Perioperative outcomes among chronic opioid users who receive lobectomy for non–small cell lung cancer

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ABSTRACT

Objective: We sought to identify whether chronic opioid users are at increased risk for complications or hospital readmission following lobectomy for non–small cell lung cancer.

Methods: The National Cancer Institute Surveillance, Epidemiology, and End Results-Medicare database was queried to identify patients older than age 65 years who received a lobectomy for non–small cell lung cancer. Chronic opioid users were identified through Medicare Part D records and were defined as those with >120 cumulative days of opioid supply for the year before surgery. A systematic 1:2 propensity matching was performed among chronic opioid users.

Results: Six thousand four hundred thirty-seven patients were identified, among whom 3627 (56%) were opioid naïve, 1866 (29%) were intermittent opioid users, and 944 (15%) were chronic opioid users. After propensity matching, 30-day mortality and 90-day mortality were nearly 2-fold higher among chronic opioid users compared with nonchronic users. In addition, length of stay and hospital charges were increased among chronic opioid users (median, 6 vs 7 days and mean increase, \$12,526, respectively). Multivariable analysis revealed that intermittent opioid users and chronic opioid users were associated with an increased risk of 90-day hospital readmission compared with opioid-naïve patients (odds ratio, 1.35; 95% confidence interval, 1.07-1.71 and odds ratio, 1.72; 95% confidence interval, 1.40-2.12, respectively), predominantly burdened by infectious, renal, and pulmonary causes.

Conclusions: Patients who chronically use opioids before lobectomy represent high-risk patients. The risk of 30- and 90-day mortality, length of stay, hospital charges, and 90-day readmission after lobectomy among chronic opioid users are substantially elevated. (J Thorac Cardiovasc Surg 2020;159:691-702)

Propensity matched 30-day mortality among chronic users of opioid drugs.

Central Message

Patients who chronically use opioids before lobectomy represent high-risk surgical patients.

Perspective

In a propensity score-matched analysis, we found that chronic opioid use before lobectomy was associated with a nearly doubled 30- and 90-day risk of mortality. In addition, chronic opioid use was associated with prolonged length of stay, increased hospital charges, and increased 90-day hospital readmission. Screening to identify chronic opioid use before elective lobectomy should be performed.

See Commentary on page 703.

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Opioid use has drastically risen during the past 2 decades, with hydrocodone use increasing by more than 2-fold and oxycodone use increasing by 5-fold.¹ Although the prevalence of opioid addiction has increased substantially, the influence of chronic opioid use before surgery on perioperative outcomes of patients undergoing general

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Abbreviations and Acronyms

NSCLC	= non–small cell lung cancer
OME	= oral morphine equivalent
SEER	= Surveillance, Epidemiology, and End Results

thoracic surgery remains to be well described. Several retrospective studies have highlighted increased costs and morbidity encountered among opioid users who undergo surgery.²⁻⁴ Although these results may represent other factors intrinsic to those who chronically use opioids, they nonetheless highlight increased perioperative burden among this population. Furthermore, opioid use may promote immunosuppression,⁵ raise the risk of sepsis in animal models,⁶ and are also implicated in impaired wound healing.⁷ The purpose of this study was to characterize early perioperative outcomes, including morbidity, mortality, and readmission burden among chronic opioid users who undergo lobectomy for non–small cell lung cancer (NSCLC). We hypothesized that chronic opioid users demonstrate worse perioperative outcomes compared with intermittent or naïve opioid users.

METHODS

Database Information

A query of the National Cancer Institute Division of Cancer Control and Population Sciences Surveillance, Epidemiology and End Results (SEER)–Medicare linked database (<https://healthcaredelivery.cancer.gov/seermedicare/>) was performed. Medicare eligibility includes 97% of those who are aged 65 years or older with claims data available for linkage with those who have fee-for-service coverage. The SEER database is supported by the National Cancer Institute and maintains cancer incidence and survival data from population-based cancer registries.⁸ Approximately 35% of the US population is covered by the SEER database. The SEER-Medicare linkage led to 93% of persons who are aged 65 years and older and registered within the SEER database to be matched to the Medicare database. Part D coverage, which provides additional coverage for prescription medications, is available for approximately 60% of Medicare beneficiaries. This study was approved by the MD Anderson Cancer Center Institutional Review Board with a waiver of informed consent.

Patient Selection Criteria

Patients who were older than age 65 years and who received a lobectomy for NSCLC between 2008 to 2013 were selected for analysis. To ensure complete claims data, including prescription records, enrollment in Medicare parts A, B, and D for 12 months before surgery without enrollment in an health maintenance organization was required. Patients were required to have histologic confirmation of diagnosis and to undergo surgery within 6 months of diagnosis or be diagnosed as late as 30 days after surgery. Patients who were diagnosed at autopsy or death certificate were excluded.

Variable Definitions

Opioid use was identified by Part D records according to the name of opioid drug prescribed, dose, and quantity filled. Patients were

categorized as chronic opioid users if at least 120 cumulative days of supply were filled 1 year before surgery. Opioid-naïve patients were those with no filled opioid prescription for the year before surgery, and intermittent opioid users filled <120 cumulative days of supply. We excluded opioid prescriptions filled within 30 days of surgery because some surgeons will provide patients with an opioid prescription intended to treat postoperative pain in preparation for surgery. These definitions reflect those previously used.⁹

NSCLC histology was identified using International Classification of Diseases for Oncology, 3rd Edition, histology codes (Appendix E1 and Table E1). Charlson comorbidity scores were calculated using Medicare Provider Analysis and Review, National Claims History, and outpatient claims for 1 year before surgery as described using the Klabunde algorithm.^{10,11} Adjuvant chemotherapy and radiation therapy was identified using Medicare claims. Stage was defined according to the American Joint Committee on Cancer Collaborative Staging Manual, sixth edition, collaborative stage. Education level, poverty level, and residence in an urban or rural environment were identified through use of census data corresponding to the ZIP code of residence of the patient. To protect the confidentiality of Medicare beneficiaries and according to SEER–Medicare database guidelines, cells with counts <11 were suppressed.

