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Acute dialysis risk in living kidney donors

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Abstract

Background. Reduced kidney function confers a higher risk of acute kidney injury at the time of an inciting event, such as sepsis. Whether the same is true in those with reduced renal mass from living kidney donation is unknown.

Methods. We conducted a population-based matched cohort study of all living kidney donors in the province of Ontario, Canada who underwent donor nephrectomy from 1992 to 2009. We manually reviewed the medical records of these living kidney donors and linked this information to provincial health care databases. Non-donors were selected from the healthiest segment of the general population.

Results. There were 2027 donors and 20 270 matched non-donors. The median age was 43 years (interquartile range 34–50) and individuals were followed for a median of 6.6 years (maximum 17.7 years). The primary outcome was acute dialysis during any hospital stay. Reasons for hospitalization included infectious diseases, cardiovascular diseases and hematological malignancies. Only one donor received acute dialysis in follow-up (6.5 events per 100 000 person-years), a rate which was statistically no different than 14 non-donors (9.4 events per 100 000 person-years).

Conclusions. These results are reassuring for the practice of living kidney donation. Longer follow-up of this and other donor cohorts will provide more precise estimates about this risk.

Keywords: acute kidney injury; administrative health database; dialysis; living kidney donors

Introduction

At the time of an inciting event such as sepsis, reduced kidney function confers a higher risk of acute kidney injury. This robust association was recently summarized in a collaborative meta-analysis of three general population cohorts [1]. Over a follow-up period of between 2 and 8 years, the risk of acute kidney injury (defined as ICD-9 Code 584 as the primary or additional discharge code) increased with lower baseline estimated glomerular filtration rate (eGFR). Compared with an eGFR of over 60 mL/min/1.73 m^2, the hazard ratio for acute kidney injury was 2.6 [95% confidence interval (95% CI) 2.2–3.1] for an eGFR of 45–59 mL/min/1.73 m^2 and 7.9 (95% CI 7.1–8.7) and 16.7 (95% CI 14.7–18.9) for an eGFR of 30–44 mL/min/1.73 m^2 and 15–29 mL/min/1.73 m^2, respectively.

It is currently unknown whether this same risk extends to the over 22 000 registered individuals who donate a kidney worldwide each year. All living kidney donors lose 50% of their renal mass. In the decade following donation, ∼40% have a new baseline measured glomerular filtration rate (GFR) of 60–80 mL/min/1.73 m^2 and 12% have a GFR of 30–59 mL/min/1.73 m^2 [2]. To our knowledge, the risk of acute kidney injury in living kidney donors has only been reported once before [3]. In this Japanese study, two acute kidney injury events were observed among 1519 living kidney donors, one of whom received acute hemodialysis (0.07%), 9.6 months post-donation after a serious traffic accident resulted in cardiogenic shock. We conducted the current study to better understand the risk of acute kidney injury in living kidney donors, studying donors from the largest province in Canada. Reasons for better knowledge of long-term donor outcomes include understanding the physiology of nephrectomy, improving informed consent and maintaining public trust in the transplantation system. We focused on severe acute kidney injury treated with acute dialysis, as this outcome is well ascertained in our data sources and is the most worrisome event.

Materials and methods

Study design and setting

We conducted a population-based matched cohort study using manual chart review and linked health care databases in Ontario, Canada. Ontario currently has ∼13 million residents who have universal access to hospital care and physician services (Statistics Canada, 2010). We conducted this study according to a pre-specified protocol, which was approved by the research ethics board at Sunnybrook Health Sciences Centre (Toronto, Ontario, Canada). The reporting of this study follows guidelines set out for observational studies as outlined by the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement [4].

Data sources

We ascertained individual characteristics, covariate information and outcome data from records in six databases. Living kidney donors were identified from the Trillium Gift of Life Network (TGLN), a central organ and tissue donor registry. This database is unique in that it captured all living kidney donor activity in the province. We manually reviewed the medical charts of all living kidney donors who underwent donor nephrectomy at all five major transplant centers in Ontario between 1992 and 2009 to ensure accuracy of the information in the TGLN database. Baseline characteristics, such as age and gender, were determined by accessing the Registered Persons Database. Diagnostic and procedural information during hospital admissions was gathered from the Canadian Institute for Health Information Discharge Abstract Database and Same Day Surgery, while information regarding emergency room visits was gathered from the National Ambulatory Care Reporting System Emergency Department. Patients receiving dialysis were identified using the Ontario Health Insurance Plan database which contains health claims for both inpatient and outpatient physician services. The databases were essentially complete for all variables used in this study.

