Title

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Prescription Patterns of Opioids and Non-Steroidal Anti-Inflammatory Drugs in the First Year After Living Kidney Donation: An Analysis of U.S. Registry and Pharmacy Fill Records

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Abstract

We examined a novel database linking national donor registry identifiers to records from a U.S. pharmaceutical claims warehouse (2007–2015) to describe opioid and NSAID prescription patterns among LKDs during the first year postdonation, divided into three periods: 0–14 days, 15–182 days, and 183–365 days. Associations of opioid and NSAID prescription fills with baseline factors were examined by logistic regression (adjusted odds ratio, $_{LCL}aOR_{UCL}$). Among 23,565 donors, opioid prescriptions were highest during days 0–14 (36.6%), but 12.6% of donors

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filled opioids during days 183–365. NSAID prescriptions rose from 0.5% during days 0–14 to 3.3% during days 183–365. Women filled opioids more commonly than men, and black donors filled both opioids and NSAIDs more commonly than white donors. After covariate adjustment, significant correlates of opioid prescription fills during days 183–365 included obesity (aOR, $_{1.24}1.38_{1.53}$), less than college education (aOR,$_{1.19}1.31_{1.43}$), smoking (aOR,$_{1.33}1.45_{1.58}$), and nephrectomy complications (aOR,$_{1.11}1.29_{1.49}$). NSAID prescription fills in year-one were not associated with differences in estimated glomerular filtration rate, incidence of proteinuria or new-onset hypertension at the first and second year postdonation. Prescription fills for opioids and NSAIDs for LKDs varied with demographic and clinic traits. Future work should examine longer-term outcome implications to help inform safe analgesic regimen choices after donation.

INTRODUCTION

Since 1954, when living donor nephrectomy was performed for the first successful kidney transplant,[1] surgical techniques for donor nephrectomy have improved, most notably with development of the laparoscopic approach, as initially described by Ratner *et al.* in1995.[2] Laparoscopic donor nephrectomy is associated with reduced postsurgical pain compared with open nephrectomy[3] and is now the standard of care approach[4]; it also helped support increased living donation rates.[5,6] Although recovery is typically faster with the laparoscopic approach, early postsurgical pain management is needed, and some providers recommend a multimodal analgesic approach including both opioids and non-steroidal anti-inflammatory drugs (NSAIDs).[7–13] A recent single-center study reported that 5.7% of living kidney donors (LKDs) may experience chronic postsurgical pain at a mean follow-up of 6 years.[14] Despite the importance of pain management in this population, data are limited regarding patterns of analgesic use beyond the surgical hospitalization, or regarding the impact of NSAIDs on outcomes of the remaining kidney after donation.

Opioid analgesics, although effective, have many adverse effects, ranging from gastrointestinal complaints to respiratory depression that can result in death in cases of overdose.[15] We previously reported that predonation opioid use is an independent risk factor for re-admission after donor nephrectomy,[16] and that opioid fill rates were 32.3 and 32.4 per 100 person-years between 1 to 4 years and > 4 years postdonation, respectively.[17] In the United States, opioid dependence has been recognized as a major health crisis and the federal government released guidelines designed to limit opioid prescription.[18] Opioid prescription patterns are now strictly scrutinized by local and federal authorities, which may result in restricted access to this class of analgesics. Hence, alternative, effective analgesic strategies are needed across clinical scenarios.

Classic NSAID-related nephrotoxicity, first described by Spuhler and Zollinger in 1953, involves renal papillary necrosis and chronic interstitial nephritis.[19] Many small studies suggested higher risk of acute kidney injury (AKI) and more rapid progression of chronic kidney disease (CKD) attributable to NSAID use, usually at high doses.[20–24] Despite general consensus that NSAIDs should be avoided in CKD, the evidence supporting this belief remains mixed. Some larger studies with longer follow-up time (up to 11–14 years), with middle-aged healthy participants, more similar to LKDs, found that NSAID use was not

associated with higher risk of decline in kidney function.[25,26] Nevertheless both the Canadian and the American Societies of Nephrology "Choosing Wisely" campaigns recommend against using NSAIDs in individuals with CKD.[27,28]

LKDs are a special group with surgical reduction in glomerular filtration rate (GFR), in whom the remaining kidney undergoes hyperfiltration adaptation that begins immediately after donation and is sustained for many years postdonation.[29] Hence, data from the general population and from patients with CKD may not be directly applicable. To advance understanding of pain medication use in LKDs, we examined a novel linkage of national U.S. transplant registry data with records from a pharmacy claims warehouse. Our goals were to examine opioid and NSAID prescription patterns during the first postdonation year, and associations of NSAIDs with postdonation renal-related outcomes.

METHODS

Data Sources

We conducted a retrospective cohort study using a novel linkage of national transplant registry and pharmaceutical claims database (PCD) records. LKD data were obtained from the Scientific Registry of Transplant Recipients (SRTR), which includes data on all donors, waitlisted candidates, and transplant recipients in the U.S., submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services, provides oversight of the activities of the SRTR and OPTN contractors.

Pharmacy fill data were assembled by linking SRTR records for LKDs with billing claims from a large U.S. PCD warehouse that maintains prescription drug fill records including self-paid fills and those reimbursed by private and public payers. The PCD comprises National Council for Prescription Drug Program 5.1-format prescription claims aggregated from multiple sources including data clearinghouses, 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, PCD records were linked with SRTR records for LKDs.

A deterministic de-identification strategy with Health Information Portability and Accountability Act and Health Information Technology for Economic and Clinical Health (HITECH)-certified encryption technology from Symphony Health Solutions was applied, wherein patient identifiers (last name, first name, sex, date of birth, and ZIP code of residence) were transformed before delivery to the Saint Louis University researchers. The patient de-identification 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.

Population and Covariates

We included all adult LKDs in the SRTR registry who donated between January 2007 and December 2015 and had linked pharmacy claims covering the donation event date through the first year postdonation. (The sampling criteria for this study are distinct from our prior publication examining LKDs in the University HealthSystem Consortium.[16]) Baseline donor demographic and clinical characteristics were identified from the SRTR registry (as reported by transplant centers) and included age, sex, race, body mass index (BMI), predonation estimated GFR (eGFR, based on the CKD Epidemiology Collaboration [CKD-EPI] equation), education level, employment status, insurance status, donor/recipient relationship, past or current smoking, hypertension, year of donation, nephrectomy approach (open or laparoscopic), surgical complications, and nephrectomy laterality. Unknown or missing response status to SRTR variables was represented in analytic models as an "unknown" indicator.

