Identifying Risk Factors for Graft Loss within 90 Days of Kidney Transplantation in the Modern Era: A Review of Single Center and UNOS Databases

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ABSTRACT

Aim: Our aim was to clarify the risk factors for graft loss within the first 90 days of kidney transplantation.

Methods: We performed an IRB-approved, retrospective review of the United Network for Organ Sharing database (2010-2015) and our own single center database (2004-2015). We analyzed risk factors for Early Graft Loss (EGL). EGL was defined as graft loss due to patient death, graft thrombosis, acute rejection, or primary non-function within 90 days of transplantation.

Results: At our center, 30 of 676 recipients experienced EGL (4.4%). The most common cause of EGL at our center was recipient death. Demographic variables associated with EGL included: expanded criteria donor (p<0.001), older donors (p=0.003), donors with higher BMI (p=0.004), and higher KDPI (p=0.001). One-, 3-, and 5-year patient survival was lower in recipients with EGL (all p<0.001). Multivariate analysis suggested expanded criteria donor and donor BMI were predictors of EGL (p<0.001).

The rate of EGL among patients in the UNOS database was 3.35%, with patient death being the most common cause. Multivariate analysis of the UNOS database revealed only recipient age was a predictor of EGL due to patient death (p<0.001). There were no predictors of EGL due to thrombosis. Previous kidney transplant and recipient age were predictors of EGL due to acute rejection (p=0.002 and p<0.001).

Conclusion: Overall between our center and UNOS database, patient death was the most common cause of EGL. Single center and UNOS data suggest that EGL occurs more frequently in recipients of sub-optimal allografts. Additionally, older age and previous transplant are associated with increased risk for EGL.

INTRODUCTION

Kidney transplantation is the most effective treatment available for patients with End-Stage Renal Disease (ESRD). However, in 2014, only 17,107 kidney transplants were performed in the United States leaving over 80,000 people waiting for a transplant [1]. Because of the need for more donors, there has been increasing utilization of suboptimal kidneys, which are associated with inferior outcomes [2,3]. Additionally, it has been suggested that the use of these allografts is linked to Early Graft Loss (EGL) [4].

EGL is defined as graft loss occurring within 90 days of kidney transplantation. It is relatively rare, occurring after approximately 5% of transplantations [5]. Causes of EGL include: patient death, renal artery or vein thrombosis, acute rejection (AR), and Primary Non-Function (PNF). Very short-term outcomes after kidney transplantation are understudied. Additionally, there have been few reports on risk factors for EGL, and those that have been published are limited to single center analyses [4,5].

Thus, our aim was to clarify those risk factors. Additionally, we sought to determine if there was a difference in the risk factors associated with each specific cause of EGL. We utilized the United Network for Organ Sharing (UNOS) database and our own single center database for our analysis. We hypothesized that the rate of EGL nationwide would be similar to that reported in prior single center analyses.

MATERIALS AND METHODS

1. UNOS database

Data containing kidney transplant donor and recipient (n= 56,883) information from June 6, 2011 through June 30, 2015 was extracted from the UNOS database. Recipients of living donor organs and simultaneous liver, pancreas, intestine, lung or heart transplants were excluded. Details regarding the recipient and donor demographics were queried. Recipient characteristics obtained

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included age, gender, BMI, time on waitlist, dialysis status, clinical status (ICU vs hospitalized vs home) and mechanical ventilatory needs at time of transplantation. Donor characteristics obtained included age, gender, race, BMI, creatinine, bilirubin, Donor Risk Index (DRI), Expanded Criteria Donor (ECD), and Donation after Cardiac Death (DCD). Additional perioperative details were queried, including Human Leukocyte Antigen (HLA) mismatch level, warm ischemia time, and cold ischemia time.

2. Study population and variables

Primary outcome of this study was rate of EGL due to any cause at 7-, 30-, and 90-days post-transplant. Causes of EGL were further analyzed and classified into primary graft dysfunction/nonfunction, graft thrombosis (renal artery and vein), acute and chronic rejection, or others. Secondary outcome includes patient death from any cause.