Population

We included all living kidney donors who were permanent residents of Ontario. The date of their nephrectomy served as the start date for donor follow-up and was designated the index date. Donors undergo a rigorous medical screening and selection process and are, thus, inherently healthier than the general population. Selecting the appropriate non-donors is central to any study of reporting relative risks associated with donor nephrectomy [5]. To address this issue, we used techniques of restriction and matching to select the healthiest segment of the general population. We randomly assigned an index date to the entire general population according to the distribution of index dates in donors. We then looked for comorbidities and measures of health care access from the beginning of available database records (1 July 1991) to the index date. This provided an average of 11 years of medical records for baseline assessment, with 99% of individuals having at least 2 years of data for review. Among the general population, we excluded any adult with any medical condition prior to the index date, which would preclude donation. This included evidence of diagnostic, procedural or visit codes for any of the following: diabetes, hypertension, cardiovascular disease or procedure, cancer, pulmonary, liver or genitourinary disease, systemic lupus erythematosus or rheumatoid arthritis, HIV, gestational diabetes or pre-eclampsia. Those who had a nephrectomy, renal biopsy or a previous nephrology consultation or evidence of frequent physician visits (greater than four visits in the previous 2 years) were also excluded. As well, we excluded any individual who failed to see a physician at least once in the 2 years prior to

index date (given that Ontario has a physician shortage, we wanted to ensure that non-donors had evidence of access for routine health care needs including preventive health measures). From a total of 9 643 344 adult Ontarians during the period of interest, this selection procedure resulted in the exclusion of 85% of adults ($n = 8\,216\,058$) as possible non-donors. From the remaining adults, we matched 10 non-donors to each donor. We matched on age (within 2 years), sex, index date (within 6 months), rural (population <10 000) or urban residence and income (categorized into quintiles, using average neighborhood income on the index date).

Outcome

The primary outcome was acute dialysis during any hospital stay. Similar to other procedures in Ontario, acute dialysis is a fee-for-service physician claim that is recorded with high accuracy [6]. All patients were followed until 31 March 2010, emigration from the province, death or receipt of acute dialysis.

Statistical analysis

We assessed differences in baseline characteristics between donors and non-donors using standardized differences. Differences of >10% may suggest meaningful imbalance [7]. We used a two-sided log-rank test stratified on matched sets to compare differences in acute dialysis outcomes between donors and non-donors. We used Cox regression stratified on matched sets to calculate the hazard ratio with 95% CI. The proportional hazards assumption was met (non-significant donor × follow-up time interaction term, P = 0.47). We conducted all analysis with SAS (Statistical Analysis Software) version 9.2.

Results

Baseline characteristics

Baseline characteristics for 2027 living kidney donors and 20 270 matched non-donors are presented in Table 1. The median age was 43 years [interquartile range (IQR) 34–50] and 60% were women. As expected, donors had more physician visits in the year prior to the index date compared to non-donors. Such visits are a necessary part of the donor evaluation process.

The majority of living kidney donors was siblings of the recipients (35% of donors), followed by spouses (19%), parents (14%) and children (13%). Thirteen percent of donors were unrelated to their recipients. Forty-three percent (43%) of the nephrectomies were performed laparoscopically and the rest were done with an open procedure. Prior to donation, the median serum creatinine was 75 μmol/L (0.85 mg/dL) (IQR 66–86 μmol/L; 0.75–0.97 mg/dL) with a median eGFR of 98 mL/min/1.73 m^2 (IQR 86–109 mL/min/1.73 m^2) based on the Chronic Kidney Disease Epidemiology Collaboration equation [8].

The median length of follow-up was 6.6 years (donors 6.9 years, non-donors 6.5 years and maximum 17.7 years). The median age at the time of last follow-up was 50 years (IQR 42–58). Of the 22 297 total individuals (2027 donors and 20 270 non-donors), 20 712 (92.9%) reached the end of the study follow-up (31 March 2010), 1223 individuals (5.5%) were censored at the time of emigration from the province, 347 individuals [1.5%, 13 donors (0.6%) and 334 non-donors (1.6%)] were censored at the time of death and the remainder experienced an acute dialysis event. The total person-years of follow-up was 163 636 (15 302 donors and 148 334 non-donors).

Outcomes

Only one living kidney donor of 2027 (0.05%) received acute dialysis representing an event rate of 6.5 per 100 000 person-years. This rate was statistically no different from the 14 non-donors who received acute dialysis (0.07%), with an event rate of 9.4 per 100 000 person-years. With only 15 events, the CI for the risk of acute dialysis in donors compared to non-donors was wide (hazard ratio 0.58, 95% CI 0.08–4.47, P = 0.61). Individuals receiving acute dialysis in our follow-up period did so at a median of 8.9 years after their index date (IQR 5.5–12.7). The type of dialysis received was either continuous veno-venous hemodialysis or intermittent hemodialysis. Seven individuals subsequently died in follow-up, six within 90 days of the initial acute dialysis treatment. Reasons for hospitalization resulting in acute dialysis included infectious causes, cardiovascular diseases, hematological malignancies as well as one episode of each of the following: acute glomerulonephritis, pre-

Table 1. Baseline characteristics of living kidney donors and matched non-donors[a]