NSAID and Opioid Use Exposure Measures

Since the need for pain control is expected to be highest early postdonation, and to decline over the first year, we divided the first year postdonation into three time periods: 0–14 days, 15–182 days, and 183–365 days. Prescription fills for NSAIDs and opioids during each of these periods were ascertained from the PCD (SDC, Table S1). Opioid fills were normalized to morphine equivalents (MEs), according to conversion ratios, as previously described (SDC, Table S1).[30–34] We calculated cumulative dose exposure for each LKD who filled NSAIDs in the first year postdonation using the equation, [drug strength x total tablets filled during first postdonation year/defined daily dose (DDD)], as previously described.[24] This translates to the total number of DDDs of NSAIDs each LKD is exposed to during the first year postdonation. DDD for each NSAID was obtained from the World Health Organization Collaborating Centre for Drug Statistics Methodology.[35] For LKDs who filled opioids, we calculated cumulative drug exposure with regard to normalized MEs, using conversion ratios previously described.[31]

Renal Outcome Measures

Proteinuria, eGFR (based on the CKD-EPI equation), and new diagnosis of hypertension requiring anti-hypertensive medications at the first year and second year postdonation were ascertained from the SRTR, as reported by transplant centers to the OPTN on the living donor follow-up form. Proteinuria was defined as a urine dipstick positivity for protein or a spot urine protein-to-creatinine ratio > 150 mg/g.

Statistical Analyses

Distributions of baseline characteristics across NSAID and opioid prescription fills were compared using the chi-square test. Adjusted correlates of NSAID and opioid prescription fills during the first year postdonation were assessed using multivariate logistic regression models, with medication fill as the outcome. All baseline demographic and clinical characteristics listed above were included in these models.

To assess whether prescription NSAID use was associated with eGFR, proteinuria, or hypertension at the first year and second year anniversary, we used linear regression and

logistic regression for univariate associations, and fit multivariate linear regression and logistic regression models with covariate adjustment. In these models, eGFR, proteinuria, and hypertension at the first anniversary were the outcomes, and any NSAID prescription fills during the first year postdonation was the exposure. In addition to adjusting for baseline demographic and clinical characteristics, we adjusted for immediate postdonation eGFR. Statistical Analysis Software (SAS) for Windows, version 9.4 (SAS institute Inc., Cary, NC) was used for data management and analyses. In all exploratory and outcome analyses, we interpreted 2-tailed *P*-values < 0.05 as statistically significant.

RESULTS

Baseline Characteristics

Between January 2007 and December 2015, 55,121 adult LKDs were recorded in the SRTR database. Of these, 23,565 had linked PCD records in the first postdonation year. Most of the donors (75%) were aged 31 to 59 years, 68% were women, 11% were black, 23% were obese, 67% had an education level higher than high school, 18% were unemployed, and 26% had a smoking history. Almost 50% donated to a biologically related recipient, 13% had hypertension, and 11% underwent right nephrectomy. These characteristics were generally similar to those of the entire cohort of LKDs recorded in the SRTR in the study period, except for higher predonation eGFR and more college level education in the study cohort (SDC, Table S2).

Patterns of Opioid Prescription Fills

During days 0–14, 15–183, and 183–365, 36.6% (n=8,623), 14.7% (n=3,464) and 12.6% (n=2,974) LKDs, respectively, filled at least one opioid prescription (Figure 1A). The median daily doses and interquartile ranges (ME, mg/day) were 16.1 (9.8), 1.3 (1.8), and 1.2 (2.6), respectively. The unadjusted frequency of opioid prescription fills during days 0–14 postdonation ranged from 31.8% in 2007 to a peak of 38.5% in 2011, and showed a slight downtrend to 35.4% in 2017.

Among the 8,623 LKDs who filled opioid prescriptions during days 0–14, 2,483 (28.8%) filled opioids again, during days 15–182 or 183–365. Among the 3,464 LKDs who filled opioid prescriptions during days 15–182, 48.3% (n=1,673) had no record of opioid fills during days 0–14, and 34.4% (n=1,193) filled opioid prescriptions again during days 183–365. Among the 2,974 LKDs who filled opioids during days 183–365, 36.6% (n=1,089) were new fillers and had no record of opioid fills during days 0–14 or 15–182 (Figure 1B).

Patterns of NSAIDs Prescription Fills

During days 0–14, 15–183, and 183–365, 0.5% (n=113), 2.2% (n=509), and 3.3% (n=774) LKDs, respectively, filled at least one NSAID prescription (Figure 2A). The cumulative NSAID dose filled by all NSAID fillers was less than 100 DDDs for the first year postdonation. For example, those who filled Ibuprofen filled less than 100 DDDs of Ibuprofen during the first postdonation year. As the DDD for Ibuprofen is 1200 mg, or six tablets of 200 mg strength, LKDs who filled Ibuprofen filled less than 600 tablets of 200 mg during the first year postdonation, i.e., less than two tablets (or 400 mg) per day. Medians

and interquartile ranges for DDDs during days 0–14, 15–182, and 183–365 were 7.0 (8.3), 28 (30), and 22.5 (30), respectively.

Among the 113 LKDs who filled NSAID prescriptions during days 0–14, only 11.5% (n=13) filled them again, during days 15–182 or 183–365. Among the 509 who filled NSAID prescriptions during days 15–182, 98.2% (n=500) were new NSAIDs users, having filled none during days 0–14, and 26.5% (n=135) repeated NSAID prescription fills during days 183–365. Among the 774 who filled NSAID prescriptions during days 183–365, 82.0% (n=635) were new fillers, having filled no NSAIDs during days 0–14 or 15–182 (Figure 2B).

