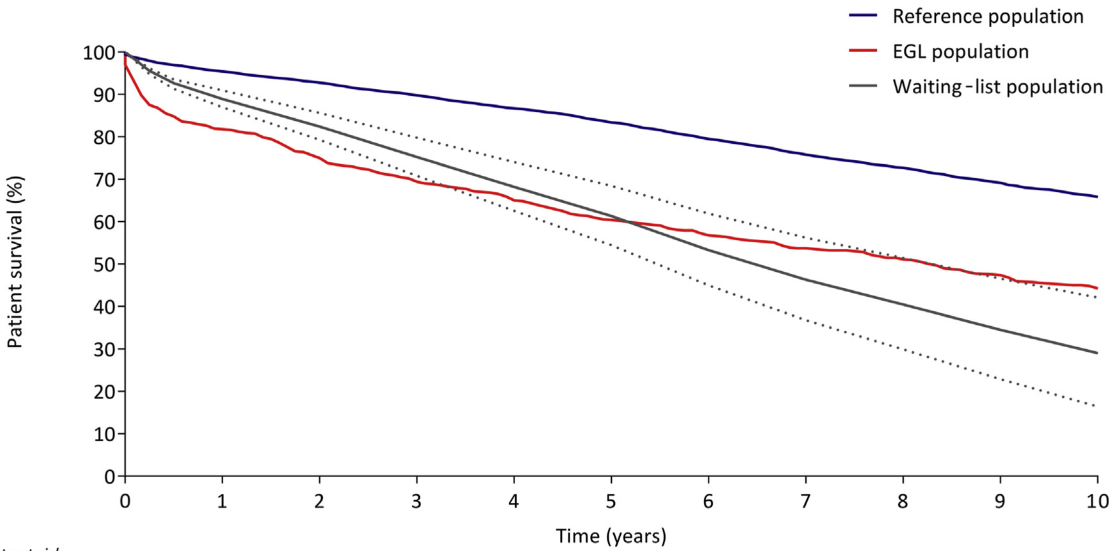
[a]Also includes patients who refused further dialysis treatment.
Data are presented as n (%).

DISCUSSION

This nationwide evaluation characterizes EGL as a medical catastrophe that associates with a substantial short-term recipient mortality and poor long-term outcomes.

The profound benefits of kidney transplantation over dialysis on patient survival, quality of life, and costs—along with an aging population—have resulted in accruing waiting lists and increased waiting list associated mortality.[3–6] Attempts to expand the donor pool come with higher incidences of delayed graft function (DGF), inferior function at 12 months, and (early) graft failure. Yet, although DGF is often regarded as a major impediment, recent cohort studies show that for DCD grafts, DGF does not impair long-term graft and patient survival and, consequently, that DGF in DCD grafts should be regarded an acceptable complication.[7–9] Graft failure, on the other hand, is considered a disastrous complication of kidney transplantation. As such, an increased risk of graft failure—and particularly early graft failure—should be considered the primary impediment for a liberal use of deceased donor kidneys.

Yet, although several cohort studies show that EGL has a negative impact on patient survival,[10–13] only 2 single-center, medium-sized (50 and 109 EGL cases, respectively) studies from the United Kingdom and Ireland systematically evaluated the further wide-ranging consequences of EGL.[1,2] However, these studies were underpowered. Moreover, EGL was defined as graft nephrectomy or loss of transplant function within 30 days after transplantation.[1,2] Although 30-day outcomes are generally used as primary outcomes for surgical complications, this time point may not accurately reflect the actual incidence of EGL. DGF may extend beyond 30 days,[14–16] and a



Number of patients at risk

	0	1	2	3	4	5	6	7	8	9	10
Reference population	7812	7421	7001	6492	5949	5425	4921	4424	4010	3634	3288
EGL population	699	569	511	463	422	373	342	316	292	259	239

Figure 3 | The impact of early graft loss on time to benefit for primary transplantations. Reference population: recipients without early graft loss after the first kidney transplant procedure. Early graft loss (EGL) population: recipients with early graft loss after the first kidney transplant procedure. Waiting-list population: simulated patient survival curve of active waitlisted (kidney-only) patients in The Netherlands. The bottom and top dashed lines represent the corresponding 10th and 90th percentiles, respectively.

