Better Understanding Live Donor Risk through Big Data

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In the context of the organ shortage, kidney transplantation from living donors has increased markedly over the last several decades. This growth in living donation has been accompanied by changes in donor characteristics, including greater racial and ethnic diversity and more unrelated donors (1). Recent studies also suggest an increase in donation from persons with baseline medical complexity, including obesity, hypertension, glucose intolerance, and even reduced renal function (2,3). However, capture of early complications by the national transplant registry has suffered from frequent missing data and under-reporting. Early postoperative complications reported by transplant centers to the Organ Procurement and Transplantation Network (OPTN) on the living donor registration form (submitted at discharge or within 6 weeks of the donation hospitalization) in 2000–2012 indicated the need for blood transfusion in 0.4%, vascular complications in 0.3%, readmission in 2.1%, reoperation in 0.5%, and other interventions in 0.8% (4). These center-reported frequencies are markedly lower than estimates of 3%–6% for major complications and 18%–22% for minor complications based on application of the Clavien classification system to sources such as a prospective Norwegian donor registry and United States hospital coding data (5).

On the background of uncertainty regarding the true distribution of perioperative complications after donor nephrectomy, a new article by Schold *et al.* illustrates an innovative approach (6). Using data from the Nationwide Inpatient Sample (NIS), an all-payer inpatient care database comprising a stratified sample of 20% of nonfederal United States hospitals from participating states, the investigators identified living kidney donors in 1998–2010 on the basis of International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis and procedure codes. Baseline comorbidity and complications during the hospitalization of the nephrectomy procedure (and thus presumably related to it, although timing of the various codes is not specified in NIS) were ascertained by diagnosis codes, and the frequency of complications was compared with that among patients who underwent appendectomy, cholecystectomy, and nephrectomy for nonmetastatic cancer. The authors reported a sample equivalent of 69,117 donors. Of note, in studies of NIS the actual number of patients from whom inferences are drawn is usually about one tenth the size of the sample equivalent size. In other words, one would estimate that approximately 7000 actual donors were identified and studied (similar to subject counts of 6300–9400 in recent studies identifying donor nephrectomies from the NIS directly in comparable time periods without the use of weighting [7,8]), but these represented about 70,000 donors nationally because of the sampling scheme used by NIS (and the weighted sample is more representative of the national population than an unweighted sample).

Among donors identified in NIS, the proportion of documented baseline comorbid conditions was <5% but increased over the study period, including rises in hypertension (0.4% in the first 4 years to 3.1% in the last 4 years) and depression (from 1.5% to 3.0%). Complications were recorded in 7.9% of the sample and, in contrast with baseline comorbidity, declined over the study period, as did length of stay. Complications were more common among men than women, African-American than white donors and those of other races, and those with hypertension. The complication rate associated with donor nephrectomy was similar to that associated with appendectomy and cholecystectomy, but lower than after nephrectomy for carcinoma. Overall, this study provides valuable information that, when framed in the context of its limitations, can be used to advance the counseling and informed consent of living donors; centers can also use this information to guide their own quality assessment and process improvement benchmarking for donor outcomes.

The current study also nicely illustrates the limitations of NIS, suggesting that this secondary data source will not provide all that donors need to know about the clinical characteristics and perioperative complications of nephrectomy. Interpretation of these, and all secondary, data by practitioners and policymakers must consider limitations specific to the datasets, particularly those relating to sampling and use of surrogate outcome measures. As Schold and colleagues point out, the NIS is a sample of 20% of United States hospitals, not a comprehensive registry. Although the sample represented a population that was approximately 89% of living donors in the United States during the same timeframe, and clinical characteristics were relatively concordant with the national transplant registry, living-donor status was not confirmed by patient-level linkages to the registry itself. Of note, observed perioperative mortality was 0.17%, which, although low, is more than five times the mortality estimates generated by OPTN reports or linkage of the OPTN registry to

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national death records (9,10). This finding suggests that some patients who were not actually donors may have been inadvertently included in the study sample, or it could possibly identify a bias in the sample population. The current study also lacked details of the surgical procedure, such as laparoscopic versus open approach and side of nephrectomy, that are tracked in the OPTN registry and may be relevant to early complication rates. Linkage of national donor registry data to other information sources, including death records, Centers for Medicare & Medicaid Services ESRD reporting forms, and administrative billing claims, has been performed and illustrates an important method for validating donor status as well as integrating baseline demographic and clinical information reported by centers to the OPTN into a study database (10–12); unfortunately, NIS is de-identified and does not support such linkage. Finally, NIS is not a longitudinal registry, so any complications that might have occurred on readmission would not have been captured.

