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Survival implications of prescription opioid and benzodiazepine use in lung transplant recipients: Analysis of linked transplant registry and pharmacy fill records

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KEYWORDS:
lung transplant;
benzodiazepines;
opioids;
mortality;
pharmacy fills

BACKGROUND: Prescription opioid and benzodiazepine use have been associated with morbidity and mortality among some groups of solid organ transplant recipients, but implications for outcomes among lung transplant patients are not well described.

METHODS: We conducted a retrospective cohort study using linked national transplant registry and pharmaceutical records to characterize the associations between benzodiazepine and opioid prescription fills in the years before and after lung transplant (2006-2017), with risk-adjusted posttransplant survival (adjusted hazard ratio, $_{LCL}aHR_{UCL}$).

RESULTS: Among 11,568 recipients, 33.7% filled an opioid prescription, and 25.8% filled a benzodiazepine prescription before transplant. Compared to patients without prescriptions, those who filled both short- and long-acting benzodiazepine prescriptions before transplant had 2-fold higher mortality in the first year posttransplant (aHR, $_{1.39}2.12_{3.21}$), after adjustment for baseline factors and opioid fills, while pretransplant opioid fills were not associated with posttransplant mortality after adjustment for benzodiazepine fills. Pretransplant opioid and benzodiazepine use strongly predicted more use after transplant. Fills of both short- and long-acting benzodiazepines in the first year posttransplant were

Abbreviations: aHR, adjusted hazard ratio; ECMO, extracorporeal membrane oxygenation; FEV1, forced expiratory volume; HR, hazard ratio; HRSA, Health Resources and Services Administration; IRB, Institutional Review Board; LAS, Lung Allocation Score; MEs, morphine equivalents; OPTN, Organ Procurement and Transplantation Network; SRTR, Scientific Registry of Transplant Recipients

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associated with 77% increased mortality >1-to-2 years posttransplant (aHR, $_{1.06}1.77_{2.96}$). Compared with no posttransplant opioid fills, there was a dose-dependent association between first-year opioid fills and subsequent adjusted mortality risk (level 2: aHR, $_{1.17}1.50_{1.92}$ to level 4: aHR, $_{1.56}2.01_{2.59}$). These effects were independent, and interactions were not detected.

CONCLUSIONS: Benzodiazepine prescription fills before and after lung transplant, and opioid fills after transplant, are independently associated with posttransplant mortality. Review of benzodiazepine and opioid use history is relevant to risk-stratifying patients before and after lung transplant.

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Opioid prescriptions for relief of acute and chronic pain are complicated by addiction, overdose, and mortality.[1-3] Benzodiazepine use may exacerbate the risk of adverse outcomes due to depressant effects on the central nervous system. Among Medicare recipients, concurrent use of benzodiazepines and opioids was associated with 5 times the risk of opioid-related overdoses as opioid use alone.[4] Concurrent opioid and benzodiazepine use also increases the rate of emergency department visits and hospitalizations for overdoses and mortality.[4-6] Consequently, the 2016 US Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain recommends that clinicians avoid coprescribing benzodiazepines and opioids whenever possible.[7]

Lung transplant recipients may be particularly vulnerable to complications of prescription opioids and benzodiazepines. Long-term opioid use increases respiratory and cardiovascular risks in patients with advanced pulmonary disease.[8,9] However, because prescription opioids are a recommended therapy for end-stage dyspnea, lung transplant candidates may receive these agents for symptom management.[10-13] Benzodiazepines may also be prescribed to manage anxiety related to chronic disease and dyspnea.[14] In a cohort of 425 lung transplant candidates, Vahidy et al[15] identified opioid use in 14% at listing. However, pretransplant opioid use did not correlate with the risk of death or retransplant over 10 years of follow-up at this center.[15] Conversely, in a single-center study of 21 lung transplant patients, posttransplant opioid use was associated with decreased forced expiratory volume (FEV1) and increased mortality over 4 years.[16]

Of importance, lung transplant recipients with histories of long-term opioid and benzodiazepine use may experience difficulty weaning from mechanical ventilation or have higher rates of other complications, such as delirium, ileus, and infections.[17] These patients may also require higher doses of sedation for ambulatory procedures (eg, posttransplant bronchoscopies), increasing the risk of complications. However, uncertainty of clinical outcomes in patients with pretransplant opioid and benzodiazepine use has prevented development of clinical practice standards. In a survey of 34 US lung transplant programs, only 33% had written policies regarding opioid use, and respondents expressed strong interest in a national consensus on opioid use in this population.[18]

In the current study, we linked US transplant registry data with pharmaceutical fill records to examine the impact of opioid and benzodiazepine use on lung transplant patient survival. We sought to quantify medication exposure before and after transplant, characterize utilization patterns, and assess the relationships of pre- and posttransplant opioid and benzodiazepine use with posttransplant mortality.

Methods

Ethics and data sources

This study was approved by the Saint Louis University Institutional Review Board (IRB protocol #23190). The study followed international standards for ethics in human research, including the Declaration of Helsinki, guidelines of the World Health Organization, and the International Society of Heart and Lung Transplantation Ethics Statement.

We linked data from the Scientific Registry of Transplant Recipients (SRTR) on lung transplant recipients and their outcomes to pharmacy prescription fill records. The SRTR system includes data on all donors, waitlist 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, oversees the activities of OPTN and SRTR contractors.

Pharmacy fill records were assembled by linking SRTR records for lung transplant recipients with billing claims from Symphony Health Solutions, a large US pharmaceutical claims data warehouse that maintains prescription drug fill records, including self-paid fills and those reimbursed by private and public payers. The fill records comprise National Council for Prescription Drug Program format prescription claims aggregated from multiple sources, including claims warehouses, retail pharmacies, and prescription benefit managers for approximately 60% of US retail pharmacy transactions. Individual claim records include the date of a given pharmacy fill with the national drug code identifying agent and dosage. After IRB and HRSA approvals, we linked pharmacy fill data with SRTR records for lung transplant recipients. We applied a deterministic deidentification strategy in which patient identifiers were transformed before delivery to the Saint Louis University researchers with Health Information Portability and Accountability Act and high-tech certified encryption technology. The patient deidentification software employs multiple encryption algorithms in succession to guarantee that the resulting "token," which contains encrypted patient identifiers, can never be decrypted. However, the algorithm yields the same results for a given set of data elements, enabling linkages by unique anonymous tokens. We removed all direct identifiers before the final dataset was available for analysis.