Statistical Analysis

Comparisons between cohorts among categorical variables were performed using either χ^2 test or Fischer exact test. Length of stay was compared using Kruskal-Wallis test. Charges were compared using a generalized linear model with a log-link and gamma distribution. Monthly oral morphine equivalent (OME) was calculated as the quantity of the opioid filled multiplied by the OME of each opioid drug. Monthly OME was reported as the mean of the cohort. Monthly OME use was compared using the Wilcoxon signed-rank test. A propensity score model predicting the likelihood of chronic opioid use before surgery was constructed using an a priori selected multivariable logistic regression model. Variables included in the propensity score model were age, race/ethnicity, sex, year of diagnosis, urban/rural environment, marital status, poverty level, education level, Charlson comorbidity score, tumor histology, tumor size, tumor grade, stage, surgical approach (video-assisted thoracoscopic surgery vs open), and receipt of any neoadjuvant therapy. After propensity score matching, cohorts were well balanced with standardized mean differences <10% (Figures E1 and E2). In addition, there were no significant differences between cohorts (Table E2). Statistical tests were 2-sided. All statistical analysis was performed with use of SAS version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Characteristics of Chronic Opioid Users

Six thousand four hundred thirty-seven patients were identified as having undergone a lobectomy for NSCLC between 2008-2013 (Figure 1). Among these, 3627 patients (56%) were opioid-naïve for the year before surgery. One thousand eight hundred sixty-six patients (29%) were intermittent opioid users, and 944 patients (15%) were chronic opioid users (Table 1). Chronic opioid use was defined as filling >120 cumulative days' worth of opioid drugs during the year before surgery. Chronic opioid use before surgery was independently associated with younger age, female sex, unmarried status, worse comorbidities, residence in a ZIP code with higher poverty level, race/ethnicity, and squamous cell histology (Table 2).

Operative Morbidity and Mortality Is Higher Among Chronic Opioid Users Who Undergo Lobectomy

Complications, length of stay, and hospital charges were significantly higher among chronic opioid users compared with either naïve or intermittent opioid users (Table 3). In addition, 30-day and 90-day mortality were significantly higher among chronic opioid drug users.

The 90-day mortality was 5.5% among opioid-naïve patients, 6.4% among intermittent opioid users, and 9.4% among chronic opioid users ($P = .001$). The 90-day hospital readmission rate was 20% among opioid-naïve patients, 24% among intermittent opioid users, and 31% among chronic opioid users ($P < .001$). Chronic opioid users demonstrated an increased readmission burden

FIGURE 1. Study flowchart indication patient selection criteria. *SEER*, Surveillance, Epidemiology, and End Results; *PUF*, Participant User Files; *NSCLC*, non-small cell lung cancer; *HMO*, health maintenance organization.

TABLE 1. Unmatched patient, tumor, and treatment characteristics

Characteristic	No preoperative chronic opioid use (n = 5493)		Preoperative chronic opioid use (n = 944)	P value
	Opioid naïve (n = 3627)	Intermittent opioid use (n = 1866)		
Age (y)				<.001
66-70	1067 (29)	653 (35)	384 (41)	
71-75	1092 (30)	570 (31)	295 (31)	
76-80	880 (24)	406 (22)	186 (20)	
>80	588 (16)	237 (13)	79 (8)	
Sex				.002
Male	1588 (44)	765 (41)	355 (38)	
Female	2039 (56)	1101 (59)	589 (62)	
Year of diagnosis				.601
2008	633 (17)	306 (16)	162 (17)	
2009	596 (16)	324 (17)	145 (15)	
2010	607 (17)	314 (17)	153 (16)	
2011	570 (16)	299 (16)	165 (17)	
2012	574 (16)	315 (17)	168 (18)	
2013	647 (18)	308 (17)	151 (14)	
Race/ethnicity				<.001
Non-Hispanic white	2968 (82)	1593 (85)	800 (85)	
Non-Hispanic black	180 (5)	99 (5)	76 (8)	
Hispanic	171 (5)	87 (5)	55 (6)	
Non-Hispanic other	308 (8)	87 (5)	13 (1)	
Urban/rural				<.001
Big metro	2093 (58)	960 (51)	444 (47)	
Less urban	323 (9)	219 (12)	120 (13)	
Metro	943 (26)	512 (27)	275 (16)	
Rural/unknown	88 (2)	44 (2)	41 (4)	
Urban	180 (5)	131 (7)	64 (7)	
Marital status				<.001
Married	1927 (53)	976 (52)	407 (43)	
Not married	1567 (43)	807 (43)	509 (54)	
Unknown	133 (4)	83 (4)	28 (3)	
% Below poverty line within ZIP code				<.001
0-5.4	1001 (28)	466 (25)	136 (14)	
5.4-10.3	843 (23)	383 (26)	276 (29)	
10.3-18.8	970 (27)	455 (24)	176 (19)	
≥18.8	813 (50)	462 (25)	356 (38)	
% With no high school education within ZIP code				<.001
0-5.8	1013 (28)	452 (24)	140 (15)	
5.8-11.0	872 (24)	443 (24)	284 (30)	
11.0-20.0	926 (26)	481 (26)	195 (21)	
≥20.0	816 (23)	490 (26)	325 (34)	
Charlson comorbidity score				<.001
0	1697 (47)	722 (39)	252 (27)	
1	1168 (57)	603 (32)	294 (31)	
2+	762 (21)	541 (29)	398 (42)	
Histology				<.001
Adenocarcinoma	2310 (64)	1148 (62)	521 (55)	
Squamous	981 (27)	539 (29)	337 (36)	
Large cell	80 (2)	37 (2)	34 (4)	
Other/NOS	256 (7)	142 (8)	52 (6)	

