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Predonation Prescription Opioid Use: A Novel Risk Factor for Readmission After Living Kidney Donation

K. L. Lentine[1,*], N. N. Lam[2], M. A. Schnitzler[1], G. P. Hess[3,4], B. L. Kasiske[5], H. Xiao[1], D. Axelrod[6], A. X. Garg[7], J. D. Schold[8], H. Randall[1], N. Dzebisashvili[9], D. C. Brennan[10] and D. L. Segev[11]

[1]Center for Abdominal Transplantation, Saint Louis University School of Medicine, St. Louis, MO
[2]Division of Nephrology, University of Alberta, Edmonton, AB, Canada
[3]Symphony Health, Pittsburgh, PA
[4]Leonard Davis Institute for Health Economics, University of Pennsylvania, Philadelphia, PA
[5]Division of Nephrology, Hennepin County Medical Center, Minneapolis, MN
[6]Division of Abdominal Transplantation, Department of Surgery, Brody School of Medicine, Greenville, NC
[7]Division of Nephrology, Western University, London, ON, Canada
[8]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH
[9]Dickson Advanced Analytics, Carolinas HealthCare System, Charlotte, NC
[10]Transplant Nephrology, Washington University School of Medicine, St. Louis, MO
[11]Division of Transplantation, Department of Surgery, Johns Hopkins School of Medicine, Baltimore, MD
**Corresponding author: Krista L. Lentine, lentinek@slu.edu*
Institution at which work was performed: Saint Louis University, St. Louis, MO, USA.

Implications of opioid use in living kidney donors for key outcomes, including readmission rates after nephrectomy, are unknown. We integrated Scientific Registry of Transplant Recipients data with records from a nationwide pharmacy claims warehouse and administrative records from an academic hospital consortium to quantify predonation prescription opioid use and postdonation readmission events. Associations of predonation opioid use (adjusted odds ratio [aOR]) in the year before donation and other baseline clinical, procedural, and center factors with readmission within 90 days postdonation were examined by using multivariate logistic regression. Among 14 959 living donors, 11.3% filled one or more opioid prescriptions in the year before donation. Donors with the highest level of predonation opioid use (>305 mg/year) were more than twice as likely as nonusers to be readmitted (6.8% vs. 2.6%; aOR 2.49, 95% confidence interval 1.74–3.58). Adjusted readmission risk was also significantly ($p < 0.05$) higher for women (aOR = 1.25), African Americans (aOR = 1.45), spouses (aOR = 1.42), exchange participants (aOR = 1.46), uninsured donors (aOR = 1.40), donors with predonation estimated glomerular filtration rate <60 mL/min/1.73 m^2 (aOR = 2.68), donors with predonation pulmonary conditions (aOR = 1.54), and after robotic nephrectomy (aOR = 1.68). Predonation opioid use is independently associated with readmission after donor nephrectomy. Future research should examine underlying mechanisms and approaches to reducing risks of postdonation complications.

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HRSA, Health Resources and Services Administration; ICD-9, International Classification of Diseases, Ninth Revision; ME, morphine equivalents; mGFR, measured glomerular filtration rate; NEC, not elsewhere classified; NIS, Nationwide Inpatient Sample; OPTN, Organ Procurement and Transplantation Network; SAS, Statistical Analysis Software; SHS, Symphony Health Solutions; SID, State Inpatient Databases; SRTR, Scientific Registry of Transplant Recipients; UHC, University HealthSystem Consortium

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Introduction

In the United States, approximately 6000 living kidney donations occur every year to help meet the growing demand for available organs (1). Over time, the characteristics of accepted donors have changed, including older age, greater racial and ethnic diversity, and more common predonation comorbidity including obesity, hypertension, and even reduced renal function (2,3). Despite the importance of understanding the outcomes of an evolving donor population, identification of short- and long-term complications by the national transplant registry has been hampered by frequent missing data and underreporting. Readmission after surgical procedures is a commonly used measure of care quality and

healthcare utilization that may serve as a proxy for subsequent morbidity and reduced quality of life (4). The Organ Procurement and Transplantation Network (OPTN) registry for U.S. kidney donors reported that from 2005 to 2012, 2.1% of donors were readmitted within 6 weeks of nephrectomy (5). Unfortunately, transplant center reporting to the OPTN underestimates early surgical complications (5), supporting a need to expand collection of postdonation outcomes with other information sources.

Using the State Inpatient Databases (SID) from four U.S. states, Schold et al identified a sample of 4524 living kidney donors from 2005 to 2010 based on *International Classification of Diseases, Ninth Revision* (ICD-9) diagnosis and procedure codes (6). Readmission within 1 year occurred for 5% of donors and was more common among women, African American and Hispanic donors, and donors with predonation depression or hypothyroidism. Similarly, using the Nationwide Inpatient Sample (NIS), perioperative mortality was estimated as 0.17%, which, while low, is more than five times greater than the 90-day mortality estimates generated from linking the OPTN registry to national death records (7,8). This suggests that the lack of confirmation of donor status through patient-level linkages to the national transplant registry may lead to inadvertent inclusion of patients who underwent nephrectomy for indications unrelated to donation. These studies also lacked some information collected in the national transplant registry, such as type of surgical procedure and transplant center donor nephrectomy volume.

