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Potential opioid-related adverse events following spine surgery in elderly patients

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ABSTRACT

Objective: Understanding the clinical and economic impact of opioid-related adverse drug events (ORADEs) within spine surgery may guide both the clinician's and hospital administration's approach to treating perioperative pain, thus improving patient care and reducing hospital costs. The objective of this analysis is to understand how potential ORADEs after spine surgery in elderly patients affect length of stay, hospital revenue and their association with comorbid conditions.

Patients and methods: We conducted a retrospective study utilizing the Center for Medicare/Medicaid Services Administrative Database to analyze Medicare discharges between April 2016 and March 2017 involving 14 spine surgery DRGs for major spine procedures in order to identify potential ORADEs. An analysis was conducted using this database to identify the incidence of potential ORADEs as well as their impact on mean hospital length of stay and hospital revenue.

Results: There were 177,432 discharges during the study period. The ORADE rate in patients undergoing spine surgery was 13.9% (24,642/177,432). The mean length of stay (LOS) for discharges with an ORADE was 3.13 days longer than without an ORADE (6.29 days with an ORADE vs 3.16 days without an ORADE). The adverse post-operative outcomes most strongly associated with potential ORADEs included shock, pneumonia, and septicemia. The mean hospital revenue per day with an ORADE was $3,076 less than without an ORADE ($7,263 with an ORADE vs $10,339 without an ORADE).

Conclusion: Potential ORADEs in spine surgery in elderly patients are common and are associated with longer hospitalizations and decreased hospital revenue. Perioperative pain management strategies that reduce ORADEs may improve patient care and increase hospital revenue.

1. Introduction

Inadequately managed postoperative pain extends hospital stays, impairs functional recovery, and is associated with higher rates of readmission and increased cardiopulmonary complications [1–3]. Sufficient pain management contributes to improved overall outcomes, higher patient satisfaction, and decreased healthcare resource use and cost [4]. Typical treatment of postoperative pain relies on opioid analgesics; it has been shown that nearly all surgical patients and half of all inpatients receive opioids during their hospitalization [4–6]. The use of opioids is unfortunately limited by well-known deleterious side effects including respiratory depression, bowel dysmotility, oversedation, nausea, vomiting, and urinary retention, and overreliance on opioids thereby incurs higher risk of opioid-related adverse events (ORADEs) [7].

ORADEs encompass a heterogenous group of complications pertaining to multiple organ systems, rendering reliable quantification of their impact difficult. A universally accepted definition or metric allowing measurement of ORADEs does not currently exist [8]. While some research groups have focused on the most severe ORADEs, i.e. respiratory arrest requiring naloxone administration and cardiopulmonary resuscitation, this strategy ignores the significant morbidity and subsequent increases in hospital length of stay (LOS) and costs associated with less severe but common ORADEs such as pruritus,

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Table 1
ICD-10 diagnosis codes commonly associated with ORADEs.

