The Evolution of Renal Graft Failure Risk: The Power of the Proximal

S. Mohan[1], T. Mayne[2], R. Nordyke[2], W. Wang[3], X. Zhu[3], J. Schold[4]

[1]Columbia University Medical Center, New York, NY [2]Angion Biomedica Corp, San Francisco, CA [3]Genesis Research, Hoboken, NJ [4]Cleveland Clinic, Cleveland, OH

Background

Renal function, as measured by eGFR, is a well-established a predictor of long-term kidney transplantation (KT) outcomes.[1-5] However, the role of intercurrent clinical events (ICE), and how they affect the relationship between eGFR and outcomes, has not been fully characterized. Schnitzler [3] has previously established that acute rejection (AR) events from discharge to 12-months post-transplant are an important predictor of subsequent graft failure, in addition to 12-month eGFR. Little is known about the potential impact that additional clinical events, such as cardiovascular events (including acute myocardial infarct and stroke) or serious infections may have on graft survival predictions.

Objectives

Evaluate graft failure hazard ratios for 12-month eGFR values with and without adjusting for intercurrent clinical events.

Methods

Study Design

A retrospective cohort analysis was conducted using the Organ Procurement and Transplantation Network (OPTN) patient registry STAR files linked with the United States Renal Data System (USRDS) administrative claims databases. The overall study period was 2012-2016, with KT performed 2012-2015 and allowing for at least 1-year of follow-up. Approval for the linkage was granted by OPTN/HRSA and the study protocol approved by the Columbia University IRB.

Study Population

Patients age 18 and older with:

- Single-organ KT procedure Jan 2012-Dec 2015
- Medicare as primary payer by date of transplant
- Graft survival ≥1 year post-transplant with available data for eGFR calculation at 12-months

Outcome

Death-censored graft failure more than 1-year post-transplant

Key Predictors

- eGFR at 12-months post-transplant (by CKD-EPI equation), treated as cubic-splined variable to account for the non-linear relationship between eGFR and graft failure [1-5]
- Intercurrent events with at least one administrative claim code: AR, cardiovascular events (CVE, including stroke and AMI), cytomegalovirus (CMV) infections, and non-CMV infections (including pneumonias, influenzas, and other infectious diseases).

Table 1: Cohort Attrition

	Criteria (applied sequentially)	N	%
Step 1	Kidney transplant from 2012-2015	67,363	100.0%
Step 2	Patients aged 18 and older at time of transplant	64,490	95.7%
Step 3	Excluding patients with multi-organ transplants	62,375	92.6%
Step 4	Patients with no kidney transplants prior to 2012	54,677	81.2%
Step 5	Patients with deceased donors only	35,626	52.9%
Step 6	Patients with MPP prior to date of transplant	11,820	17.5%
Step 7	EXCLUDE pre-emptive transplant (no dialysis prior)	11,404	16.9%
Step 8	EXCLUDE Patients who died within 12 months post-transplant	10,497	15.6%
Step 9	EXCLUDE Graft Failure within 12 months post-transplant	10,154	15.1%
Step 10	Patients with SCr levels 365 days post-transplant	9,942	14.8%
Step 11	EXCLUDE missing donor BMI, age or weight, PRA, HLA and CIT	9,665	14.3%

Results

9,665 patients met study selection criteria. Of these, 784 (8%) experienced graft failure during follow-up. Baseline demographic and clinical characteristics for patients are shown in **Table 2**.

Table 2: Demographic and Clinical Characteristics

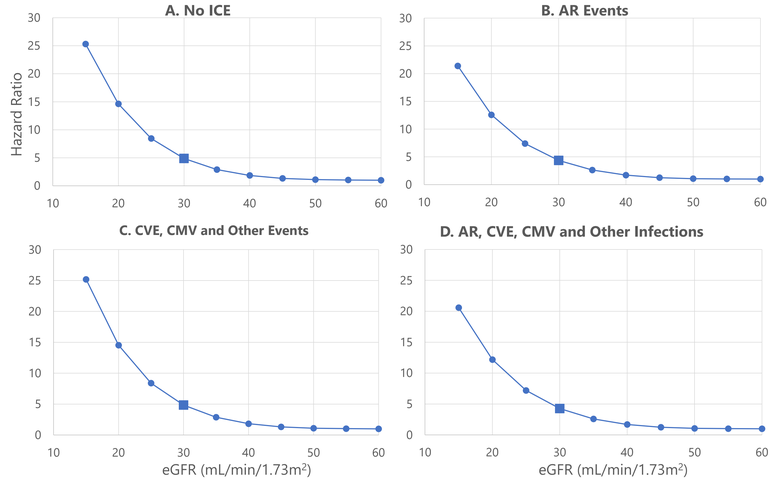
	Total Cohort	Graft Failure	No Graft Failure
N	9665	784	8881
12-month eGFR (by CKD-EPI), ml/min/1.73m^2	61.1	47.0	62.3
Follow Up Time from 1-Year after Transplant, days	1373	1140	1394
Mean age, years	53.1	50.9	53.3
Male gender, %	62.3	64.7	62.1
Black race, %	41.0	51.2	40.1
Years since Dialysis Start	5.2	5.4	5.2