Because of the large sample size, the necessity for anonymity of the patients studied, and the nonintrusive nature of the research, a waiver of informed consent was granted per the Department of

Health and Human Services Code of Federal Regulations (Title 45, Part 46, Paragraph 46.116).

Population and measures

We enrolled all patients who underwent lung transplant between 2006 and 2017 with 1 year of linked pre- and/or posttransplant pharmacy prescription fill records. We ascertained patient, donor, and transplant clinical and demographic characteristics from the OPTN Transplant Candidate Registration and Transplant Recipient Registration forms (Table 1). Cause of end-stage lung disease was categorized according the diagnosis groups (A, B, C, and D) defined in OPTN allocation policy.[19,20]

We queried outpatient pharmacy fills for opioids and benzodiazepines in the year before lung transplant to define pretransplant exposure. Separately, we quantified posttransplant use through the first anniversary, excluding early postsurgical fills in the first 90 days after transplant, as previously described.[21-23] Opioid prescription fills were normalized to morphine equivalents (MEs), according to established conversion ratios (Table S1),[24,25] as previously described.[23,26,27] We aggregated pre- and posttransplant MEs separately within each period for each recipient, expressed as dose (mg) of ME exposure over the year. We categorized annual ME exposure as follows: level 1, >0 to 200 mg; level 2, >200 to 600 mg; level 3, >600 to 2,700 mg; level 4, >2,700 mg, to rank by approximate quartiles of use, similar to previous methods.[21-23,26,28] We categorized benzodiazepine prescription fills as either short- or long-acting according to their elimination half-life, as per previous methods.[6]

The primary outcome was all-cause mortality, as reported by transplant programs to OPTN, and supplemented with the Social Security Death Master File. Graft loss, as reported by programs to the OPTN, was a secondary endpoint. Patients were followed until the end of the study period (June 1, 2018).

Statistical analyses

We merged and analyzed datasets using Statistical Analysis Software (SAS) version 9.4 (SAS Institute Inc., Cary, NC); R for Windows was used for Kaplan-Meier graphics (ggplot; https://www.r-project.org/). We compared distributions of clinical and demographic traits among recipients with each level of opioid exposure with no opioid use, using the Chi-square test. Using multivariate logistic regression, we constructed propensity score models for the likelihood of any opioid fills in the pretransplant period and in the first year posttransplant with data summarized in Table 1. We estimated event incidence using the Kaplan-Meier method, with use of the log-rank test to assess the statistical significance of unadjusted differences. With multivariate Cox regression, including adjustment for recipient, donor, and transplant clinical factors, we quantified adjusted associations of pre- and posttransplant opioid fills with posttransplant death (adjusted hazard ratio with 95% upper and lower confidence limits, $_{LCL}aHR_{UCL}$), stratified by quintile of propensity score, as per previous methods.[20,26,27] We assessed the proportionality assumption by examining Schoenfeld residuals and assessed the effects of benzodiazepine fills separately and concomitantly with opioid fills, including testing for interactions. In all outcome analyses, we interpreted 2-tailed p values <0.05 as statistically significant. In the analysis of pretransplant medication fills, we assessed outcomes to the first transplant anniversary, using the date of transplant as the origin for assessment. In the analysis of posttransplant medication fills, we assessed outcomes from >1-to-2 years posttransplant, using the first anniversary as the origin. Observation time was censored at the end of follow-up (June 1, 2018). Sensitivity analyses examined posttransplant survival from >1-to-5 years posttransplant.

Results

Baseline characteristics of lung transplant recipients

In the study period, 18,595 US adult lung transplants were recorded in the SRTR database. Of these, 11,568 (62.2%) also had available pretransplant medication fill data and were included in the study sample. Characteristics of the study cohort were generally similar to those of patients without linked pharmacy fill records, although small differences were statistically significant due to the large sample size (Table S2). The most notable difference was variation in distributions of the year of transplant across the study period for the included cohort (e.g., fewer transplanted in 2008-2010) compared with the excluded cohort.

Among the study sample, 33.7% filled an opioid prescription in the year before transplant. The highest pretransplant level of opioid prescription use (level 4) was more common among patients who were women, Black, had lower educational attainment, and had public or other insurance. Level 4 prescription opioid use was also more common among patients with lower functional status, history of extracorporeal membrane oxygenation (ECMO), and transplant in recent years (Table 1). Patterns of posttransplant prescription opioid fills according to clinical traits were similar (Table S3).

Of the study cohort, 25.8% also filled a benzodiazepine prescription in the pretransplant year (short-acting: 19.5%; long-acting: 4.2%; or both: 2.1%). Pretransplant benzodiazepine fills, including short-acting medications, long-acting medications, or both, were higher among patients with level 4 opioid fills (56.2%) than among those without opioid fills (18.8%) (Figure S1).

Mortality according to pretransplant opioid and benzodiazepine use

Overall, 6.1% of lung transplant recipients died, and 6.7% experienced graft failure within the first year after transplant; most graft failures were concomitant with death. Reported causes of death included 18.3% graft failure, 17.1% pulmonary, 16.0% infection, 8.8% cardiovascular/cerebrovascular, 7.8% malignancy, 16.0% other, and 16.0% unknown. Compared with lung transplant recipients with no pretransplant opioid fills, those with level 4 fills had increased mortality (8.2% vs 6.0%, p = 0.02; Figure 1). After adjustment for demographic and clinical factors and propensity for opioid fills, level 4 pretransplant opioid use was associated with a 41% increased risk of death in the first posttransplant year (aHR, $_{1.09}1.41_{1.82}$) compared with no fills (Table S4). With adjustment for demographic and clinical factors, fills of short-acting, long-acting, and both classes of benzodiazepines in the pretransplant year were

Table 1 Pretransplant Opioid Use Levels According to Baseline Clinical Characteristics of Lung Transplant Recipients

