Survival Implications of Opioid Use Before and After Liver Transplantation

Henry B. Randall,[1] Tarek Alhamad,[4] Mark A. Schnitzler,[1] Zidong Zhang,[1] Sophia Ford-Glanton,[2] David A. Axelrod,[5] Dorry L. Segev,[6] Bertram L. Kasiske,[7] Gregory P. Hess,[8,9] Hui Yuan,[3] Rosemary Ouseph,[1] and Krista L. Lentine[1]

[1]Center for Abdominal Transplantation, [2]Department of Surgery and [3]Department of Anesthesia, Saint Louis University School of Medicine, St. Louis, MO; [4]Transplant Nephrology, Washington University School of Medicine, St. Louis, MO; [5]Division of Abdominal Transplantation, Department of Surgery, Brody School of Medicine, Greenville, NC; [6]Division of Transplantation, Department of Surgery, Johns Hopkins School of Medicine, Baltimore, MD; [7]Division of Nephrology, Hennepin County Medical Center, Minneapolis, MN; [8]Symphony Health, Pittsburgh, PA; and [9]Leonard Davis Institute for Health Economics, University of Pennsylvania, Philadelphia, PA

Implications of prescription opioid use for outcomes after liver transplantation (LT) have not been described. We integrated national transplant registry data with records from a large pharmaceutical claims clearinghouse (2008-2014; n = 29,673). Opioid fills on the waiting list were normalized to morphine equivalents (MEs), and exposure was categorized as follows: > 0-2 ME/day (level 1), > 2-10 ME/day (level 2), > 10-70 ME/day (level 3), and >70 ME/day (level 4). Associations (adjusted hazard ratio [aHR], $_{95\%\ LCL}$ aHR $_{95\%\ UCL}$) of pretransplant ME level with patient and graft survival over 5 years after transplant were quantified by multivariate Cox regression including adjustment for recipient, donor, and transplant factors, as well as propensity adjustment for opioid use. Overall, 9.3% of recipients filled opioids on the waiting list. Compared with no use, level 3 (aHR $_{1.06}1.28_{1.55}$) and 4 (aHR $_{1.16}1.52_{1.98}$) opioid use during listing were associated with increased mortality over 5 years after transplant. These associations were driven by risk after the first transplant anniversary, such that mortality >1-5 years increased in a graded manner with higher use on the waiting list (level 2, aHR, $_{1.00}1.27_{1.62}$; level 3, aHR, $_{1.08}1.38_{1.77}$; level 4, aHR, $_{1.49}2.01_{2.72}$). Similar patterns occurred for graft failure. Of recipients with the highest level of opioids on the waiting list, 65% had level 3 or 4 use in the first year after transplant, including 55% with use at these levels from day 90-365 after transplant. Opioid use in the first year after transplant also bore graded associations with subsequent death and graft loss >1-5 years after transplant. Opioid use history may be relevant in assessing and providing care to LT candidates.

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Liver transplantation (LT) candidates undergo evaluation of the severity and complications of liver disease, comorbid conditions, overall fitness, and psychosocial status. The intent is to select candidates with acceptable anticipated risks of perioperative and longer-term complications who are expected to benefit from transplant. Pharmaceutical care as indicated by the medication list is often reviewed to identify health problems, assess special care such as anticoagulation, and identify possible drug interactions that might occur after transplant. Use of pharmaceutical care information to assess the severity of comorbid conditions and inform expectations for clinical outcomes after LT has not been well established. The current US transplant registry does not include measures of pharmaceutical care. Thus, novel approaches to supplement the registry, such as integrated measures of pharmaceutical care, are needed to advance understanding of the relationships of comorbid conditions and pharmaceutical care with posttransplant outcomes.[1-4]

Abbreviations: ACGF, all-cause graft failure; aHR, adjusted hazard ratio; COPD, chronic obstructive pulmonary disease; ESLD, end-stage liver disease; HRSA, Health Resources and Services Administration; LCL, lower confidence limit; LT, liver transplantation; ME, morphine equivalent; MELD, Model for End-Stage Liver Disease; OPTN, Organ Procurement and Transplantation Network; SHS, Symphony Health Solutions; SRTR, Scientific Registry of Transplant Recipients; UCL, upper confidence limit.

