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Chronic opioid analgesic usage post-kidney transplantation and clinical outcomes

Kulshrestha S, Barrantes F , Samaniego M, Luan FL. Chronic opioid analgesic usage post-kidney transplantation and clinical outcomes.

Abstract: Chronic opioid usage (COU) is common among patients with end-stage renal disease (ESRD) qualified for kidney transplantation and associated with inferior post-transplant outcomes. The magnitude of COU after kidney transplantation and its impact on transplant outcomes remain unknown. We performed a single-center retrospective study aimed to describe the prevalence of COU during the first year, to identify the predictors of COU and to determine the impact of COU on post-transplant outcomes including the rates of hospitalization and acute rejection during the first year, as well as long-term patient and graft survival. Among 1045 kidney transplant patients, 119 (11.4%) had required continued outpatient prescription of opioid analgesics during the first year after kidney transplantation, mostly for non-surgery-related pain (85%). A positive history of COU prior to transplantation was the strongest predictor of COU in the first year post-transplantation (adjusted odds ratio [AOR] 4.31, $p < 0.001$). Patients with COU had more often hospital admission during the first year (AOR 2.48, $p = 0.001$, for 1 or 2 admissions, and AOR 6.03, $p < 0.001$ for ≥ 3 admissions), but similar rate of acute rejection (19.3% vs. 15.7%, $p = 0.31$). During long-term follow-up, however, the patient and/or death-censored kidney survival was not different. COU early post-kidney transplantation, when clinically indicated and properly supervised, does not appear to affect the risk of death and death-censored graft failure.

Satyarth Kulshrestha[a], Fidel Barrantes[b], Milagros Samaniego[a] and Fu L. Luan[c]

[a]Division of Nephrology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, [b]Presbyterian Kidney Transplant Center, Albuquerque, NM and [c]Department of Kidney and Pancreas Transplantation, St. Barnabas Medical Center, Livingston, NJ, USA

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Corresponding author: Satyarth Kulshrestha, 3914 Taubman Center, 1500 E Medical Center Drive, SPC 5364, Ann Arbor, MI 48109-5364, USA.
Tel.: +1 734 763 9041;
fax: +1 734 232 4160;
e-mail: Satyarth@med.umich.edu

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Kidney transplantation is the treatment of choice for a large majority of patients with end-stage renal disease (ESRD) as it provides survival advantage and improvement in the quality of life compared to the dialysis therapy (1, 2). Patient and kidney graft survival has improved over the years with the modern immunosuppression and dedicated patient management (3). Consequently, the issues pertaining to health-related quality of life are now attaining more recognition. Chronic pain is one such issue that is highly prevalent in the chronic dialysis population and reported by nearly half of the patients with ESRD undergoing maintenance dialysis therapy (4, 5).

The management of chronic pain among patients with ESRD is often inadequate. The patients on dialysis are seen weekly but focus is primarily on the adequacy of dialysis and factors directly related to delivery of dialysis. Nephrologists are perceived to be reluctant in delving into chronic pain problem and in prescribing nonsteroidal anti-inflammatory drugs (NSAIDs) to these patients (6, 7). Opioids are the alternative analgesics with up to 36% of dialysis patients being prescribed opioid analgesics chronically in the USA (7, 8). The use of opioid analgesics, both short term and long term, is associated with a variety of adverse effects that are dose dependent and often enhanced in the setting of renal failure (9–11). We have recently observed that a history of chronic opioid analgesic usage (COU) prior to kidney transplantation was associated with inferior patient survival post-transplantation (12).

There are few studies examining the presence of chronic pain and the use of analgesics for the management of pain after kidney transplantation. One recent observational study suggested no major difference in the point-prevalence of chronic pain reported by ESRD patients on dialysis (63%) and by stable kidney transplant patients (62%). In this study, 15% of dialysis patients and 37% of kidney transplant patients received no analgesics for their pain relief (13). To date, there are no published data on the magnitude of opioid analgesic usage

after kidney transplantation and its potential impact on the transplant outcomes. To fill this knowledge gap, we performed a single-center observational study investigating the magnitude of opioid analgesic usage during the first year post-transplantation and its impact on both the short- and the long-term post-transplant outcomes.