3. Statistical analysis

Descriptive statistics of clinical and demographic characteristics were summarized using one-way ANOVA and t-test for continuous variables and chi-square test for categorical variables. Missing variables were omitted from the statistical analysis. For continuous variables, compliance with the normality assumption was tested using Shapilo-Wilk diagnostic test, and Kruskal Wallis rank test was performed when the normality assumption was violated. Patients who did not experience any of the end points were censored on the last follow-up date or on June 30th, 2015. Multivariate Cox-regression analyses were conducted to investigate adjusted risk factors. Those included donor and recipient demographics, peri- and post-operative factors, factors linked to organ quality, and organ share type (local, regional, or national).

4. Single center database

We analyzed our database of 676 patients who received kidney transplants and were induced with Alemtuzumab(ALE) at the University of Toledo Medical Center in Toledo, Ohio between March 2004 and November 2015. Patient data was reviewed using TransChart electronic medical record software (TransChart LLC, Dublin, Ohio). Donor information included: gender, age, ethnicity, presence of hypertension, presence of diabetes mellitus, type of donor and terminal creatinine. Recipient information included: gender, age, ethnicity, blood type, type of graft received, Panel Reactive Antibody (PRA), and number of transplants (Table 6). EGL was defined as the occurrence of renal artery or vein thrombosis, AR, or PNF within the first 90 days post-transplantation.

Prior to transplantation, patient profiles were cross-matched for T and B cell status via flow cytometry. All patients included in our study were negative cross-matches for both T and B cells. All cases of acute rejection were biopsy-proven.

Patients were pretreated with 25 mg of diphenhydramine intravenously (IV). At the time of the procedure, induction immunosuppression with methylprednisolone 500 mg (IV) (Solu-Medrol, Pfizer, New York, NY), mycophenolate sodium 540 mg by mouth (PO) (Myfortic, Novartis Pharmaceuticals, Basel, Switzerland) and ALE 30 mg IV was administered.

The post-operative steroid taper consisted of: methylprednisolone 250 mg IV on post-operative day 1, methylprednisolone 125 mg IV on post-operative day 2, prednisone 60 mg PO on post-operative day 3, prednisone 40 mg PO on post-operative day 4, and, finally, prednisone 20 mg PO on post-operative day 5. Patients at high-risk for rejection were continued indefinitely on prednisone 5-10 mg PO.

Starting on post-operative day 1, Tacrolimus 1.5 mg PO (Prograf, Astellas Pharma, Tokyo, Japan) and mycophenolate sodium 540 mg PO twice per day were given. Tacrolimuslevels were measured and titrated to the correct dose. Side effects permitting, mycophenolate sodium was increased to 720 mg PO at discharge.

Table 6: Recipient and Donor Demographics - Single Center.

Recipient Factors	EGL	Control	Sig.
Age at Transplant (yrs)	56.8	52	0.073
Elderly (>65 yrs)	7 (23.3%)	115 (17.8%)	0.465
Male gender (n,%)	21 (70%)	408 (62.3%)	0.562
White (n,%)	18 (60%)	461 (71.4%)	0.217
African American (n,%)	8 (26.7%)	144 (22.3%)	0.654
Hispanic (n,%)	3 (10%)	28 (4.3%)	0.153
Asian (n,%)	1 (3.3%)	13 (2%)	0.474
Re-transplant (n,%)	9 (30%)	172 (26.6%)	0.676
PRA>20% (n,%)	7 (23.3%)	118 (18.5%)	0.477
Donor Factors	**EGL**	**Control**	**Sig.**
Deceased (n,%)	25 (83.3%)	476 (73.7%)	0.291
Expanded criteria donor (n,%)	11 (44%)	49 (10.3%)	p<0.001
Donor after cardiac death (n,%)	1 (4.2%)	48 (10.1%)	0.496
Donor age (yrs)	46.5	38.3	0.003
Donor hypertension (n,%)	13 (46.4%)	123 (19.1%)	0.001
Donor diabetes mellitus (n,%)	4 (14.3%)	35 (5.4%)	0.075
Donor cancer (n,%)	1 (3.6%)	16 (2.5%)	0.521
Smoker Donor (n,%)	8 (27.6%)	156 (24.3%)	0.662
Alcoholic Donor (n,%)	6 (25%)	83 (17.5%)	0.41
Donor BMI (kg/m2)	30	26.9	0.004
KDPI	60.4	38.9	0.001
Terminal Creatinine (mg/dL)	1.2	0.955	0.034
Cold ischmic time (hrs)	13.9	11.5	0.629
Warm ischemic time (hrs)	0.83	1.02	0.196