Associations of Baseline Traits with Opioid and NSAIDs Prescription Fills

During days 0–14 postdonation, LKDs who filled opioids were more commonly aged 19–44 years, of black race, obese, and uninsured, with a smoking history, donation in 2011–2013, and surgical complications of nephrectomy. Those who underwent laparoscopic nephrectomy (versus open) and left (versus right) nephrectomy were also more likely to fill opioids during days 0–14. Donor factors associated with opioid fills remained overall similar during days 15–182 and 183–365, except that female sex, education less than college level, and lack of insurance were associated with increased filling, while laparoscopic nephrectomy was associated with less likelihood of opioid fills beyond the first 14 days (Table 1). After covariate adjustment, many of these associations remained statistically significant. During days 15–182, age 60 years was associated with 43% lower likelihood of opioid fills compared with age 19–30 years (aOR, $_{0.48}0.57_{0.68}$), black race was associated with 22% higher likelihood of fills compared with white race (aOR, $_{1.09}1.22_{1.37}$), smoking history was associated with 63% increased likelihood of fills (aOR, $_{1.51}1.63_{1.77}$), and surgical complications of donor nephrectomy with 75% increased likelihood (aOR, $_{1.54}1.75_{1.99}$) (Table 2). Compared with men, women were more likely to fill opioids across the observation periods.

Very few LKDs filled NSAIDs during days 0–14, and only black race and lack of biological relationship to the recipient were associated with higher likelihood of fills. During days 183–365, LKDs who were female, black, Hispanic, obese, with education level less than college, or uninsured were more likely to fill NSAIDs (Table 1). In the multivariate models, statistically significant correlates of increased NSAID fills included: female sex, 26% and 31% higher likelihood than men during days 15–182 and 183–365 (aOR, $_{1.03}1.26_{1.54}$; $_{1.11}1.31_{1.55}$), respectively; black race, more than twice the likelihood compared with white race during days 0–14 (aOR, $_{1.52}2.54_{4.11}$), and 55% to 81% increased likelihood in later periods; obesity, 79% increased likelihood compared with normal BMI during days 15–182 (aOR, $_{1.40}1.79_{2.29}$), and 50% increased likelihood during days 183–365; and less than college education, 41% increased likelihood compared with college level education during days 15–183 (aOR, $_{1.15}1.41_{1.72}$), and 53% higher likelihood during days 183–365. Smoking history was associated with 25% increased likelihood of filling during days 15–182, and donation in 2011–2013 (versus 2007–2010) with trends towards lower NSAID fills across the first year postdonation (Table 2).

Associations of NSAIDs Fills with eGFR, Proteinuria, and Hypertension at 1 Year and 2 Years Postdonation

For these outcomes, LKDs who filled at least one NSAID prescription at any point during the first year postdonation were considered exposed to NSAIDs. Mean eGFR at the first anniversary for LKDs who filled NSAIDs was 67.2 mL/min per 1.73 m^2, comparable to 65.8 mL/min per 1.73 m^2 for those who did not, with a difference of 1.4 mL/min per 1.73 m^2 (β, $_{0.22}1.40_{2.58}$). In multivariable linear regression modeling, there was no statistically significant difference in eGFR at the first anniversary between LKDs who filled NSAIDs and those who did not (aβ, $_{-0.90}$-0.11$_{0.68}$; Table 3). There was also no difference in incidence of proteinuria at the first anniversary between NSAID fillers and non-fillers in both univariate, 4.5% vs. 5.1% (OR, $_{0.64}0.87_{1.16}$), and multivariate logistic regression models (aOR, $_{0.61}0.83_{1.12}$; Table 3). After excluding LKDs with hypertension at the time of donation ($n = 2849$), incidence of new onset hypertension at the first anniversary was similar between NSAIDs fillers and non-fillers, 0.7% vs. 0.9% (OR, $_{0.34}0.80_{1.59}$). In the multivariate logistic regression model, NSAID prescription use was not significantly associated with new-onset hypertension (aOR, $_{0.37}0.87_{1.74}$; Table 3). Similarly, in a subset of patient with available 2-year follow-up data (n= 18 603), NSAID use in the first year was not associated with two-year eGFR (aβ, $_{-1.47}$-0.62$_{0.23}$), likelihood of proteinuria (aOR, $_{0.59}0.83_{1.13}$) or new onset hypertension (aOR, $_{0.56}1.11_{1.96}$).

DISCUSSION

We examined linked national living donor registry and pharmacy claims data to quantify patterns of NSAID and opioid prescription fills during the first year postdonation. Opioid prescription filling was highest, as expected, in the first two weeks after nephrectomy (36.6%). Although opioid prescription fills declined in the subsequent follow-up periods, approximately 13% of donors filled opioids during days 183–365 postdonation. NSAID prescriptions increased from 0.5% during days 0–14 to 3.3% during days 183–365. Women filled opioids more commonly than men, and black donors filled both opioids and NSAIDs more commonly than white donors. Significant correlates of opioid prescription fills during days 183–365 also included obesity, less than college education, smoking history, and nephrectomy complications. NSAID fills in the first year were not associated with adverse renal outcomes (eGFR, proteinuria, or hypertension) at 1 and 2 years postdonation.

While opioid analgesics may be effective in achieving pain control, they have the potential for serious adverse effects, including risk of developing opioid use disorder and overdose, which can in some cases result in death.[15] We previously showed that predonation opioid prescription use was an independent risk factor for early re-admission after donor nephrectomy (6.8% vs. 2.6%; aOR, $_{1.74}2.49_{3.58}$).[16] In the CKD population, Novick et al. recently demonstrated that receiving prescription opioids was associated with a higher risk of death and hospitalizations compared with receiving prescription NSAIDs.[36] In the general population, the U.S. has witnessed a dramatic increase in opioid overdose-related deaths in the past 15 years, with 47,600 deaths in 2017, accounting for 67.8.4% of all overdose deaths.[37] The Centers for Disease Control and Prevention (CDC) released data from 11 states participating in the Enhanced State Opioid Overdose Surveillance program, and noted that

up to 35% of opioid overdose deaths may be related to prescription opioids.[38] In response to this increasing trend of opioid-related unintentional deaths, the CDC issued opioid prescription guidelines that require limiting the number of opioid tablets prescribed for acute pain, including pain after surgical procedures.[18] Undergoing a surgical procedure may represent first exposure to opioid drugs for many patients in the general population, and has been associated with higher risk of opioid use disorder; the risk seems to be higher for those exposed at a younger age.[39–41] Opioid prescription patterns after surgery are higher in the U.S. compared with other countries.[42] Given these concerns, surgeons appear to have already changed their practices regarding prescription opioids, prescribing them at lower rates than in previous years.[43] In our study, there was no significant difference in prescription rates of opioids during the first two weeks postdonation in recent years of donation, and incidence of persistent opioid prescription fills after the early postdonation period was 28.8%. We previously reported that prescription opioid fill rates were 32.3 and 32.4 per 100 person-years between 1–4 years and > 4 years postdonation.[17] Future studies should assess risk of perioperative opioid use and subsequent opioid use disorder among LKDs.