Address reprint requests to Krista L. Lentine, M.D., Ph.D., Center for Abdominal Transplantation, Saint Louis University School of Medicine, 1402 South Grand Boulevard, St. Louis, MO, 63104. Telephone: 314-577-8765; E-mail: lentinek@slu.edu

Opioid analgesics serve an important role in management of both acute and chronic pain, but heightened awareness of an "epidemic" of complications related to the misuse, abuse, and inherent potential toxicity of prescription opioids is a timely topic.[5-8] Concerns about opioid-related toxicity are even greater with regard to patients with end-stage organ failure due to altered drug protein binding, metabolism, and excretion, leading to accumulation of parent agents and potentially toxic metabolites.[9,10] We recently linked the national transplant registry with pharmacy fill records and found that prescription opioid fills before kidney transplant were associated with increased risk of complications after the transplant procedure.[2,11]

Patients with end-stage liver failure present with pain due to multiple comorbid conditions and may be prescribed opioids to assist with pain control. To advance understanding of the frequency and outcomes implications of prescription opioid use in LT candidates, we examined a novel database that integrates national transplant registry data with pharmacy fill records. Our goals were to quantify fills for prescription opioids on the waiting list, identify correlates of opioid use, and determine whether prescription opioid exposure before and after transplant is associated with posttransplant outcomes.

This work was conducted under the auspices of the Minneapolis Medical Research Foundation, contractor for the Scientific Registry of Transplant Recipients (SRTR), as a deliverable under contract no. HHSH250201000018C (US Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation). As a US government-sponsored work, there are no restrictions on its use. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the US government. The opinions, results, and conclusions reported in this article are those of the authors and are independent of the funding sources.

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Patients and Methods

DATA SOURCES

We conducted a retrospective cohort study using linked health care databases in the United States to ascertain patient characteristics, pharmacy fill records, and outcome events for LT recipients. This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services, provides oversight of the activities of the OPTN and SRTR contractors. Baseline demographic information ascertained for LT recipients from OPTN included age, sex, and race as reported by the transplant centers.

Pharmacy fill data were assembled by linking SRTR records for LT recipients with billing claims from Symphony Health Solutions (SHS), a large US pharmaceutical claims data warehouse that collects prescription drug fill records including self-paid fills and those reimbursed by private and public payers. SHS aggregates National Council for Prescription Drug Program format prescription claims from multiple sources including claims warehouses, retail pharmacies, and prescription benefit managers for approximately 60% of US retail pharmacy transactions. Individual claim records include the pharmacy fill date with the National Drug Code identifying agent and dosage. After institutional review board and HRSA approvals, SHS records were linked with SRTR records for LT recipients. 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 employs 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. This study was approved by the Saint Louis University institutional review board.

POPULATION, COVARIATES, AND OUTCOMES

LT recipients who were eligible for the study had SRTR records of LT, underwent transplant between 2007 and 2014, and had available pharmaceutical fill records while on the transplant waiting list. Pharmacy fills for opioids while on the waiting list were normalized to morphine equivalents (MEs) according to the conversion ratios in Supporting Table 1. ME based on pharmacy fills during listing were aggregated for each transplant recipient and expressed as ME per day of listing. Opioid users were categorized according to level of opioid use as follows: level 1, > 0-2 ME/day; level 2, > 2-10 ME/day; level 3, > 10-70 ME/day; and level 4, > 70 ME/day. Recipient clinical and demographic characteristics, and characteristics of the donated organ and other transplant factors, were defined by the OPTN Transplant Candidate and Recipient Registration forms (Table 1). The primary outcomes were all-cause mortality and graft failure after transplant.

STATISTICAL ANALYSES

Data sets were merged and analyzed with SAS, version 9.4 (SAS Institute Inc., Cary, NC). Distributions of clinical and demographic traits among recipients with each level of opioid exposure on the waiting list versus no opioid use were compared by the χ^2 test.

The log-rank test was used to assess the statistical significance of differences in unadjusted incidence of all-cause graft failure (ACGF) and patient death across opioid use levels over 5 years after transplant. At-risk time for all models was censored at study end (January 31, 2015). Adjusted associations of ME exposure on the waiting list with posttransplant graft failure and death (adjusted hazard ratio [aHR], $_{95\%\ LCL}$ aHR $_{95\%\ UCL}$) were quantified by multivariate Cox regression including adjustment for recipient, donor, and transplant clinical factors. Outcome models were also stratified by quintile of propensity for opioid use to control for confounding by indication, as previously described.[2,11] Primary analyses considered risk from transplant to 5 years after transplant. Because mortality is highest in the first year after transplant and likely has drivers other than risk after the first anniversary, we also examined risk partitioned in the early (0-1 year) and later (>1-5 years) posttransplant periods. In secondary analyses, we examined associations of opioid use in the first year, and from day 90 to 365 (to exclude perioperative fills) on subsequent mortality and graft loss >1-5 years after transplant.