(Continued)

TABLE 1. Continued

Characteristic	No preoperative chronic opioid use (n = 5493)		Preoperative chronic opioid use (n = 944)	P value
	Opioid naïve (n = 3627)	Intermittent opioid use (n = 1866)		
Grade				.037
Well	591 (16)	295 (16)	123 (13)	
Moderate	1553 (43)	749 (40)	409 (43)	
Poor	1220 (34)	664 (36)	347 (37)	
Unknown	263 (7)	158 (8)	65 (7)	
Stage				.647
I	2383 (66)	1184 (63)	603 (64)	
II	452 (12)	224 (12)	121 (13)	
III	509 (14)	295 (16)	148 (16)	
IV	133 (4)	83 (4)	39 (4)	
Unknown/0	145 (4)	80 (31)	33 (3)	
Tumor size (cm)				.083
<2	925 (26)	517 (28)	248 (26)	
2-3	1011 (28)	512 (27)	261 (27)	
3-5	1080 (30)	495 (27)	289 (27)	
≥5	611 (17)	342 (18)	146 (15)	
Approach				<.001
Open	2036 (56)	1123 (60)	609 (65)	
Video-assisted thoracoscopic surgery	1591 (44)	743 (40)	335 (35)	
Chemotherapy				<.001
None	2595 (72)	1314 (70)	660 (70)	
Neoadjuvant	143 (4)	145 (8)	71 (8)	
Adjuvant	889 (25)	407 (22)	213 (23)	
Radiation				<.001
None	3097 (85)	1549 (83)	804 (85)	
Neoadjuvant	54 (2)	81 (4)	26 (3)	
Adjuvant	476 (13)	236 (13)	114 (12)	

Values are presented as n (%). NOS, Not otherwise specified.

related to infectious, renal, and pulmonary causes, with no relationship identified between preoperative opioid use and cardiac, hematologic, neurologic, or gastrointestinal reasons for readmission.

Propensity-Matched Operative Outcomes Among Chronic Opioid Users

Chronic opioid use remained associated with a nearly 2-fold increase in 30-day and 90-day mortality after propensity matching (Table 4). There were no longer differences in the complication rate or 30-day readmission rate ($P = .079$ and $P = .301$, respectively). However, length of stay and hospital charges were significantly higher among chronic opioid users as opposed to opioid-naïve or intermittent opioid users ($P = .002$ and $P < .001$, respectively). Readmissions relating to infectious, renal, pulmonary, and cardiac causes were also significantly higher among chronic users of opioid drugs ($P < .05$ for all), with no significant differences in hospital readmissions relating to hematologic, neurologic, or gastrointestinal causes.

Factors Associated With 90-Day Readmission Among Matched Cohort

Compared with the opioid-naïve patients, intermediate and chronic opioid use before surgery were both associated with significant increases in 90-day hospital readmission (intermittent: odds ratio [OR], 1.35; 95% confidence interval [CI], 1.07-1.71, and chronic: OR, 1.72; 95% CI, 1.40-2.12). In addition, compared with those who chronically use opioids before surgery, intermittent opioid use was associated with a significant reduction in 90-day hospital readmission (OR, 0.79; 95% CI, 0.62-0.99). Other factors that were associated with 90-day hospital readmission included sex, marital status, residence in a ZIP code with a lower high school graduation rate, tumor grade, Charlson comorbidity score, and open approach (Table 5). However, age, year of diagnosis, race/ethnicity, American Joint Committee on Cancer stage, tumor histology, and receiving neoadjuvant therapy were not associated with 90-day hospital readmission.

TABLE 2. Factors associated with chronic opioid use before surgery

Factor	Multivariable Odds ratio (95% Confidence interval)	P value
Age group (y)		<.001
>80	Reference	
66-70	2.35 (1.80-3.06)	
71-75	1.82 (1.39-2.39)	
76-80	1.53 (1.15-2.04)	
Sex		<.001
Male	Reference	
Female	1.33 (1.14-1.56)	
Race/ethnicity		<.001
Non-Hispanic white	Reference	
Hispanic	0.99 (0.72-1.36)	
Non-Hispanic black	0.97 (0.72-1.29)	
Non-Hispanic other	0.19 (0.11-0.34)	
Year of diagnosis		.433
2008	Reference	
2009	0.88 (0.68-1.13)	
2010	0.97 (0.76-1.25)	
2011	1.08 (0.85-1.39)	
2012	1.13 (0.88-1.44)	
2013	0.95 (0.74-1.22)	
Urban/rural		.825
Big metro	Reference	
Metro	1.04 (0.87-1.24)	
Urban	1.02 (0.75-1.39)	
Less urban	0.92 (0.72-1.19)	
Rural	1.16 (0.78-1.73)	
Marriage status		.002
Married	Reference	
Not married	1.29 (1.10-1.51)	
Unknown	0.84 (0.55-1.28)	
% with no high school education within ZIP code		.138
0-5.66	Reference	
5.66-10.5	1.12 (0.88-1.43)	
10.5-19.35	1.35 (1.04-1.74)	
≥19.35	1.26 (0.94-1.68)	
% Below poverty line within ZIP code		<.001
0-5.24	Reference	
5.24-10.03	1.17 (0.91-1.50)	
10.03-18.19	1.81 (1.39-2.35)	
≥18.19	2.18 (1.63-2.91)	
Stage		.898
I	Reference	
0	0.69 (0.08-5.87)	
II	1.12 (0.90-1.41)	
III	1.10 (0.89-1.36)	
IV	1.09 (0.75-1.59)	
Unknown	1.02 (0.65-1.59)	