Antimicrobial prophylaxis was started post-operatively with sulfamethoxazole (800 mg)-trimethoprim (160 mg) 1 tab PO (Bactrim DS, AR Scientific, Philadelphia, PA) 3 times per week and clotrimazole troche 10 mg dissolved in the mouth 4 times per day following oral care. In the event of a Cytomegalovirus (CMV) mismatch, daily valgancyclovir 450 mg PO (Valcyte, Hoffman-La Roche, Basel, Switzerland) was prescribed. The diagnosis of CMV mismatch was made by determining the IgM antibodies to CMV by Polymerase Chain Reaction (PCR).

Continuous variables were presented in medians and were compared using t-tests or the Mann-Whitney U test when appropriate. Categorical variables including gender, ethnicity, education level, delayed graft function, and early rejection were presented in terms of percentage of the total number within the group. They were compared with Pearson's Chi-square or Fisher's Exact Test. Multivariate survival analysis was done using Cox regression analysis with multivariate factors selected from univariate results and with patient ethnicity included for comparison. Type I error level was set at 0.05. All statistical analyses for single center were conducted using IBM SPSS ver23 (IBM Corp., Armonk, NY) and analyses for UNOS data were conducted using Stata ver14 (StataCorp LLC, College Station, TX).

MATERIALS AND METHODS

1. UNOS database

The rate of EGL in the UNOS database was 1,903 (3.35%) out of 56,883 patients. Increased age, elevated BMI, and recipient diabetes were significantly associated

with higher rates of EGL due to patient death when compared to the non-EGL group (p<0.001, p=0.0220, and p<0.001, respectively) (Table 1).

Patients who were at home directly prior to transplantation experienced EGL due to thrombosis at a significantly higher rate compared to the non-EGL group (p=0.045) (Table 2). Multivariate analysis revealed no significant predictors of EGL due to thrombosis.

EGL due to PNF was significantly more common in female recipients and recipients without diabetes (p=0.004 and p=0.01, respectively) (Table 3).

Table 1: Comparison of Recipient Characteristics between EGL-Patient Death and Non-EGL – UNOS.

Recipient Characteristics	EGL-Pt death	Non-EGL	P-value
Age at Transplant, mean (SD)	59.21 (11.48)	52.11 (13.55)	0.000
Male, n (%)	590 (63.85%)	33,488 (60.91%)	0.069
BMI, mean (SD)	28.54 (5.35)	28.13 (5.37)	0.0220
Diabetes, n (%)	487 (52.71%)	21,847 (39.75%)	0.000
Causes of kidney disease			
Hepatitis C, n (%)	60 (6.49%)	2,867 (5.21%)	0.083
Hepatitis B, n (%)	86 (9.31%)	4,553 (8.28%)	0.262
Days on Waiting List	1016.45 (785.25)	936.71 (774.01)	0.0019
Status / Location at time of Transplant, n (%)			
ICU	**3 (0.32%)**	**45 (0.08%)**	**0.012**
Hospitalized	11 (1.19%)	392 (0.71%)	0.089
Home	866 (93.72%)	50,578 (91.99%)	0.054
HLA mismatch level, mean (SD)	4.12 (1.54)	4.08 (1.58)	0.4239
Graft failure causes, n (%)			
Primary non-function	33 (3.57%)	47 (0.09%)	0.000
Acute rejection	20 (2.16%)	622 (1.13%)	0.003
Vascular Thrombosis	30 (3.25%)	32 (0.06%)	0.000