Results

SAMPLE CHARACTERISTICS AND CORRELATES OF PRETRANSPLANT OPIOID USE

Between 2007 and 2014, 46,547 adult recipients of liver-only transplants were recorded in the SRTR database. Of these, 29,673 had linked pharmacy claims covering their time on the transplant waiting list. Mean and median durations of time from listing to transplant were 75 and 174 days, respectively. Overall, 9.3% of the eligible study sample filled opioids while on the waiting list, including 1039 with level 1, 787 with level 2, 689 with level 3, and 233 with level 4 exposure, respectively. Distributions of clinical traits according to opioid use level on the waiting list are shown in Table 1. Compared with transplant recipients who did not use opioids on the waiting list, those with level 4 use were more likely to be aged 46-60 years, to be male and of white race, to have hepatocellular carcinoma and hepatitis C as etiology for liver failure, and to have received a previous transplant. Recipients with level 4 use on the waiting list were more likely to not be working, to not have private insurance, to have a low Model for End-Stage Liver Disease (MELD) score (6-9, 10-14, and 15-19), and to have undergone transplant in the later period of the study (2011-2014).

PATIENT AND GRAFT SURVIVAL ACCORDING TO LEVEL OF OPIOID USE ON THE WAITING LIST (PRETRANSPLANT)

Over 5 years after transplant, unadjusted patient death was higher ($P < 0.05$) for patients with level 3 (30%) and level 4 (43%) of opioid use on the waiting list compared with nonusers (22%; Fig. 1A). Similarly, unadjusted graft failure was higher ($P < 0.05$) over 5 years for patients with level 3 (31%) and level 4 (45%) of opioid use compared with nonusers (23%; Fig. 1B). After multivariate adjustment for recipient, donor, and transplant factors, and propensity adjustment for the likelihood of opioid use (Supporting Table 2), recipients at level 3 of opioid use during listing had a higher risk of death (aHR, $_{1.06}1.28_{1.55}$) compared with nonusers over 5 years after transplant, and a near-significant trend toward higher all-cause graft loss (aHR,

TABLE 1. Distributions of Clinical Traits in the Study Sample According to Opioid Use Level on the Waiting List

Characteristics	No Use	Opioid Use on Waiting List: Level 1 (>0-2 ME/day)	Level 2 (>2-10 ME/day)	Level 3 (>10-70 ME/day)	Level 4 (>70 ME/day)
Recipient factors					
Age, years		*	†	*	†
18-30	4.1	3.8	4.8	2.9	4.7
31-45	11.6	9.1	9.8	11.0	9.4
46-60	55.4	53.1	60.0	63.1	66.1
>60	29.0	34.1	25.4	22.9	19.7
Male	66.4	67.1	71.7†	69.8	79.0*
Race			*	*	*
White	72.1	72.3	77.4	83.5	84.1
Black	10.4	10.0	10.3	7.0	8.6
Hispanic	12.5	13.0	9.4	8.0	5.2
Other race	5.1	4.7	2.9	1.6	2.2
ABO blood type		*			
A	36.7	39.2	39.1	37.9	38.6
AB	5.1	2.6	4.6	4.5	6.9
B	13.9	11.7	13.7	12.1	11.6
O	44.3	46.5	42.6	45.6	42.9
Body mass index, kg/m^2					
<18.5	2.1	1.4	2.0	1.9	1.3
18.5-24.9	28.3	29.8	26.1	31.8	29.6
25-30	33.6	35.5	35.7	32.8	34.8
>30	34.3	31.9	34.7	32.5	33.5
Unknown	1.7	1.4	1.5	1.0	0.9
Education		†	*		
Grade/high school	44.0	44.5	47.9	46.2	46.8
College and higher	45.5	47.6	46.5	45.3	45.5
Unknown	10.5	8.0	5.6	8.6	7.7
Employment status		†		†	†
Working	15.4	18.5	15.1	10.9	9.9
Not working	80.1	77.7	80.8	84.3	83.7
Unknown	4.6	3.9	4.1	4.8	6.4
Cause of ESLD		*	*	*	*
Hepatocellular carcinoma	22.5	31.2	34.8	30.6	35.2
Hepatitis C	25.5	31.4	28.2	32.4	37.8
Hepatits B	1.8	0.6	0.6	0.4	0.0
Alcoholic	13.7	8.4	7.6	9.1	5.6
Metabolic	2.5	1.2	1.1	1.7	1.3
Other	33.9	27.3	27.6	25.7	20.2
Comorbidities					
Diabetes	25.6	29.4†	24.8	22.4	24.0
Hypertension	22.2	23.5	22.2	22.6	22.8
Cerebrovascular diseases	0.8	0.8	1.1	0.3	1.2
Peripheral vascular diseases	0.7	1.2	0.5	0.7	0.4
COPD	2.0	1.7	2.5	2.8	3.0
Coronary artery disease/angina	2.3	1.7	1.7	2.3	2.6
Calculated MELD at transplant		*	*	*	*
0-9	12.5	18.0	18.7	18.1	27.0
10-14	18.5	25.0	24.1	25.0	20.2
15-19	23.2	27.2	25.8	24.1	27.9
20-24	19.8	16.9	16.4	17.9	12.9
25-29	13.7	6.8	8.4	8.7	8.6
30-34	8.7	4.5	4.7	4.8	3.0
35-39	2.9	0.9	1.8	1.3	0.4
≥40	0.8	0.6	0.1	0.2	0.0
Primary payer at transplant		†	†	*	†
Public	40.5	44.4	44.9	48.8	51.5
Private	58.7	55.0	54.8	50.9	48.1
Other payer	0.8	0.7	0.4	0.3	0.4