considerable number of graft losses may only be diagnosed after 30 days.[1,17] As a consequence, the 30-day time frame is too short to justify a robust medical decision, as the clinical diagnosis of EGL may be made at a time point beyond 30 days. In this context, we considered the 90-day time frame more appropriate, as regulations within Eurotransplant allow recipients with graft failure within 90 days to retain their initial pre-transplantation waiting times in case of relisting. Consequently, the 90-day time point hallmarks a strong external impetus for clinical decision-making with respect to the diagnosis of EGL. As such, it was decided to define EGL as functional graft loss within 90 days after transplantation. Based on this definition, we identified almost 700 recipients with EGL after their first kidney transplant in the national registry and performed a systematic, in-depth evaluation of the overall impact of EGL.

Although the overall incidence of EGL (8.2%) in this evaluation suggests a 2.5-fold higher incidence than in the United States (3.4%),[11] it is important to bear in mind that this is partly due to a time-dependent effect with higher incidences of EGL in the earlier years.[1] In fact, the incidence of EGL in The Netherlands for the corresponding time period (i.e., 2011 to 2015) is 5.4%. The moderately higher incidence presumably reflects a more liberal attitude toward accepting DCD kidneys[18] and the fact that the donors (for the 2011–2015 timeframe) are approximately 16 years older in The Netherlands than in the United States.[11] It has to be noted that, although multivariate analyses mainly identified donor characteristics as risk factors for the development of EGL (Tables 3 and 4), the models only cover 14% (for DCD) and 13% (for DBD) of the variation by the explanatory variables as estimated by Nagelkerke R^2.[19] This implies that the majority of causative factors are not captured by the current database and that, apart from donor and procedural factors, recipient factors also associate with the development of EGL. A notable aspect is the observed significant risk of EGL in recipients who received grafts from diabetic DCD donors (Table 3). Although this alarming finding obviously requires external confirmation, it calls for restraint in use of these donors. Although of interest, the available registry data did not allow further exploration of the negative impact of diabetes in DCD donors. One possible explanation for the phenomenon is that donor diabetes interferes with superior resilience responses observed in DCD donor kidneys.[20]

This study confirms the findings of earlier studies with regard to the profound impact of EGL on patient survival. Whereas the Dutch registry data indicate a 30- and 90-day mortality rate of 1% and 2%, respectively, in the non-EGL group, an almost 7-fold higher incidence was observed in the EGL group. Although this high mortality may obviously be a direct consequence of EGL,[2,21] the EGL-associated 90-day mortality also includes EGL that results from a recipient's death. To be more specific, grafts in patients who died perioperatively are denied the opportunity to regain their function. Although the increased mortality may directly be related to surgical complications,[2,22] it presumably also involves accumulation of recipient-related risk factors such as a higher age, poor (cardio)vascular status, and/or an increased frailty.[23]

Apart from the immediate impact of EGL on mortality, the data indicate far-reaching, long-term consequences. Based on data from the Eurotransplant registry, 25% of the recipients