	Total $N = 22\,297$	Donor $N = 2027$	Non-donors $N = 20\,270$
Age, years	43 (34–50)	43 (34–50)	43 (34–50)
Female	13 376 (60%)	1216 (60%)	12 160 (60%)
Income, lowest quintile	3311 (15%)	301 (15%)	3010 (15%)
Rural residence	3047 (14%)	277 (14%)	2770 (14%)
Physician visits in prior year[b]	1 (0–2)	11 (8–15)	1 (0–2)
Year			
1992–1995	2387 (11%)	217 (11%)	2170 (11%)
1996–2000	5846 (26%)	531 (26%)	5315 (26%)
2001–2005	7504 (34%)	682 (34%)	6822 (34%)
2006–2009	6560 (29%)	597 (29%)	5963 (29%)

[a]Data presented as median (IQR) or as number (percent). The time of transplantation is also referred to as the index date and was randomly assigned to non-donors to establish the time follow-up began.
[b]Indicates a standardized difference between donors and non-donors >10%. Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled SD; a value >10% is interpreted as a meaningful difference between the groups. As expected, donors had more physician visits in the year prior to index date compared to non-donors, as such visits are a necessary part of the donor evaluation process.

eclampsia, acute pancreatitis, hepatorenal syndrome and drug overdose.

Discussion

Acute kidney injury frequently occurs in the setting of acute infection or cardiac disease. When it is most severe, acute dialysis is needed to maintain life. In this study, we found no evidence of a higher risk of acute dialysis in the decade following living kidney donation. The overall incidence of acute dialysis is very small and will not occur in over 99.99% of donors in the decade following donation. During this time, living kidney donors are unlikely to suffer from the inciting events that may pre-dispose to acute kidney injury. As well, when such events do occur, it is possible the remaining kidney adequately compensates to prevent severe acute kidney injury. These results provide safety re-assurances to potential donors, their recipients and transplant professionals.

The results also add to the consistent evidence in the literature supporting the safety of long-term renal outcomes following living kidney nephrectomy. For example, the risk of end-stage renal disease (ESRD) in living kidney donors appears to be similar to that of the general population. In one Swedish study, 1112 living kidney donors were followed for a median of 14 years and 6 donors progressed to ESRD (0.5%) [9]. In a larger study from Minneapolis in the USA, 11 of 3698 (0.30%) living kidney donors developed ESRD an average of 22 years after donation, a rate of 18.0 cases per 100 000 person-years as compared with a rate of 26.8 per 100 000 person-years in the general population [10]. In our study, almost half of the individuals who received acute dialysis died within the subsequent 90 days, and others recovered their renal function. Thus, examining events of acute dialysis contributes to the assessment of long-term renal outcomes after donation as these patients would not have been captured in ESRD registries.

Our study has a number of strengths. It was made possible by the province of Ontario's universal health care benefits, with the collection of all health care encounters for all citizens. This reduces concerns about selection and information biases. We also manually reviewed over 2000 consecutive medical charts to ensure the accuracy of donor information presented in this study. For the period of interest, this essentially represents all living donation activity for the largest province in Canada. We used techniques of restriction and matching to select appropriate non-donors to whom donor outcomes could be reliably compared. We followed many individuals over a span of a decade and, for some, as long as 17 years. Loss to follow-up, a concern in many long-term donor follow-up studies, was minimal in our setting (<6% of participants emigrated from the province in follow-up). The assessment of acute dialysis was also accurate and reliable.

However, there are some limitations to our study. We were unable to confidently use health care database codes for acute kidney injury in the absence of receiving dialysis, as we had no data to show such codes are valid in patients with previous nephrectomy [11]. Laboratory values of serum creatinine during hospitalization or emergency room visit were also not available in our data sources. Thus, we could not study milder forms of acute kidney injury nor could we describe the severity of the acute kidney injury according to modern staging systems [12]. However, we did know that the injury was severe enough to receive acute dialysis. Similarly, a lack of serum creatinine measurements in follow-up precluded an assessment of acute dialysis risk according to donor eGFR after donation. Accurate racial information was also not available. Given that 75% of Ontario residents are Caucasian, these results may generalize less well to non-Caucasian donors (Statistics Canada, 2006 census). Finally, the number of acute dialysis events was low which resulted in wide CIs. We did not rule out a clinically important risk that could become apparent as more donors enter an older age range in follow-up or manifest an eGFR <60 mL/min/1.73 m^2 in the decades following donation. Although the maximum length of follow-up was 17 years, the median length of follow-up was 6.6 years, while the median length of time to acute dialysis was 8.9 years. For this reason, ongoing follow-up of this and other cohorts is warranted. At this time, our results are re-assuring for the practice of living kidney donation among carefully selected donors.

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Conflict of interest statement. None declared.

(See related article by Wolters and Vowinkel. Risks in life after living kidney donation. *Nephrol Dial Transplant* 2012; 27: 3021–3023.)

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