Presurgical use of opioid analgesics is increasingly recognized as a predictor of postoperative complications and resource utilization in diverse patient populations, including those undergoing general and orthopedic surgery procedures (9,10). Pharmacy fill records offer a nonobtrusive measure of medication use in epidemiologic investigations of populations, including living donors and transplant recipients (11–13). We recently linked the national transplant registry with fill records from a large pharmacy claims clearinghouse and found that prescription opioid fills in the year before kidney transplantation were associated with increased risk of complications after the transplant procedure (14,15). Given the growing concern about risks related to use of prescription opioids in the general population (16), we sought to examine whether prescription opioid use before living kidney donation was associated with readmission as a measure of postdonation morbidity and resource utilization needs. Opioid fills were considered with regard to total exposure over 1 year predonation and the timing of fills in relation to donation. We also assessed whether readmission risk varied with other demographic, clinical, procedure, and center factors. To do this, we examined a unique database combining the national transplant registry with hospital administrative and pharmacy fill records.

Methods

Data sources

We conducted a retrospective cohort study using linked healthcare databases in the United States to ascertain patient characteristics, pharmacy fill records, and outcome events for living kidney donors. This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR system includes data on all donors, waitlist candidates, and transplant recipients in the United States, submitted by the members of the OPTN. The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors. Baseline demographic information ascertained for living kidney donors from the OPTN at the time of donation included age, sex, and race as reported by the transplant center.

Pharmacy fill data were assembled by linking SRTR records for living kidney donors with billing claims from Symphony Health Solutions (SHS), a large U.S. pharmaceutical claims data warehouse that captures prescription drug fill records including self-paid fills and those reimbursed by private and public payers. SHS includes National Council for Prescription Drug Program format prescription claims aggregated from multiple sources including claims warehouses, retail pharmacies, and prescription benefit managers for approximately 60% of U.S. retail pharmacy transactions. Individual claim records include the date of a given pharmacy fill with the national drug code identifying agent and dosage. After institutional review board and HRSA approvals, SHS records were linked with SRTR records for living kidney donors. We applied a deterministic deidentification strategy wherein patient identifiers (last name, first name, date of birth, sex, and ZIP code of residence) were transformed before delivery to the Saint Louis University researchers with Health Information Portability and Accountability Act and HITECH-certified encryption technology from SHS. The patient deidentification software uses multiple encryption algorithms in succession to guarantee that the resulting "token" containing encrypted patient identifiers can never be decrypted. However, the algorithm yields the same results for a given set of data elements, such that linkages by unique anonymous tokens are possible.

Baseline comorbid conditions and readmission events were ascertained from the University HealthSystem Consortium (UHC). The UHC is an alliance of 107 academic medical centers and 234 of their affiliated hospitals (approximately 90% of the nation's nonprofit academic medical centers, including approximately 50% of U.S. transplant centers). UHC administrative records are based on data submitted from the UB-04 billing forms, which include patient demographics and the ICD-9 diagnosis and procedure codes. The data from UHC were linked to the SRTR using transplant center, date of donation, and donor age and sex. Residential ZIP codes were available for verification of duplicate matches (no duplicates were identified for this sample). All direct identifiers were removed before the final data set was available for analysis.

Population and covariates

Figure 1 and Table S1 summarize information for the study covariates including the source databases, definitions, and sample frequencies. We included all living kidney donors who donated between 2008 and 2012 at UHC centers and who had 1 year of predonation pharmacy fill records in SHS. Baseline donor demographic and clinical information ascertained from the SRTR at the time of donation included age, sex, race, donor–recipient relationship, presence of health insurance, body mass index (BMI), estimated glomerular filtration rate (eGFR, based on the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation), physical limitations, education level, employment status, hypertension (defined as a reported condition, use of hypertension medication, systolic blood