TABLE 1. *Continued*

Characteristics	No Use	Opioid Use on Waiting List: Level 1 (>0-2 ME/day)	Level 2 (>2-10 ME/day)	Level 3 (>10-70 ME/day)	Level 4 (>70 ME/day)
Transplant and donor factors					
Donor risk index					
1.5-2.0	1.0	1.0	1.7	0.7	1.3
2.0-2.5	2.4	2.2	2.4	3.5	4.7
≥2.5	2.5	3.1	2.3	2.3	2.2
Unknown	94.1	93.7	93.7	93.5	91.9
Previous transplant	6.5	4.0*	5.7	7.4	9.9†
Living donor	3.3	3.4	3.7	4.1	3.9
Transplant year		*	*	*	†
2007-2010	41.2	17.1	24.9	25.4	33.9
2011-2014	58.8	82.9	75.1	74.6	66.1

NOTE: Data are given in column percentages. Total >100% or 99.9% reflect rounding.
*$P < 0.001$.
†$P < 0.05$-0.001.

$_{0.99}1.19_{1.42}$). Recipients at level 4 of pretransplant opioid use had a higher risk of death (aHR, $_{1.16}1.52_{1.98}$) and all-cause graft loss (aHR, $_{1.10}1.42_{1.84}$) compared with nonusers over 5 years (Fig. 2). Death-censored graft loss was uncommon (3.81% by 5 years) and was not associated with opioid exposure.

Considered by risk period, mortality and graft loss over the first year after transplant did not differ significantly according to level of opioid use during listing (Fig. 2A). However, in longer-term follow-up, recipients with level 2, level 3, and level 4 of opioid use during listing had 27% (aHR, $_{1.00}1.27_{1.62}$), 38% (aHR, $_{1.08}1.38_{1.77}$), and 101% (aHR, $_{1.49}2.01_{2.72}$) increased relative hazards of posttransplant death, respectively, compared with nonusers. The risk of ACGF had similar associations with opioid use on the waiting list. Specifically, recipients at level 2, level 3, and level 4 of opioid use on the waiting list had 34% (aHR, $_{1.06}1.34_{1.68}$), 37% (aHR, $_{1.07}1.37_{1.75}$), and 105% (aHR, $_{1.52}2.05_{2.76}$) increased relative hazards of all-cause graft loss compared with nonusers over >1-5 years posttransplant (Fig. 2B). Other risk factors for recipient death and graft failure in the first year after transplant included older age, black race, high body mass index, higher MELD score, nonworking status, comorbid conditions (diabetes and chronic obstructive pulmonary disease [COPD]), end-stage liver disease (ESLD) due to hepatocellular carcinoma or hepatitis C, previous transplant, and undergoing transplant between 2007 and 2010 (Supporting Table 3). Other risk factors associated with patient death and graft failure over longer-term follow-up included age older than 60 years, black race, low body mass index at transplant, comorbid conditions (diabetes, coronary artery disease, and COPD), retransplant status, nonworking and public payer insurance, and undergoing transplant between 2007 and 2010 (Supporting Table 4).

OPIOID USE PATTERNS BEFORE AND AFTER TRANSPLANT

We examined a subgroup of recipients with identified pharmacy claims extending from start of listing to 1 year after transplant (n = 27,973) to characterize the persistence of pretransplant opioid use patterns after transplant (Fig. 3). A graded pattern of posttransplant opioid use was noted based on use on the waiting list. Recipients at level 4 of opioid use during listing continued to use large amounts of opioids in the first year after LT; 33% were at level 4 of use and 32% were at level 3 of use after transplant. Overall, level of opioid use increased after transplant, likely affected by requirements for pain medication after major surgery. Among recipients at level 1 of opioid use prelisting, 39% increased their use to levels 2, 3, and 4 after transplant. In a similar trend, 26% of recipients at level 2 of prelisting opioid use increased their use to levels 3 and 4 after transplant (Fig. 3A). To exclude early fills for the management of postoperative pain after discharge from the transplant surgery, we also examined patterns of opioid use from day 90 to 365 after transplant. Similarly, a graded pattern of posttransplant opioid use after the perioperative period was noted based on opioid use during listing. Fifty-five percent of patients with level 4 opioid use during listing had level 3 or 4 opioid use from 90 to 365 days after transplant. Only