	Opioid Use within 1-Year Before Lung Transplant					
	No use (*N* = 7,665) %	Level 1 (*N* = 1,023) %	Level 2 (*N* = 944) %	Level 3 (*N* = 969) %	Level 4 (*N* = 967) %	*p* Value
Recipient clinical factors						
Age, years						
18-30	58.4	9.9	11.5	10.0	10.1	0.19
31-44	59.0	9.0	9.5	9.5	13.1	Reference
45-59	62.2	9.1	8.8	9.5	10.4	0.11
≥60	71.3	8.5	7.0	7.3	5.9	<0.0001
Sex						
Female	64.2	8.6	8.6	9.3	9.3	<0.0001
Male	67.7	9.0	7.9	7.7	7.7	Reference
Race						
White	66.7	8.6	8.0	8.3	8.4	Reference
Black	61.2	10.7	10.2	8.4	9.4	0.004
Hispanic	64.3	9.3	8.6	10.0	7.8	0.48
Other	73.7	8.5	5.5	7.2	5.1	0.15
Education						
College and higher	67.1	9.2	8.4	8.0	7.3	Reference
Grade/high schools	65.1	8.1	7.9	9.1	9.9	<0.0001
Unknown	65.7	10.9	7.7	7.1	8.6	0.38
Primary payer						
Private	66.5	9.1	8.9	8.6	6.9	<0.0001
Public	66.1	8.7	7.4	8.1	9.8	Reference
Other	59.5	2.7	2.7	16.2	18.9	0.06
UNOS lung transplant diagnosis group						
A: Obstructive lung disease	69.0	8.3	6.2	7.8	8.7	Reference
B: Pulmonary vascular disease	56.0	11.0	11.9	9.9	11.2	<0.0001
C: Cystic fibrosis, or immunodeficiency disorder	61.3	9.5	9.2	9.1	11.0	<0.0001
D: Restrictive lung disease	66.6	8.9	8.8	8.4	7.3	<0.0001
Functional status						
No assistance	69.5	8.5	7.3	7.7	7.0	Reference
Some assistance	66.5	9.5	8.1	7.5	8.5	0.05
Total assistance	64.3	8.4	8.7	9.6	9.0	<0.0001
Six minute-walk test, feet						
≤699	65.5	7.8	8.8	8.8	9.1	Reference
700-1,060	67.6	8.5	7.5	8.2	8.3	0.20
≥1061	68.3	9.3	8.8	7.3	6.3	0.0005
Unknown	64.8	9.4	7.9	8.9	9.1	0.16
Diabetes mellitus						
Yes	64.2	8.8	8.9	9.0	9.1	0.12
No	66.8	8.9	8.0	8.2	8.2	Reference
Assisted ventilation						
On waitlist	60.2	7.0	10.5	12.3	10.1	<0.0001
At transplant	61.3	7.9	9.5	12.1	9.2	<0.0001
After transplant	66.3	8.9	8.2	8.3	8.4	0.11
ECMO support						
Yes	56.4	8.5	11.1	15.1	9.0	<0.0001
No	66.6	8.9	8.1	8.2	8.3	Reference
Predicted FEV1, %						
≤21	68.1	8.3	7.0	8.2	8.5	Reference
22-53	65.2	8.9	8.6	8.5	8.8	0.03
≥54	66.3	9.4	8.7	8.3	7.3	0.03
Cardiac index, L/min						
≤2.58	67.8	9.4	7.4	8.0	7.4	Reference
2.59-3.10	67.0	8.9	8.2	7.6	8.3	0.39
≥3.11	64.8	8.2	8.4	9.1	9.4	0.001
Unknown	64.1	9.0	9.3	9.5	8.1	0.04

(*continued on next page*)

Table 1 (*Continued*)

	Opioid Use within 1-Year Before Lung Transplant					
	No use (*N* = 7,665) %	Level 1 (*N* = 1,023) %	Level 2 (*N* = 944) %	Level 3 (*N* = 969) %	Level 4 (*N* = 967) %	*p* Value
Pulmonary artery systolic pressure, mm Hg						
≤34	66.3	8.3	8.7	8.4	8.4	Reference
35-43	66.4	9.4	7.2	8.6	8.3	0.12
≥44	66.6	8.8	8.5	7.9	8.3	0.86
Unknown	60.7	10.0	8.6	11.1	9.7	0.19
Mean pulmonary artery pressure, mm Hg						
≤22	66.0	9.1	8.5	8.4	8.0	Reference
23-29	66.5	8.7	7.7	8.4	8.7	0.58
≥30	67.2	8.6	8.2	7.6	8.3	0.59
Unknown	62.3	9.1	8.4	11.5	8.7	0.09
PCO_2, mm Hg						
≤41	66.4	9.5	8.9	8.3	6.8	Reference
42-50	67.0	8.7	8.0	8.3	8.0	0.15
≥51	64.9	8.7	7.8	8.5	10.1	<0.0001
Unknown	68.8	6.8	6.8	8.1	9.6	0.006
Most recent serum creatinine, mg/dL						
≤0.70	65.5	8.2	8.4	8.8	9.1	Reference
0.71-0.90	67.2	9.1	7.8	8.5	7.4	0.03
0.91-1.29	67.4	9.1	7.9	7.5	8.2	0.10
≥1.30 or dialysis	61.0	10.4	9.8	9.0	9.8	0.13
Total bilirubin, mg/dL						
≤0.37	62.8	8.8	8.7	9.6	10.2	Reference
0.38-0.57	67.6	8.7	7.4	8.1	8.2	0.0002
≥0.58	68.2	9.0	8.3	7.6	6.9	<0.0001
LAS levels						
≤46	67.8	8.9	7.3	7.7	8.2	Reference
47-59	64.8	9.1	8.8	8.9	8.5	0.07
≥60	62.1	8.5	10.5	10.2	8.7	<0.0001
Transplant year						
2008-2010	70.2	7.5	7.7	7.3	7.3	Reference
2011-2013	65.3	8.3	8.9	9.0	8.5	0.001
2014-2017	65.1	10.0	7.8	8.4	8.8	<0.0001

Abbreviations: ECMO, extracorporeal membrane oxygenation; FEV1, forced expiration volume in one second; LAS, lung allocation score; mg, milligram; PCO2, partial pressure of carbon dioxide; UNOS, United Network for Organ Sharing.