Recipients on the waitlist for longer periods of time had a significantly higher incidence of EGL due to patient death compared to the non-EGL group (p=0.0019) (Table 1). Patients who were in the ICU or hospital at the time of transplant experienced EGL due to patient death at a significantly higher rate compared to the non-EGL group (p=0.012) (Table 1). Upon multivariate analysis, only recipient age was a significant predictor of EGL due to patient death (HR: 1.04, CI: 1.03-1.04, p<0.001).

Incidence of EGL due to thrombosis was significantly more common in males and in recipients without diabetes (p=0.004 and p=0.017, respectively) (Table 2).

Table 2: Comparison of Recipient Characteristics between EGL-Thrombosis and Non-EGL – UNOS.

Recipient Characteristics	EGL-Thrombosis	Non-EGL	P-value
Age at Transplant, mean (SD)	50.96 (14.23)	52.11 (13.55)	0.1310
Male, n (%)	171 (53.11%)	33,488 (60.91%)	0.004
BMI, mean (SD)	28.29 (5.52)	28.13 (5.37)	0.5947
Diabetes, n (%)	107 (32.23%)	21,847 (39.74%)	0.017
Causes of kidney disease			
Hepatitis C, n (%)	13 (4.04%)	2,867 (5.21%)	1.000
Hepatitis B, n (%)	21 (6.52%)	4,553 (8.28%)	0.253
Days on Waiting List	877.16 (710.15)	936.71 (774.01)	0.1685
Status / Location at time of Transplant, n (%)			
ICU	**0 (0%)**	**45 (0.08%)**	**0.608**
Hospitalized	4 (1.24%)	392 (0.71%)	0.261
Home	306 (95.03%)	50,578 (91.99%)	0.045
HLA mismatch level, mean (SD)	4.04 (1.57)	4.08 (1.58)	0.3209
Graft failure causes, n (%)			
Primary non- function	322 (100%)	47 (0.09%)	0.000
Acute rejection	0 (0%)	622 (1.13%)	0.055
Vascular Thrombosis	-	32 (0.06%)	-

Table 3: Comparison of Recipient Characteristics between EGL-PNF and Non-EGL – UNOS.

Recipient Characteristics	EGL-PNF	Non-EGL	P-value
Age at Transplant, mean (SD)	51.43 (14.12)	52.11 (13.55)	0.3479
Male, n (%)	191 (53.50%)	33,488 (60.91%)	0.004
BMI, mean (SD)	28.53 (5.67)	28.13 (5.37)	0.1588
Diabetes, n (%)	118 (33.05%)	21,847 (39.74%)	0.010
Causes of kidney disease			
Hepatitis C, n (%)	14 (3.92%)	2,867 (5.21%)	0.273
Hepatitis B, n (%)	21 (5.88%)	4,553 (8.28%)	0.101
Days on Waiting List, mean (SD)	891.79 (726.94)	936.71 (774.01)	0.2743
Status / Location at time of Transplant, n (%)			
ICU	**0 (0%)**	**45 (0.08%)**	**0.589**
Hospitalized	4 (1.12%)	392 (0.71%)	0.363
Home	334 (93.56%)	50,578 (91.99%)	0.278
HLA mismatch level, mean (SD)	4.08 (1.57)	4.08 (1.58)	0.9446
Graft failure causes, n (%)			
Primary non-function	-	47 (0.09%)	-
Acute rejection	0 (0%)	622 (1.13%)	0.043
Vascular Thrombosis	322 (90.20%)	32 (0.06%)	0.000

Recipient age was found to be marginally protective for recipients with EGL due to PNF (HR: 0.99, CI: 0.98-0.99, p=0.039). EGL due to AR was significantly more common in recipients with elevated BMI (p=0.0003) (Table 4).