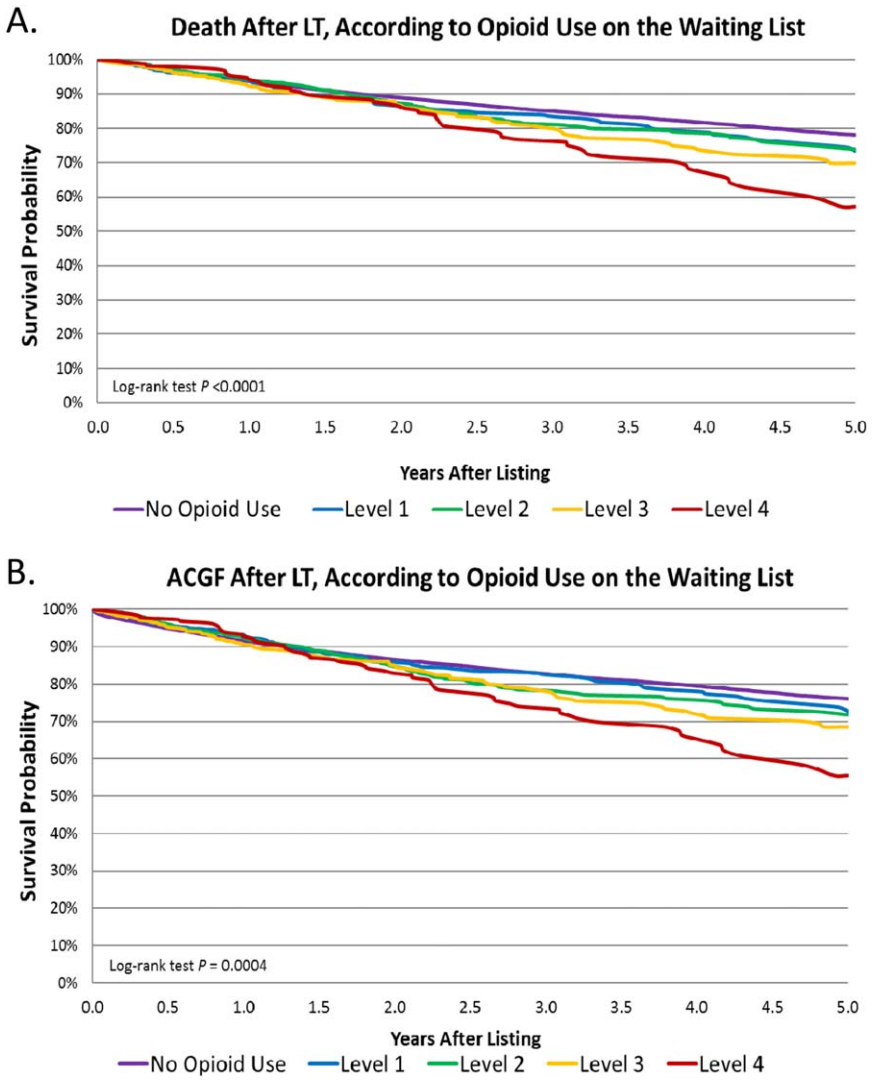

FIG. 1. Death and graft failure after LT according to prescription opioid use on the waiting list. Level 1, > 0-2 ME/day; level 2, > 2-10 ME/day; level 3, > 10-70 ME/day; and level 4, > 70 ME/day.

10% of nonusers during listing had level 3 or 4 opioid use between 90 and 365 days (Fig. 3B).

PATIENT AND GRAFT SURVIVAL ACCORDING TO OPIOID USE AFTER LT

Level 2 or higher opioid use in the first year after transplant was associated with a 40%-50% higher risk of death and graft failure over >1-5 years after transplant. Specifically, recipients with level 2, level 3, and level 4 opioid use in the first year after transplant had 42% (aHR $_{1.28}1.42_{1.58}$), 39% (aHR $_{1.21}1.39_{1.59}$), and 53% (aHR $_{1.33}1.53_{1.75}$) increased risk of death compared with nonusers over >1-5 years after transplant. Similarly, recipients with level 2, level 3, and level 4 opioid use in the first year after transplant had 44% (aHR $_{1.29}1.44_{1.60}$), 42% (aHR $_{1.24}1.42_{1.63}$), and 55% (aHR $_{1.35}1.55_{1.78}$) increased risk of graft failure >1-5 years after transplant (Fig. 4A). Risk relationships were stronger when posttransplant opioid use was considered from day 90 to 365 after transplant, such that level 4 use in this period was associated with twice the risk of subsequent death (aHR $_{1.72}2.00_{2.32}$) and graft failure (aHR $_{1.73}2.01_{2.33}$), respectively (Fig. 4B).