Percentages are row percentages.

Opioid use levels (annual ME): Level 1, >0 to 200 mg; Level 2, >200 to 600 mg; Level 3, >600 to 2,700 mg; Level 4, >2,700 mg.

p values: for comparison of distributions of each level of opioid use vs no use in a given clinical category.

associated with 29%, 35%, and 117% increased risk of death in the first posttransplant year, respectively (aHR, $_{1.07}1.29_{1.56}$; aHR, $_{0.94}$ $1.35_{1.94}$; and aHR, $_{1.44}2.17_{3.26}$, respectively) (Table S4).

Although associations were stronger when considering opioid or benzodiazepine use alone, some independent effects were present when both medications were assessed in the same model (Table 2). Including adjustment for opioid use, fills of short-acting or both classes of benzodiazepines were associated with 25% and 102% increased risk of death in the first posttransplant year (aHR $_{1.03}1.25_{1.52}$ and aHR $_{1.33}2.02_{3.07}$, respectively; Figure 2). However, the association of pretransplant opioid use with posttransplant mortality was not significant after adjustment for benzodiazepine fills. Interactions between opioid and benzodiazepine fills on mortality risk were not observed. Other recipient characteristics associated with death within 1 year of transplant included OPTN diagnosis class B (aHR, $_{1.10}1.61_{2.34}$), need for mechanical ventilation after surgery (aHR, $_{1.02}1.64_{2.64}$), and elevated serum creatinine ≥1.3 mg/dL or the need for dialysis (aHR, $_{1.23}1.64_{2.21}$) (Table 2).

Patterns of posttransplant opioid and benzodiazepine use

Among the cohort, 40.1% filled an opioid prescription in the year after transplant, and 17.9% filled a benzodiazepine prescription (short-acting: 12.5%; long-acting: 3.9%; or

both: 1.5%). Overall, 60.0% of lung transplant recipients who filled an opioid prescription in the pretransplant year continued to fill opioid prescriptions in the posttransplant year. The level of pretransplant opioid use strongly predicted posttransplant opioid use (Figure 3a). Eighty percent of patients with level 4 pretransplant opioid use also filled opioid prescriptions posttransplant, including 50% who filled at level 4 posttransplant. Pretransplant benzodiazepine use was also correlated with posttransplant use, such that 59.8% of lung transplant patients who filled prescriptions for both agents pretransplant also filled a benzodiazepine prescription posttransplant (Figure 3b). Posttransplant benzodiazepine use rose progressively with higher levels of posttransplant opioid use, to 42.1% in those with level 4 opioid use (Figure S1).

Mortality according to posttransplant opioid and benzodiazepine use

Overall, 6.1% of lung transplant recipients died >1-to-2 years posttransplant, and 6.7% experienced graft loss. Compared to those without opioid fills, patients with all levels of posttransplant opioid use had increased risk of subsequent death (Figure 1) and graft loss, especially those with level 4 opioid use vs no use (death incidence: 10.3% vs 4.8%, $p < 0.0001$; graft loss incidence: 10.8% vs 5.5%, $p < 0.0001$). In years >1-to-2 posttransplant, deaths attributed to pulmonary causes were more common in lung transplant recipients with levels 3 and 4 opioid use than in recipients without opioid prescription fills (21.9% and 20.6% vs 16.5%, $p < 0.05$). Pulmonary (26.2% vs 16.9%, $p < 0.05$) and infection-related (17.4% vs 12.3%, $p < 0.05$) deaths were more common among lung transplant patients who filled long-acting benzodiazepines than in recipients with no use (Figure S2).

After adjustment for demographic and clinical factors and propensity for opioid fills, risk of death >1-to-2 years posttransplant increased with higher levels of opioid use in the first year after transplant (level 1 aHR, $_{0.87}$ $1.22_{1.72}$; level 2 aHR, $_{1.23}1.57_{2.02}$; level 3 aHR, $_{1.28}1.62_{2.04}$; level 4 aHR, $_{1.78}2.27_{2.89}$; Table S4). Similarly, after adjustment for demographic and clinical factors, prescription fills of short-acting, long-acting, and both classes of benzodiazepines were associated with 63%, 63%, and 131% increased risk of death >1-to-2 years posttransplant, respectively (Table S4).

Independent effects of first-year opioid and benzodiazepine fills with subsequent mortality were also present when both medications were assessed simultaneously. After adjustment, including benzodiazepine use, the risk of death >1-to-2 years posttransplant increased with higher first-year opioid fill levels (level 2 aHR, $_{1.17}1.50_{1.92}$; level 3 aHR, $_{1.19}1.50_{1.90}$; and level 4 aHR, $_{1.56}2.01_{2.59}$; Figure 2). After adjustment for opioid use, fills of short-acting (aHR, $_{1.12}1.40_{1.75}$) and both classes of benzodiazepines (aHR, $_{1.06}1.77_{2.96}$) in the first year after transplant were independently associated with increased risk of death >1-to-2 years posttransplant (Figure 2). These effects were independent,