Table 6 | Comparison analyses of recipient characteristics

	Recipients with early graft loss after a first kidney transplant procedure								Reference population, n = 7812	
	Patients died ≤90 d after transplantation, n = 82		Non-relisted, n = 154		Relisted, not retransplanted, n = 142		Relisted and retransplanted, n = 298			
Age (yr)	57.3 ± 11.6 60.0 [50.0–65.0]		57.5 ± 12.6 60.0 [50.8–68.0]		50.6 ± 13.6 53.5 [42.5–60.0]		46.6 ± 14.2 48.0 [36.0–58.0]		51.6 ± 14.1 54.0 [43.0–63.0]	
Sex (% male)	50 (61)		82 (53)		81 (57)		183 (61)		4698 (60.1)	
Body mass index (kg/m^2)	26.8 ± 4.8		27.2 ± 4.9		26.6 ± 4.8		25.7 ± 4.4		24.8 ± 4.2	
Preemptive primary transplantation (% yes)	0		6 (4)		5 (4)		8 (3)		215 (2.8)	
Previous dialysis time before primary transplantation (yr)	4.8 ± 2.3 4.6 [3.2–6.2]		4.1 ± 2.0 3.8 [2.7–5.2]		4.4 ± 2.7 4.0 [2.3–5.8]		4.0 ± 2.0 4.0 [2.6–5.1]		3.8 ± 2.2 3.6 [2.3–5.0]	
PRA	n[a]	%	n[a]	%	n[b]	%	n[b]	%	n[a]	%
>5 and <85%	5	6	26	17	64	45	135	45	707	9
≥85%	0	0	2	1	34	24	71	24	63	1
Cause of renal failure	n	%	n	%	n	%	n	%	n	%
Chronic renal failure, etiology unknown	9	11	27	18	22	15	39	13	1197	15
Diabetes mellitus	12	15	16	10	12	8	15	5	740	10
Glomerulonephritis	6	7	14	9	14	10	45	15	785	10
Hypertension	16	20	20	13	12	8	30	10	881	11
IgA nephropathy	1	1	3	2	4	3	13	4	412	5
(Poly)cystic kidney disease	11	13	22	14	20	14	47	16	1184	15
Pyelonephritis	4	5	8	5	5	4	38	13	620	8
Miscellaneous	20	24	38	25	42	30	66	22	1651	21
Not specified	3	4	6	4	11	8	5	2	342	4

PRA, panel reactive antibodies.
[a]Most recent registered PRA percentage before the primary transplant procedure.
[b]Maximum PRA percentage registered after primary transplant procedure.
Data are presented as mean (±SD), median [interquartile range], or n (%).

with EGL were not relisted for re-transplantation. Reasons for not relisting are not captured in the Netherlands Organ Transplant Registry (NOTR) and Eurotransplant registry, and considerations are generally missing from patient records. Specified motivations for not relisting included patients' preferences or recipient's health status such as overall functional status or frailty, cardiovascular status or vascular condition.[24] These aspects are reflected by the approximately 10-year older age of the non-relisted versus the relisted patients (Table 6).

One-third of the patients relisted after EGL did not undergo re-transplantation. Although this might be a slight overestimation, owing to some recipients with more recent EGL may be still awaiting re-transplantation, the majority of recipients is most likely removed from the waiting list because of worsening clinical condition or death. Although no specific information was available to what extent sensitization determines eligibility for relisting, sensitization status did not seem to influence the probability of re-transplantation among the relisted patients, as the number of immunized and highly immunized patients was equally distributed between the re-transplanted and not–re-transplanted groups.

Only 43% of the EGL patients had undergone re-transplantation. Outcomes for these re-transplantations are inferior compared with those of first kidney transplants. Noticeably, re-transplantation was associated with a doubled incidence of EGL (16.8% vs. 8.2% for primary transplantations and 9.1% for re-transplantations following late graft loss). This presumably reflects the convergence of risk factors within the individual patient, indicating that patients with EGL after a first transplant should be considered a high-risk recipient. This increased risk of recurrent EGL will obviously compromise the time to benefit for re-transplantations,[24–29] an aspect that should be accounted for when considering re-transplantation.

In the light of the profound impact of EGL, the question arises whether a risk of EGL outweighs the waiting-list mortality. Although such an analysis is prone to confounding by indication,[30] the cohort data allowed us to estimate the impact of the 8.2% *a priori* risk of EGL at the population level. It was concluded that, despite the profound impact of EGL for the individual recipient, the 8.2% incidence affected the population risk minimally. On this basis, it can be concluded that an optimal trade-off between the risk of EGL and waiting-list mortality is beyond an *a priori* EGL risk of 8.2% and that a policy aimed at minimizing incident EGL will lead to avoidable deaths as a result of longer waiting-list times.