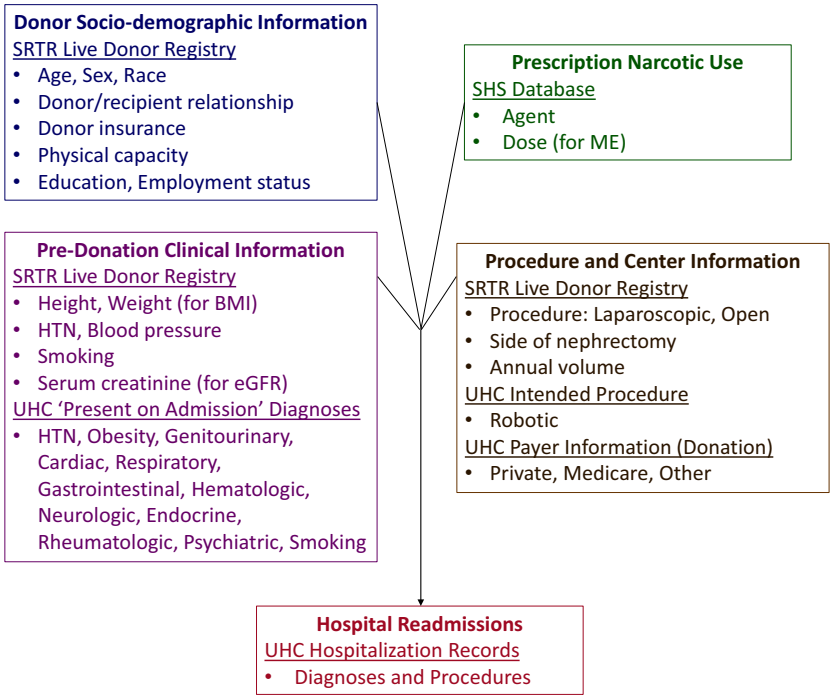

Figure 1: Data integration to capture baseline donor characteristics, procedure information, and hospital readmissions. BMI, body mass index; eGFR, estimated glomerular filtration rate; HTN, hypertension; ME, morphine equivalents; SHS, Symphony Health Solutions; SRTR, Scientific Registry of Transplant Recipients; UHC, University HealthSystem Consortium.

pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg), and history of smoking as reported by the transplant center.

Baseline comorbid conditions were augmented from UHC diagnosis codes indicated as "present on admission" including supplementation of SRTR-reported hypertension, obesity, and smoking; additional clinical conditions were categorized by organ system (Table 1). Intended procedure type (laparoscopic or open) and side of nephrectomy (left or right) were identified from the SRTR registry; further characterization of robotic-assisted nephrectomy procedures was based on ICD-9 procedure codes from the UHC database. The payer for donation (which in the U.S. health system is the recipient's insurance) was classified as commercial, Medicare, or other per UHC reports. Average annual living donor nephrectomy volume for the included centers was obtained from SRTR reports.

Pharmacy fills for opioid analgesics in the year before donation were ascertained from the SHS records. Opioid use was normalized to morphine equivalents (ME), according to conversion ratios, as previously described (17,18) (Table S2). Predonation ME were aggregated for each living donor and expressed as dose (mg) of ME exposure over the year. We ranked annual ME exposure among donors who filled opioid prescriptions predonation by tertiles as <130, 130–305, and >305 mg/year, similar to previous methods (14,15). We performed sensitivity analyses considering any opioid fill and filling patterns within 6 months and in months 7–12 before donation. Additional sensitivity analyses were performed among a subset of donors who had 2 years of predonation prescription drug eligibility in SHS, considering associations with both quantity of exposure (as defined by ME level) and filling patterns within each of the 2 years before donation.

Outcome measurements

The primary outcome was hospital readmission within 90 days after donor nephrectomy, as identified by the UHC database. UHC records also include (ICD-9) diagnosis codes associated with the readmission events. We performed sensitivity analyses by using hospital readmission rates within 180 days and 1 year after donation as the outcome.

Statistical analyses

Data sets were merged and analyzed with the use of SAS (Statistical Analysis Software) version 9.4 (SAS Institute Inc., Cary, NC). Distributions of clinical and demographic traits among donors with each level of predonation opioid exposure, versus no opioid use, were compared by use of the χ^2 test. Associations of predonation opioid use (adjusted odds ratio [aOR]) and other baseline clinical, procedural, and center factors with readmission events within 90 days postdonation were examined using multivariate logistic regression. In all outcome analyses, we interpreted two-tailed p-values <0.05 as statistically significant.

Results

Baseline characteristics of the living donor sample

Between 2008 and 2012, 30 026 living kidney donors in the United States were recorded in the SRTR database. Of these, 14 959 (49.8%) were also found in the linked UHC and SHS records. The baseline characteristics of the study sample were similar to those of all donors recorded in the SRTR database during the same period (Table S3). In the study sample, mean age at the time of donation was 42.1 years (standard deviation, 11.8 years); 61.7% were female, 72.6% were white, and 11.7% were African American (Table 1). Nearly half of donors were unrelated to their recipients, including exchange

Table 1: Baseline characteristics of the living kidney donor sample by level of predonation opioid use