With regard to the accuracy of study measures, billing claims are surrogate measures of clinical diagnoses and procedures, and coding errors in the form of both under- and over-reporting are possible. Billing claims have been demonstrated to provide sensitive measures of diabetes and cardiovascular diagnoses in general populations (13,14) but to under-represent the burden of some complications, such as kidney dysfunction, compared with laboratory-based measures (15). In the current study, as nicely identified by the authors, claims-based indication of obesity among 3.7% of recent donors compared with the reported prevalence of body mass index >30 kg/m^2 in 22% of donors in the OPTN registry indicates that the sensitivity of billing claims for capture of obesity was inadequate. The accuracy of administrative claims probably varies by condition and population, and measures-validation studies comparing claims with other information sources, such as medical records, will be important for advancing optimal use of claims data for donor outcomes assessments; these validation studies will be explored as a component of the new multicenter National Institutes of Health–funded WHOLE-DONOR (Wellness and Health Outcomes in LivE DONORs) study (R01-DK096008; principal investigator, D.L.S.). Furthermore, although overall complications were categorized by affected organ system, the current study did not provide information on the severity of complications or need for interventions, such as transfusions, surgery, or invasive procedures. Presumably, severity grading could be possible by applying the Clavien system for administrative data, and identification of postdonation interventions such as reoperation could be possible if based on query of procedure codes.

To improve the practical utility of the data generated by the current study for donor counseling, future work should seek to define implications of both baseline comorbidity and perioperative complications for longer-term health outcomes. In the current study, male sex, baseline hypertension, and African American race were independently associated with perioperative complications in multivariable models. These same characteristics have also been associated with increased risk of later medical complications, ESRD, and death within other donor cohorts (10–12). Whether early complications play a mediating role in the long-term risks needs to be defined in data sources (or primary studies) capturing longitudinal outcomes. Further, comparisons of long-term outcomes in living donors versus controls with similar baseline demographic and clinical profiles are critical for quantifying the risks attributable to donation—*i.e.*, for discriminating the risks related to kidney donation itself in the context of a given clinical or demographic profile from the risks among individuals of that given profile who do not serve as organ donors.

As policies for informed consent, medical evaluation, and follow-up of living organ donors are receiving increased attention and formalization by the organizations that guide and regulate transplantation practice, ongoing efforts to strengthen the available evidence are needed. New national policy effective February 2013 includes mandated thresholds for the collection of clinical information at follow-up points of 6 month, 1 year, and 2 years, including some complications such as death, readmission, kidney complications, dialysis, and loss of insurance, as well medical conditions such as diabetes and hypertension (16). Although more thorough center reporting of these clinical data to the OPTN will strengthen the available information on postdonation health, limitations of the registry will persist, including the scope and granularity of the collected data elements, the $<100\%$ final mandated thresholds for data collection (established as 80% of the center's donors by December 2014 for clinical data), and limitation of the follow-up survey to 2 years after donation. Thus, collection of primary data in dedicated, funded research studies of live donors, and examination of secondary data sources, will remain important and has been endorsed by a 2010 consensus conference convened to evaluate "Living Kidney Donor Follow-up: State-of-the-Art and Future Directions" (17) and by individual experts in living donor care (18). We believe that advances in the use of secondary data for understanding donor outcomes will include data integration approaches for sample confirmation when possible, as well as efforts to quantify and refine the accuracy of claims-based algorithms for event detection based on direct linkages or comparisons to other information sources for external validation. Ultimately, by improving understanding of the short- and long-term health outcomes among representative, diverse samples of living donors, the transplant community can meaningfully improve the processes of consent, selection, and care that are vital priorities.

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