(Continued)

TABLE 2. Continued

Factor	Multivariable Odds ratio (95% Confidence interval)	P value
Histology		.043
Adenocarcinoma	Reference	
Large cell	1.50 (0.98-2.29)	
Other/NOS	0.85 (0.60-1.20)	
Squamous	1.18 (1.00-1.40)	
Tumor size (cm)		.371
<2	Reference	
2-3	0.96 (0.79-1.17)	
3-5	1.04 (0.86-1.27)	
≥5	0.85 (0.67-1.09)	
Approach		.089
Open	Reference	
Video-assisted thoracoscopic surgery	0.87 (0.74-1.02)	
Neoadjuvant therapy		.065
No	Reference	
Yes	1.31 (0.98-1.74)	
Grade		.895
Well differentiated	Reference	
Moderately differentiated	1.07 (0.84-1.35)	
Poorly differentiated	1.02 (0.80-1.31)	
Unknown	0.97 (0.68-1.37)	
Charlson comorbidity score		< .001
0	Reference	
1	1.51 (1.26-1.81)	
2+	2.80 (2.34-3.34)	

NOS, Not otherwise specified.

DISCUSSION

We identified that chronic opioid use before lobectomy was associated with significantly increased hospital charges, length of stay, 30- and 90-day mortality, and hospital readmissions. To our knowledge, this represents the first large population-based study to investigate the influence of opioid use before lung surgery.

A propensity-matched study of 5.7 million adults who underwent cardiac surgery showed that an opioid use disorder before cardiac surgery was associated with a higher incidence of major complications, including blood transfusions, pulmonary embolism, prolonged mechanical ventilation, and pain.² Similarly, worse perioperative outcomes among those who abuse or are dependent on opioid drugs have been reported among surgeries at several other sites,¹²⁻¹⁸ with increased costs, longer length of stay, increased morbidity, mortality, and 30-day readmission having all been reported. Complications or reason for readmission among these studies were predominantly infectious, pulmonary, and pain-related.^{12,13,18} In other studies, any amount of preoperative opioid use has also been

TABLE 3. Unmatched early operative outcomes according to preoperative opioid use

Outcome	No preoperative chronic opioid use (n = 5493)		Preoperative chronic opioid use (n = 944)	P value
	Opioid naïve (N = 3627)	Intermittent opioid use (n = 1866)		
Complications	2037 (56)	1116 (59)	610 (64)	<.001
Length of hospital stay (d)	6 (4-9)	6 (4-9)	7 (5-10)	<.001
Discharge status				<.001
Home	3004 (83)	1521 (82)	689 (73)	
Skilled nursing facility	372 (10)	215 (12)	140 (15)	
Long-term care hospital	54 (1)	23 (1)	29 (3)	
Rehabilitation facility	82 (2)	39 (2)	26 (3)	
Not applicable/expired	74 (2)	44 (2)	36 (4)	
Other	41 (1)	24 (1)	24 (3)	
Mean hospital charges (\$)	104,781	107,375	119,253	<.001
30-d mortality	127 (3.5)	72 (3.9)	58 (6.1)	.001
90-d mortality	201 (5.5)	120 (6.4)	89 (9.4)	<.001
30-d hospital readmission	427 (12)	262 (14)	152 (16)	<.001
90-d hospital readmission	741 (20)	448 (24)	290 (31)	<.001
90-d hospital readmission rate according to readmission diagnosis*				
Pulmonary	371 (10)	233 (12)	147 (16)	<.001
Cardiac	260 (7)	140 (8)	85 (9)	.163
Hematologic	94 (3)	56 (3)	36 (4)	.129
Renal	284 (8)	155 (8)	114 (12)	<.001
Infectious	320 (9)	206 (11)	143 (15)	<.001
Neurologic	46 (1)	27 (1)	17 (2)	.452
Gastrointestinal	24 (<1)	15 (<1)	<11 (<1)	.612
Pain	11 (<1)	<11†	<11†	.158

Values are presented as n (%) or median (interquartile range). *More than one category may be present per patient; 287 patients were uncategorized. †Cells representing ≤10 were suppressed per Surveillance, Epidemiology and End Results–Medicare guidelines.

independently associated with increased operative morbidity, length of stay, 30-day readmissions, and costs.^{3,4,19,20}

Although methods to adjust for confounding were used for the above studies, patients who use opioid drugs before surgery harbor high-risk characteristics, as shown in our study and in other articles. Those who use opioid drugs before surgery are younger, are more likely to be a smoker or use illicit drugs, have worse pain, higher rates of depression, worse fibromyalgia scores, lower life satisfaction, and more medical comorbidities.²¹ Separately, younger age, race, female sex, and body mass index have been shown to be associated with chronic preoperative opioid use.²² In addition, opioid use has also been shown to be associated with poor compliance with treatment recommendations.²³