Baseline characteristics	Full cohort (N = 14 959)	No use (n = 13 267)	Level 1 (n = 550)	Level 2 (n = 614)	Level 3 (n = 528)
Age at donation, years	42.1 (11.8)	42.1 (11.8)	40.7 (11.4)*	41.8 (11.5)	43.5 (11.3)*
Female	61.7	60.9	68.9†	69.7‡	65.5*
Race			*	*	‡
White	72.6	72.0	72.6	76.6	82.6
African American	11.7	11.5	15.8	12.1	11.2
Hispanic	10.9	11.3	8.2	9.1	4.2
Other	4.9	5.2	3.5	2.3	2.1
Donor–recipient relationship					*
First-degree relative	45.3	45.8	43.6	41.9	37.7
Other biological relative	7.6	7.5	7.8	8.6	8.5
Spouse/partner	12.6	12.5	10.9	14.5	14.4
Paired/nondirected	9.4	9.4	9.8	9.3	10.4
Other unrelated	25.1	24.8	27.8	25.7	29.0
Donor health insurance					
Insured	73.1	73.0	72.6	74.8	73.3
Uninsured	11.6	11.6	13.1	10.8	10.8
Not reported	15.4	15.4	14.4	14.5	15.9
Body mass index, kg/m^2					*
<18.5	1.1	1.1	0.7	1.0	1.5
18.5 to <25	34.3	34.7	33.3	30.8	29.9
25 to <30	40.1	40.2	38.4	39.9	38.3
≥30	21.1	20.7	23.3	24.1	25.4
Not reported	3.4	3.2	4.4	4.2	4.9
Predonation eGFR, mL/min per 1.73 m^2					
>90	67.5	67.5	68.9	67.8	65.7
60–90	29.5	29.5	28.4	29.0	30.3
<60	1.5	1.5	1.3	1.5	2.1
Not reported	1.5	1.5	1.5	1.8	1.9
Physical capacity				*	‡
No limitations	96.2	96.2	95.8	98.1	95.8
Limitations	0.4	0.3	0.2	0.3	1.9
Not reported	3.4	3.5	4.0	1.6	2.3
Highest level of education					†
College or higher	64.5	65.0	62.9	63.2	55.1
Grade school or high school	25.6	25.3	27.5	26.6	31.8
Not reported	9.9	9.7	9.6	10.3	13.1
Employment status					*
Working	80.1	80.4	79.6	79.0	76.0
Not working	16.8	16.6	16.6	17.9	20.5
Not reported	3.1	3.0	3.8	3.1	3.6
Comorbid conditions					
Hypertension	12.2	12.1	12.2	11.7	13.8
Genitourinary	2.0	1.9	2.0	2.0	3.4*
Cardiac	0.9	0.9	0.9	0.7	1.5
Respiratory	5.5	5.2	7.5*	7.5*	8.0*
Gastrointestinal	8.1	7.9	9.1	9.0	11.4*
Hematologic	1.6	1.6	2.0	2.0	2.1
Neurologic	0.3	0.3	0.0	0.5	0.8
Endocrine	11.8	11.6	13.3	13.2	14.8*
Rheumatologic	0.2	0.2	0.2	0.3	0.2
Psychiatric	7.3	7.0	9.3*	9.8*	11.2†
Smoking	8.9	8.5	11.1*	10.4	13.8‡
Procedure and center characteristics					
Nephrectomy approach, intended					
Open	3.7	3.6	4.2	3.3	5.5
Laparoscopic (non-robotic)	93.9	94.0	92.7	94.3	91.3
Laparoscopic (robotic)	2.4	2.4	3.1	2.4	3.2

(*Continued*)

Table 1. Continued

Baseline characteristics	Full cohort (N = 14 959)	No use (n = 13 267)	Level 1 (n = 550)	Level 2 (n = 614)	Level 3 (n = 528)
Side of nephrectomy					
Left	86.3	86.5	84.2	84.9	84.7
Right	13.7	13.5	15.8	15.2	15.3
Payer for donation				*	*
Private	29.5	29.7	30.6	27.9	24.6
Medicare	13.7	13.5	13.3	17.4	16.7
Other	56.8	56.8	56.2	54.7	58.7
Average annual center volume					
≤10	1.8	1.9	1.3	1.3	1.7
11–50	41.4	41.1	40.4	44.1	44.9
>50	56.8	57.0	58.4	54.6	53.4

Data presented as percentages (%) except for age, which is presented as mean (standard deviation).
eGFR, estimated glomerular filtration rate.
*p < 0.05–0.002; †p = 0.001–0.0001; ‡p < 0.0001.

participants or nondirected donations (9.4%). Nephrectomy procedures were predominantly laparoscopic (93.9%); 2.4% were robotic, and 3.7% were planned open procedures.