Discussion

The global burden of opioid-related health problems, disabilities, and premature death has been estimated to approach 11 million life-years lost.[8] The United States and Canada are 2 of the highest prescription

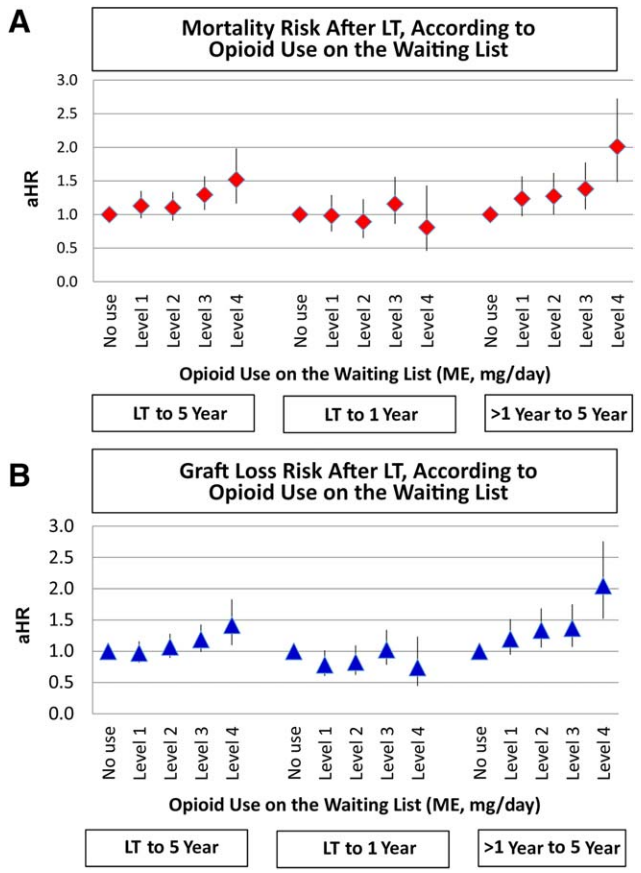

FIG. 2. Adjusted associations of opioid use on the waiting list with posttransplant death and graft failure. Level 1, > 0-2 ME/day; level 2, > 2-10 ME/day; level 3, > 10-70 ME/day; and level 4, > 70 ME/day.

opioid consumers in the world,[5,12,13] and recent estimates demonstrate a 300% increase in US opioid prescriptions from 1999 to 2010.[14] In 2014 alone, US retail pharmacies dispended 245 million prescriptions for opioids.[15] Patients with ESLD have an increased burden of conditions associated with chronic pain but are also at high risk for opioid-related complications due to impaired drug metabolism. In the context of the prescription opioid epidemic, little is known about the impact of opioid use on outcomes after LT. We examined a unique linkage of national transplant registry data with outpatient pharmacy fill records from a pharmaceutical claims clearinghouse to characterize the frequency of prescription opioid use among patients awaiting LT and to determine whether exposure on the waiting list predicted posttransplant outcomes. During the 5-year follow-up period, we found that recipients with the highest levels of opioid use on the waiting list had 20%-50% higher adjusted risks of death and graft loss than nonusers. These associations were driven by risk after the first transplant anniversary, such that while opioid use during listing was not associated with first-year outcomes, mortality and graft loss >1-5 years increased in a graded manner with higher use on the waiting list, with the highest level of use associated with twice the risk of these adverse outcomes.

The lack of associations of opioid use during listing with early posttransplant outcomes might be related to the higher rates of mortality and surgical complications in the first year after LT, which may mask the effect of opioids over short-term follow-up. In addition, the longer-term effects of pretransplant opioid use may be in part driven by patterns of sustained opioid use after transplant. Sixty-five percent of recipients at the highest level of opioid use during listing filled at level 3 or level 4 over the first year after transplant, including 55% with use at these levels from day 90 to 365 after transplant. Data on patterns of prescription opioid use after LT are lacking, but a previous meta-analysis examining the use of illicit drugs after transplant (mainly LT) found that 4 out of 100 former substance users relapsed their illicit drug use during a year of follow-up.[16] In the current study, opioid use in the first year after transplant had prognostic implications, bearing graded associations with subsequent death and graft loss >1-5 years after transplant. High-level use beyond the perioperative period (from day 90 to 365) was associated with twice the risk of subsequent death and graft loss.