Results of Cox proportional hazard regression models with and without ICE are shown in **Table 3**. Predictors without statistically significant results (p>0.05) in any model are not shown. Notable transplant features that do not predict graft failure among 1-year survivors are cold ischemia time (CIT), delayed graft function (DGF), and received on pump.

Table 3: Results for regression models with/without intercurrent events (HRs, *=p<0.01)

	A. No ICE		B. AR Events		C. CVE, CMV and Other Infections		D. AR, CVE, CMV and Other Infections	
Recipient Variables								
Age: 30 to 44 (Ref: <30)	0.45	*	0.47	*	0.46	*	0.48	*
Age: 45 to 59	0.28	*	0.30	*	0.28	*	0.30	*
Age: 60 to 74	0.26	*	0.29	*	0.25	*	0.28	*
Age: 75+	0.31	*	0.34	*	0.31	*	0.34	*
Male (Reference: Female)	1.18		1.18		1.19		1.19	
Black (Reference: Non-Black)	1.42	*	1.42	*	1.42	*	1.42	*
Years on Dialysis (ln)	1.14		1.14		1.13		1.13	
Donor Variables								
History of HTN: Yes (Ref: No)Yes	1.18		1.21		1.19		1.22	
History of HTN: Unknown	0.82		0.74		0.82		0.75	
History of Diabetes: Yes (Ref: No)	1.45	*	1.44	*	1.44	*	1.43	*
History of Diabetes: Unknown	1.15		1.31		1.17		1.43	
Transplant Variables								
Year: 2013 (ref: 2012)	0.85		0.86		0.85		0.86	
Year: 2014	0.72	*	0.75	*	0.71	*	0.74	*
Year: 2015	0.65	*	0.67	*	0.62	*	0.63	*
# HLA Mismatches: <5 (Ref: 6)	1.25		1.24		1.27		1.26	
# HLA Mismatches: 5	0.97		0.97		0.97		0.97	
Intercurrent Events -Discharge to 12 Months								
AR events: Yes (Ref: No)	.		1.72	*			1.65	*
AR events: Unknown	.		1.32				1.30	
CV Events: Yes (Ref: None)	.		.		0.61		0.68	
CMV Infections: Yes (Ref: No)	.		.		1.10		1.09	
Other Infections: Yes (Ref: No)	.		.		1.43	*	1.38	*

Figure 1: Adjusted Hazard Ratios by eGFR value for models with/without ICE



- For Models A and B in Figure 1, the addition of AR events reduces adjusted HRs for 12-month eGFRs at eGFR values below 30 mL/min (■ marker); at 20 mL/min ΔHR=2.0, e.g. HRs above 30 are essentially unchanged. Trends between 12-month eGFR and graft failure are similar above 30mL/min for all models.
- The additional ICEs of CV Events, CMV, and other infection events (Model C) add no predictive power as compared to Model A.
- The addition of other ICE to AR (Model D) does not change the HR curve relative to Model B.

Discussion

- 12-month eGFR is a well-established predictor of long-term graft outcomes. [1-5]
- AR events have been previously shown to reduce the graft failure adjusted HRs for 12-month eGFR measures at relatively low levels of renal function (below 30-35 ml/min) [3]. Those results are confirmed here, reducing the failure HRs for 12-month eGFR by 1-2 points at low eGFR values.
- Characteristics of the transplant procedure, including cold ischemia time, delayed graft function, or organ received on a pump were not significant predictors of graft survival after 1 year
- This analysis shows that the only ICE to affect the strength of the relationship between eGFR and graft survival is AR, and that eGFR remains the strongest predictor of graft survival even when ICE are added to the predictive model. These data support eGFR as a strong surrogate of graft failure.

Conclusions

At 12-months post-transplant, renal function as measured by eGFR, is the strongest predictor of graft failure even when the influence of intercurrent clinical events are accounted for.

REFERENCES: [1] Kasiske BL, et al. AJKD. 2011 Mar;57(3):466-75. **[2]** Schnitzler MA, et al. Transpl Int. 2012(A);25(2):179-191. **[3]** Schnitzler MA, et al. Transplantation. 2012(B); Jan 27;93(2):172-81.**[4]** Schnitzler, MA et al. Transplantation. 2011; 91(12):1347-56. **[5]** Loupy A, et al. BMJ. 2019;366:l4923.