A further question is whether patients who sustained EGL would have been better off with remaining on the waiting list. Although the data herein imply a time to benefit of 5 years after EGL, this poor outcome is actually a reflection of asymmetrical outcomes, with a strikingly high 6-month mortality for a subgroup of EGL recipients but favorable

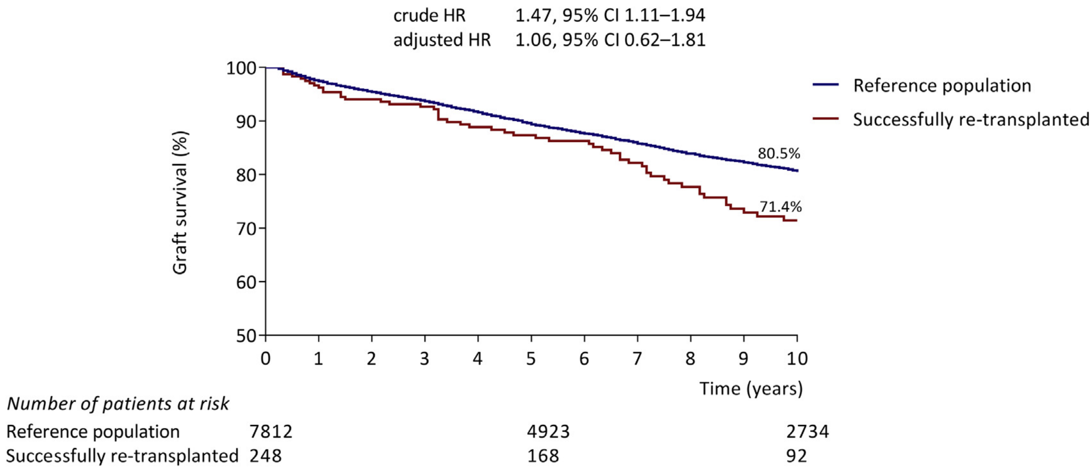


Figure 4 | Death censored 10-year graft survival. Reference population: recipients without early graft loss after the first kidney transplant procedure. Successfully re-transplanted: recipients with early graft loss after the first transplant procedure and without early graft loss after re-transplantation. The model adjusted for clinically relevant variables and variables with $P < 0.1$ in the univariate analysis: donor type, donor age, sex, height, body mass index, last creatinine, cause of death, hypertension, diabetes, recipient age, sex, cause of renal failure, panel reactive antibodies, mismatch human leukocyte antigen (HLA)–A and HLA-B, cold ischemic time, graft anastomosis time, and year of transplant procedure. CI, confidence interval; HR, hazard ratio.

outcomes for EGL recipients surviving 6 months. One could speculate that the early mortality affects a subgroup of vulnerable recipients who were, in retrospect, better off staying on dialysis. In this context, accurate prediction tools aimed at identifying patients at risk of early death after EGL are an unmet medical need.[30]

Our study has some limitations, as this is a registry-based study. Although the NOTR is a mandatory registry for all 8 Dutch transplant centers, and several quality checks are performed, there are remaining missing data and registration errors. In addition, recipient factors of potential relevance, such as frailty, comorbidities, and cardiac and vascular state, are not included in the registry. Another limitation is that the vast majority of the patients in this evaluation are Caucasian. Given the profound impact of race on transplant outcomes, conclusions may not fully apply to non-Caucasians.[31] Finally, conclusions are influenced by medical decision-making; kidneys with an anticipated risk of EGL are often declined before organ procurement (selection bias by allocation), and only a selective group of patients are considered eligible for relisting and re-transplantation (selection bias by indication).