In the midst of the opioid crisis epidemic and concerns about prescribing opioids for pain, NSAID analgesics, which have been regarded with caution due to the potential for adverse renal effects, may be viable options for alternative pain control.[44] Increased use of NSAIDs has been recently observed in the general population.[45] Studies exploring safe incorporation of NSAID analgesics during the perioperative period after living donor nephrectomy are emerging. In a single-center randomized control study, Grimsby et al. reported that eGFRs for LKDs who received continuous infusion of Ketorolac for the first 24 hours were similar at 1 year postdonation to those for LKDs who received saline (89.29 vs. 87.94 mL/min per 1.73m^2; $P = 0.58$).[11] In contrast, another single-center retrospective study reported that Ketorolac (15 or 30 mg) started intra-operatively and continued for the first 24 hours after living donor nephrectomy was associated with significantly lower eGFR at 1 year compared with no Ketorolac exposure (62 ml/min per 1.73 m^2 vs. 73 ml/min per 1.73 m^2, $P < 0.01$).[12] Literature is limited regarding patterns of NSAID use among LKDs beyond discharge from the nephrectomy hospitalization. While our finding of 3.3% of LKDs filling prescriptions NSAIDs during days 183–365 postdonation is interesting, since many transplant centers recommend that LKDs not take NSAIDs,[12,46] the rates are lower than in the general population, where NSAID prescription rates were up to 15%.[20,47] NSAID fill rates in our LKD study sample were also lower than in the CKD population. Among participants who responded to over-the-counter (OTC) and prescription NSAID use ($n = 12,065$) in the National Health and Nutrition Examination Survey (1999–2004), NSAID use was 5% in moderate-severe CKD (stages 3 and 4),[48] and a single-center study of 2,157 patients (age 18 years), all with CKD (eGFR < 60 mL/min per 1.73 m^2) reported a 12.2% NSAID prescription rate at office visits, and nephrologists were less likely to prescribe NSAIDs than primary care physicians (9.6% vs. 15%).[49] In prospective longitudinal study of chronic renal insufficiency cohort (2003–2008) participants ($n = 3872$), Zhan et al. reported any NSAID use of 24%; interestingly, being seen by a nephrologist was associated with lower odds of starting NSAIDs (aOR, $_{0.46}0.61_{0.81}$), and stopping NSAIDs was associated with increased odds of starting opioid analgesics (aOR, $_{1.04}1.46_{2.03}$).[50] Since LKDs are generally counseled

against taking NSAIDs during their evaluation and may be followed by transplant centers in the first year postdonation, this may explain low rates of prescription NSAID fills in the study sample. Because of the low frequency of prescription NSAID use, we were unable to study interactions of NSAID prescriptions and opioid prescriptions. Future studies should explore whether NSAID use among LKDs affects rates of opioid use.

Data on the safety of NSAIDs among LKDs are limited, especially after the initial postoperative period. Our findings of lack of an association of NSAID fills with lower eGFR, higher proteinuria, or increased hypertension at first or second yeasr postdonation are reassuring. These results, though novel, should be interpreted with caution as the cumulative exposure to prescription NSAIDs was quite low, and follow-up was limited to 2 years postdonation. Notably, however, the association of NSAID use with adverse outcomes even in the general population and patients with traditional CKD is inconsistent. Higher cumulative doses for longer periods of time may be associated with worse renal outcomes. For example, 700 mg of Ibuprofen daily, continuously, for 3 years, in older patients was associated with a 26% increased risk for eGFR reduction by 15 mL/min per 1.73 m^2 or more (aOR: $_{1.04}1.26_{1.53}$).[24] Another recent study of active duty U.S. army soldiers from 2011–2014, who were young, showed that those who used high doses of NSAIDs (> 7 DDDs in a month) experienced statistically significant but modest higher risk of AKI (aHR, $_{1.1}1.2_{1.4}$) and CKD (aHR, $_{1.0}1.2_{1.3}$).[51] In contrast, two other general population studies, the Nurses' Health study and the Physicians' Study that included apparently healthy women aged 44–69 years and men aged 40–84 years, respectively, showed no significant association with decline in renal function with NSAID use.[25,26] Regarding hypertension as an adverse outcome with NSAID use, in the Nurses' Health study, NSAID use was associated with a 35% higher likelihood of a diagnosis of hypertension (aOR $_{1.25}1.35_{1.46}$) at 8 years follow-up.[52] On the other hand, in the Physicians' Study, NSAID use was not associated with higher risk of hypertension (aOR $_{0.97}1.12_{1.31}$).[53] Factors affecting the lack of associations between NSAID prescription fills and adverse outcomes in the current study may include that living donors are relatively young, lack comorbidity, and filled NSAIDs at lower doses, and that the follow-up period was short.

Our study has strengths. First, we expand the understanding of patterns of NSAID and opioid prescription fills among LKDs and associations of NSAIDs with renal outcomes. Second, using pharmacy prescription fills as a measure of NSAID and opioid use is an objective method not subject to recall bias. Third, our cohort of LKDs for whom we were able to access prescription fills was overall similar to the entire U.S. living donor cohort. Our study also has limitations, including inability to identify over-the-counter NSAID use or illicit opioid use. Moreover, some transplant centers may dispense pain medications without processing prescriptions on discharge, and donors who filled opioid or NSAID prescriptions may not have taken all dispensed pills, contributing to misclassification bias. Our follow-up duration was short, and we lacked access to measures of AKI, hyperkalemia, or non-renal side effects of NSAIDs such as gastritis. We were unable to evaluate specific indications for pain medication use or define which NSAIDs and opioid prescriptions were related to the nephrectomy. Notably, a recent survey of 512 LKDs from a single center in the Netherlands reported that chronic postsurgical pain related to nephrectomy was 12.2% between 3 and 24

months.[14] If LKDs in our cohort also had similar rates of chronic surgical pain, many analgesic prescriptions could have been due to surgical pain.

