OPTN Kidney Transplantation Committee
Biopsy Best Practices Workgroup
Meeting Summary
August 23, 2021
Conference Call

Andrew Weiss, MD, Chair

Introduction

The Biopsy Best Practices Workgroup (the Workgroup) met via teleconference on 08/23/2021 to discuss the following agenda items:

1. Review Project Timeline
2. Biopsy, Anatomy, and Resistance Effects on Transplant Outcomes (BARETO) Study Presentation

The following is a summary of the Workgroup's discussions.

1. Review Project Timeline

The Workgroup reviewed the project scope, goals, and timeline leading up to public comment.

Summary of discussion:

The Workgroup had no questions or comments.

2. Biopsy, Anatomy, and Resistance Effects on Transplant Outcomes (BARETO) Presentation

The Workgroup received a presentation on the UNOS led, Mendez-funded BARETO study.

Data Summary:

Over the last 30 years, the kidney discard rate has risen, remaining between 18 percent and 20 percent for the last decade. The number one reason cited for discard over the last few decades has been biopsy findings, with between 30 and 40 percent of discards citing biopsy as the main reason for discard.

While many believe that biopsies contribute to the refusal of useful organs, others suggest that the clinical information provided by biopsies is critical to prevent negative outcomes and to better match potential recipients.

A recent behavioral study[1] using an organ offer simulation tool, SimUNet, focused on examining how biopsy findings influence organ offer decisions. The findings of the behavioral study showed two interesting trends:

- In the context of high KDPI, ECD kidneys, the data suggests that biopsies are being used to "rule out" kidneys for transplant
    - "Poor" biopsy findings were influential in decision making; all else equal, the acceptance rates with a "poor" biopsy shown were below 50 percent. If those results were withheld, acceptance rates rose to about 70 percent.

[1] Stewart DE, Garcia VC, Rosendale JD, Klassen DK, Carrico BJ. Diagnosing the Decades-Long Rise in the Deceased Donor Kidney Discard Rate in the U.S. Transplantation. 2016.

    - When these kidneys were shown with “good” biopsy findings, the acceptance rates didn’t increase much beyond the 70 percent acceptance rate for these kidneys presented without biopsy results.
- In the context of AKI kidneys, the data suggests that biopsies were used to “rule in” kidneys for transplant
    - When no biopsy was reported, acceptance rates were below 30 percent. However, when a kidney had “good” biopsy results, the acceptance rates rose 2-3 fold, with statistically significant results

The literature on biopsies over the last 20 or 30 years has had several limitations, including:

- Small sample sizes, as many are single or few center
- Unrealistic sampling, as formalin-fixed paraffin embedded samples are not practical in post-procurement environments, where frozen samples are most commonly used
- Limited focus, typically to glomerular sclerosis
- Arbitrary categorization of glomerular sclerosis, as opposed to a continuum
- Focus on short-term outcomes as opposed to long-term outcomes

The study itself is a retrospective observational study of biopsied ECD kidneys, looking at about 6000 transplants occurring between 2008-2012. The study focuses on glomerular sclerosis, interstitial fibrosis, and vascular changes as the biopsy exposure variables, and 10-year all cause graft survival recipient outcomes, utilizing rigorous causal inference methodology, including multivariable regression, propensity score inverse probability weighting, and doubly robust regression.

The study adjusted for a robust set of clinical parameters, based on literature review, correlations, and clinical hypothesis generation:

- Donor factors – age, KDPI, body mass index (BMI), sex, terminal creatinine, race/ethnicity, hypertension history, and diabetes history
- Kidney graft factors – interstitial fibrosis, chronic vascular changes, arterial plaque, and aortic plaque
- Recipient factors – estimated post-transplant survival score (EPTS), functional status, calculated panel reactive antibodies (CPRA)/sensitization, immunosuppression, and induction
- Transplant/matching factors – cold ischemia time, pumped (yes or no), and donor-recipient sex mismatch

The preliminary findings from the study:

- Unadjusted 10-year Kaplan Meier analysis on graft survival by glomerular sclerosis show a dose-response relationship for 0-5 percent, 6-10 percent, and 11+ percent glomerulosclerosis
    - Unadjusted, the 10-year hazard of graft survival by glomerulosclerosis aligns with the unadjusted Kaplan Meier curves for 11+ percent and 0-5 percent (reference group) – there is a 1.29 hazard ratio
    - There is a 29 percent higher hazard of graft failure compared to the reference group for the 11+ percent group, with a 5 percent confidence interval
- Adjusted, the effects of glomerulosclerosis are tempered to some degree, but a meaningfully large and statistically significant effect still remains, with a hazard ratio of 1.18 and a confidence interval that shows clear difference from the null hypothesis
- Looking at percent glomerulosclerosis on a spectrum, the unadjusted curve shows an increasingly statistically significant increasing hazard of graft failure as glomerulosclerosis goes from 0 percent to 10 percent

    - Adjusted, the results are very similar. The increasing hazard tapers offs dramatically beyond 10 percent
    - Comparing this to the discard rate as a function of glomerulosclerosis, there appears to be a disconnect between the flattening of the dose-response relationship between glomerulosclerosis and graft failure hazard, and utilization practices as the discard rate continues to precipitously rise beyond 10 percent
- Looking at interstitial fibrosis and long term graft survival in an unadjusted framework via Kaplan Meier curves, there is a weak effect showing graft survival decreasing with increasing degree interstitial fibrosis
    - Adjusted, the effect is significantly attenuated, with a wider confidence interval for the moderate/several degree of interstitial fibrosis, due to fewer cases in that category
- Looking at vascular changes and long term graft survival in an unadjusted framework, the trend is almost identical to that of the interstitial fibrosis Kaplan Meier curves.
    - Adjusted, the effect is significantly attenuated.