ICD-10 Code	Brief Description
Gastrointestinal ORADEs	
K567	Ileus, unspecified
K560	Paralytic ileus
K590.0	Constipation, unspecified
K590.9	Other constipation
K590.3	Drug induced constipation
K590.1	Slow transit constipation
K918.9	Other postprocedural complications and disorders of digestive system
R112	Nausea with vomiting, unspecified
K910	Vomiting following gastrointestinal surgery
Central Nervous System ORADEs	
R400	Somnolence
R410	Disorientation, unspecified
R418.2	Altered mental status, unspecified
R401	Stupor
G978.2	Other postprocedure complications and disorders of nervous sys
H814.9	Vertigo of central origin, unspecified ear
H814.3	Vertigo of central origin, bilateral
H814.1	Vertigo of central origin, right ear
H814.2	Vertigo of central origin, left ear
Respiratory ORADEs	
J960.1	Acute respiratory failure with hypoxia
J960.0	Acute respiratory failure, unspecified with hypoxia or hypercapnia
J958.21	Acute postprocedural respiratory failure
J960.2	Acute respiratory failure with hypercapnia
J969.0	Respiratory failure, unspecified, unspecified with hypoxia or hypercapnia
J969.1	Respiratory failure, unspecified with hypoxia
J952	Acute pulmonary insufficiency following nonthoracic surgery
J951	Acute pulmonary insufficiency following thoracic surgery
J969.2	Respiratory failure, unspecified with hypercapnia
J958.22	Acute and chronic postprocedural respiratory failure
J962.1	Acute and chronic respiratory failure with hypoxia
J962.0	Acute and chronic respiratory failure, unspecified with hypoxia or hypercapnia
J962.2	Acute and chronic respiratory failure with hypercapnia
R068.9	Other abnormalities of breathing
J80	Acute respiratory distress syndrome
R060.0	Dyspnea, unspecified
R060.9	Other forms of dyspnea
R090.2	Hypoxemia
J958.9	Other postprocedure complications and disorders of respiratory system, NEC
J182	Hypostatic pneumonia, unspecified organism
Urinary ORADEs	
R339	Retention of urine, unspecified
R338	Other retention of urine
R330	Drug induced retention of urine
N998.9	Other postprocedural complications and disorders of GU sys
Other ORADES	
L299	Pruritus, unspecified
T402.X5A	Adverse effect of other opioids, initial encounter
T406.05A	Adverse effect of unspecified narcotics, initial encounter
T404.X5A	Adverse effect of other synthetic narcotics, initial encounter
T406.95A	Adverse effect of other narcotics, initial encounter
T402.X5S	Adverse effect of other opioids, sequela
T400.X5A	Adverse effect of opium, initial encounter
T406.05S	Adverse effect of unspecified narcotics, sequela
T404.X5S	Adverse effect of other synthetic narcotics, sequela
T406.95S	Adverse effect of other narcotics, sequela
R682	Dry mouth, unspecified
T400.X5S	Adverse effect of opium, sequela
W183.0XA	Fall on same level, unspecified, initial encounter
W183.9XA	Other fall on same level, initial encounter
W06.XXXA	Fall from bed, initial encounter
W04.XXXA	Fall while being carried or supported by other persons, initial
W04.XXXD	Fall while being carried or supported by other persons, subsequent
W183.1XD	Fall on same level due to stepping on an object, subsequent encounter

sedation, nausea, vomiting, and ileus [6,9–11]. Researchers have applied the severe and broader definitions in studies examining ORADEs both at the local level and by using a combination of administrative database searches in concert with confirmatory retrospective chart review [5,12–14]. The definition of ORADEs used by the current study includes respiratory dysfunction, ileus, nausea, vomiting, changes in mental status, urinary retention, diarrhea, falls, and pruritus not present on admission, all of which have been previously associated with opioids and specific *International Classification of Diseases, Ninth Revision* (ICD-10) codes. Multiple recent studies have applied this methodology to define ORADEs with validation via manual review of locally available data.

The rates of spine surgery are increasing dramatically alongside the increasing prevalence of low back pain in the United States [15]. The Agency for Healthcare Research and Quality (AHRQ) estimated a 40% increase in spinal fusions in a 7 year period, and Deyo and colleagues reported a 15-fold increase in the rates of spinal fusion from 2002 to 2007 [16]. Spinal procedures are associated with higher levels of postoperative pain compared to other surgeries [17]. In a review of 179 surgical subtypes, three of the top six most painful procedures were spinal surgeries: lumbar fusion (1–2 levels), lumbar fusion (> 3 levels), and complex spinal reconstruction [18]. Elevated post-surgical pain in these populations thereby amplifies the risk of ORADEs.