In light of the recent opioid overdose epidemic in the United States, prescription rates for opioids may decline among LKDs and non-opioid analgesics may become an increasingly important therapeutic option for pain control.[50] Although our analysis did not detect an association between prescription NSAID fills at low doses with adverse effects on kidney function, hypertension, or proteinuria in the short-term, we cannot conclude that NSAIDs are completely safe, especially at higher doses and beyond 1 year postdonation." Future studies should examine the long-term effects of analgesics use in LKDs and define best practices for pain control in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

LDN	laparoscopic donor nephrectomy
BMI	body mass index
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
eGFR	estimated glomerular filtration rate
HRSA	Health Resources and Services Administration
NCPDP	National Council for Prescription Drug Program
NSAIDs	non-steroidal anti-inflammatory drugs
OPTN	Organ Procurement and Transplantation Network
aOR	adjusted odds ration

aHR	adjusted hazards ration
PCD	pharmaceutical claims database
SAS	Statistical Analysis Software
SRTR	Scientific Registry of Transplant Recipients
U.S.	United States
AKI	acute kidney injury
OTC	over the counte

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A.

Prescription Opioid Fill Patterns in First Year Postdonation, by Class and Time Period

B.

Frequency of LKDs with New or Repeated Opioid Fills in First Year Postdonation, by Time Period
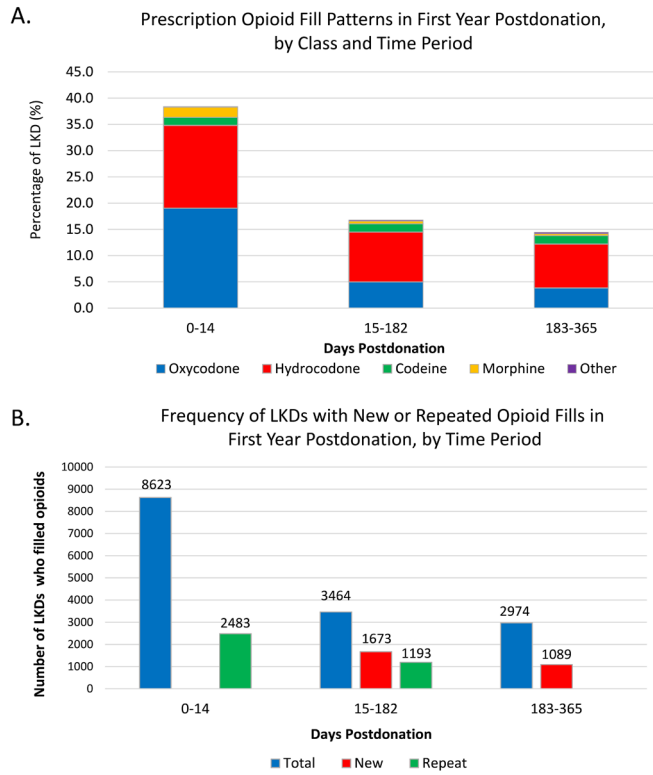
Figure 1.
(A) Frequency of opioid prescription fills among living kidney donors in the first year postdonation. **(B)** Patterns of opioid prescription fills among living kidney donors during their first year postdonation. LKD, living kidney donor.
"Total": Refers to the total number of LKDs who filled opioids during each of the three follow up periods in the first year postdonation: 0–14 days, 15–182 days, and 183–365 days. "New": Refers to LKDs who filled opioids during days 15–182 and 183–365 but have no record of filling opioids in previous periods. "Repeat": Refers to LKDs who filled opioids during days 0–14 or 15–182 who repeated opioids fills in later periods

A. Prescription NSAID Fills Patterns in First Year Postdonation, by Class and Time Period

Legend: Propionic acid derivative, Salicylic acid derivative, Acetic acid derivative, Enolic acid derivative, COX2 Inhibitor, Anthranilic acid derivative

B. Frequency of LKDs with New or Repeated NSAID Fills in First Year Postdonation, by Time Period

Legend: Total, New, Repeat

Figure 2.
(A) Frequency of NSAID prescription fills among living kidney donors in the first year postdonation. **(B)** Patterns of NSAIDs prescription fills among living kidney donors during their first year postdonation. LKD, living kidney donor; NSAID, non-steroidal anti-inflammatory drug.

"Total": Refers to the total number of LKDs who filled NSAIDs during each of the three follow-up periods in the first year postdonation: 0–14 days, 15–182 days, and 183–365 days. "New": Refers to LKDs who filled NSAIDs during days 15–182 and 183–365 but have no record of filling NSAIDs in previous periods. "Repeat": Refers to LKDs who filled NSAIDs during days 0–14 or 15–182 who repeated NSAID fills in later periods.

Table 1.

Opioid and NSAID fill percentages among the whole cohort of living kidney donors (N = 23 565), by donor factors, across three periods of first year postdonation.