Table 4: Comparison of Recipient Characteristics between EGL-Acute Rejection and Non-EGL – UNOS.

Recipient Characteristics	EGL-Acute Rejection	Non-EGL	P-value
Age at Transplant, mean (SD)	53.20 (13.66)	52.11 (13.55)	0.3865
Male, n (%)	80 (68.97%)	33,488 (60.91%)	0.076
BMI, mean (SD)	29.95 (5.74)	28.13 (5.37)	0.0003
Diabetes, n (%)	40 (34.48%)	21,847 (39.74%)	0.248
Causes of kidney disease			
Hepatitis C, n (%)	13 (11.21%)	2,867 (5.21%)	0.004
Hepatitis B, n (%)	12 (10.34%)	4,553 (8.28%)	0.421
Days on Waiting List, mean (SD)	1193.52 (964.64)	936.71 (774.01)	0.0004
Status / Location at time of Transplant, n (%)			
ICU	**0 (0%)**	**45 (0.08%)**	**0.758**
Hospitalized	1 (0.86%)	392 (0.71%)	0.849
Home	112 (96.55%)	50,578 (91.99%)	0.071
HLA mismatch level, mean (SD)	4.08 (1.66)	4.08 (1.58)	0.9789
Graft failure causes, n (%)			
Primary non-function	0 (0%)	47 (0.09%)	0.753
Acute rejection	-	622 (1.13%)	-
Vascular Thrombosis	0 (0%)	32 (0.06%)	0.795

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EGL due to AR was also significantly more common in recipients who had longer times spent on the waitlist (1193.52±964.64 days vs. 936±774.01 days; p=0.0004) (Table 4). Previous kidney transplant (HR: 2.12, CI: 1.32-3.42, p=0.002) and recipient age (HR: 1.03, CI: 1.02-1.05, p<0.001) were risk factors for EGL due to AR according to multivariate analysis.

Donor characteristics can be found in Table 5.

Table 5: Comparison of Donor Characteristics between EGL and Non-EGL – UNOS.

Donor Characteristics	EGL-Pt. Death	EGL-Thrombosis	EGL-PNF	EGL-Acute Rejection	Non-EGL
Age, mean (SD), p-value	44.04 (15.12), 0.0000	40.61 (13.63), 0.1390	41.76 (13.66) , 0.0021	43.62 (14.64) , 0.0016	39.43 (14.28)
Male, n (%), p-value	572 (61.90%), 0.667	187 (58.07%), 0.250	210 (58.82%), 0.356	73 (62.93%), 0.704	33,653 (61.21%)
Race, n (%), p-value					
African American	141 (5.26%), 0.191	41 (12.73%), 0.592	47 (13.17%), 0.743	16 (13.79%), 0.993	7,568 (13.77%)
White	610 (66.02%), 0.101	232 (72.05%), 0.177	256 (71.71%), 0.199	78 (67.24%), 0.763	37,685 (68.54%)
Hispanic	134 (14.50%), 0.333	39 (12.11%), 0.496	43 (12.04%), 0.451	15 (12.93%), 0.881	7,371 (13.41%)
Asian	23 (2.49%), 0.925	7 (2.17%), 0.757	7 (1.96%), 0.558	3 (2.59%), 0.919	1,342 (2.44%)
Other	16 (1.73%), 0.801	3 (0.93%), 0.224	4 (1.12%), 0.310	4 (3.45%), 0.200	1,014 (1.84%)
BMI, mean (SD), p-value	28.93 (7.08), 0.0000	28.67 (7.34), 0.0324	28.68 (7.30) , 0.0216	27.79 (6.50) , 0.8784	27.88 (6.53)
Creatinine, mean (SD), p-value	**1.14 (0.67), 0.2716**	**1.14 (0.68), 0.5358**	**1.17 (0.71) , 0.9684**	**1.09 (0.54) , 0.3426**	**1.17 (0.94)**
Bilirubin, mean (SD), p-value	0.96 (1.32), 0.3717	0.83 (1.09) , 0.0325	0.88 (1.31) , 0.0887	1.02 (0.64) , 0.9219	1.01 (1.44)
DRI, mean (SD), p-value	42.20 (116.72), 0.9755	49.30 (118.51) , 0.2252	49.71 (117.62), 0.1771	52.14 (133.18), 0.3091	42.09 (106.28)
Donor after cardiac death, n (%), p-value	167 (18.07%), 0.032	64 (19.88%), 0.030	73 (20.45%), 0.010	19 (16.38%) 0.793	8,519 (15.49%)
Expanded criteria donor, n (%), p-value	252 (27.27%), 0.000	54 (16.77%), 0.325	66 (18.49%), 0.052	29 (25.00%), 0.002	8,145 (14.81%)
Warm ischemia time in minutes, mean (SD), p-value	23.50 (16.54), 0.0168	24.16 (13.97) , 0.0628	24.41 (22.72) , 0.0335	17.58 (9.41) , 0.3115	20.82 (13.97)
Cold ischemia time in hours, mean (SD), p-value	18.01 (9.14), 0.0001	18.82 (8.66) , 0.0001	18.73 (8.75) , 0.0001	16.50 (8.72) , 0.6591	16.87 (8.93)