This retrospective study utilized the Center for Medicare and Medicaid Services (CMS) administrative claims database to identify potential ORADEs and their incremental cost among Medicare discharges following spine surgery. The impact of opioid based analgesia in spine surgery specifically has not been well characterized. Little is known about the effect of ORADEs following spine surgery on LOS, hospital revenue, and relevant associations with clinical disease states, especially in the elderly. The purpose of this study was to determine the incidence of ORADEs in Medicare patients undergoing spine surgery, and to quantify the impact of these adverse events on clinical and economic outcomes. We hypothesized that ORADEs are associated with increased LOS, decreased hospital revenue, and display significant associations with certain comorbidities and demographic factors. Awareness of the clinical and economic impact of ORADEs will allow healthcare administrators and clinicians to determine the subgroups of spine surgery most likely to benefit from postoperative pain quality improvement efforts, potentially reducing cost and improving patient outcomes.

2. Materials and methods

2.1. Study design

This retrospective study utilized data from the Medicare Limited Data Sets (LDS), an administrative claims database from the (CMS) [19]. LDS effectively contains data from all hospitals in the United States that provide care for patients with Medicare, totaling approximately 30–35% of all inpatient hospital discharges. The CMS database has been used in previous quality improvement initiatives, and outcomes have been tied to hospital reimbursement [20]. In an effort to

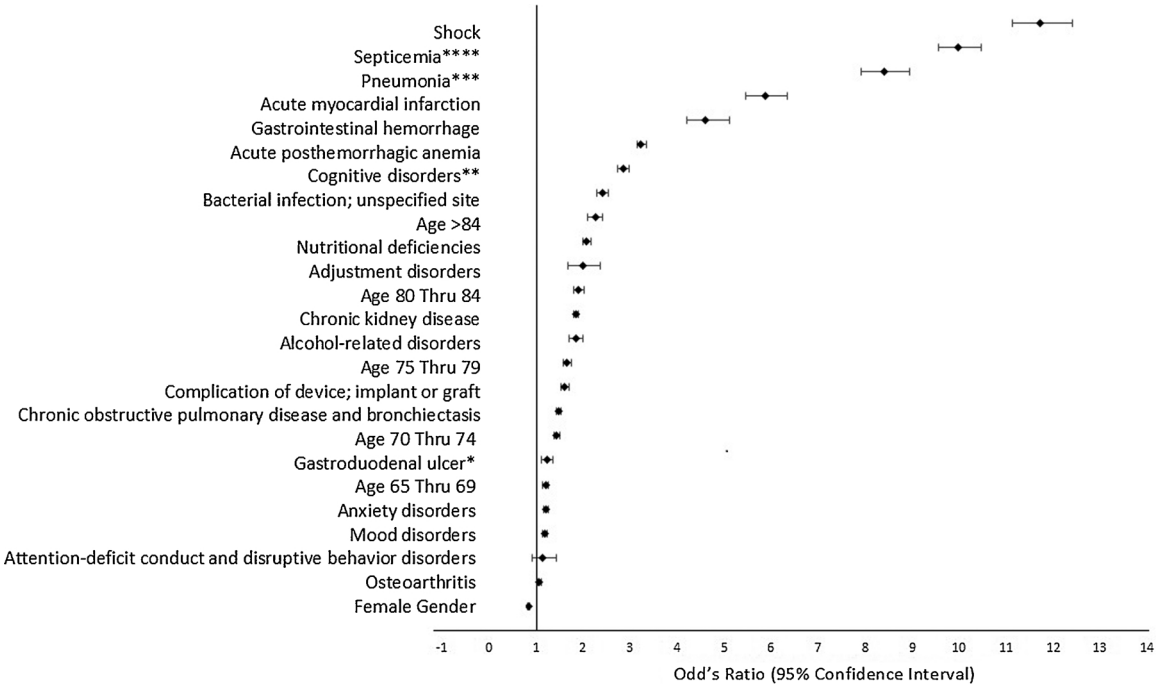

Fig. 1. Multivariable association between potential ORADEs and Agency for Healthcare Research and Quality (AHRQ) Clinical Classification Software (CCS) categories among spine surgery DRGs 453–460, 471–473, 518-520.
****except in labor.
***except that caused by tuberculosis or sexually transmitted disease.
**Cognitive disorders include delirium, dementia, and amnestic and other cognitive disorders.
*except hemorrhage.