Materials and methods

Study design and patient population

This is a single-center observational study that included all adult patients who received a kidney transplant between January 1, 2004 and December 31, 2008 with follow-up through December 31, 2012. Patients were excluded if they received simultaneous multi-organ transplants, died, or lost their kidney transplant before three months. The period of initial three months was chosen to allow for considerable duration of opioid usage after transplantation. This study was approved by the institutional review board (IRB).

Demographic and baseline characteristics of the study population as well as subsequent follow-up information including the number of hospital admission and biopsy-documented acute rejection during the first year, patient and kidney graft survival were obtained from the institutional electronic medical record database. A history of chronic pain and chronic opioid analgesics use prior to kidney transplantation was ascertained at the time of initial kidney transplantation evaluation and during subsequent pre-transplant follow-up as part of the evaluation process by a multidisciplinary team composed of transplant nephrologists, surgeons, and social workers. Additional baseline characteristics included a history of past illicit drug abuse and psychiatric diagnosis among others. However, none of the patients reported active recreational drug abuse because active drug abuse is an exclusion clause for kidney transplantation in our center's recipient selection policy. Similarly, any patient with a positive psychiatric history, which included mood disorders, schizophrenia, and personality disorders would have to have symptoms under stable control prior to be considered as a suitable candidate to receive kidney transplantation.

Assessment of chronic opioid usage and pain first year post-transplantation

We determined the active use of opioid analgesics by documenting the presence of opioid analgesic prescription in the outpatient setting, associated with the complaint of pain, at three time intervals: four to eight wk, three to six months, and 10–12 months after transplantation through detailed review of institutional electronic medical records. The standard definition of opioid analgesics was used (14). Chronic opioid usage (COU) was defined as active use of opioid analgesics at all the three time intervals or first two time intervals if the patient had an event (death and/or graft loss) between three and 12 months. Transient opioid administration for acute events in an inpatient setting was not counted. We also did not include the opioid usage during the first four wk, because all our patients were prescribed as-needed opioid analgesics upon the discharge from the initial hospitalization and the prescription stays active in the electronic chart for four wk. Effort was made to include only those who had unequivocal documentation of continued opioid analgesic use.

The cause of pain was classified into four categories: iatrogenic, arthritis/degenerative joint disease, neuropathic and others. The first category comprised all pain descriptions suggesting location to be site of the invasive procedure, namely pain in the area with recent surgical intervention was classified as iatrogenic. Any pain characterized to be joint pain was classified as arthritis/degenerative joint disease, documented neuropathic pain was classified as such. All other cases were put into "other" category.

Assessment of clinical correlates of COU and post-transplant outcomes

We separated the study population into two groups according to COU status (yes or no). We assessed the potential association of various demographic and baseline characteristics with COU. We compared the frequency of hospital readmission (none, 1 or 2, 3 or more) and biopsy-documented acute rejection during the first year, the patient and death-censored kidney graft survival during subsequent follow-up between the two groups.

Statistical analysis

Categorical variables were expressed as proportions and compared using chi-square (χ^2) test. Continuous variables were expressed as mean $\pm$ SD and compared using the Student's *t*-test. Logistic regression analyses were performed to identify the predictors of COU and its association with hospital admissions and acute rejection during the first year post-kidney transplantation. Kaplan–Meier survival and Cox regression analyses were performed to compare patient and/or

death-censored kidney graft survival between the groups with and without COU. All patient, donor, and transplant characteristics were considered for inclusion in the multivariate models. Final models included those variables with $p < 0.10$ after backward selection.

All statistical tests were two-sided, and a p value equal to or <0.05 was considered significant. Statistical analyses were conducted using SAS 9.3. (Cary, NC, USA).

Results

Study patient population

Among 1045 solitary kidney transplant patients who met the inclusion criteria, everyone had an active opioid prescription during the first month (center's policy). During the second month, 261 patients (24.5%) had active opioid use, 176 patients (16.8%) between three and six months, and 148 patients (14.6%) between 10 and 12 months post-transplantation, respectively, had active opioid analgesic use. COU during the first year (Fig. 1) was noted in 119 of 1045 patients (11.4%). Mean age of our recipients' cohort was 49.3 ± 13.2 yr with 62.8% (668) being males and 18.1% (193) being African Americans. The most commonly prescribed opioid analgesic was hydrocodone (59.4%) followed by oxycodone (29.8%), hydromorphone (5.2%), fentanyl (2.9%), and others (2.7%) (Fig. 2A). The most common cause of pain for which the opioid analgesics were prescribed was related to pre-existent arthritis (57%) followed by neuropathic pain (19%), iatrogenic pain (15%), and others (9%) (Fig. 2B).