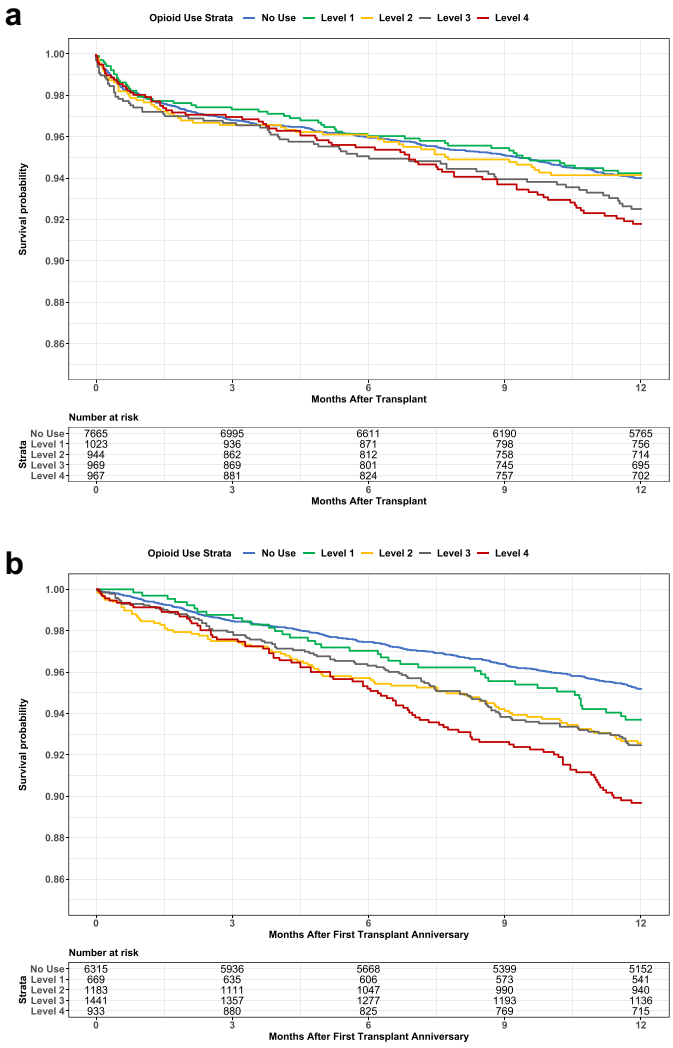
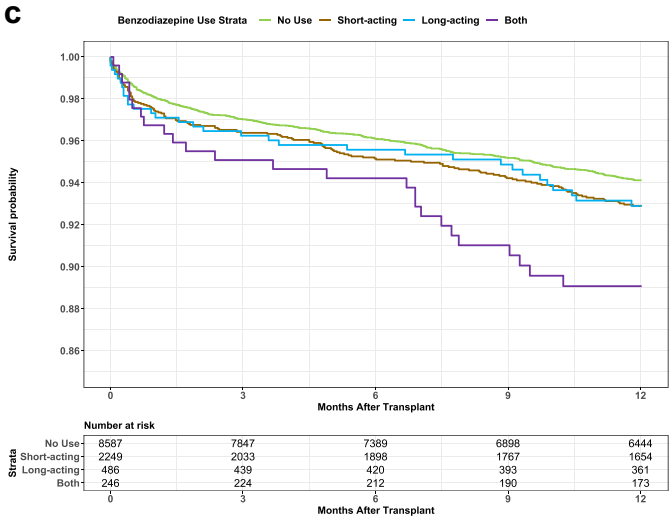


Figure 1 Patient survival according to opioid and benzodiazepine prescription fills before and after lung transplant. (a) First-year posttransplant mortality according to pretransplant opioid use. (b) Mortality >1-to-2 years posttransplant according first-year posttransplant opioid use. (c) First-year posttransplant mortality according to pretransplant benzodiazepine use. (d) Mortality >1-to-2 years posttransplant according first-year posttransplant benzodiazepine use. Opioid use levels (annual morphine equivalents): Level 1, >0 to 200 mg; level 2, >200 to 600 mg; level 3, >600 to 2,700 mg; level 4, >2,700 mg.

and interactions between opioids and benzodiazepines on mortality risk were not observed. The adverse impact of first-year opioid and benzodiazepine fills persisted with follow-up to the fifth transplant anniversary, including significant and graded effects across all levels of opioid use (Table S5).

Discussion

Patients with end-stage lung disease are often prescribed opioids for pain or dyspnea and benzodiazepines for anxiety. In this study, we found that 33.7% filled an opioid prescription and 25.8% filled a benzodiazepine prescription in



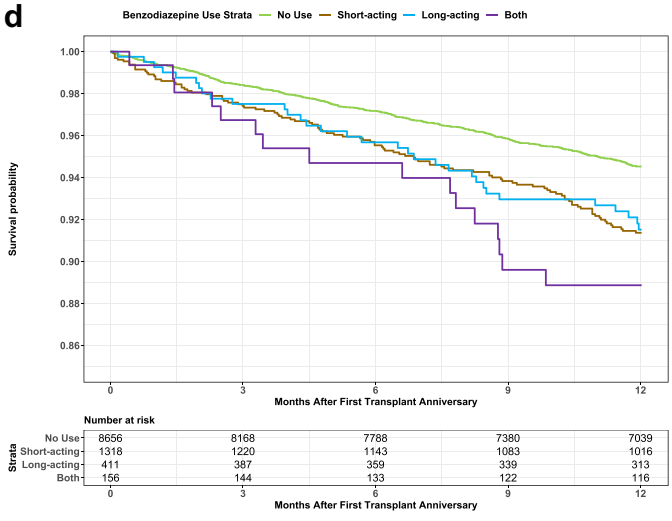


Figure 1 Continued.

the year before lung transplant. Compared to patients without prescription fills, those who filled both short- and long-acting benzodiazepines before transplant had a 2-fold increase in mortality in the first posttransplant year, independent of opioid use. Associations of pretransplant opioid use with mortality were not significant after adjustment for benzodiazepine fills. Pretransplant opioid and benzodiazepine use strongly predicted more common use after transplant. Fills of both short- and long-acting benzodiazepine use during the first year posttransplant were associated with 77% increased mortality >1-to-2 years posttransplant, and higher levels of posttransplant opioid fills were independently associated with graded mortality risk, including 2-fold increased mortality for those with the highest level of posttransplant opioid use.

Lung transplant patients could be expected to be at increased risk for opioid and benzodiazepine use and associated consequences.[10-13] We found that prescription opioid use in lung transplant recipients was similar to that among kidney and heart transplant recipients but higher than among liver transplant recipients.[21-23] A recent study from Canada reported lower opioid use at the time of listing for lung transplant, possibly reflecting different definitions of prescription opioid use and practice patterns.[15] In the Canadian study, opioid use was defined based on review of medications at the time of listing, and some "nonusers" may have received prescriptions in the period between listing and transplant.[15] Electronic pharmacy fill records have been shown to be highly accurate records of physician prescriptions and overcome some of the limitations of other methods of prescription quantification, such as self-reported medication use.[29-31] Despite the lower prevalence of outpatient opioid use in the Canadian study, patient characteristics associated with opioid use were similar to those in the current study, including higher use in patients who required pretransplant ECMO and mechanical ventilation.[15]

The risks associated with prescription opioid use in lung transplant patients identified in this study, particularly after transplant, are similar to those from previous observations in the heart, liver, and kidney transplant populations.[21,23,27] Our results are also consistent with a recent single-center study of 21 lung transplant recipients by Drees et al[16] who reported that posttransplant opioid use was associated with a 16% decrease in FEV1 and with increased mortality (HR, $_{1.1}7.1_{45}$), with up to 4 years of posttransplant follow-up.