Table 2A
Total discharges and ORADE rate following spine surgery.

DRG	DRG Description	Total Discharges (Apr 2016 to March 2017)	ORADE Rate
453	Combined Anterior/Posterior Spinal Fusion With Mcc	1,897	57.6
454	Combined Anterior/Posterior Spinal Fusion With Cc	6,220	23.6
455	Combined Anterior/Posterior Spinal Fusion Without Cc/Mcc	5,690	7.9
456	Spinal Fusion Except Cervical With Spinal Curvature Or Malignancy Or Infection Or Extensive Fusions With Mcc	1,703	54.1
457	Spinal Fusion Except Cervical With Spinal Curvature Or Malignancy Or Infection Or Extensive Fusions With Cc	4,636	24.3
458	Spinal Fusion Except Cervical With Spinal Curvature Or Malignancy Or Infection Or Extensive Fusions Without Cc/Mcc	1,811	10.2
459	Spinal Fusion Except Cervical With Mcc	6,126	47.1
460	Spinal Fusion Except Cervical Without Mcc	79,389	12.0
471	Cervical Spinal Fusion With Mcc	3,797	40.4
472	Cervical Spinal Fusion With Cc	17,717	9.1
473	Cervical Spinal Fusion Without Cc/Mcc	25,030	3.5
518	Back And Neck Procedures Except Spinal Fusion With Mcc Or Disc Device Or Neurostimulator	3,894	22.2
519	Back And Neck Procedures Except Spinal Fusion With Cc	8,880	15.6
520	Back And Neck Procedures Except Spinal Fusion Without Cc/Mcc	10,642	6.8
	All DRGs	177,432	13.9

ORADE = opioid-related adverse drug event; DRG = diagnosis-related group; Mcc = major complications or comorbidities; Cc = complications or comorbidities.

promote transparency to health care consumers, CMS has made certain metrics from its database publicly available at https://www.medicare.gov/hospitalcompare/search.html [21]. Fourteen admission diagnosis-related groups (DRGs) were selected to compare the impact of ORADEs on specific measures such as hospital revenue, mean LOS, and the association of specific comorbidities with potential ORADEs within the study population.

2.2. Study population

The study population included all hospitalizations between April 2016 and March 2017 in which patients with Medicare underwent one of the major spine procedures included in the analysis: combined anterior/posterior spinal fusion with major complications or comorbidities (DRG 453), combined anterior/posterior spinal fusion with complications or comorbidities (DRG 454), combined anterior/posterior spinal fusion without complications or comorbidities (DRG 455), spinal fusion except cervical with spinal curvature or malignancy or infection or extensive fusions with major complications or comorbidities (DRG 456), spinal fusion except cervical with spinal curvature or malignancy or infection or extensive fusions with complications or comorbidities (DRG 457), spinal fusion except cervical with spinal curvature or malignancy or infection or extensive fusions without complications or comorbidities (DRG 458), spinal fusion except cervical

Table 2B
The impact of potential ORADEs on hospital lengh of stay following spine surgery.