The demographic and baseline characteristics between patients with and without COU are shown in Table 1. The patients from two groups were comparable with regard to age, gender, BMI,

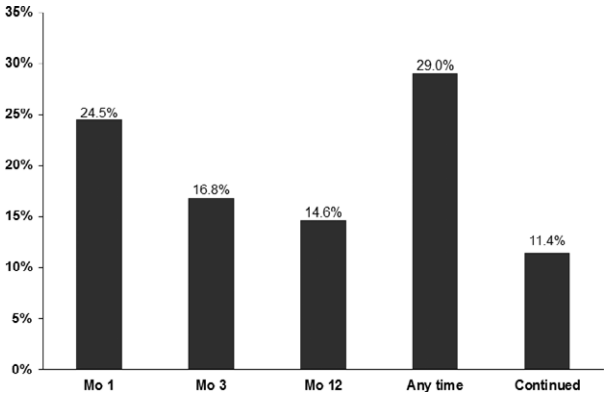

Fig. 1. Opioid use at various time-points.

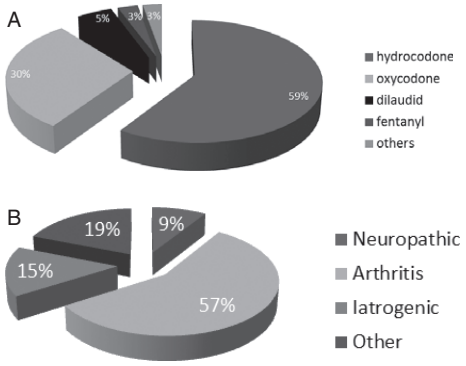

Fig. 2. (A) Opioid usage pattern among the post-transplant chronic opioid user. (B) Characteristics of pain in post-transplant chronic opioid users.

underlying diabetes mellitus, HCV sero-status, college education, proportion receiving first kidney transplant and PRA ≥ 20%. The COU patients more frequently had a positive history of pre-transplant chronic opioid usage (33.6% vs. 7.0%, $p < 0.001$), chronic pain (66.4% vs. 39.2%, $p < 0.001$), psychiatric disorders (52.1% vs. 27.5%, $p < 0.001$), illicit drug usage (21.9% vs. 10.8%, $p = 0.001$), and alcohol abuse (16.0% vs. 10.2%, $p = 0.05$) prior to transplantation. The COU patients were more often African American (25.2% vs. 17.7%, $p = 0.05$) and a former or current smoker (64.7% vs. 48.3%, $p = 0.001$), longer dialysis vintage (3.2 ± 3.3 vs. 2.3 ± 2.6 yr, $p = 0.004$), less likely to be employed (26.1% vs. 44.0%, $p < 0.001$), and to have private health insurance (28.6% vs. 44.6%, $p = 0.001$). They (COU) were less likely to receive a preemptive kidney transplant (15.1% vs. 26.7%, $p = 0.006$) and a living donor kidney transplant (35.3% vs. 52.3%, $p = 0.001$). The COU patients received ECD (20.2% vs. 12.2%, $p = 0.02$) and/or DCD kidney (13.5% vs. 6.5%, $p = 0.006$) more often. Finally, COU patients had longer initial hospital stay (7.4 ± 5.8 vs. 5.2 ± 3.6 d, $p < 0.001$), experienced more delayed graft function (27.2% vs. 12.9%, $p < 0.001$), and received more frequently induction with rabbit antithymocyte globulin (rATG) (31.9% vs. 23.2%, $p = 0.04$).

Predictors of COU during the first year after transplantation

As shown in Table 2, among all the demographic and baseline characteristics, a history of pre-transplant COU was the strongest predictor of post-transplant COU (adjusted odds ratio [AOR] 4.31, 95% CI 2.60, 7.16, $p < 0.001$). Additional predictors included a positive history of psychiatric

