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Foretelling the Future: Predicting Graft Outcome by Evaluating Kidney Baseline Transplant Biopsies

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Kidney allografts typically have had a previous life and often show donor-derived “wear and tear,” with signs of hypertension-induced arteriomegaloerosclerosis and occasionally other renal diseases that may affect graft survival. “Procurement” and “zero-hour implantation” biopsies are performed at time of grafting to assess donor disease. Procurement biopsy samples are primarily collected to give information on organ suitability for transplantation, and zero-hour implantation biopsies are performed to provide insight into pre-existing diseases relevant for comparative analyses after transplantation and for overall prognosis. Thus, the diagnostic implications from both biopsy types overlap, which is why the term “baseline transplant biopsy” is often used synonymously. As of yet, generally accepted and predictive scoring systems for the evaluation of such baseline kidney transplant biopsy specimens have not been established.¹

Most examinations of procurement biopsy specimens are limited to frozen sections of subcapsular wedges, which have pitfalls in the interpretation. Ideally, at least 25 glomeruli (from as deep in the cortex as possible) should be studied, and subcapsular scar tissue should be excluded. Importantly, a wedge biopsy is often not representative because it includes mostly outer cortex, the zone where glomerulosclerosis and fibrosis due to vascular disease are most severe. Arteriosclerosis, in contrast, most prominently affects arcuate and larger-caliber arteries and therefore is under-represented in a wedge biopsy.²–⁴ Zero-hour implantation biopsy specimens are commonly obtained by needle core biopsy that has to be of specific size (16-gauge needle, two cores) to render optimal results. Thus, proper histologic evaluation of all baseline biopsy specimens can be challenging.

The use of procurement biopsies increases with donor age: 5% at age 20, 20% at age 45, 40% at age 55, and 60% at age 65.⁵ There is general agreement that normal donor kidneys fare well after transplantation, whereas severely altered organs with marked chronic injury and sclerosis or with a diffuse crescentic GN have an ominous prognosis and are generally unsuited for grafting. Uncertainty, however, still exists on the fate and suitability of donor kidneys with moderate to severe pre-existing changes in glomeruli, the tubulo-interstitial compartment, and blood vessels. What lesion is most significant prognostically, what other factors should be considered, who is the best-suited recipient, and, most important, should the organ be used at all?

Many studies have correlated donor characteristics and findings in baseline biopsy specimens (from procurement or implantation biopsy) with outcome. The study by De Vusser et al. in this issue of JASN is the latest one in an entire series.⁶ It is clear that some abnormalities do not measurably affect long-term prognosis, in part because of other, more severe causes of graft loss (e.g., rejection, cardiovascular disease, infection; Figure 1).

GN has been evaluated in many studies as an indicator for organ suitability. The results are contradictory. A seminal report showed that allografts with good function at 6 months had less global glomerulosclerosis in the baseline biopsy specimen than those with poor function (2% versus 20%),⁶ and a threshold of <20% glomerulosclerosis characterized a group with a lower rate of delayed graft function and graft loss. These findings contributed to the proposed 20% cutoff that gained subsequent support.⁷ However, a large study of 387 baseline biopsy found that glomerulosclerosis was not an
independent predictor of outcome if age was included in a multivariate analysis.\textsuperscript{8}

In a large United Network for Organ Sharing study of 3444 baseline biopsies of cadaveric donor organs, glomerulosclerosis over 20% predicted decreased graft survival only when associated with decreased creatinine clearance in the donor.\textsuperscript{9} According to this study, glomerulosclerosis should not be the sole criterion for discarding donor kidneys. A recent single-center study from Baltimore, Maryland, analyzed a series of 371 baseline biopsy specimens, mainly collected from an “expanded donor organ pool” with relatively long ischemia times that had been rejected by other transplant centers. In this cohort of mostly “marginal donor organs,” five histologic features (glomerulosclerosis, periglomerular fibrosis, arteriosclerosis, arteriolar hyalinosis, and scar formation) were weighted and incorporated into a cumulative chronic histologic scoring index. Overall graft survival was 90% at 1 year; at 5 years it ranged from 53% in organs with high cumulative chronicity indices up to 90% in those with low indices.\textsuperscript{10} In this series more than 50% of organs with relatively marked sclerosis and chronic injury functioned 5 years after grafting. The data from Baltimore underscore that even marginal donor organs can be beneficial for some recipients, particularly in “old-for-old” or dual-organ transplantation programs.\textsuperscript{11–15} Another study found a high donor-recipient age ratio (i.e., old donor organ into young recipient) to be associated with an increased risk for subsequent allograft failure.\textsuperscript{16} Thus, chronic injury, including the percentage of globally sclerosed glomeruli, does not provide universal guidelines for the suitability of donor kidneys in a diverse recipient population ranging from young to old.