DRG	DRG Description	Mean LOS (days)	Mean LOS with Orade	Mean LOS without Orade	Difference in Mean LOS with and without ORADE ($p < 0.001$)
453	Combined Anterior/Posterior Spinal Fusion With Mcc	10.42	11.18	9.39	1.79
454	Combined Anterior/Posterior Spinal Fusion With Cc	5.26	6.36	4.92	1.44
455	Combined Anterior/Posterior Spinal Fusion Without Cc/Mcc	3.22	4.17	3.14	1.03
456	Spinal Fusion Except Cervical With Spinal Curvature Or Malignancy Or Infection Or Extensive Fusions With Mcc	11.19	11.8	10.47	1.33
457	Spinal Fusion Except Cervical With Spinal Curvature Or Malignancy Or Infection Or Extensive Fusions With Cc	6.1	7.11	5.77	1.34
458	Spinal Fusion Except Cervical With Spinal Curvature Or Malignancy Or Infection Or Extensive Fusions Without Cc/Mcc	3.57	4.27	3.5	0.77
459	Spinal Fusion Except Cervical With Mcc	7.41	8.52	6.43	2.09
460	Spinal Fusion Except Cervical Without Mcc	3.29	4.6	3.12	1.48
471	Cervical Spinal Fusion With Mcc	8.42	10.18	7.22	2.96
472	Cervical Spinal Fusion With Cc	3.01	5.15	2.8	2.35
473	Cervical Spinal Fusion Without Cc/Mcc	1.64	2.7	1.6	1.1
518	Back And Neck Procedures Except Spinal Fusion With Mcc Or Disc Device Or Neurostimulator	4.93	8.55	3.89	4.66
519	Back And Neck Procedures Except Spinal Fusion With Cc	3.92	5.35	3.66	1.69
520	Back And Neck Procedures Except Spinal Fusion Without Cc/Mcc	2.16	3.28	2.08	1.2
	All DRGs	3.59	6.29	3.16	3.13

ORADE = opioid-related adverse drug event; LOS = length of stay; DRG = diagnosis-related group; Mcc = major complications or comorbidities; Cc = complications or comorbidities.

with major complications or comorbidities (DRG 459), spinal fusion except cervical without complications or comorbidities (DRG 460), cervical spinal fusion with major complications or comorbidities (DRG 471), cervical spinal fusion with complications or comorbidities (DRG 472), cervical spinal fusion without complications or comorbidities (DRG 473), back and neck procedures except spinal fusion with major complications or comorbidities or disc device or neurostimulator (DRG 518), back and neck procedures except spinal fusion with complications or comorbidities (DRG 519), or back and neck procedures except spinal fusion without complications or comorbidities (DRG 520).

In total, this comprised a cohort of 177,432 Medicare discharges associated with one of these 14 DRGs.

2.3. Measures

The data provided by the LDS database was catalogued by DRGs. Within each DRG, data were further organized by total discharges within each DRG, total CMS payments, ORADE rate, mean LOS (total, with ORADEs, and without ORADEs), and mean hospital revenue per day (total, with ORADEs, and without ORADEs). Using these values, the difference in both hospital revenue and in mean LOS with and without ORADEs were determined, thus allowing for the assessment of potential ORADEs on patient care.

Within this data set, hospital revenue is defined as the CMS reimbursement payment and was obtained from the LDS database. More specifically, the hospital revenue per day for each DRG was calculated by totaling the Medicare payments for the DRG cohort and dividing by the total hospitalization days for that specific DRG. Hospital LOS was defined as the total number of days from admission to discharge in both hospitalization with and without ORADEs. Due the LDS database restrictions on the use of specific hospitalization dates, we were not able to calculate specific postsurgical LOS.

Potential ORADEs were determined by identifying ICD-10 diagnosis codes that were both not present on admission and are commonly associated with ORADEs as listed in Table 1. The ICD-10-CM codes selected were defined and utilized previously in similar studies using validated methodologies [5,7,13,22,23].

While utilizing the LDS database and ICD codes, further analysis was also conducted to understand the association of specific comorbidities present in the study population to potential ORADEs. By using the Agency of Healthcare Research and Quality (AHRQ) Clinical Classification Software (CCS), tens of thousands of ICD codes (over 69,800 diagnosis codes and 71,900 procedure codes) were categorized into groups more suitable for statistical analysis compared to individual ICD-10-CM/PCS codes. From these groups, 21 categories were selected based on their clinical relevance and statistical significance as related to potential ORADEs within spine surgery DRGs 453–460, 471–473, and 518–520.