We observed that persistent use of opioids and benzodiazepines before and after lung transplant was common. Indeed, we found that 50% of patients with the highest level of pretransplant opioid use continued high-level use after transplant. Higher-level opioids fills were correlated with benzodiazepine use, possibly reflecting comorbid pain, dyspnea, and anxiety. We found that pretransplant benzodiazepine use may be the stronger risk factor, while use of either or both medications after lung transplant increases risk. Because opioids may be necessary for symptom management pretransplant, clinicians may want to concentrate on decreasing pretransplant benzodiazepine use while considering limiting both after lung transplant, when opioids are no longer needed for symptom control. However, a prospective study is needed to validate this hypothesis and confirm benefits of changes in medication use patterns on patient outcomes.

The associations in our study cannot prove cause and effect. The inferior outcomes associated with opioid and benzodiazepine prescription fills may be due to worse baseline illness severity, despite adjustment for covariates in the national registry.[32] However, regardless of causality, the significance and magnitude of the effect sizes support that use of these medications is prognostically important in the lung transplant population. In addition, use of prescription opioids and benzodiazepines may be associated with patient behaviors that mediate adverse outcomes, such as nonadherence with immunosuppressive medications or other treatments or care plans.[33,34] Further research is needed to understand the factors contributing to the increased risk of death in lung transplant recipients prescribed benzodiazepines and opioids, especially after transplant.

This study has limitations. Pharmacy data are not available for all lung transplant recipients in the SRTR registry. While the study sample was generally similar to patients

Table 2 Adjusted Associations of Opioid and Benzodiazepine Fills with Mortality Risk After Lung Transplant

	Death in the first year after transplant aHR (95% CL)	Death >1-to-2 years after transplant aHR (95% CL)
Opioid use		
No opioid use	Reference	Reference
Level 1	0.94 (0.71-1.25)	1.20 (0.86-1.68)
Level 2	0.93 (0.69-1.24)	1.50 (1.17-1.92)[a]
Level 3	1.15 (0.88-1.50)	1.50 (1.19-1.90)[b]
Level 4	1.25 (0.96-1.63)	2.01 (1.56-2.59)[c]
Benzodiazepine use		
No use	Reference	Reference
Short-acting	1.25 (1.03-1.52)[a]	1.40 (1.12-1.75)[a]
Long-acting	1.29 (0.90-1.87)	1.39 (0.96-2.00)
Both	2.02 (1.33-3.07)[b]	1.77 (1.06-2.96)[a]
Recipient clinical factors		
Age, years		
18-30	Reference	Reference
31-44	0.64 (0.39-1.03)	0.71 (0.48-1.06)
45-59	1.19 (0.75-1.89)	0.63 (0.41-0.97)[a]
≥60	1.44 (0.89-2.32)	0.84 (0.55-1.30)
Female	1.02 (0.85-1.22)	1.15 (0.95-1.38)
Race		
White	Reference	Reference
Black	0.99 (0.75-1.31)	1.10 (0.82-1.49)
Hispanic	1.06 (0.75-1.48)	0.64 (0.41-0.99)[a]
Other	1.06 (0.63-1.79)	1.22 (0.71-2.09)
Education		
College/graduate	Reference	Reference
Grade/high school	0.97 (0.83-1.15)	0.98 (0.82-1.17)
Unknown	1.22 (0.89-1.68)	0.97 (0.69-1.35)
Primary payer		
Public	Reference	Reference
Private	0.90 (0.77-1.05)	0.87 (0.73-1.03)
Other	1.71 (0.55-5.39)	2.47 (0.91-6.69)
UNOS lung transplant diagnosis group		
A: Obstructive lung disease	Reference	Reference
B: Pulmonary vascular disease	1.61 (1.10-2.34)[a]	0.77 (0.47-1.27)
C: Cystic fibrosis, or immunodeficiency disorder	1.00 (0.64-1.56)	0.85 (0.56-1.30)
D: Restrictive lung disease	0.99 (0.78-1.26)	0.90 (0.70-1.15)
Functional status		
No assistance	Reference	Reference
Some assistance	1.01 (0.81-1.25)	0.91 (0.73-1.13)
Total assistance	1.14 (0.92-1.42)	1.07 (0.86-1.33)
Six minute-walk test, feet		
≤699	Reference	Reference
700-1060	1.03 (0.83-1.28)	1.04 (0.84-1.31)
≥1061	0.79 (0.62-1.00)	1.12 (0.88-1.41)
Unknown	0.90 (0.72-1.12)	0.93 (0.72-1.19)
Diabetes mellitus	1.00 (0.82-1.22)	1.18 (0.95-1.45)
Assisted ventilation		
On waitlist	1.30 (0.80-2.11)	1.56 (0.87-2.80)
At transplant	1.29 (0.81-2.06)	0.53 (0.29-0.98)[a]
After transplant	1.64 (1.02-2.64)[a]	1.06 (0.74-1.51)
ECMO support	1.07 (0.69-1.67)	0.88 (0.48-1.60)
Predicted FEV1, %		
≤21	Reference	Reference
22-53	1.20 (0.95-1.51)	1.03 (0.82-1.30)
≥54	1.14 (0.86-1.52)	1.04 (0.77-1.39)
Cardiac Index, L/min		
≤2.58	Reference	Reference
2.59-3.10	0.93 (0.76-1.13)	1.03 (0.83-1.29)
≥3.11	0.96 (0.78-1.18)	1.04 (0.82-1.30)
Unknown	1.30 (1.01-1.68)[a]	1.31 (1.01-1.70)[a]
Pulmonary artery systolic, mm Hg		
≤34	Reference	Reference
35-43	1.22 (0.96-1.57)	1.31 (1.01-1.70)[a]
≥44	1.25 (0.91-1.73)	1.35 (0.96-1.89)
Unknown	1.11 (0.58-2.16)	1.15 (0.62-2.13)