In conclusion, the results in this nationwide study show that EGL after kidney transplantation is associated with

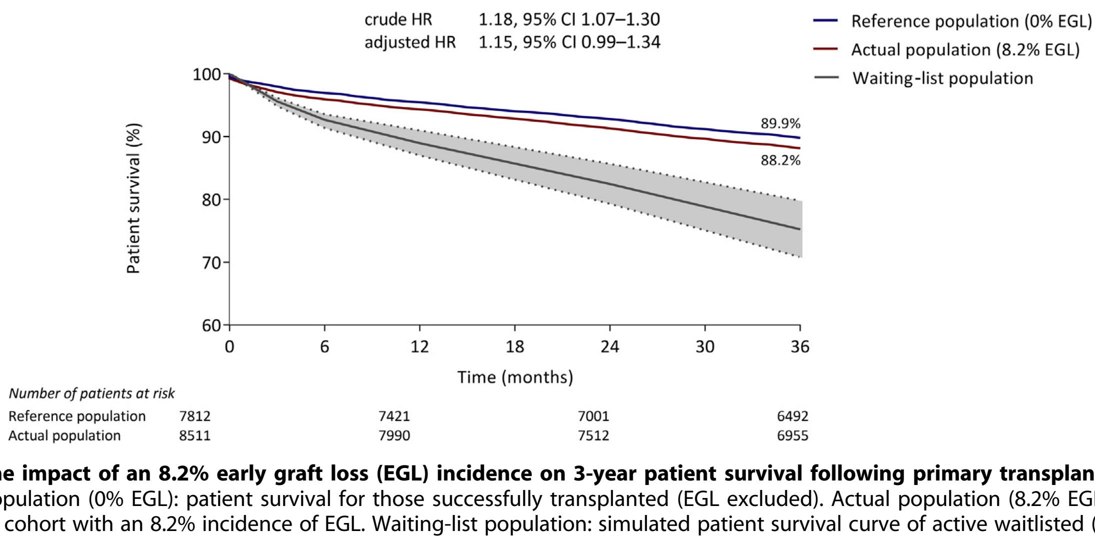


Figure 5 | The impact of an 8.2% early graft loss (EGL) incidence on 3-year patient survival following primary transplantation. Reference population (0% EGL): patient survival for those successfully transplanted (EGL excluded). Actual population (8.2% EGL): patient survival for a cohort with an 8.2% incidence of EGL. Waiting-list population: simulated patient survival curve of active waitlisted (kidney-only) patients in The Netherlands. The bottom and top dashed lines represent the corresponding 10th and 90th percentiles, respectively. The 3-year mortality risk for a population with an 8.2% EGL risk was estimated in a Cox proportional hazards model (actual population vs. reference population) that adjusted for clinically relevant variables and variables with $P < 0.1$ in the univariate analysis: donor age, sex, height, body mass index (BMI), cause of death, hypertension, smoking, cardiac arrest, and recipient age; sex; height; BMI; cause of renal failure; time on dialysis; panel reactive antibodies; mismatch human leukocyte antigen (HLA)–DR, HLA-A, and HLA-B; and graft anastomosis time. CI, confidence interval; HR, hazard ratio.

significant detrimental consequences. These consequences include profound short-term and long-term mortality rates, a reduced chance of relisting and re-transplantation, and—for those re-transplanted—an increased risk of recurrent EGL. Although the development of EGL and the associated poor outcomes are generally attributed to the use of suboptimal kidney grafts, the data in this study also imply convergence of recipient risk factors in patients with EGL. As such, these recipient factors should specifically be accounted for when estimating the optimal trade-off at which the impact of EGL is balanced by maximizing the donor pool–size. With respect to the donor and procedural factors, the multivariate analyses performed show that, after the medical decision to accept the graft for donation, traditional risk factors minimally associate with incident EGL. Hence, there is an urgent need for complementary risk-assessment tools, such as biomarkers or *ex vivo* functional organ assessment, and possibly more extended risk prediction models.

METHODS

Study population

This study was approved by the local ethics committee of the Leiden University Medical Center. Data from all 11,415 deceased donor kidney transplant procedures performed between 1990 and 2018 were retrieved from NOTR. This nationwide, mandatory registry contains the data of all 8 Dutch kidney transplant centers. Registry follow-up is conducted at 3 months and 1 year after transplantation and annually thereafter. Procedures in recipients younger than 12 years of age (n = 261), combined organ procedures (n = 635), and uncontrolled circulatory death-donor procedures (Maastricht category 1, dead on arrival; and category 2, unsuccessful resuscitation) (n = 212) were excluded. The remaining 10,307 deceased donor kidney transplants were included in the analyses. For validation purposes and for correction of missing data, additional data of recipients with EGL was retrieved from Eurotransplant and Renal Replacement Registry (RENINE), the mandatory dialysis registry of The Netherlands, and incorporated in the final database.