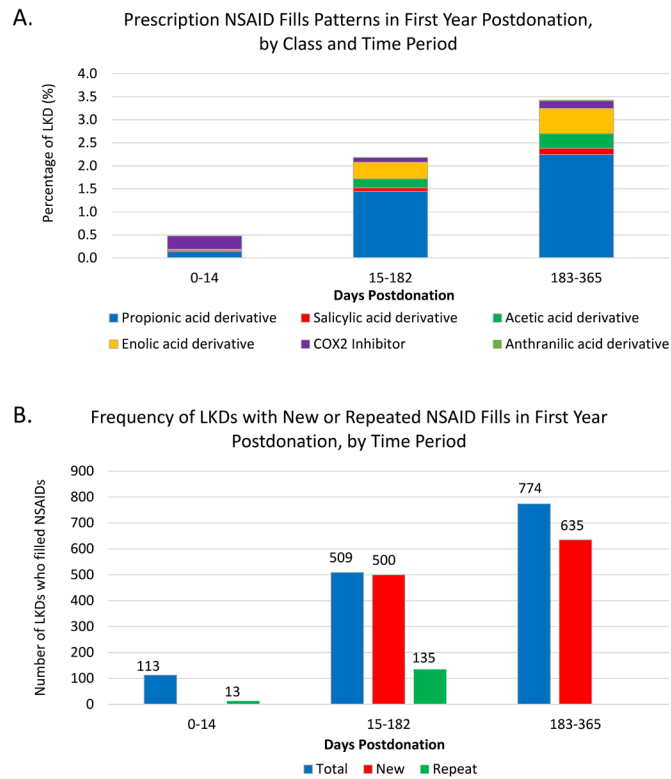| Donor Factors	Opioid prescription fills			NSAID prescription fills		
	0–14 d	15–182 d	183–365 d	0–14 d	15–182 d	183–365 d
Age (years)	‡	‡	*			
19–30	40.0	15.8	13.1	0.4	2.2	3.6
31–44	38.0	15.8	13.4	0.4	2.1	3.6
45–59	34.8	14.2	12.1	0.6	2.2	3.0
60	32.1	10.3	10.8	0.5	2.2	2.7
Sex		†	‡			†
Male	36.0	13.4	11.4	0.4	1.9	2.7
Female	36.9	15.3	13.2	0.5	2.3	3.5
Race	‡	‡	‡	*	‡	‡
White	36.5	14.6	12.7	0.4	1.9	2.8
Black	39.6	17.9	15.1	0.9	2.9	5.4
Hispanic	36.7	13.8	10.9	0.3	3.5	4.9
Other	29.6	9.5	8.8	0.6	1.9	2.6
Body mass index (kg/m^2)	†	‡	‡		‡	‡
<18.5	33.6	12.7	13.2	0.0	1.4	1.8
18.5–24.9	35.4	13.3	11.0	0.5	1.5	2.6
25–30	36.2	14.7	12.9	0.4	2.3	3.4
>30	39.2	16.7	14.5	0.6	2.8	4.1
Unknown	34.3	16.5	12.1	0.0	3.7	4.0
Preoperative eGFR (mL/min per 1.73 m^2)	‡	*	*			*
>90	38.1	15.3	13.1	0.5	2.2	3.5
60–90	33.9	13.7	11.7	0.5	2.0	2.8
<60	33.6	11.7	11.7	0.2	2.1	2.5
Unknown	35.7	13.5	15.8	0.0	4.7	1.8
Smoking history	‡	‡	‡			
Smoker	38.7	19.9	16.2	0.5	2.5	3.4
Non-smoker	35.9	12.9	11.4	0.5	2.1	3.3
Hypertension history						
Yes	35.7	13.8	12.0	0.4	2.3	3.0
No	36.7	14.8	12.7	0.5	2.1	3.3
Education level		‡	‡		‡	‡
College	36.1	13.4	11.5	0.4	1.8	2.8
K-12	37.6	18.2	15.2	0.6	2.9	4.6
Unknown	37.1	14.9	13.8	0.7	2.6	3.6
Employment status		‡	*			†

Donor Factors	Opioid prescription fills			NSAID prescription fills		
	0–14 d	15–182 d	183–365 d	0–14 d	15–182 d	183–365 d
Employed	36.8	14.1	12.3	0.5	2.1	3.1
Unemployed	35.6	17.3	14.0	0.5	2.4	4.1
Insurance status	‡	*	*			*
Insured	35.5	14.4	12.5	0.5	2.1	3.2
Uninsured	43.6	17.1	14.3	0.4	2.4	4.3
Unknown	38.4	14.8	12.2	0.2	2.6	3.4
Donor/Recipient Relationship	†		*	*		
Biologically Related	35.6	14.5	12.2	0.4	2.1	3.3
Not Biologically Related	37.6	14.9	13.1	0.6	2.2	3.3
Complications		‡	‡			
Yes	38.1	23.1	16.0	0.1	1.9	3.5
No	36.5	14.1	12.4	0.5	2.2	3.3
Nephrectomy approach	‡	*				
Laparoscopic	36.9	14.6	12.6	0.5	2.2	3.3
Open operation	28.8	18.0	12.9	0.7	2.3	4.0
Nephrectomy side	‡	*				
Right	33.0	12.9	12.0	0.6	2.2	3.0
Left	37.0	14.9	12.7	0.5	2.2	3.3
Year of donation	†				†	
2007–2010	35.0	14.6	12.7	0.5	2.6	3.5
2011–2013	37.8	14.8	12.2	0.4	1.7	3.0
2014–2016	36.9	14.6	13.3	0.5	2.3	3.5

Data in the cells represent row percentages. P-values:

*
p<0.05–0.002;

†
p=0.001–0.0001;

‡
p<0.0001. eGFR: estimated glomerular filtration rate. K-12: Finished high school. Complications: surgical complications including reoperation for any reason, and readmission after initial discharge. Open operation: conversion from laparoscopic to open donor nephrectomy.

Table 2.

Adjusted associations of opioid and NSAID prescription fills with baseline donor factors the whole cohort of living kidney donors (N = 23 565), by periods of fills.