Donor age was significantly increased in recipients who experienced EGL due to death (44.04±15.12 years; p<0.0001), EGL due to PNF (41.76±13.66 years; p=0.0021), and EGL due to AR (43.62±14.64 years; p=0.0016) compared to the non-EGL group (39.43±14.28 years). Donor BMI was also significantly elevated in recipients who experienced EGL due to death (28.93±7.08 kg/m2; p<0.0001), EGL due to thrombosis (28.93±7.08 kg/m2; p=0.0324), and EGL due to PNF (28.68±7.30 kg/m2; p=0.0216) compared to the non-EGL group (27.88±6.53 kg/m2). DCD donors were used significantly more often in recipients who experienced EGL due to death (18.07%; p=0.032), EGL due to thrombosis (19.88%; p=0.03), and EGL due to PNF (20.45%; p=0.01) compared to the non-EGL group (15.49%). ECD donors were used significantly more often in recipients who experienced EGL due to PNF (18.49%; p=0.05) and EGL due to AR (25%; p=0.002) compared to the non-EGL group (14.81%). Warm Ischemia Time (WIT) was significantly longer in recipients who experienced EGL due to death (23.50±16.54 min; p<0.0001), and EGL due to PNF (24.41±22.72 min; p=0.0335) compared to the non-EGL group (20.82±13.97 min). Cold Ischemia Time (CIT) was significantly longer in recipients who experienced EGL due to death (23.5±16.54 hrs. ; p=0.0001), EGL due to thrombosis (18.82±8.66 hrs.; p=0.0001), and EGL due to PNF (18.73±8.75 hrs.; p=0.0001) compared to recipients who did not experience EGL (16.87±8.93 hrs).

2. Single center

A total of 676 patients underwent kidney transplantation at our institution during the study period. 30 (4.4%) patients had EGL (Table 7).

Table 7: Cause of Graft Failure - Single Center.