Most studies show a correlation of glomerulosclerosis, interstitial fibrosis, and arteriosclerosis with donor age. In deceased donors age 40 years or younger, 54% of renal biopsy findings were normal, in contrast to only 7% after age 40.\textsuperscript{17} At the University of North Carolina at Chapel Hill, we found evidence of arterionephrosclerosis in approximately 68% of our conventional donor pool organs. In 19% of organs, moderate chronic changes were noted at a relatively young mean donor age of 37 years. Unexpected moderate to severe arterionephrosclerosis was also found in 19% of organs of living donors, suggestive of clinically undiagnosed episodes of hypertension. On the other hand, even septuagenarians can have kidneys with relatively minor sclerosis.\textsuperscript{18,19} Thus, age alone is only an imperfect predictor of the overall degree of nephrosclerosis and the suitability of an organ for transplantation.

At present, approximately 15%–20% of all kidneys harvested in the United States are discarded (the Organ Procurement and Transplantation Network reports that in the United States in 2011, 94,000 patients were waitlisted for a kidney-kidney/pancreas transplant, but only 17,600 kidney-kidney/pancreas transplants were performed). According to the National Kidney Foundation, the most common reason for discarding donor

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**Figure 1.** Factors influencing outcome of kidney transplants. CMV, cytomegalovirus; DSA, donor-specific antibodies.
organs is an abnormal biopsy finding; such findings led to 42.8% of kidney discards from 2005 to 2009, up from 37.2% during 1995–1999. Currently there is great concern that rigid and arbitrarily set morphologic criteria for the evaluation of procurement biopsy specimens result in the unnecessary discard of kidneys.1,11

In this context, De Vusser and colleagues propose a novel scoring system, the Leuven Donor Risk Score that predicts 5-year graft survival with 81% sensitivity and 85% specificity.3 The proposed score is a sum score based on known histologic (glomerulosclerosis, interstitial fibrosis, tubular atrophy) and demographic (donor age) characteristics that are, as noted above, individually associated to varying degrees with graft survival. The strengths of De Vusser and colleagues’ study include a large cohort of patients, long-term follow-up data, in-depth statistical analyses, and comparative evaluation of historical, previously published alternative scoring systems.

Although these data are intriguing, it is important to note that they have certain limitations, some of which are outlined by the authors themselves. The analysis is based on single center central European observations accounting for region-specific demographic characteristics. The authors report excellent graft survival, 94% at 2 years and 90% at 5 years, thereby leaving only relatively few patients in the “failed transplant group” used for statistical analysis. Important histologic changes, such as the degree of arteriosclerosis, are probably underestimated because of the use of subcapsular wedge biopsy specimens, which often lack large caliber vessels. Additionally, it would have been informative to learn more about allograft function after transplantation in order to determine what impact a high Leuven score might have on serum creatinine levels and GFR over time.

The most significant limitation of De Vusser and colleagues’ study is, however, the lack of information on post-transplantation events, such as rejection, polymavirus infections, and recurrence of renal disease, that adversely affect graft survival (Figure 1). This short-coming, present in previously published scoring systems, such as the Maryland Aggregate Pathology Index,1,10 raises doubts regarding the robustness and predictive value of the suggested scoring criteria.

It is clear that many factors influence graft survival (Figure 1) and that the needs of individual transplant recipients, young or old, may differ. Interestingly, Munivenkatappa and colleagues from Maryland showed that >50% of donor kidneys with a high burden of chronic injury functioned for 5 years.10 Possibly, dual transplantation of marginal donor organs could be a strategy to further improve outcome. Thus, as emphasized by De Vusser and colleagues, scoring systems should not be primarily used to reject potential donor organs but rather to guide their targeted allocations. In this context, the Leuven scoring system outlines a new strategy to predict “the future” (i.e., graft survival) and to use donor organs most efficiently. It also becomes clear that there may not be a single best universal scoring system that optimally works in all donor organs—normal or sclerosed—and meets all the specific needs of a diverse population of organ recipients. Possibly different scoring approaches are required. De Vusser and colleagues’ report comes at a time of intensified discussion on the best use of donor organs and fair allocations,20 and it provides much-needed information for a broad debate. As with all important studies, that by De Vusser et al. prompts new questions: Is the overall effect of chronic, pre-existing donor disease on long-term graft survival underestimated in all current series/statistical analyses, including data reported by the United Network for Organ Sharing?

DISCLOSURES
None.

REFERENCES

allocation of marginal kidney allografts to elderly recipients combined with modified immunosuppression gives good results. Transplantation 80: 953–958, 2005