Opioid drugs may plausibly increase morbidity through their immunosuppressive properties.⁵ In a mouse sepsis model with *Streptococcus pneumoniae* inoculation, chronic morphine treatment resulted in suppression of nuclear factor kappa light chain enhancer of activated B cells as well as modulation of macrophage inflammatory protein 2 and

inflammatory cytokines.⁶ Delayed neutrophil recruitment, increased bacterial burden in the lung, spleen, and blood, and increased mortality was observed. Among observational studies, opioid drugs have been shown to be associated with an increased risk of community-acquired pneumonia²⁴ and also invasive pneumococcal disease.²⁵ In addition, peripheral opioid receptors regulate wound healing through multiple levels, including modulating keratinocyte differentiation, migration, and adhesion.^{26,27} Mice treated with chronic morphine demonstrated delayed neutrophil and macrophage recruitment to wound sites, downregulation of neurokinin-1 neurokinin-2, decreased wound closure, and increased bacterial sepsis.²⁸⁻³⁰ Morphine decreases expression of hypoxia inducible factor 1-alpha and vascular endothelial growth factor, suppresses angiogenesis, and resulted in decreased wound closure in a rat model.^{31,32} Lastly, topical naloxone given to rats with type 1 diabetes show hastened wound closure with stimulation of angiogenesis.³³ Perhaps not surprising based on these findings, postoperative opioid use remained an independent predictor of wound dehiscence after

TABLE 4. Matched early operative outcomes according to preoperative opioid use

Outcome	Naïve or intermittent preoperative opioid use (n = 1816)	Chronic preoperative opioid use (n = 908)	P value
Complications	1103 (61)	583 (64)	.079
Length of hospital stay (d)	6 (4-9)	7 (5-10)	.002
Discharge status			<.001
Home	1462 (81)	665 (73)	
Skilled nursing facility	215 (12)	136 (15)	
Long-term care hospital	34 (2)	25 (3)	
Rehabilitation facility	43 (2)	26 (3)	
Not applicable/expired	37 (2)	34 (4)	
Other	25 (1)	22 (2)	
Mean hospital charges (\$)	106,405	118,931	<.001
30-d mortality	60 (3)	54 (6)	.001
90-d mortality	99 (5)	85 (9)	<.001
30-d hospital readmission	257 (14)	142 (16)	.301
90-d hospital readmission	415 (23)	275 (30)	<.001
90-d hospital readmission rate according to readmission diagnosis*			
Pulmonary	213 (12)	139 (15)	.009
Cardiac	121 (7)	80 (9)	.043
Hematologic	44 (2)	34 (4)	.051
Renal	143 (8)	105 (12)	.002
Infectious	182 (10)	136 (15)	<.001
Neurologic	27 (1)	15 (2)	.741
Gastrointestinal	15 (<1)	<11 (<1)	.882
Pain	<11†	<11†	.135

Values are presented as n (%) or median (interquartile range). *More than one category may be present per patient; 287 patients were uncategorized. †Cells representing ≤10 were suppressed per Surveillance, Epidemiology and End Results–Medicare guidelines.

abdominopelvic surgery.⁷ In addition, opioid dose among 450 patients was independently associated with delayed time to healing for chronic wounds, after taking into account pain level.³⁴ Lastly, in a large, propensity-matched analysis of the SEER-Medicare database, opioid use after lobectomy for stage I NSCLC was associated with decreased survival and decreased cancer-specific survival.³⁵

Opioid using patients have been shown in other studies to demonstrate an increased burden of cardiovascular disease. An analysis of 29,025 patients enrolled in the Reasons for Geographic and Racial Differences in Stroke prospective cohort study revealed that, after adjustment for coronary risk factors, prescription opioid use was associated with an increased risk of cardiovascular death during the study duration.³⁶ In addition, chronic analgesia use with opioid or cyclooxygenase-2 therapy has been shown to be associated with a higher risk of myocardial infarction.^{37,38}

Separately, without adjusting for opioid use, chronic pain has been shown to be associated with an increased risk of cardiovascular disease.³⁹ Plausible mechanisms may include decreased vascular endothelial growth factor expression among cultured myocytes subject to hypoxia,^{40,41} increased arterial stiffness,⁴² or other unidentified pathways.

Opioid use-reduction strategies are actively being developed, largely in the postoperative setting. The implementation of an enhanced recovery after thoracic surgery pathway, which included the use of multimodal analgesia, was associated with a significant reduction in opioid use after surgery.⁴³ Other interventions have also been successful, including an intervention bundle consisting of patient and provider education that included the use of multimodal analgesia and resulted in a significant reduction in prescribed opioid drugs without an increase in postoperative pain.⁴⁴ A large quality improvement study involving a regional health system over a 16-month period with more than a million clinical encounters also resulted in a rather substantial 58% reduction in prescribed opioid medications.⁴⁵

There are several limitations to this retrospective study. Although we performed a detailed propensity score-matching analysis, there is a risk of confounding with variables that were not measured with Medicare claims files. These may include preoperative functional status, physiologic reserve, detailed psychiatric illness, and comorbid conditions predisposing to chronic pain that are not included in the Charlson comorbidity score. In addition, our study population represents a population-based cancer registry with those individuals enrolled in Medicare and older than age 65 years, which may represent different kinds of patients than those sampled in other database studies. Strengths of this study include the use of detailed and comprehensive prescription records, SEER cancer registry data, and large population-level analysis.

CONCLUSIONS

We identified that chronic opioid users represent high-risk patients, with nearly doubled 30-day and 90-day mortality as well as increased 90-day hospital readmissions. Readmissions relating to infectious, renal, pulmonary, and cardiac causes were significantly higher among chronic users of opioid drugs. Patients undergoing elective lobectomy for lung cancer should be screened to identify chronic opioid use, and these patients should be optimized medically preoperatively. Consideration should be given toward preoperative opioid use-reduction strategies. Because of the higher rate of readmissions in this patient cohort, careful discharge planning and vigilant postoperative follow-up should be undertaken.