(*continued on next page*)

Table 2 (*Continued*)

	Death in the first year after transplant aHR (95% CL)	Death >1-to-2 years after transplant aHR (95% CL)
Mean pulmonary artery pressure, mm Hg		
≤22	Reference	Reference
23-29	0.86 (0.67-1.10)	0.71 (0.55-0.93)[a]
≥30	0.96 (0.70-1.32)	0.80 (0.57-1.12)
Unknown	0.85 (0.54-1.32)	0.91 (0.57-1.43)
PCO2, mm Hg		
≤41	Reference	Reference
42-50	1.02 (0.84-1.23)	0.86 (0.69-1.06)
≥51	0.96 (0.78-1.20)	0.91 (0.72-1.15)
Unknown	0.66 (0.45-0.98)[a]	0.93 (0.68-1.28)
Most recent serum creatinine, mg/dL		
≤0.70	Reference	Reference
0.71-0.90	1.03 (0.84-1.26)	1.09 (0.88-1.35)
0.91-1.29	1.30 (1.04-1.62)[a]	1.16 (0.92-1.48)
≥1.3 or dialysis	1.64 (1.23-2.21)[b]	1.39 (0.99-1.95)
Total bilirubin, mg/dL		
≤0.37	Reference	Reference
0.37-0.57	1.21 (0.98-1.49)	0.88 (0.71-1.10)
≥0.58	1.37 (1.13-1.66)[a]	1.12 (0.92-1.36)
LAS levels		
≤46	Reference	Reference
47-59	1.02 (0.81-1.28)	1.48 (1.18-1.87)[b]
≥60	0.95 (0.75-1.21)	1.27 (0.98-1.65)
Donor and transplant factors		
Age, year		
<18	1.01 (0.75-1.35)	1.13 (0.84-1.52)
18-30	Reference	Reference
31-44	0.93 (0.76-1.13)	0.95 (0.76-1.18)
45-59	1.05 (0.86-1.27)	1.14 (0.92-1.40)
≥60	0.97 (0.66-1.44)	1.22 (0.82-1.81)
Donor/recipient height ratio		
≤0.99	Reference	Reference
1.00-1.03	0.79 (0.66-0.95)[a]	0.92 (0.74-1.13)
≥1.04	0.75 (0.61-0.93)[a]	1.06 (0.85-1.32)
Donor/recipient weight ratio		
≤0.91	Reference	Reference
0.92-1.19	0.79 (0.65-0.95)[a]	1.01 (0.82-1.24)
≥1.20	0.92 (0.74-1.14)	0.91 (0.72-1.15)
Total ischemic time, minutes		
≤260	Reference	Reference
261-344	0.96 (0.80-1.15)	0.78 (0.64-0.96)[a]
≥345	0.90 (0.74-1.09)	0.97 (0.79-1.19)
Transplant year		
2008-2010	Reference	
2011-2013	0.91 (0.75-1.12)	
2014-2017	0.83 (0.66-1.04)	
2006-2010		Reference
2011-2013		0.88 (0.72-1.07)
2014-2016		1.00 (0.80-1.26)

Abbreviations: ECMO, extracorporeal membrane oxygenation; FEV1, forced expiration volume in one second; LAS, lung allocation score; mg, milligram; PCO2, partial pressure of carbon dioxide; UNOS, United Network for Organ Sharing.

Opioid use levels (annual morphine equivalents): Level 1, >0 to 200 mg; Level 2, >200 to 600 mg; Level 3, >600 to 2,700 mg; Level 4, >2,700 mg.

For models of death in the first year after transplant, opioid and benzodiazepine use was examined within 1 year before transplant. For models of death in the >1-to-2 years after transplant, opioid and benzodiazepine use was examined in the year after transplant (excluding the first 90 days, to remove surgery-related use). There were no significant interactions between opioid and benzodiazepine use in the mortality models.

p values:

[a] $p < 0.05$ to 0.002.

[b] $p = 0.001$ to 0.0001.

[c] $p < 0.0001$.