Eurotransplant data for the 2009–2018 interval indicate a 1-year waiting list mortality of 11.03% ± 1.41% per year (mean ± SD) for patients on the active waiting list (kidney only) in The Netherlands,[32] implying a relative risk of death of 2.51 compared with those successfully transplanted (observed 1-year mortality rate, 4.40%). Based on this relative risk, waiting-list survival curves were constructed using the Kaplan-Meier method to estimate waiting list survival times and 10- to 90-percentile intervals. This strategy was chosen, as waiting-list survival analyses may not be reliable beyond 1-year follow-up.[30]

The Modification of Diet in Renal Disease (MDRD) equation was used to estimate GFR in the recipient.[33,34] The eGFR in donors was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[35]

Definitions

In this study, EGL was defined as graft loss within 90 days after transplantation. Kidney transplant recipients who died within 90 days with a functioning kidney graft were not considered as EGL recipients. Recipients without EGL after their first kidney transplant procedure were considered the reference population. For ischemic periods of the donor kidneys, the following definitions were used: The first warm ischemic time in kidneys donated after circulatory death (DCD) is the time following the no-touch period after circulatory arrest and asystole until cold flush-out in the donor is commenced; the cold ischemia time is defined as the time from start of cold flush-out until the start of the vascular anastomosis at time of implantation in the recipient; the graft anastomosis time is the time from organ removal from static cold storage or hypothermic machine perfusion to reperfusion in the recipient. Immunized patients are patients who have PRA ranges of ≥6% and <85%.[36] Highly immunized patients have PRAs of ≥85%.[36]

Statistical analysis

IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY) was used for statistical analysis. Differences in donor, recipient, and transplant characteristics were analyzed using the Mann-Whitney rank test for nonparametric data, independent Student's *t* test for normal distributed data and the chi-square test for categorical data. A multivariate regression analysis was used to identify factors associated with EGL. Variables with a $P < 0.1$ in the univariate analysis were entered in the multivariate regression analysis. Cox proportional hazards analyses, adjusted for clinically relevant variables (recipient age and sex) and statistical relevant variables ($P < 0.1$ in the univariate analysis), were performed to evaluate differences in patient- and death-censored graft survival. Patient survival was calculated from the date of transplant to the date of death (event), and patients were censored on the last day of follow-up, which was October 17, 2018. Survival time was truncated at 3 months or 10 years. Graft survival was calculated from the date of transplant to the registered date of graft failure (event). Patients were censored at the time of patient's death or at the time of last day of follow-up. Kaplan-Meier survival curves were generated for all groups of interest. Results are represented as aHR for the patient and graft survival analyses, and as odds ratio (OR) for the multivariate regression analysis with the corresponding 95% CI. In this study, missing data—coded as *unknown* for categorical variables—were excluded from analyses. For variables of primary interest (EGL, cause of EGL, and short-term patient and graft survival), there were no missing values. The frequency of missing data for secondary variables is shown in Supplementary Table S1. To exclude a possible missing data-related bias, additional sensitivity analyses were performed for different timeframes. P values < 0.05 were considered statistically significant.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Proportion of missing data.

Table S2A. Multivariate sensitivity analysis including data from 2002 to 2018 (odds ratio [95% CI]): risk factors associated with early graft loss after a first DCD transplant procedure.

Table S2B. Multivariate sensitivity analysis including data from 2002 to 2018 (odds ratio [95% CI]): risk factors associated with early graft loss after a first DBD transplant procedure.

Table S3. Time-related changes in incidence and consequences of early graft loss.

Figure S1. Landmark analysis of short-term and long-term patient survival following rejection resp. nonrejection-related EGL.

Figure S2. Death censored 10-year graft survival following successful re-transplantation after primary rejection resp. nonrejection-related EGL.

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