Regarding correlates of opioid use before transplant, we found that LT recipients at the highest level of prelisting opioid use were less likely to be working and less likely to have private insurance compared with nonusers. A previous study showed that in the general population, high-level opioid users were more likely to have lower education and lower income, and more likely to receive disability pensions compared with short-term opioid users;[17] we observed similar patterns among kidney transplant recipients.[2,11] Such groups warrant focused attention regarding prescription opioid use patterns before and after organ transplant.

With the growing use of prescription opioids, a definition of opioid use disorder was recently established in the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association to increase health care provider awareness about opioid misuse. Opioid use disorder is defined as a repeated

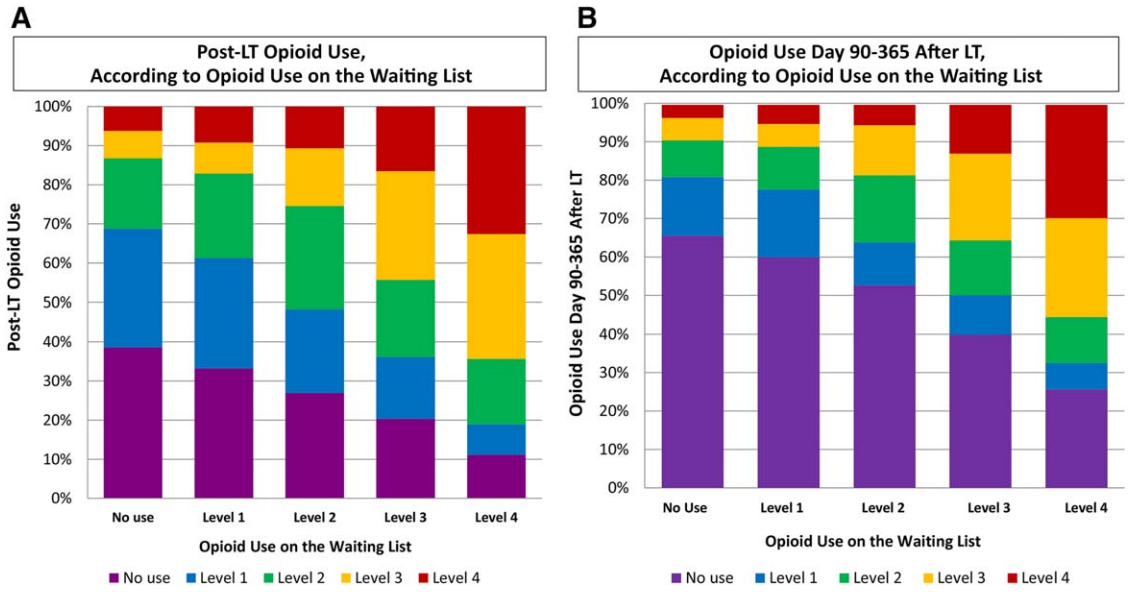

FIG. 3. (A) Opioid use in the first year after LT according to opioid use on the waiting list. Level 1, > 0-2 ME/day; level 2, > 2-10 ME/day; level 3, > 10-70 ME/day; and level 4, > 70 ME/day. (B) Opioid use day 90-365 after LT, according to opioid use on the waiting list.

occurrence within a 12-month period of 2 or more of 11 problems, including withdrawal symptoms, use in increased amounts or longer than intended, need for increased doses for effects, continued use despite resulting conditions, strong desire or urge to use, and excessive time spent using opioids.[18,19] Although we were not able to define opioid use disorder, we were able to show a strong association of pretransplant opioid use with persistent high-level use after LT, indicating that transplant may not resolve requirements for pain medication in patients with end-stage liver failure. Furthermore, we found that opioid use in the first year after transplant was associated with 40%-50% higher risk of subsequent death and graft loss, and that risk relationships were stronger when posttransplant opioid use was considered after the perioperative period (from day 90 to 365 after transplant).

To the best of our knowledge, ours is the first study to describe an association between opioid use before and after transplant with outcomes after LT. We previously reported that pretransplant prescription opioid use before kidney transplant was associated with increased risks of posttransplant death and graft loss.[2] 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, and living kidney donation.[2,11,20-22] The current work extends these associations to identify prognostic implications of prescription opioid use prior to LT. Factors typically examined during evaluation for LT include cardiovascular and pulmonary disorders, extrahepatic malignancy, renal failure, active alcohol or drug use, and nutritional and psychosocial status. Our results support adding examination of pharmaceutical care history including prescription opioid use to better assess potential risk after transplant.