TABLE 5. Factors associated with 90-day readmission in matched cohort

Factor	Univariable	P value	Multivariable	P value
	Odds ratio (95% Confidence interval)		Odds ratio (95% Confidence interval)	
Opioid use		<.001		<.001
Naïve	Reference		Reference	
Intermittent	1.40 (1.12-1.74)		1.35 (1.07-1.71)	
Chronic	1.67 (1.36-2.04)		1.72 (1.40-2.12)	
Age group (y)		.088		.098
>80	Reference		Reference	
66-70	0.76 (0.56-1.04)		0.75 (0.54-1.04)	
71-75	0.73 (0.53-1.01)		0.72 (0.51-1.00)	
76-80	0.92 (0.66-1.29)		0.91 (0.64-1.30)	
Sex		<.001		<.001
Male	Reference		Reference	
Female	0.72 (0.60-0.86)		0.71 (0.59-0.87)	
Race		.982		.408
Non-Hispanic white	Reference		Reference	
Hispanic	1.00 (0.69-1.47)		0.82 (0.54-1.25)	
Non-Hispanic black	0.96 (0.69-1.34)		0.76 (0.53-1.09)	
Non-Hispanic other	0.88 (0.42-1.86)		0.83 (0.38-1.84)	
Year of diagnosis		.256		.274
2008	Reference		Reference	
2009	0.99 (0.73-1.34)		1.00 (0.73-1.37)	
2010	1.10 (0.82-1.48)		1.10 (0.80-1.49)	
2011	1.21 (0.91-1.61)		1.26 (0.93-1.70)	
2012	0.89 (0.66-1.20)		0.90 (0.66-1.23)	
2013	0.89 (0.66-1.20)		0.93 (0.68-1.28)	
Urban/rural		.183		.059
Big metro	Reference		Reference	
Metro	1.12 (0.92-1.37)		1.01 (0.79-1.29)	
Urban	0.83 (0.58-1.20)		0.70 (0.46-1.06)	
Less urban	0.88 (0.66-1.16)		0.71 (0.50-1.02)	
Rural/unknown	0.72 (0.45-1.14)		0.59 (0.35-0.99)	
Marriage status		.161		.044
Married	Reference		Reference	
Not married	1.19 (0.99-1.42)		1.28 (1.05-1.56)	
Unknown	1.15 (0.71-1.86)		1.23 (0.74-2.05)	
Education		.038		.044
0-5.66	Reference		Ref	
5.66-10.5	1.33 (0.98-1.80)		1.42 (1.02-1.97)	
10.5-19.35	1.17 (0.88-1.57)		1.35 (0.95-1.92)	
≥19.35	1.46 (1.10-1.93)		1.68 (1.15-2.47)	
Poverty		.435		.726
0-5.24	Reference		Reference	
5.24-10.03	0.90 (0.67-1.22)		0.85 (0.61-1.19)	
10.03-18.19	0.86 (0.65-1.13)		0.84 (0.60-1.19)	
≥18.19	1.01 (0.78-1.32)		0.90 (0.62-1.32)	
Stage		.068		.185
I	Reference		Reference	
0	1.52 (0.14-16.9)		2.32 (0.20-26.8)	
II	1.22 (0.94-1.58)		1.18 (0.90-1.56)	
III	0.97 (0.76-1.24)		0.95 (0.73-1.23)	
IV	1.65 (1.10-2.48)		1.53 (1.00-2.34)	
Unknown	0.71 (0.42-1.20)		0.72 (0.39-1.32)	

(Continued)

TABLE 5. Continued

Factor	Univariable	P value	Multivariable	P value
	Odds ratio (95% Confidence interval)		Odds ratio (95% Confidence interval)	
Tumor histology		.004		.416
Adenocarcinoma	Reference		Reference	
Large cell	1.53 (0.97-2.41)		1.23 (0.75-2.00)	
Other/NOS	1.08 (0.74-1.59)		1.14 (0.74-1.76)	
Squamous	1.38 (1.15-1.66)		1.18 (0.96-1.45)	
Tumor size (cm)		.514		.968
<2	Reference		Reference	
2-3	1.12 (0.88-1.42)		1.03 (0.81-1.33)	
3-5	1.16 (0.92-1.47)		1.01 (0.79-1.30)	
≥5	1.21 (0.92-1.59)		0.96 (0.71-1.31)	
Surgery approach		.003		.005
Open	Reference		Reference	
Video-assisted thoracoscopic surgery	0.75 (0.62-0.90)		0.75 (0.61-0.92)	
Neoadjuvant therapy		.548		.851
No	Reference		Reference	
Yes	1.10 (0.80-1.52)		1.03 (0.73-1.46)	
Grade		<.001		.018
Well differentiated	Reference		Reference	
Moderately differentiated	1.46 (1.08-1.98)		1.31 (0.95-1.80)	
Poorly differentiated	1.97 (1.45-2.66)		1.64 (1.18-2.30)	
Unknown	1.64 (1.08-2.51)		1.50 (0.95-2.38)	
Charlson comorbidity score		<.001		<.001
0	Reference		Reference	
1	1.21 (0.96-1.53)		1.16 (0.91-1.48)	
2+	1.75 (1.40-2.17)		1.58 (1.25-2.00)	

NOS, Not otherwise specified.

Webcast

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Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: lung cancer, lobectomy, opioid dependency, perioperative morbidity

Discussion

Dr Michael J. Liptay (Chicago, Ill).
I would like to congratulate Dr Nelson and his colleagues for a well-presented and timely study. Thanks also for providing the manuscript well beforehand.

The opioid crisis is front and center and recognized as a major challenge facing our health care system. Surgeons are often unwitting contributors—a presentation just yesterday concluded that 1 out of 14 patients undergoing major cardiothoracic surgeries become chronic opioid users. You have shown with your data today the serious potential risk for increased complications and mortality if a future lobectomy is needed.