Cause	EGL	Control	DGF	90 Day Rejection
Acute rejection	4 (13.8%)	22 (15.2%)	2 (13.3%)	6 (20.7%)
Chronic rejection	0	21 (14.5%)*	1(6.7%)	4 (13.8%)
Graft thrombosis	7 (24.1%)	1 (0.7%)*	0*	1 (3.4%)*
Other allograft complication	1 (3.4%)	1 (0.7%)	0*	0
Death	11 (36.7%)	68 (46.9%)	8 (53.3%)	7 (24.1%)
Recurrent disease	0	9 (6.2%)	1 (6.7%)	2 (6.9%)
Primary non-function	7 (24.1%)	0*	0*	0*
Other	0	23 (15.9%)*	3 (20%)*	9 (31%)*

*= Significant difference at p<0.05, either to control (EGL) or to EGL (DGF, 90 day rejection)

Recipients of Expanded Criteria Donor (ECD) grafts had a significantly higher rate of EGL compared to controls (44% and 10.3%, respectively; p<0.001, Table 6). Patients who experienced EGL received grafts from significantly older donors compared to controls (46.5 years and 38.3 years, respectively; p=0.003, Table 6). Donor Body Mass

Index (BMI) was significantly higher in recipients with EGL compared to controls (30 kg/m2 and 26.9 kg/m2, respectively; p=0.004, Table 6). Recipients with EGL received grafts from donors with significantly higher Kidney Donor Profile Indices (KDPI) compared to controls (60.4 and 38.9, respectively; p=0.001, Table 6). All other recipient and donor demographics are listed in Table 6.

Graft loss due to graft thrombosis was significantly higher in recipients with EGL compared to controls (24.1% and 0.7%, respectively; p<0.05). Graft loss because of AR was not significantly different in the EGL group compared to controls (13.8% and 15.2%, respectively; p>0.05). The rate of death as a cause of graft loss did not differ significantly between recipients with EGL and controls (36.7% and 46.9%, respectively; p>0.05; Table 7).

1-, 3-, and 5-year patient survival was significantly lower in recipients with EGL compared to controls (63%, 50%, 50% and 97.5%, 91.4%, 86%, respectively; all p<0.001) (Table 8).

Table 8: Negative Outcomes for EGL and Comparison Groups - Single Center.

Factor	EGL	Control	Sig
Patient survival	15 (50%)	557 (86.2%)	p<0.001
- 1 year	17 (63%)	594 (97.5%)	p<0.001
- 3 year	10 (50%)	417 (91.4%)	p<0.001
- 5 year	10 (50%)	313 (86%)	p<0.001
Rejection rate	10 (33.3%)	172 (26.6%)	0.406
Median Survival	EGL	Control	Sig
Rejection-free	14.9	1340.7	p<0.001
Patient	1067.6	1743.9	p<0.001
Days until	EGL	Control	Sig
Rejection	**18.8**	**308.4**	**0.001**
Death	327.9	1145.8	p<0.001

There was no significant difference in the rate of rejection between recipients with EGL and controls (33.3% and 26.6%, respectively; p=0.406). The median number of days until rejection in the EGL group was significantly less than controls (18.8 days and 308.4 days, respectively; p=0.001). The median number of days until the death for those with EGL was significantly less than controls (327.9 days and 1145.8 days, respectively; p<0.001). Multivariate analysis suggested that ECD (HR=5.163, CI=2.217-12.027, p<0.001) and donor BMI (HR=1.148, CI=1.069-1.232, p<0.001) were significant predictors of EGL.

DISCUSSION

EGL after kidney transplantation is a relatively rare, yet catastrophic event, occurring at rates of 4.4% at our center and 3.35% among UNOS patient data. Thus, it is important to understand the risk factors associated with EGL in order to better inform clinical decision-making. We defined EGL as renal artery or vein thrombosis, ACR, AMR, PNF, or recipient death occurring within 90 days of kidney transplantation. Other reports defined EGL as occurring within 30 days of kidney transplantation [4,5]. We chose a 90-day window because any patients who lost their allograft during this time period would be able to retain their pre-transplantation listing time.