Given the potential adverse effects of opioids,[23-26] a pathophysiological connection with mortality is plausible, although contributions from unmeasured comorbidity and compliance/behavior are also possible. Potential adverse effects of opioid analgesics include central nervous system depression, respiratory depression, constipation, urinary retention, tolerance, physical dependence, and less commonly, cardiac arrhythmias, hepatotoxicity, nephrotoxicity, and even death.[23-26] Aberrant behaviors including drug-seeking and diversion may also correlate with both opioid analgesics use and poor clinical outcomes.[27] We recently found that opioid use before kidney transplant was associated with increased risk of an array of complications after kidney transplant, including ventricular arrhythmias, cardiac arrest, hypotension, hypercapnia,

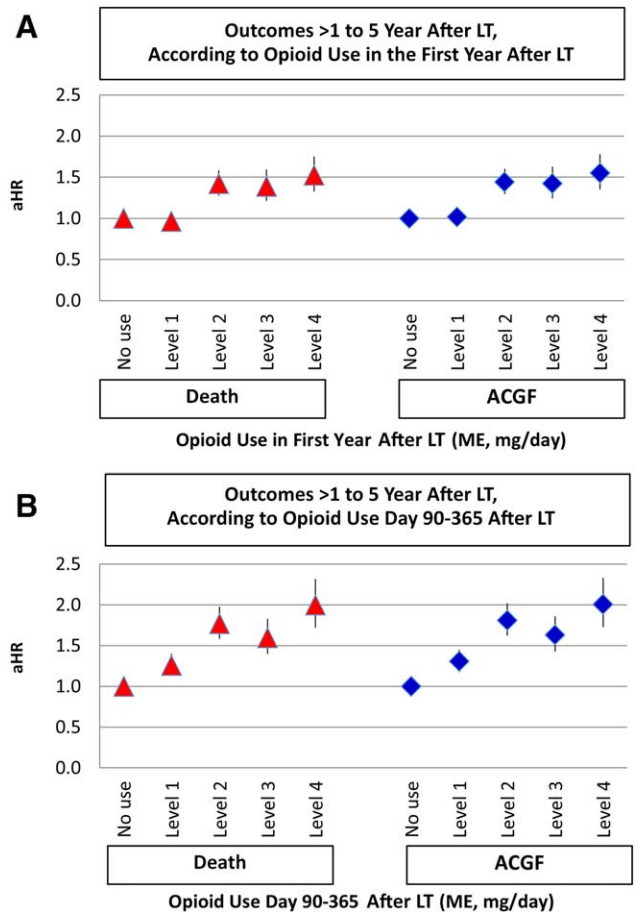

FIG. 4. Adjusted associations of opioid use in the first year after transplant with posttransplant death and graft failure over 2-5 years after LT. Level 1, > 0-2 ME/day; level 2, > 2-10 ME/day; level 3, > 10-70 ME/day; and level 4, > 70 ME/day.

mental status changes, drug abuse/dependence, alcohol abuse, accidents, and noncompliance.[11] Regardless of the mechanisms of association, identification of novel markers of posttransplant outcomes is a timely concern to help transplant programs better assess and manage risk at a programmatic level. Transplantation in the United States is an increasingly regulated field with a high level of public reporting. Centers are graded for recipient and graft survival using risk-adjusted equations developed by SRTR to predict expected 1-year and 3-year posttransplant patient and graft survival.[28] Importantly, the SRTR equations do not adjust for chronic pain or pretransplant opioid use as risk factors for posttransplant death or graft failure. Thus, centers performing transplants in patients who require opioid analgesics before transplant should be aware of unidentified risk that will not be recognized by SRTR, and in addition to attempting to modify opioid dependence before transplant, should consider extra monitoring and focused posttransplant care.

Our study has limitations. First, its retrospective design can identify associations but not prove causation. Second, the available data do not include some relevant clinical information to identify opioid use disorder. We could not examine illegal drug use or alcohol drinking habits to determine any associations with opioid use in LT recipients. Our pharmacy claims data included ~60% of US retail pharmacies, and so our results may not generalize to the full population of US LT recipients. Electronic pharmacy claims, our 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.[29-32] However, we were unable to account for illicit drug use or "pharmacy shopping" behaviors, possibly underestimating true drug exposure. We were also not able to identify markers of physical dependence or addiction. Despite these important caveats and limitations, this work is of value in demonstrating that supplementing national transplant registry data with pharmacy claims may identify novel risk markers for adverse events after transplant.

In summary, although associations may in part reflect underlying conditions, the need for high levels of opioids before and after LT is a marker for increased risk of posttransplant complications, especially over longer-term follow-up. Our study informs transplant teams that many patients receiving opioids prior to transplant will continue to use or increase their use after LT. Further work should seek to identify underlying mechanisms, assess the impact of decreasing opioid use before transplant, and determine management approaches to improving patient outcomes. For now, these data suggest that transplant candidates who require high levels of opioids warrant careful evaluation of pain management strategies, perhaps by a multidisciplinary team including a pain management specialist, as well as focused monitoring of clinical status after transplant.

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