It was interesting to me that more than half of patients in all the groups underwent a thoracotomy and not a minimally invasive approach. The chronic opioid users who seemingly would benefit most from a minimally invasive approach underwent a video-assisted thoracoscopic

surgical approach only 35% of the time compared with 44% of the opioid naïve cohort. I know this isn't your institution—it's a database review—but do you have any thoughts on that?

Dr David B. Nelson (*Houston, Tex*). That is a great question. A benefit of looking at Surveillance, Epidemiology and End Results–Medicare data is you look at what happens nationwide as opposed to at an experienced tertiary care center.

Dr Liptay. I don't know what the lag is in entering data, but you looked at data from 2008 to 2013. Do you think if you looked at data from 2013 to 2018 it would be different?

Dr Nelson. That's certainly a possibility. Others have published data showing that the use of minimally invasive approaches in general, including robotic surgery, is still increasing, with fewer open cases being performed. There is an update in the Surveillance, Epidemiology and End Results–Medicare file to 2015, which may help clarify this. Certainly, the use of VATS might be higher more recently.

Dr Liptay. You noted that using video-assisted thoracoscopic surgical approach translated into a decreased risk of 90-day readmissions of a hazard ratio of 0.75, I think.

You say in your Conclusions that you would need to optimize medically these chronic opioid users before taking them to surgery, but you also mention that chronic opioid

users are often of poor economic status, less educated, continue to smoke, and are less compliant with recommendations. How do you medically optimize these people in your practice?

Dr Nelson. It may be difficult to tease out the differences of the effect of opioids use on readmission opposed to other factors that could be contributing, such as smoking or medication compliance. It may be the case that, even without knowing opioid use status, a provider would know whether or not a patient needs medical optimization. Obviously, if you are still smoking and other factors you mentioned, those are risk factors that need to be targeted. I think everything you can do to optimize a patient before surgery is important. Among these factors—based on our research—may be opioid reduction.

Dr Liptay. Thanks very much.

Dr Nelson. Thank you.

Dr Felix Fernandez (*Atlanta, Ga*). Very well presented and certainly a very timely topic. Did you also query postoperative opioid use in the different patient cohorts in the Surveillance, Epidemiology and End Results–Medicare dataset to look at how that may have influenced or been associated

with the outcomes as well?

Dr Nelson. We haven't looked at that for morbidity. That's a great question.

APPENDIX E1. COMMON PROCEDURAL TERMINOLOGY (CPT)/INTERNATIONAL CLASSIFICATION OF DISEASES, 9TH EDITION (ICD-9)/INTERNATIONAL CLASSIFICATION OF DISEASES FOR ONCOLOGY, THIRD EDITION (ICD-O-3)/NATIONAL DRUG CODE (NDC) CODE IDENTIFICATION

1. Non–small cell lung cancer

Histology code 8010-8015, 8020-8022, 8030-8040, 8046, 8050-8052, 8070-8084, 8090-8110, 8120-8131, 8140-8156, 8160-8162, 8170-8175, 8180, 8190-8221, 8230-8231, 8240-8263, 8270-8280, 8290-8337, 8340-8347, 8350-8390, 8400-8562, 8570-8576, 8580-8671, 8940-8941

2. Surgery codes

a. Pneumonectomy

- i. VATS: 32.5, 32.50; CPT: 32671
- ii. Open: 32.59; CPT: 32440, 32445, 32488

b. Sleeve lobectomy

- i. Open: CPT: 32486
- ii. No ICD-9 code
- iii. No VATS equivalent

c. Sleeve pneumonectomy

- i. Open: CPT: 32442
- ii. No ICD-9 code
- iii. No VATS equivalent

d. Lobar resection

- i. VATS: 32.4, 32.41; CPT: 32663
- ii. Open: 32.49, CPT: 32480

e. Sublobar resection

- i. VATS wedge: 32.20; CPT: 32602, 32607, 32608, 32657, 32666, 32667, 32668
- ii. Open wedge: 32.29; CPT: 32095, 32096, 32097; 32505, 32506, 32507
- iii. VATS segmentectomy: 32.3, 32.30; CPT: 32669
- iv. Open segmentectomy: 32.39; CPT: 32484

3. Opioid (by generic name)

f. Flag

- i. Oxycodone
 - ii. Tramadol
 - iii. Codeine
 - iv. Dihydrocodeine
 - v. Fentanyl
 - vi. Oxymorphone
 - vii. Morphine
 - viii. Methadone
 - ix. Meperidine
 - x. Hydromorphone
 - xi. Hydrocodone
 - xii. Tapentadol
 - xiii. Pentazocine
 - xiv. Butorphanol
 - xv. Nalbuphine
 - xvi. Pentazocine
 - xvii. Buprenorphine
 - xviii. Propoxyphene
 - xix. Levorphanol
- g. Without the following flags**

- i. Butalbital
- ii. Guaifenesin
- iii. Homatropine
- iv. Phenylephrine
- v. Pseudoephedrine

FIGURE E1. Mirror histograms indicating propensity score distribution before and after propensity matching.

FIGURE E2. Standardized mean differences before and after propensity matching.