2.4. Statistical analysis

CMS payments are expressed in U.S. dollars as the total sum of all revenue from hospital discharges within each DRG. LOS is expressed as days and is the mean of all hospital discharges within each DRG. A multivariable regression analysis was utilized to determine the odds ratio (OR) of a potential ORADE for each specific CCS category. A p-value of < 0.05 was considered statistically significant for all analyses, which were performed using RStudio (Boston, MA). This multivariable regression analysis was compiled into a forest plot as demonstrated by Fig. 1. In this multivariable analysis, the reference CCS categories were “male” and “age < 65,” which were thus not included in Table 3 or in Fig. 1.

3. Results

Tables 2A–2C summarize the ORADE rate in spine surgery, the impact of potential ORADEs on LOS, and its effect on hospital revenue in spine surgery. The overall ORADE rate in the 14 DRG groups for spine surgeries was 14.1% (26,695 out of 189,328 records analyzed). The mean LOS of discharges with an ORADE was 1.69 days longer than without an ORADE (5.35 days with an ORADE vs 3.65 days without an ORADE; $p < 0.001$).

As demonstrated by the above tables, each DRG group represents a class of spinal procedures. The categories encompass a broad range of spinal procedures, with fusions comprising the bulk. The procedures are further characterized by the severity of co-existing comorbidities or complications; DRG 471, for instance, represents cervical spinal fusions with major complications or comorbidities (MCC), whereas DRG 472 represents cervical spinal fusions with complications or comorbidities (CC), and 473 is cervical spinal fusions without major complications or comorbidities. This classification allows the authors to analyze each DRG and the associated impact potential ORADEs may have on hospital

Table 2C
The impact of potential ORADEs on hospital revenue following spine surgery.

DRG	DRG Description	Total CMS Payments (USD)	Mean Revenue/Day with ORADE (USD)	Mean Revenue/Day without ORADE (USD)	Mean Difference in Hospital Revenue/day with and without ORADE ($p < 0.001$), USD
453	Combined Anterior/Posterior Spinal Fusion With Mcc	$151,112,253	$7,355	$8,108	$752
454	Combined Anterior/Posterior Spinal Fusion With Cc	$345,732,638	$9,239	$11,100	$1,861
455	Combined Anterior/Posterior Spinal Fusion Without Cc/Mcc	$222,637,039	$9,968	$12,399	$2,431
456	Spinal Fusion Except Cervical With Spinal Curvature Or Malignancy Or Infection Or Extensive Fusions With Mcc	$122,437,867	$6,272	$6,629	$357
457	Spinal Fusion Except Cervical With Spinal Curvature Or Malignancy Or Infection Or Extensive Fusions With Cc	$234,565,582	$7,353	$8,671	$1,318
458	Spinal Fusion Except Cervical With Spinal Curvature Or Malignancy Or Infection Or Extensive Fusions Without Cc/Mcc	$63,525,583	$8,614	$9,981	$1,368
459	Spinal Fusion Except Cervical With Mcc	$250,307,558	$5,041	$6,072	$1,032
460	Spinal Fusion Except Cervical Without Mcc	$1,937,648,204	$5,569	$7,781	$2,212
471	Cervical Spinal Fusion With Mcc	$128,464,065	$3,474	$4,540	$1,066
472	Cervical Spinal Fusion With Cc	$318,523,207	$3,798	$6,375	$2,578
473	Cervical Spinal Fusion Without Cc/Mcc	$323,662,349	$5,072	$8,041	$2,970
518	Back And Neck Procedures Except Spinal Fusion With Mcc Or Disc Device Or Neurostimulator	$70,609,960	$2,486	$4,427	$1,941
519	Back And Neck Procedures Except Spinal Fusion With Cc	$92,539,628	$2,105	$2,806	$701
520	Back And Neck Procedures Except Spinal Fusion Without Cc/Mcc	$69,209,643	$2,210	$3,105	$894
	All DRGs	$4,330,975,575	$7,263.00	$10,339.00	$3,076.00

ORADE = opioid-related adverse drug event; DRG = diagnosis-related group; CMS = Centers for Medicare and Medicaid; USD = United States Dollar; Mcc = major complications or comorbidities; Cc = complications or comorbidities.

revenue and LOS within DRGs. DRG 518 demonstrates the largest difference in mean LOS between discharges with an ORADE versus without, at 4.66 days. The smallest difference is found in DRG 458, with a difference in LOS of 0.77 days between DRGs with and without an ORADE. The difference in mean hospital revenue per day with and without an ORADE was highest for DRG 473, at $2,790, and smallest for DRG 456, at $357.