Table 1. Demographic and baseline characteristics of study population

	COU, No (n = 926)	COU, Yes (n = 119)	p
Recipient characteristics			
Age, years (SD)	49.1 (13.4)	50.6 (12.0)	0.24
Gender, male, n (%)	584 (63.1)	72 (60.5)	0.59
African American, n (%)	164 (17.7)	30 (25.2)	0.05
BMI, kg/m^2 (SD)	28.4 (5.6)	28.6 (6.4)	0.68
First transplant, n (%)	797 (86.1)	104 (87.4)	0.69
HCV-positive serology, n (%)	39 (4.2)	9 (7.6)	0.10
Preemptive transplant, n (%)	247 (26.7)	18 (15.1)	<0.01
Dialysis duration, years (SD)	2.3 (2.6)	3.2 (3.3)	<0.01
Employed, n (%)	407 (44.0)	31 (26.1)	<0.01
Private health insurance, n (%)	413 (44.6)	34 (28.6)	0.01
Diabetes mellitus, n (%)	312 (33.7)	47 (39.5)	0.21
Psychiatric history, n (%)	255 (27.5)	62 (52.1)	<0.01
Positive smoking history, n (%)	447 (48.3)	77 (64.7)	<0.01
History of chronic pain, yes (%)	363 (39.2)	79 (66.4)	<0.01
COU prior to transplantation, yes (%)	65 (7.0)	40 (33.6)	<0.01
History of alcohol abuse, n (%)	94 (10.2)	19 (16.0)	0.05
History of illicit drug use, n (%)	100 (10.8)	26 (21.9)	<0.01
College education, n (%)	444 (48.0)	58 (48.7)	0.87
PRA ≥ 20%, n (%)	204 (22.0)	27 (22.7)	0.87
Donor characteristics			
Age, years (SD)	39.7 (13.3)	38.2 (14.6)	0.22
Gender, male (%)	486 (52.5)	65 (54.6)	0.66
Living donor, n (%)	484 (52.3)	42 (35.3)	<0.01
ECD, n (%)	113 (12.2)	24 (20.2)	0.02
DCD, n (%)	60 (6.5)	16 (13.5)	<0.01
Transplant characteristics			
CMV D+/R−, n (%)	191 (20.6)	20 (16.8)	0.33
Cold ischemia time, hours (SD)	7.7 (6.8)	9.7 (6.9)	<0.01
HLA mm, n (SD)	3.2 (1.9)	3.2 (1.9)	0.87
Initial hospital stay, days (SD)	5.2 (3.6)	7.4 (5.8)	<0.01
CNIs, CsA, n (%)	846 (91.4)	113 (95.0)	0.18
Delayed graft function, n (%)	120 (13.0)	31 (26.1)	<0.01
Induction with rATG, n (%)	215 (23.2)	38 (31.9)	0.04

COU, chronic opioid usage.

Table 2. Predictors of chronic opioid usage (COU) after transplantation

Variables	AOR	95% CI	p
COU prior to transplantation, yes	4.31	2.60, 7.16	<0.01
Positive psychiatric history, yes	2.27	1.49, 3.45	<0.01
Chronic pain prior to transplantation, yes	2.04	1.30, 3.20	<0.01
History of illicit drug use, yes	1.98	1.14, 3.43	0.01
Induction with rATG, yes	1.82	1.15, 2.88	0.01
Prior or current smoking habit, yes	1.60	1.03, 2.47	0.04
Length of initial inpatient stay, days	1.10	1.05, 1.14	<0.01

disorders (AOR 2.27; 95% CI 1.49, 3.45, p < 0.001), chronic pain before transplantation (AOR 2.04, 95% CI 1.30, 3.20, p = 0.002), illicit drug abuse (AOR 1.98, 95% CI 1.14, 3.43, p = 0.01), the use of induction therapy with rATG (AOR 1.82, 95% CI 1.15, 2.88, p = 0.01), prior or current smoking history (AOR 1.60, 95% CI 1.03, 2.47, p = 0.04), and length of initial inpatient stay (days) (AOR 1.10, 95% CI 1.05, 1.14, p < 0.001).

COU and clinical outcomes

Hospitalizations. There were 1131 hospital admissions documented during the first year among 1045 patients: 518 with no admission, 384 with 1 or 2 admissions and 143 with 3 or more admissions, respectively. There were more hospital admissions among patients with COU than patient with no COU (χ^2, p < 0.001) (Fig. 3). In fact, patients with COU were twice more likely to have 1 or 2 admissions (AOR 2.48, 95% CI 1.49, 4.13, p = 0.001) and 6 times more likely to have multiple (≥3) admissions (AOR 6.03, 95% CI 3.39, 10.75, p < 0.001) during the first year post-transplantation.