In the study sample, 11.3% of donors filled one or more opioid prescriptions in the year before donation. Compared with donors who did not use opioids before donation, those with the highest level of use (level 3) were more often women, of white race, spouses of their recipients, obese, and less likely to be employed (Table 1). These donors were also more likely to have genitourinary, respiratory, gastrointestinal, psychiatric, and endocrine diseases and a smoking history. Length of stay for the initial nephrectomy hospitalization was modestly but significantly longer in donors with level 3 predonation opioid use compared with nonusers (2.8 vs. 2.7 days, p = 0.008).

Incidence of postdonation hospital readmission according to predonation opioid use level

Median time from donation to any readmission within 1 year was 12 days (mean 53 days). Overall, 2.9% of donors were readmitted to hospital within 90 days of donation. After adjustment for demographic, clinical, and procedure factors, the lowest level of predonation opioid use was not associated with 90-day readmission (aOR 0.90, 95% confidence interval [CI] 0.52–1.55). However, living kidney donors with the second level of predonation opioid use were 92% more likely to be readmitted (5.2% vs. 2.6%; aOR 1.92, 95% CI 1.32–2.80), and those with the highest level use were more than twice as likely to be readmitted as were nonusers (6.8% vs. 2.6%; aOR 2.49, 95% CI 1.74–3.58) (Figure 2). Readmission risk was significantly (p < 0.05) higher for women than for men (3.1% vs. 2.5%; aOR 1.25, 95% CI 1.01–1.55), for African American donors than for white donors (4.1% vs. 2.8%; aOR 1.45, 95% CI 1.10–1.92), and for donors to their spouses/partners (3.5% vs. 2.5%; aOR 1.42, 95% CI 1.05–1.92) and exchange/nondirected donors (3.5% vs. 2.5%; aOR 1.46, 95% CI 1.05–2.04) than for first-degree relatives. Readmission rates were also higher for uninsured donors (3.8% vs. 2.7%; aOR 1.40, 95% CI 1.05–1.87), markedly higher for donors with predonation eGFR <60 vs. >90 mL/min/1.73 m^2 (6.5% vs. 2.8%; aOR 2.68, 95% CI 1.54–4.66), and higher after robotic versus laparoscopic nephrectomy (4.7% vs. 2.9%; aOR 1.68, 95% CI 1.00–2.81) and in donors with a predonation history of pulmonary condition (4.4% vs. 2.8%; aOR 1.54, 95% CI 1.08–2.20). Predonation cardiac conditions had a near-significant association with 90-day readmission (5.8% vs. 2.9%; aOR 2.06, 95% CI 0.99–4.30; p = 0.05). We did not detect significant associations between the risk of 90-day readmission and donor BMI, education level, employment status, side of nephrectomy, or payer for donation. There were no significant interactions of baseline factors and predonation opioid use for 90-day readmission.

Patterns were similar for associations of opioid use level in the year before donation with readmissions within 180 days and 1 year of donation, although effect sizes were attenuated compared to associations with 90-day readmission rates (Table S4). Opioid fills within 6 months (aOR 1.69, 95% CI 1.15–2.46) and in months 7–12 (aOR 1.62, 95% CI 1.11–2.36) only before donation were associated with 90-day readmission, but readmission risk was highest for donors who filled opioid prescriptions in both periods (aOR 2.19, 95% CI 1.36–3.51). Among the subsample (n = 8802) with 2 years of predonation pharmacy records, prescription opioid fills within 2 years before donation were also associated with readmission risk, although the association was significant only for those with the highest level of use (aOR 1.97, 95% CI 1.05–2.39). Considered by timing of fill, opioid fills 0–12 months before donation (aOR 1.54, 95% CI 1.11–2.13) and in both the 0–12-month and 13–24-month predonation periods (aOR 1.59, 95% CI 1.05–2.39) were associated with 90-day readmissions,