Preliminary conclusions based on these findings include:

- Despite valid limitations, procurement biopsy glomerulosclerosis is independently predictive of post-transplant graft-survival
    - The dose-relationship between graft survival and glomerulosclerosis tapers beyond 10 percent, which is discordant with kidney utilization practices
- Interstitial Fibrosis and Vascular Changes have little or no independent association with graft survival after rigorous risk adjustment
- Glomerulosclerosis and other independently predictive prognostic parameters (anatomy and pumping resistance) should be incorporated into clinical predictions such as KDPI in order to temper their impact, foster more evidence driven decision making, and help biopsy findings rule in ECD and high KDPI kidney for transplant

Summary of discussion:

The Chair of the Workgroup asked if the progressive increase in number of kidneys biopsied could be explained by the recovery of more marginal kidneys. A presenting Researcher agreed that over the 1990s and 2000s, there was a push to expand the donor pool and procure more organs, even those considered more marginal. A prior study published by UNOS (as OPTN)(1) aimed to find out if the rise in the discard rate during the 2000's was due to risk aversion, or instead was an expected consequence of an older donor pool with more comorbidities. By and large, the trends in increased discards and increased biopsy could be explained by the change in the donor pool. As the donor pool has been relatively stable, with some changes with respect to hepatitis C and opioid use, the trends have flattened. The rise in discard rates coincided with a rise in rates of performing biopsies, so it is conceivable that the increased number of biopsies is due to the recovery of marginal kidneys, although the study did not directly answer that question.

The Chair noted that the 10 percent glomerulosclerosis threshold does not align with the 20 percent or greater threshold that is often taught. The Chair continued, asking if there is an ability to hone in on that kind of split, since so many transplant programs utilize the 20 percent threshold. One presenting Researcher remarked that comment gets to one of the main goals of the study – to provide rigorously analyzed evidence that will help change acceptance practice if that practice is using the 20 percent threshold in an inordinate way. Biopsy findings should be used commensurate with their effects. The presenting Researcher also noted that the data itself has limitations, particularly with a decreasing sample size as glomerulosclerosis increases beyond 30 and 35 percent, it becomes difficult to precisely

estimate the effects on recipient outcomes. Fewer centers are transplanting at such a high level of glomerulosclerosis. Selection bias also presents an obstacle, as other donor factors could increase the comfort level of surgeons accepting and transplanting high glomerulosclerosis kidneys. In that case, there could be an unmeasured factor the analysis does not account for which could impact the results. The presenting Researcher continued, asking if that was the case, what those factors could be.

The Chair noted that there is a focus on degree of scarring when it comes to organ declines based on degree of glomerulosclerosis, particularly with the presenting values the donor has upon admission and at time of recovery. If the donor has a creatinine of 1.8 that never declines to a normal value, there is no other data available that can point to degree of scarring, other than a biopsy. The donor could always have a 1.8 creatinine or developed acute renal failure, and renal scarring plays an influential role in the acceptance decision. The Chair offered another example. With a similar ECD donor with a 0.8 creatinine who has no protein in the urine and has 20 percent sclerosis, there is still a focus on the donor's good kidney function. A recipient can still do very well with one of the two organs presenting that creatinine of 0.8. The Chair asked if a creatinine threshold, such as 1.2, could be used to study differences in offer decision making patterns. A presenting Researcher noted that the former example points to a biopsy being able to help rule in a 1.8 creatinine kidney by ruling out chronic kidney disease, while the latter example points to a situation where a biopsy should have less influence. The presenting Researcher pointed out that the behavioral study found, with ECD kidneys with creatinine levels of less 1.3, biopsy still had a profound effect on ruling out to clinicians. The behavioral study quantified how a biopsy's influence differed between clinicians, and found significant heterogeneity in terms of practice with respect to those types of clinical scenarios and how biopsy impacts decision making. One presenting Researcher remarked that the BARETO cohort does not have the detail of change in creatinine over time, and agreed that admission creatinine and change in creatinine levels may have an impact.

The Chair provided another set of examples. A donor with a creatinine of 3 that finished with a creatinine of 2.5 and had no scarring on the biopsy could be more easily considered than if the biopsy showed 20 or 25 percent glomerulosclerosis. In that way a reassuring biopsy could influence towards acceptance, but one with scarring would reinforce clinical concern. A presenting Researcher noted that potentially, the effects of glomerulosclerosis and the isolated results could potentially be stratified by presence of AKI or CKD.

Upcoming Meeting

September 14, 2021 – Teleconference
September 28, 2021 – Teleconference

Attendance

- **Committee Members**
  - Andrew Weiss
  - Dominick Santoriello
  - Catherine Kling
  - Colleen Flores
  - Julianne Kemink
  - Meg Rogers
- **HRSA Representatives**
  - Marilyn Levi
- **SRTR Staff**
  - Bryn Thompson
  - Jon Miller
  - Nick Salkowski
- **UNOS Staff**
  - Lindsay Larkin
  - Amanda Robinson
  - Kayla Temple
  - Lauren Motley
  - Ross Walton
  - Ben Wolford
  - Leah Slife
  - Nicole Benjamin
- **Other Attendees**
  - Darren Stewart, MS, UNOS, BARETO study co-PI
  - Guarav Gupta, MD, Virginia Commonwealth University, BARETO study co-PI