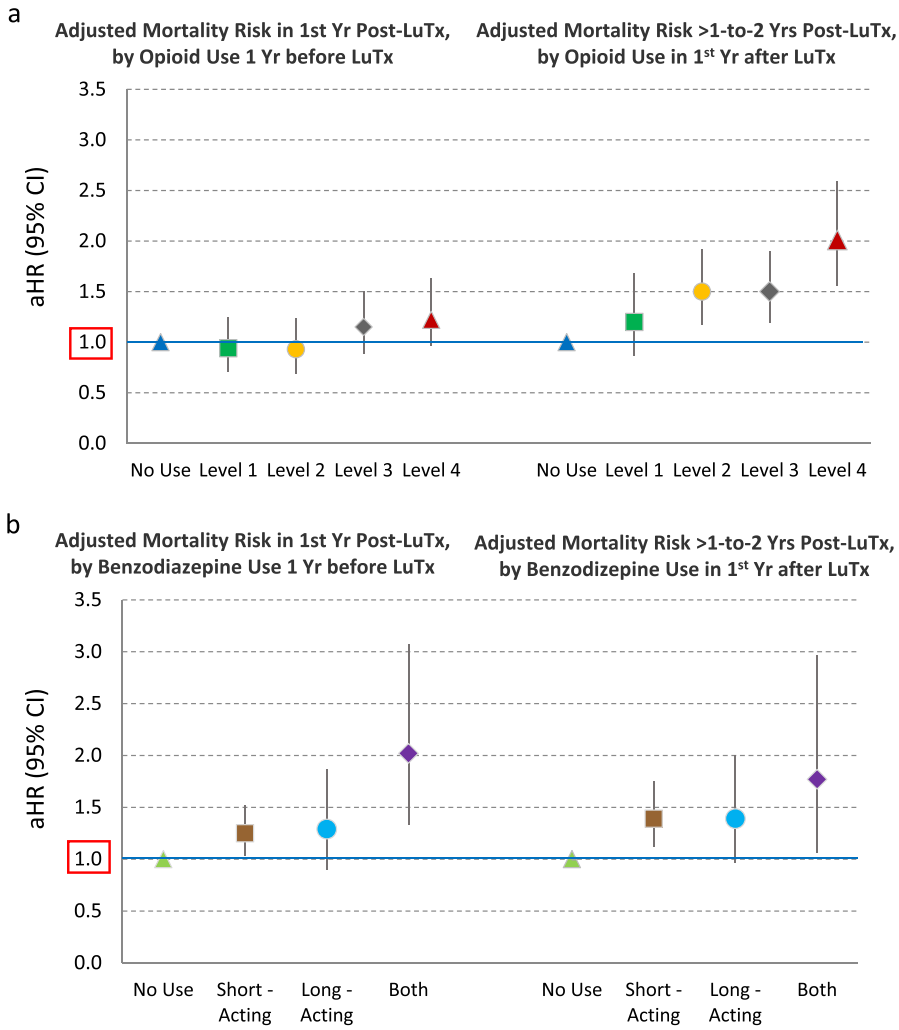


Figure 2 Adjusted associations of opioid (a) and benzodiazepine (b) prescription fills with mortality risk after lung transplant. Effects are adjusted for baseline patient, donor and transplant factors, and both classes of medications. aHR, adjusted hazard ratio; CI, confidence interval; LuTx, lung transplant.

without pharmacy data—and these data capture one of the largest and most representative samples in the literature—some differences that may limit generalizability to patients not included in the analysis. The available data lacked information on the indication for prescriptions (e.g., dyspnea vs pain, in the case of opioids). However, we adjusted for a broad spectrum of demographic, clinical, and transplant factors identified in the registry. The database may also underestimate opioid and benzodiazepine use, because we cannot account for illicit drug use, "pharmacy shopping" behaviors, or simultaneous prescription fills at pharmacies not included in the pharmacy claims data. However, this ascertainment bias would most likely skew the study toward the null hypothesis. Consequently, associations with poor outcomes likely underestimate true impacts. Some critically ill patients are hospitalized for weeks or months before lung transplant (sometimes intubated or on ECMO) and could be exposed to sedation and opioids but would not be classified as having pretransplant exposures in this analysis, because the pharmacy claims data captures only outpatient prescription fills. Our findings also may not generalize to medication use after the first transplant anniversary.

These data may not reflect actual medication use, because not all filled prescriptions may be used. Pharmacy fill records are an indirect but validated measure of medication exposure.[29-31] Last, we were unable to classify patients who have clinically identified drug dependency and other substance use disorders, although many such patients are excluded from transplant through the required comprehensive psychosocial evaluation before listing. Despite these limitations, the current study provides an assessment of opioid and benzodiazepine use in lung transplant patients in a national sample, extending inferences from single-center studies that rely on self-reported questionnaires, surveys, or chart review.[29,30] Linking national registries with pharmacy fill records allows assessment of medication exposures as novel risk markers for adverse events, adjusted for key recipient and donor and transplant characteristics, to identify potentially modifiable risk factors that may guide improved outcomes.

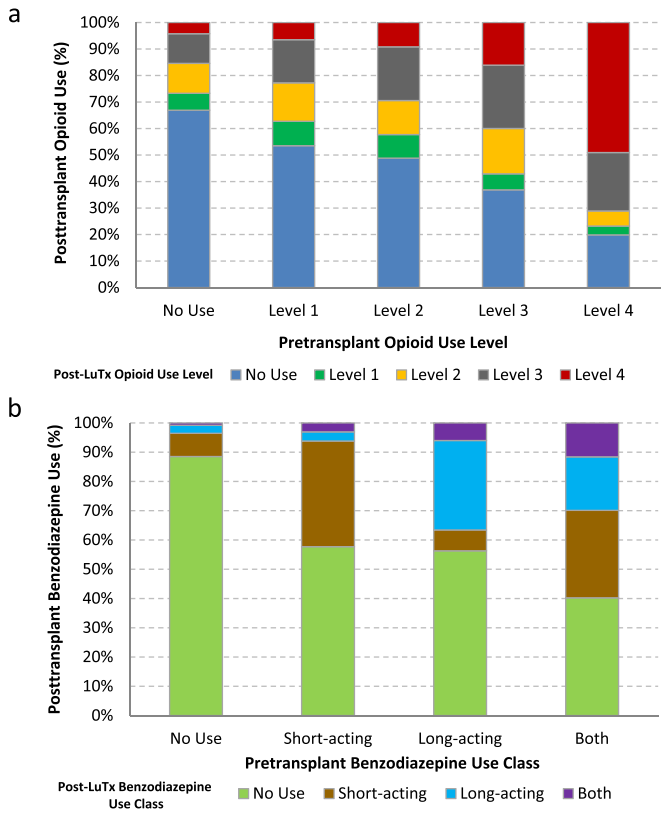


Figure 3 Posttransplant opioid (a) and benzodiazepine (b) use according to pretransplant prescription fills. Opioid prescription levels (annual morphine equivalents): Level 1, >0 to 200 mg; level 2, >200 to 600 mg; level 3, >600 to 2700 mg; level 4, >2700 mg. LuTx, lung transplant.

In summary, although associations may in part reflect underlying conditions, prescription benzodiazepine fills in lung transplant patients before and after transplant, and opioid use after transplant, are independently associated with posttransplant mortality and are relevant to the risk stratification of lung transplant patients. Our study informs transplant teams that many patients receiving pretransplant opioids and/or benzodiazepines will continue to fill these agents in the year after lung transplant. Further prospective work should seek to identify mechanisms underlying risk relationships and assess the feasibility and outcome implications of decreasing benzodiazepine and opioid use through other strategies for symptom management. For now, these data suggest that lung transplant patients who require benzodiazepines and opioids warrant careful evaluation, perhaps by a multidisciplinary team that includes anxiety and pain specialists, appropriate education on the clinical implications, and focused monitoring of clinical status after transplant.

Disclosure statement

The authors of this manuscript have no conflicts of interest to disclose.

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Data availability statement

This study was approved by the Saint Louis University Institutional Review Board. Individual participant deidentified data will not be shared by the authors due to restrictions of data use agreements. SRTR registry data can be obtained from the SRTR.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2021.02.004.

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