Donor factors	Opioid prescription fills			NSAID prescription fills		
	0–14 d	15–182 d	183–365 d	0–14 d	15–182 d	183–365 d
Age (years)						
19–30	Reference	Reference	Reference	Reference	Reference	Reference
31–44	0.92 (0.85–1.00)	1.01 (0.90–1.12)	1.01 (0.90–1.13)	0.75 (0.42–1.41)	0.97 (0.75–1.27)	1.03 (0.84–1.27)
45–59	0.82 (0.76–0.89)‡	0.89 (0.79–0.99)*	0.89 (0.79–1.01)	1.34 (0.76–2.45)	1.09 (0.83–1.44)	0.95 (0.76–1.19)
60	0.75 (0.67–0.85)‡	0.57 (0.48–0.68)‡	0.77 (0.64–0.92)*	1.17 (0.49–2.68)	1.17 (0.78–1.74)	0.87 (0.61–1.22)
Sex						
Male	Reference	Reference	Reference	Reference	Reference	Reference
Female	1.06 (1.00–1.13)*	1.20 (1.11–1.31)‡	1.24 (1.13–1.35)‡	1.46 (0.95–2.31)	1.26 (1.03–1.54)*	1.31 (1.11–1.55)†
Race						
White	Reference	Reference	Reference	Reference	Reference	Reference
Black	1.06 (0.97–1.16)	1.22 (1.09–1.37)†	1.17 (1.03–1.32)*	2.54 (1.52–4.11)†	1.55 (1.18–2.02)†	1.81 (1.47–2.21)‡
Hispanic	0.93 (0.85–1.02)	0.88 (0.77–0.99)*	0.79 (0.69–0.90)†	0.91 (0.42–1.76)	1.80 (1.39–2.29)‡	1.58 (1.28–1.94)‡
Other	0.73 (0.62–0.85)‡	0.64 (0.50–0.81)†	0.70 (0.54–0.88)*	1.53 (0.53–3.45)	1.12 (0.64–1.80)	0.95 (0.60–1.44)
Body mass index (kg/m²)						
<18.5	0.87 (0.65–1.16)	0.91 (0.60–1.35)	1.18 (0.78–1.74)	-	0.91 (0.22–2.44)	0.68 (0.21–1.63)
18.5–24.9	Reference	Reference	Reference	Reference	Reference	Reference
25–30	1.05 (0.98–1.12)	1.15 (1.05–1.26)†	1.25 (1.14–1.37)‡	0.97 (0.62–1.52)	1.53 (1.22–1.92)†	1.30 (1.09–1.56)*
>30	1.16 (1.08–1.25)‡	1.28 (1.16–1.41)‡	1.38 (1.24–1.53)‡	1.31 (0.80–2.13)	1.79 (1.40–2.29)‡	1.50 (1.23–1.83)‡
Unknown	1.00 (0.78–1.28)	1.41 (1.01–1.93)*	1.15 (0.79–1.63)	-	2.28 (1.14–4.16)*	1.55 (0.80–2.73)
Preoperative eGFR (mL/min per 1.73 m²)						
>90	Reference	Reference	Reference	Reference	Reference	Reference
60–90	0.90 (0.84–0.96)†	0.97 (0.89–1.06)	0.94 (0.86–1.02)	1.03 (0.67–1.55)	0.93 (0.76–1.14)	0.90 (0.75–1.06)
<60	0.88 (0.72–1.08)	0.82 (0.60–1.10)	0.93 (0.68–1.25)	0.44 (0.03–2.05)	0.90 (0.43–1.68)	0.77 (0.39–1.35)

Donor factors	Opioid prescription fills			NSAID prescription fills		
	0–14 d	15–182 d	183–365 d	0–14 d	15–182 d	183–365 d
Unknown	0.93 (0.68–1.28)	0.95 (0.59–1.46)	1.36 (0.88–2.04)	-	2.18 (0.97–4.24)*	0.51 (0.12–1.35)
Smoking history						
Smoker	1.11 (1.04–1.18)†	1.63 (1.51–1.77)‡	1.45 (1.33–1.58)‡	0.98 (0.63–1.50)	1.25 (1.02–1.52)*	1.04 (0.88–1.22)
Non-smoker	Reference	Reference	Reference	Reference	Reference	Reference
Hypertension history						
Yes	1.00 (0.92–1.09)	0.98 (0.88–1.10)	0.96 (0.85–1.08)	0.73 (0.38–1.29)	1.07 (0.82–1.39)	0.94 (0.74–1.17)
No	Reference	Reference	Reference	Reference	Reference	Reference
Education level						
College	Reference	Reference	Reference	Reference	Reference	Reference
K-12	1.02 (0.95–1.09)	1.30 (1.20–1.42)‡	1.31 (1.19–1.43)‡	1.39 (0.89–2.12)	1.41 (1.15–1.72)†	1.53 (1.30–1.80)‡
Unknown	1.08 (0.98–1.19)	1.10 (0.95–1.25)	1.26 (1.09–1.45)†	1.99 (1.06–3.52)*	1.29 (0.93–1.74)	1.26 (0.96–1.63)
Employment status						
Employed	Reference	Reference	Reference	Reference	Reference	Reference
Unemployed	0.93 (0.86–1.00)*	1.27 (1.16–1.40)‡	1.12 (1.02–1.24)*	1.01 (0.60–1.63)	1.01 (0.80–1.27)	1.27 (1.06–1.51)*
Insurance status						
Insured	Reference	Reference	Reference	Reference	Reference	Reference
Uninsured	1.35 (1.23–1.49)‡	1.03 (0.91–1.16)	1.04 (0.91–1.19)	0.79 (0.37–1.52)	1.03 (0.76–1.38)	1.11 (0.88–1.40)
Unknown	1.15 (1.06–1.26)†	0.95 (0.84–1.07)	0.89 (0.79–1.01)	0.31 (0.12–0.68)*	1.04 (0.79–1.35)	0.92 (0.73–1.16)
Donor/Recipient Relationship						
Biologically Related	Reference	Reference	Reference	Reference	Reference	Reference
Not Biologically Related	1.13 (1.07–1.20)‡	1.09 (1.01–1.17)*	1.12 (1.04–1.21)*	1.75 (1.19–2.61)*	1.11 (0.93–1.33)	1.11 (0.96–1.29)
Complications						
Yes	1.04 (0.94–1.16)	1.75 (1.54–1.99)‡	1.29 (1.11–1.49)†	0.26 (0.04–0.82)	0.86 (0.57–1.23)	1.02 (0.76–1.35)
No	Reference	Reference	Reference	Reference	Reference	Reference
Nephrectomy approach						
Laparoscopic	Reference	Reference	Reference	Reference	Reference	Reference
Open operation	0.73 (0.63–0.84)‡	1.38 (1.16–1.64)†	1.03 (0.84–1.25)	1.22 (0.50–2.54)	1.01 (0.63–1.53)	1.26 (0.89–1.74)

Donor factors	Opioid prescription fills			NSAID prescription fills		
	0–14 d	15–182 d	183–365 d	0–14 d	15–182 d	183–365 d
Nephrectomy side						
Right	0.89 (0.81–0.97) *	0.81 (0.71–0.92) †	0.94 (0.82–1.06)	1.35 (0.76–2.26)	1.05 (0.78–1.39)	0.92 (0.72–1.17)
Left	Reference	Reference	Reference	Reference	Reference	Reference
Year of donation						
2007–2010	Reference	Reference	Reference	Reference	Reference	Reference
2011–2013	1.13 (1.06–1.20) †	1.02 (0.94–1.11)	0.95 (0.87–1.04)	0.79 (0.52–1.20)	0.68 (0.55–0.84) †	0.85 (0.72–1.00)
2014–2016	1.11 (1.03–1.20) *	1.00 (0.91–1.11)	1.05 (0.94–1.17)	0.76 (0.45–1.26)	0.92 (0.72–1.16)	1.01 (0.83–1.23)

P-values:

*
p<0.05–0.002;

†
p=0.001–0.0001;

‡
p<0.0001. eGFR: estimated glomerular filtration rate. K-12: Finished high school. Complications: surgical complications including reoperation for any reason, and readmission after initial discharge. Open operation: conversion from laparoscopic to open donor nephrectomy.