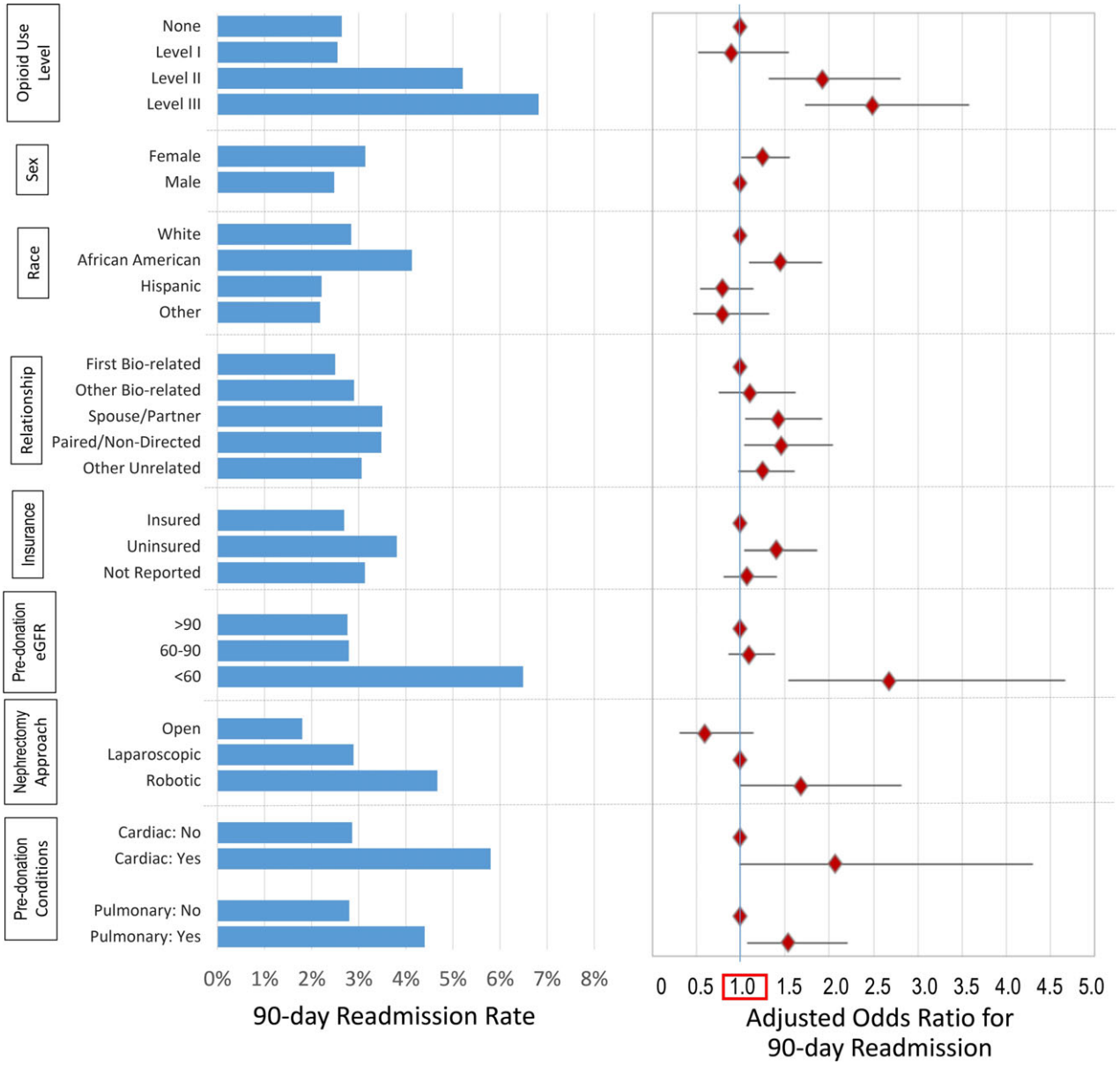

Figure 2: Readmission rates within 90 days after living donor nephrectomy according to predonation prescription opioid use and other baseline factors. Adjusted for donor age, body mass index, education, employment, and predonation comorbid conditions (as per Table 1). eGFR, estimated glomerular filtration rate.

while use only in the period 13–24 months before donation was not associated with readmission risk (aOR 1.01, 95% CI 0.67–1.50).

Among donors who did not fill opioid prescriptions before donation, the most common primary diagnoses for 90-day readmission included infection (11.7%), digestive system complications not elsewhere classified (NEC; 10.6%), constipation (7.2%), abdominal pain (6.9%), nausea with vomiting (4.3%), dehydration (4.3%), and hernia (4.0%). Among donors with the highest level of predonation opioid use, leading readmission diagnoses included infection (25.0%), a variety of gastrointestinal complaints (digestive system complications NEC [16.7%], abdominal pain [5.6%], nausea with vomiting [5.6%], paralytic ileus [5.6%], other disorders of the peritoneum [5.6%]), and hernia (7.9%) (Table S5). Among donors with the second level of predonation opioid use, opioid abuse was the diagnosis for 3.1% of hospital readmissions within 90 days of nephrectomy.

Discussion

A current understanding of the complications associated with living kidney donation is vital for tailoring the informed consent process for future potential donors and to guide development of strategies to reduce risks (19). To improve understanding of the frequency and correlates of readmission after donor nephrectomy, we integrated the national U.S. donor registry with a pharmacy claims database and administrative records from a large academic hospital consortium and identified several important, novel findings. (1) More than 11.3% of donors filled at least one opioid prescription in the year before donation. (2) While the lowest level of prescription opioid use in the year before donation was not associated with 90-day readmission, living kidney donors with the second level of opioid use were 92% more likely to be readmitted, and those with the highest level of use were more than twice as likely as were nonusers to be readmitted. (3) Considered by timing, opioid fills within 6 months and in months 7–12 only in the year before donation were associated with 90-day readmission, but readmission risk was highest for donors who filled opioid prescriptions in both periods. During a 2-year predonation timeframe, patterns of use in both the 0–12-month and 13–24-month periods, as well as use in the more recent period were associated with readmission risk, while use only in the more remote predonation period was not associated with postdonation readmission. Adjusted readmission risk was also higher for women, African Americans, spouses, exchange participants, uninsured donors, and donors with predonation eGFR <60 mL/min/1.73 m^2 or histories of pulmonary or cardiac conditions, and after robotic nephrectomy.