Acute rejection. There were 168 patients with biopsy-documented acute rejection during the first year. There was no significant difference in incidence of acute rejection during the first year between patients with and without COU (19.3% vs. 15.7%, χ^2, p = 0.31), as shown in Fig. 4.

Patient and graft survival. We investigated the occurrence of death and/or death-censored kidney graft failure in relation to COU. In univariate analysis, patients with COU appeared to be at an increased risk for death (HR 1.61, 95% CI 1.13, 2.32, p = 0.009) and death-censored kidney graft failure (HR 1.96, 95% 1.23, 3.10, p = 0.004). However, after adjusting for multiple baseline and demographic characteristics, as well as the

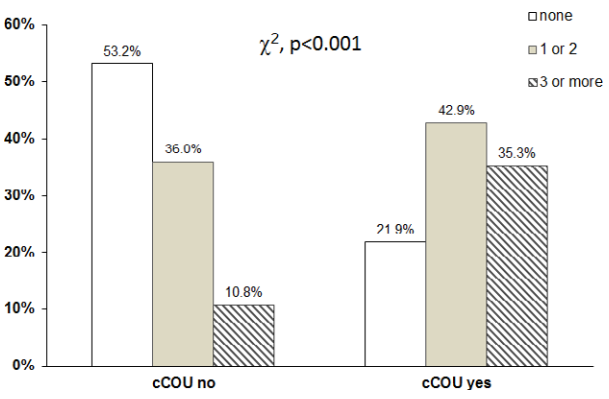

Fig. 3. Incidence of hospitalizations based on chronic opioid usage (COU) status.

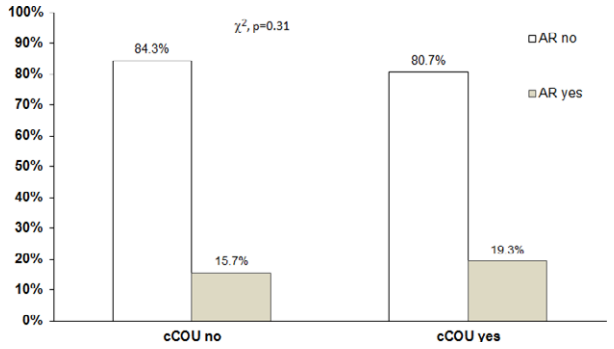

Fig. 4. Incidence of acute rejection in the first year, by chronic opioid usage status.

Table 3. Predictors of death/graft failure in first year after kidney transplant

Variables	AHR	95 % CI	p
COU after transplantation, yes	0.84	0.39, 1.81	0.66
PRA ≥ 80	3.05	1.59, 6.27	<0.01
COU prior to transplantation, yes	2.35	1.11, 4.96	0.03
Length of initial inpatient stay, days	1.05	1.01, 1.10	0.02
Private health insurance, yes	0.40	0.19, 0.83	0.01

COU, chronic opioid usage.

occurrence of acute rejection, baseline renal function and hospital admission, such association was no longer statistically significant. Results of multivariate Cox proportional hazards model for the combined outcome of death and/or graft loss are shown in Table 3. The tables 4 and 5 show the results of multivariate analysis of individual outcomes, death and death censored graft loss in the first year respectively.

Discussion

To the best of our knowledge, this is the first cohort study looking at post-transplant chronic opioid usage and its consequences in kidney transplant recipients. Our study adds to pre-existing knowledge about this issue, which has come from small cross-sectional studies that used one-time questionnaire data (4, 13). Our study showed that continued requirement for opioid prescription during the first year post-transplantation was common, observed in about 11% of patients among our cohort. Although we observed a positive association between COU and hospitalization during the first year post-transplantation, the long-term transplant outcomes and patient and death-censored kidney graft survival were similar among patients with and without COU. There was no association between COU and acute rejections in the first year.

Table 4. Multivariate analysis: predictor of death in the first year after kidney transplantation

Variable	AHR	95% CI	p
COU post-transplantation, yes	0.82	0.55, 1.24	0.35
Diabetes as cause of ESRD, yes	2.59	1.98, 3.39	<0.01
History of alcohol abuse, yes	1.82	1.29, 2.56	<0.01
COU prior to transplantation, yes	1.60	1.07, 2.39	0.02
First transplant, yes	0.49	0.33, 0.74	<0.01
Recipient age, years	1.05	1.04, 1.07	<0.01
Dialysis duration, years	1.11	1.06, 1.16	<0.01
Initial hospitalization, days	1.04	1.01, 1.07	<0.01

COU, chronic opioid usage.