Our multivariable analysis of potential ORADEs by AHRQ category is grouped by clinical condition or demographic factor in Table 3 and depicted in a Forest plot in Fig. 1. As depicted in the figure and table, the adverse post-operative outcomes that were most strongly associated with potential ORADEs included shock, septicemia, pneumonia, and acute myocardial infarction. Adverse postoperative outcomes were associated with increasing age, with individuals ages 84 and older demonstrating the highest odds ratio among age groups (OR 2.26, 95% CI 2.1–2.43), followed by individuals ages 80–84 (OR 1.91, 95% CI 1.81–2.02), ages 75–79 (OR 1.67, 95% CI 1.59–1.74), ages 70–74 (OR 1.44, 95% CI 1.38–1.5), and ages 65–69 (OR 1.21, 95% CI 1.16–1.26). Patients with cognitive disorders, including dementia and amnestic disorders, demonstrated strong associations with potential ORADEs (OR 2.86, 95% CI 2.67–3.06), followed by those with nutritional deficiencies (OR 2.08, 95% CI 1.97–2.2), adjustment disorders (OR 1.99, 95% CI 1.6–2.49), alcohol-related disorders (OR 1.85, 95% CI 1.69–2.03), and chronic kidney disease (OR 1.85, 95% CI 1.78–1.93). Of note, female gender was associated with a decreased risk of potential ORADE in comparison to male gender (OR 0.85, 95% CI 0.82-0.87).

4. Discussion

ORADEs following spine surgery are common, can negatively impact patient outcomes, and slow functional recovery. This study analyzed the impact of ORADEs in spine surgery, demonstrating an associated overall increase in mean hospital length of stay by 3.13 days and decrease in hospital revenue by $3,076 per day in the presence of ORADEs. In our study, potential ORADEs in the elderly population were most strongly associated with certain post-operative complications such as shock, septicemia, pneumonia, acute myocardial infarction, gastrointestinal hemorrhage, and acute post-hemorrhagic anemia. Several demographic factors also demonstrated significant associations with potential ORADEs. Advanced age in particular exhibited a stepwise increase in odds ratio for ORADEs from ages 65 to > 84.

Opioids remain a fundamental component of perioperative surgical analgesia. Their efficacy is limited by peripheral receptor activity which may lead to the negative consequences of ORADEs [24]. Opioid analgesia must thereby be judiciously balanced to prevent adverse effects, patient harm, and the increased cost associated with ORADEs [11,12,22].

In our study, the most commonly occurring potential ORADEs included shock, septicemia, and pneumonia. The immunomodulatory effects of opioid medication weaken patients' innate defense against infection and may promote shock or septicemia [25]. Opioids also exhibit vasodilatory effects and may exacerbate septic or hemorrhagic shock [26].

Perhaps the most well-known adverse effects of opioids, respiratory depression and hypoventilation, may contribute to pneumonia by several mechanisms. Underinflation of the lungs as a result of decreased respiratory drive can lead to atelectatic states which promote the development of infectious processes [27]. Inherent to spine surgery, many patients' respiratory effort will be diminished as a result of postsurgical pain with breathing or newly altered, more restrictive thoracic anatomy following multilevel vertebral fusions.

Based on our analysis, certain demographic factors significantly impacted the likelihood of ORADE occurrence. Increasing age, in particular, is significantly associated with increased risk of potential ORADE. Patients over the age of 84 were much more likely to suffer a potential ORADE than their younger counterparts. The causes behind

Table 3
Multivariable Association of Potential ORADEs with Clinical Classification Software (CCS) Categories within the Agency for Healthcare Research and Quality (AHRQ).