The 90-day hospital readmission rate of 2.9% in our study is comparable to that found in previous studies. Patel et al identified records for 3074 living kidney donors between 2004 and 2005 in the UHC data set (based on diagnosis and procedure codes) and reported that the incidence of hospital readmission was 1.4% at a mean of 8.7 days after initial discharge (excluding rehospitalizations for incisional hernia, which occurred at a mean of 266 days after discharge) (20). More than half of the cases (65%) were due to gastrointestinal causes, such as ileus, constipation, or emesis, and only one case of a hospital readmission was due to pain, which occurred 5 days after the initial discharge. In the previously described study by Schold et al, the 1- and 3-year cumulative incidence of rehospitalization was 5% and 11%, respectively (6). Neither of these studies linked to the transplant registry to confirm donor status.

To the best of our knowledge, ours is the first study to describe an association between predonation opioid use and postdonation readmission rates. We previously reported that pretransplantation prescription opioid use in 16 322 kidney transplant recipients was associated with a higher 3-year incidence of posttransplantation clinical complications, including adverse cardiac and respiratory events, as well as death and graft loss (14,15). Presurgical use of opioid analgesics is increasingly recognized as a predictor of postoperative complications and resource utilization in diverse populations, including those undergoing general, orthopedic, and transplant surgery procedures (9,10,14,15). The current work extends these associations to donor nephrectomy by identifying correlations of higher-level predonation prescription opioid use with slightly longer lengths of stay for the initial surgical hospitalization and substantially higher hospital readmission rates. Importantly, the pattern of use matters, as increased readmission risk was observed with higher-level opioid exposure and for fills across longer periods predonation but not for low-level exposure or use >1 year before donation that was not sustained.

In the current study, the most common diagnoses at readmission for donors with the highest predonation opioid use were for infection and gastrointestinal complaints such as digestive system complications, abdominal pain, nausea with vomiting, paralytic ileus, and other disorders of the peritoneum. Opioid use has well-established gastrointestinal side effects, which may exacerbate the risk of gastrointestinal complications postoperatively. Although the opioid receptor antagonist naltrexone has been shown to accelerate fibroblast proliferation and wound healing, classic opioid receptor agonists have not been found to impair healing (21). Our study design did not assess opioid use after donation, and it is likely that our findings, at least in part, reflect predonation opioid use as a marker for underlying patient factors associated with higher risks of perioperative complications.

In the general population, the growing use and misuse of prescription opioids have become a public health concern. The Centers for Disease Control and Prevention (CDC) issued a press release highlighting the risk of prescription opioid–related morbidity and mortality (16). As a result, the CDC proposed a new Guideline for Prescribing Opioids for Chronic Pain including recommendations for assessing risks of prescription opioid use such as opioid use disorders and overdoses (22), and the U.S. Congress is proposing legislation to address the nation's opioid epidemic (23). In an open letter to physicians about confronting the opioid crisis, the president of the American Medical Association advised that "physicians should avoid initiating opioids for new patients with chronic noncancer pain and should limit the amount of opioids prescribed in post-operative and acute settings by prescribing the lowest effective dose for the shortest period of time if opioids are necessary" (24). Our study suggests that even in the selected healthiest segment of the population, prescription opioid use is associated with adverse clinical outcomes.

With regard to other correlates of readmission risk, as in our study, Schold et al reported that rehospitalizations were more common among female and African American donors (6). The most common diagnoses at rehospitalization within 3 years were pregnancy-related causes (21%), digestive system diseases (14%), and injuries and poisoning (13%). Schold et al suggested that the increase in rehospitalizations within 3 years for female donors was largely due to pregnancy-related causes rather than excess morbidity. This does not apply to our current study, as our readmission outcomes were assessed over a period up to 1 year, when few female donors would be expected to be pregnant so close to their nephrectomy surgery, and no readmissions for pregnancy were observed. Our study confirms a higher readmission rate for African American than for white donors as previously reported by Schold et al (6). Similarly, we recently reported that African American donors were more likely to experience perioperative complications (aOR 1.26) and more severe complications (aOR 1.56) after donor nephrectomy than white donors (25). This A higher risk of perioperative complications in African Americans has been observed in other donor studies (26) and in the nondonor population after surgical procedures (27,28). The higher readmission risk in uninsured donors is notable and may reflect less access to outpatient or primary care services. Although Medicare and other insurance plans include provisions to cover early postdonation care under the recipient's insurance, these benefits generally extend only to 90 days and are limited to conditions deemed "donation-related," a designation that may be disputed. Future work should attempt to determine mediators of racial variation in early risks after donor nephrectomy and examine whether early complications correlate with longer-term risks among African American donors.