Table 5. Predictor of death-censored graft loss in the first year after kidney transplantation

Parameter	AHR	95% CI	p
Continued opioid use, yes	1.39	0.85, 2.71	0.18
Race, African American	1.95	1.32, 2.89	0.001
Private insurance, yes	0.57	0.39, 0.83	0.004
first transplant, yes	0.36	0.24, 0.55	<.001
Recipient age (years)	0.97	0.96, 0.99	<0.001
Initial hospitalization duration (days)	1.04	1.00, 1.09	0.04
smoking, yes	1.64	1.14, 2.36	0.01
eGFR of allograft, mL/min	0.98	0.96, 0.99	<0.001
Acute rejection in first year, yes	1.68	1.12, 2.51	0.01

Transplant patients report pain symptoms frequently, 43% reported it during the first year in our study. Transplant recipients' pain issues seem to be inadequately addressed; in our study, only about half of the patients reporting pain were getting treated. It is plausible that many patients did not have pain severe enough to request prescription analgesics. The tendency to prescribe opioids and avoiding NSAIDs seems common in many transplant centers in the USA and would stand out in contrast to the analgesic use pattern reported in Masajtis-Zagajewska's study (13).

We were interested to find the effect of pre-transplant opioid use on future opioid use, given the notion that quality of life improves after transplantation and pain problems could resolve in some cases. Of the 105 pre-transplant opioid users, only 40 continued to be on chronic opioids after transplant. On the other hand, one-third of the post-transplant COUs had a history of COU prior to transplant. Furthermore, we found that a history of past illicit drug usage, having a psychiatric diagnosis, the presence of chronic pain, and a positive smoking history were also associated with the post-transplant COU during the first year. These suggest that patients with post-transplant COU share some similarity with regard to certain comorbidities such as chronic pain problem and psychiat-

ric history prior to transplant and social behaviors including substance abuse and smoking habit. Only two transplant-related variables predicted COU: Longer initial hospital stay after the surgery and the use of rATG as an induction agent, potential markers for more complicated early postoperative course and for high immunological risk among those patients who subsequently required chronic opioid usage.

Barrantes et al. (12), using the same study sample, have shown that chronic opioid use prior to transplantation was associated with mortality risk post-kidney transplantation. Reason cited was higher comorbidity burden in pre-transplant chronic opioid users. We had expected to see similar findings because, as shown in Table 1, prevalence of comorbidities and factors implying complicated postoperative course such as the length of initial hospital stay and the occurrence of DGF is higher among the COU group. However, multivariate analysis showed the post-transplant COU was not an independent risk factor for death after adjusting various known risk factors. This suggests that comorbidity burden is driving the higher mortality in post-transplant COU group.

We had hypothesized that COU would be a risk factor for acute rejections, and thus, possibly death-censored graft loss because medication noncompliance is reported more frequently among patients with chronic pain and opioid analgesic use (15). Our data, once again, failed to show such link.

Our analysis of hospitalization after transplantation showed an association between COU and multiple hospitalizations, but we cannot imply causality given the design of our study. Most of repeat admissions in COU group were related to surgical complications or the need for invasive procedures. Mostly the opioids were prescribed for pain associated with these procedures by the physicians. This suggests that underlying problem was the complicated clinical course rather than opioid usage. Better understanding can only be gauged by a prospective study.

We acknowledge that the ascertainment of opioid use and outcomes through chart review is an important limitation. Verification of chronic opioid use and pain problem in transplant recipients is best assessed by a prospective study, but such a study is hard to execute in absence of preliminary data from a retrospective study like ours. It is possible that we may not have captured opioid prescriptions provided by physicians outside of our health system. This would result in underestimation of true prevalence of COU in our analysis. Our data collection about hospitalizations could potentially miss the admissions that occurred at other hospitals. We also cannot report on quality of life because these data were not recorded in charts of our institution.

In conclusion, the COU is relatively common early after kidney transplantation and not associated with negative impact on patient and kidney graft survival. Thus, when clinically indicated and under close monitoring, judicious use of opioid analgesic should be provided.

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