The limited, single-center analyses that exist on EGL to date have suggested that increased donor age, DCD donor type, ECD donor type, and increased CIT were associated with EGL [4,5]. Cox regression analysis of our single-center data confirmed that ECD donor type was a significant predictor of EGL. The results of the review of UNOS data, however, were not as straightforward. Our data suggest that increased donor age is significantly associated with only EGL due to patient death, PNF, and AR. DCD donor type is associated with EGL due to patient death, thrombosis, and PNF, but not AR. Finally, ECD donor type is significantly associated with EGL due to patient death and AR. Multivariate analysis revealed, however, that none of these factors was a significant predictor of EGL vs. non-EGL. In this regard, the results of our UNOS review differ from those of both our own single-center review and those of Hamed et al. and Phelan et al.

Given that data on EGL is limited, we sought to compare the potential risk factors presented in our data to those reported for thrombosis, AR, PNF, and patient death outside the scope of EGL to determine how our findings, in the context of EGL, compare.

Many have reported increased donor age as a risk factor for renal allograft thrombosis [6,7,8]. In the context of EGL, our data indicate that there was no significant difference in donor age between recipients who did not experienced EGL and those who experienced EGL due to thrombosis. A major risk factor for graft thrombosis is a history of thrombosis [4,7]. Unfortunately, our data did not include whether or not recipients had a history of thrombosis thus preventing us from drawing additional conclusions.

Lebranchu et al. reported that older donor age was a significant predictor of AR following transplantation. Our results correlate with their findings and further, suggest that in the context of EGL, increased donor age is also associated with an increased risk for recipient death and PNF. They also suggested that African American ethnicity and extended CIT were related to increased rates of AR. Our data, however, suggest that there was no significant difference in the number of African American recipients who experienced AR as a cause of EGL and those who did not. Additionally, there was no significant difference in CIT between the two groups. Delayed graft function is a well-known risk factor for AR [9,10]. Unfortunately we did not have data on the recipients who experienced delayed graft function.

Hamed et al. found an increased incidence of PNF in DCD kidneys, which they believed was due to warm ischemic injury as these kidneys are more vulnerable to ischemic reperfusion injury. Similarly, Snoejis, et al. noted that patients who suffered from PNF typically had impaired hemodynamic status during the time of transplant. During the surgery, these patients have a lower BP than those with delayed or immediate graft function. Our data supports these findings as an increase in WIT and CIT can increase the risk of EGL. Our results along with these studies demonstrate that PNF may reflect the quality of the donor organ more than the recipient.

Regarding patient mortality, Debout et al. demonstrated a significant proportional increase in recipient mortality for each additional hour of CIT. We report significantly longer CIT in recipients who experienced EGL due to patient death. CIT was also significantly greater in recipients who experienced EGL due to thrombosis and acute rejection. It has also been reported that recipients of ECD grafts have a higher risk of death in the early post-transplant period [12]. Our data are similar, recipients who suffered EGL due to death were significantly more likely to have received an ECD graft.

In recipients who experience EGL, it is important to know what happened to them after graft loss. In analyzing the post-EGL outcomes of patients at our own institution, we found 20 recipients who experienced EGL attributable to causes other than patient death. Of these, 3 were re-transplanted and 3 died while waiting for a re-transplant. The remaining 14 are still awaiting re-transplant to our knowledge.

Our analysis has a number of strengths. Primarily, it includes data from both a single center (similar to previous analyses on EGL) and the UNOS database. Furthermore, we were able to identify risk factors specific to certain causes of EGL using the UNOS data. Finally, we utilized a relatively large sample size. One weakness was the lack of certain data points, such as previous history of thrombosis. Additionally, the relative lack of other reports on the topic of EGL make it difficult to compare out conclusions to others.

CONCLUSION

The rates of EGL were 4.4% at our center and 3.35% among UNOS patient data. Although an obvious trend is difficult to discern, our data generally suggest that sub-optimal allografts are associated with an increase in EGL due to a variety of factors. Given these results, we believe transplant providers should use caution and increased monitoring of recipients receiving what could be considered sub-optimal allografts.

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SCIENTIFIC LITERATURE