We also identified a strong association between predonation eGFR <60 mL/min/1.73 m^2 with 170% increased readmission risk. An eGFR of ≥80 mL/min/1.73 m^2 is commonly considered to be the minimum threshold for donor acceptance (29). The SRTR registry collects predonation serum creatinine (which can be used to compute eGFR) but not other measures of renal function expected to be obtained during the donor evaluation. Currently, OPTN policy requires either measured glomerular filtration rate (mGFR, by an exogenous filtration marker) or measured creatinine clearance as part of the living donor evaluation (30). Since eGFR may underestimate mGFR at higher ranges (31), it is expected that accepted donors in our study with low eGFR had demonstrations of higher levels of renal function by other testing. Nonetheless, our findings show that low eGFR has prognostic significance for postdonation outcomes.

In our study, donors who underwent robotic nephrectomy had an increased risk of hospital readmission (aOR 1.68, compared with nonrobotic laparoscopic procedures). This likely reflects surgical experience with donor nephrectomy and management of its potential complications. In 2003, as laparoscopic nephrectomies were becoming more widely accepted, Matas et al surveyed 171 transplant centers that performed 10 828 living donor nephrectomies (5660 open nephrectomies and 5168 laparoscopic nephrectomies) between 1999 and 2001 (32). They found that the readmission rate was higher for donors who underwent laparoscopic nephrectomy than for those who underwent open nephrectomy (1.6% vs. 0.6%, $p < 0.001$), mainly due to increased gastrointestinal complications. They hypothesized that the shorter length of hospital stay for donors undergoing laparoscopic nephrectomy may be a tradeoff for a slightly increased risk of readmission. In another recent study, donors who underwent robotic laparoscopic nephrectomy had a higher risk of perioperative complications (aOR 2.07, compared with nonrobotic laparoscopic nephrectomy) (25), and in our current study, robotic laparoscopic nephrectomy was also associated with an increased risk of readmissions, suggesting that newer surgical techniques may have increased perioperative adverse outcomes initially, as experience is being developed.

An important strength of our study is the novel linkage of multiple data sources to enable investigation of the relationship between predonation opioid use and postdonation hospital readmission rates. There are also limitations to the study design. Although we were able to confirm living donor status through the SRTR registry, our linkage with an academic hospital consortium resulted in a donor cohort that represents approximately half of those registered in the SRTR in the same period. Thus, while our study is larger than prior studies, our results may not be generalizable to living donor nephrectomies performed at nonacademic hospitals where procedural and center factors may differ or to patients not identified in the pharmacy database. Notably, the baseline characteristics of the study sample were similar to characteristics of all U.S. living kidney donors registered in the SRTR during the same period (Table S3). Electronic pharmacy claims, the source of predonation opioid use information, have been shown to be highly accurate records of physician prescribing that circumvent some of the limitations of self-reported medication use, including underreporting (33–36). However, we were unable to account for illicit drug use or "pharmacy shopping" behaviors, possibly underestimating true drug exposure. For the primary outcome, we used the UHC data set rather than the national registry, which is limited to transplant center reports of donor nephrectomy complications within the first 6 weeks. Complete identification of early readmissions in UHC data was recently reported in a validation study (37). Nonetheless, readmissions in the UHC data are limited to the same center, and postdonation hospitalizations at other facilities (which may become more likely with increasing time after donation) are not

included. Last, due to the observational nature of our study design, we are only able to describe associations and we cannot prove causality or define underlying mechanisms. While high identification rates for many comorbid conditions and complications in the UHC have been reported (37), residual confounding is possible in any observational design.

In summary, linkage of the national transplant registry with administrative records from a pharmacy claims database and an academic hospital consortium enabled characterization of readmission after living donor nephrectomy in a contemporary sample, including frequency and clinical correlates. We identified predonation opioid use as a novel risk factor for readmission after donation. While associations may in part reflect opioid use as a measure of predonation comorbidity, the observation is relevant to risk stratification and counseling. Future work should investigate possible underlying mechanisms and approaches to optimizing postdonation outcomes.

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Disclosure

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1: Databases and coding definitions for baseline characteristics.

Table S2: Conversions used to standardize doses of opioid medications as morphine equivalents.

Table S3: Baseline characteristics of the study sample of living kidney donors compared with all living kidney donors recorded in the SRTR during the study period (2008–2012).

Table S4: Adjusted associations of predonation opioid fills, including use level and timing of fills, with hospital readmission within 90 days, 180 days, and 1 year of donation.

Table S5: Most common primary medical diagnoses for readmission within 90 days after donor nephrectomy, according to predonation opioid use level.