TABLE E1. International Classification of Diseases-Ninth Revision (ICD-9) diagnosis codes upon hospital readmission

Complication category	Diagnosis	ICD-9 diagnosis code
Respiratory	Chronic obstructive pulmonary disease	491.21 491.22 492.*
	Aspiration	507.* 508.8* 508.9*
	Other	997.3*
	Pleurisy	511.*
	Pneumothorax	512.*
	Pulmonary insufficiency	518.*
	Respiratory arrest	799.1*
	Respiratory distress	786.* except 786.5*
Cardiac	Myocardial infarction	410.* 411.*
	Dysrhythmias	427.0* 427.1* 427.2* 427.3* 427.4* 427.89 427.9*
	Heart failure	428.0 428.1 428.2 428.21 428.23 428.3 428.31 428.33 428.4 428.41 428.43 428.9
	Other	997.1 785.51 998.01
	Pericarditis	420.*
	Cardiac arrest	427.5
	Chest pain NOS	413.*
	Blood loss anemia	285.1*
Heme	Thromboembolic events (deep vein thrombosis and pulmonary embolism)	415.1* 453.4*
	Embolism	444.*
	Gastrointestinal bleed	578.*
Gastrointestinal	Obstruction, nausea, or vomiting	560.*, 536.*, 787.0*
Renal	Acute kidney injury	584.* 586.*
	Electrolyte/fluid	276.*
	Syncope	780.2
Infectious	Pneumonia	481.* 482.* 483.* 507.* 486.* 513.*
	Wound infection	998.5*, 998.02
	Cellulitis	682.*
	Bacteremia, septicemia or SIRS	038.* 790.7 995.9*
	Urinary tract infection	599.0
	Shock	785.5*
	Empyema	510.*
	Wound	875.*, 998.*
Neuro	Cerebrovascular attack/transient ischemic attack	434.* 435.*, 431
	Postoperative stroke or hemorrhage	997.02
	Encephalopathy	348.*
Pain	Pain	292.0 292.11, 292.12, 292.2, 292.8, 292.82, 292.83, 292.84, 292.85, 292.89, 292.9 338.12, 338.18, 338.19 786.5* 965.00, 965.01, 965.02, 965.09 967.0, 967.6, 967.8-968.0, 969.*, 970.1, 970.8, 970.81, 970.89, 970.9, 975.2, 975.4, 975.6, 976.1

NOS, Not otherwise specified; SIRS, systemic inflammatory response syndrome.

TABLE E2. Matched patient, tumor, and treatment characteristics after propensity matching 1:2 according to chronic opioid use

Characteristic	Preoperative naïve or intermittent opioid use (n = 1816)	Preoperative chronic opioid use (n = 908)	P value
Age (y)			.865
66-70	738 (41)	355 (39)	
71-75	573 (32)	290 (32)	
76-80	349 (19)	184 (20)	
>80	156 (9)	79 (34)	
Sex			.781
Male	712 (39)	351 (39)	
Female	1104 (61)	557 (61)	
Year of diagnosis			.999
2008	317 (17)	157 (17)	
2009	281 (15)	140 (15)	
2010	287 (16)	147 (16)	
2011	322 (18)	159 (18)	
2012	311 (17)	158 (17)	
2013	298 (16)	147 (16)	
Race/ethnicity			.823
Non-Hispanic white	1563 (86)	770 (85)	
Non-Hispanic black	130 (7)	73 (8)	
Hispanic	97 (5)	52 (6)	
Non-Hispanic other	26 (1)	13 (2)	
Urban/rural			.994
Big metro	860 (47)	435 (48)	
Less urban	226 (12)	112 (12)	
Metro	525 (29)	259 (29)	
Rural/unknown	83 (5)	39 (4)	
Urban	122 (7)	63 (7)	
Marital status			.690
Married	808 (44)	402 (44)	
Not married	943 (52)	479 (53)	
Unknown	65 (4)	27 (3)	
% Below poverty line within ZIP code			.985
0-5.4	268 (15)	136 (15)	
5.4-10.3	552 (30)	270 (30)	
10.3-18.8	345 (19)	176 (19)	
≥18.8	651 (36)	326 (33)	
% With no high school education within ZIP code			.731
0-5.8	254 (14)	140 (15)	
5.8-11.0	545 (30)	274 (30)	
11.0-20.0	410 (23)	194 (21)	
≥20.0	607 (33)	300 (33)	
Charlson comorbidity score			.904
0	517 (28)	252 (28)	
1	589 (32)	294 (33)	
2+	710 (39)	362 (40)	
Histology			.973
Adenocarcinoma	1017 (56)	512 (56)	
Squamous	631 (35)	314 (35)	
Large cell	56 (3)	32 (4)	
Other/NOS	107 (6)	50 (6)	

(Continued)

TABLE E2. Continued

Characteristic	Preoperative naïve or intermittent opioid use (n = 1816)	Preoperative chronic opioid use (n = 908)	P value
Grade			.975
Well differentiated	235 (13)	122 (13)	
Moderately differentiated	786 (43)	387 (43)	
Poorly differentiated	666 (37)	336 (37)	
Unknown	129 (7)	63 (7)	
Stage			.935
I	1147 (63)	582 (34)	
II	224 (12)	119 (13)	
III	303 (17)	140 (15)	
IV	74 (4)	37 (4)	
Unknown/0	68 (4)	30 (3)	
Tumor size (cm)			.981
<2	478 (26)	233 (26)	
2-3	504 (28)	254 (28)	
3-5	548 (30)	279 (31)	
≥5	286 (67)	142 (16)	
Approach			.799
Open	1177 (65)	584 (64)	
Video-assisted thoracoscopic surgery	639 (35)	324 (36)	
Chemotherapy			.737
None	1262 (69)	636 (70)	
Neoadjuvant	118 (7)	64 (7)	
Adjuvant	436 (24)	208 (23)	
Radiation			.242
None	1510 (83)	777 (86)	
Neoadjuvant	57 (3)	22 (2)	
Adjuvant	249 (14)	109 (12)	

Values are presented as n (%). NOS, Not otherwise specified.