Table 3.

Multivariate model associations for renal outcomes at first year postdonation anniversary for living kidney donors who filled at least one prescription NSAIDs any time during first year postdonation (N = 20 295).

Donor factors	eGFR at 1 year post donation (aβeta)	Proteinuria at 1 year post donation (aOR)	Hypertension at 1 year post donation (aOR); Baseline HTN excluded
NSAID fills in first yr postdonation	−0.11 (−0.90 to 0.68)	0.83 (0.61–1.12)	0.87 (0.37–1.74)
Preoperative eGFR (mL/min/1.73 m²)	0.22 (0.21 to 0.23)[‡]	1.00 (1.00–1.01)	0.99 (0.98–1.00)
Postoperative eGFR (mL/min/1.73 m²)	0.46 (0.45 to 0.48)[‡]	1.00 (0.99–1.00)	0.99 (0.98–1.01)
Age (years)			
19–30	Reference	Reference	Reference
31–44	−4.84 (−5.39 to −4.29)[‡]	1.02 (0.84–1.24)	1.30 (0.69–2.64)
45–59	−7.67 (−8.26 to −7.08)[‡]	0.98 (0.79–1.21)	2.48 (1.33–4.99)[*]
60	−9.91 (−10.72 to −9.10)[‡]	1.01 (0.74–1.36)	4.20 (1.99–9.30)[†]
Sex			
Male	Reference	Reference	Reference
Female	0.95 (0.57 to 1.34)[‡]	0.78 (0.68–0.89)[†]	0.48 (0.35–0.65)[‡]
Race			
White	Reference	Reference	Reference
Black	1.62 (1.01 to 2.23)[‡]	1.43 (1.17–1.74)[†]	0.60 (0.28–1.13)
Hispanic	1.73 (1.14 to 2.32)[‡]	1.34 (1.10–1.63)[*]	1.08 (0.62–1.77)
Other	0.41 (−0.51 to 1.33)	0.84 (0.56–1.20)	0.61 (0.15–1.62)
Body mass index (kg/m²)			
<18.5	1.01 (−0.84 to 2.87)	0.90 (0.38–1.79)	1.29 (0.07–6.14)
18.5–24.9	Reference	Reference	Reference
25–30	−0.24 (−0.65 to 0.17)	1.07 (0.92–1.25)	1.83 (1.21–2.83)[*]
>30	−0.48 (−0.96 to −0.00)[*]	1.13 (0.95–1.35)	2.18 (1.38–3.49)[†]
Unknown	−1.16 (−2.81 to 0.49)	0.67 (0.24–1.49)	1.99 (0.32–6.83)
Smoking history			
Smoker	0.39 (0.00 to 0.79)	1.06 (0.92–1.23)	1.24 (0.88–1.73)
Non-smoker	Reference	Reference	Reference
Hypertension history			
Yes	−0.17 (−0.68 to 0.34)	0.94 (0.77–1.13)	-
No	Reference	Reference	Reference
Education level			
College	Reference	Reference	Reference
K-12	0.82 (0.40 to 1.25)[†]	0.99 (0.85–1.15)	1.34 (0.94–1.90)
Unknown	−0.08 (−0.79 to 0.64)	0.50 (0.35–0.69)[‡]	0.75 (0.35–1.45)

Donor factors	eGFR at 1 year post donation (aβeta)	Proteinuria at 1 year post donation (aOR)	Hypertension at 1 year post donation (aOR); Baseline HTN excluded
Employment status			`
Employed	Reference	Reference	Reference
Unemployed	0.28 (−0.19 to 0.76)	1.01 (0.85–1.20)	0.79 (0.49–1.22)
Insurance status			
Insured	Reference	Reference	Reference
Uninsured	1.25 (0.64 to 1.85)[‡]	1.11 (0.89–1.37)	1.38 (0.80–2.25)
Unknown	1.54 (0.91 to 2.18)[‡]	1.03 (0.81–1.29)	0.98 (0.54–1.65)
Donor/Recipient Relationship			
Biologically Related	Reference	Reference	Reference
Not Biologically Related	0.14 (−0.22 to 0.49)	0.99 (0.87–1.13)	0.95 (0.69–1.30)
Complications			
Yes	−0.85 (−1.55 to −0.16)[*]	1.48 (1.18–1.83)[†]	0.70 (0.32–1.35)
No	Reference	Reference	Reference
Nephrectomy approach			
Laparoscopic	Reference	Reference	Reference
Open operation	−0.04 (−0.94 to 0.87)	1.20 (0.87–1.62)	0.28 (0.05–0.91)
Nephrectomy side			
Right	0.62 (0.06 to 1.18)[*]	1.02 (0.82–1.24)	1.29 (0.78–2.01)[*]
Left	Reference	Reference	Reference
Year of donation			
2007–2010	Reference	Reference	Reference
2011–2013	−0.56 (−0.98 to −0.15)[*]	1.43 (1.22–1.68)[‡]	1.45 (1.01–2.11)
2014–2016	−0.40 (−0.87 to 0.07)	2.05 (1.72–2.44)[‡]	1.20 (0.76–1.88)[‡]

P-values:

[*]
p<0.05–0.002;

[†]
p=0.001–0.0001;

[‡]
p<0.0001. aβeta: adjusted beta coefficient. aOR: adjusted odds ratio. eGFR: estimated glomerular filtration rate. HTN: hypertension. K-12: Finished high school. Complications: surgical complications including reoperation for any reason, and readmission after initial discharge. Open operation : conversion from laparoscopic to open donor nephrectomy.