CCS Category	Total Discharges	Number of ORADEs	ORADE rate	Odds Ratio	p-value
Shock	672	437	39.40	11.72 (9.99 - 13.74)	< 0.001
Septicemia****	861	527	37.97	9.97 (8.69 - 11.44)	< 0.001
Pneumonia***	1690	959	36.20	8.42 (7.64 - 9.28)	< 0.001
Acute myocardial infarction	597	289	32.62	5.87 (5 - 6.9)	< 0.001
Gastrointestinal hemorrhage	320	136	29.82	4.6 (3.68 - 5.75)	< 0.001
Cognitive disorders**	4115	1268	23.56	2.86 (2.67 - 3.06)	< 0.001
Acute posthemorrhagic anemia	22003	6575	23.01	3.24 (3.13 - 3.35)	< 0.001
Bacterial infection; unspecified site	3979	1097	21.61	2.42 (2.26 - 2.6)	< 0.001
> 84 years old	5174	1093	21.12	2.26 (2.1 - 2.43)	< 0.001
Nutritional deficiencies	6780	1659	19.66	2.08 (1.97 - 2.2)	< 0.001
Adjustment disorders	432	105	19.55	1.99 (1.6 - 2.49)	< 0.001
Alcohol-related disorders	2738	624	18.56	1.85 (1.69 - 2.03)	< 0.001
80 - 84 years old	12808	2369	18.50	1.91 (1.81 - 2.02)	< 0.001
Chronic kidney disease	14668	3219	18.00	1.85 (1.78 - 1.93)	< 0.001
Complication of device; implant or graft	7543	1536	16.92	1.62 (1.53 - 1.72)	< 0.001
75 - 79 years old	27773	4581	16.49	1.67 (1.59 - 1.74)	< 0.001
Chronic obstructive pulmonary disease and bronchiectasis	21757	4041	15.66	1.49 (1.44 - 1.55)	< 0.001
70 - 74 years old	41754	6084	14.57	1.44 (1.38 - 1.5)	< 0.001
Gastroduodenal ulcer*	2569	427	14.25	1.24 (1.12 - 1.38)	< 0.001
Anxiety disorders	29381	4664	13.70	1.21 (1.17 - 1.25)	< 0.001
Mood disorders	34193	5355	13.54	1.19 (1.15 - 1.23)	< 0.001
Attention-deficit conduct and disruptive behavior disorders	690	108	13.53	1.15 (0.94 - 1.41)	0.181
Female Gender	96441	12517	12.98	0.85 (0.82 - 0.87)	< 0.001
Osteoarthritis	28582	4190	12.79	1.08 (1.04 - 1.12)	< 0.001
65 - 69 years old	50864	6373	12.53	1.21 (1.16 - 1.26)	< 0.001

ORADE = opioid-related adverse drug event.
* except hemorrhage.
** Cognitive disorders include delirium, dementia, and amnestic and other cognitive disorders.
*** except that caused by tuberculosis or sexually transmitted disease.
**** except in labor.

this association are multifactorial and likely reflect the increased incidence of comorbidities and overall frailty in the elderly population, as well as heightened sensitivity to opioid medications. As patients age, physiologic changes include a decreased volume of distribution of the drug and reduced renal and hepatic metabolism [28–30]. Clinicians need to maintain awareness of the typical doses required in older patients to avoid ORADEs. The American Society of Anesthesiologists (ASA) physical status and comorbid conditions typically increase alongside increasing age; frail, geriatric patients can suffer catastrophic consequences if they experience adverse events such as pneumonia or septicemia, especially following major surgery. Likewise, postoperative recovery may be impaired by other, less severe ORADEs. In the setting of major spine surgery for the medically complex, elderly patient, it is of the utmost importance to optimize the already challenging recovery period by avoiding ORADEs.

The association between ORADEs and increased LOS most likely results from the time required to treat the broad range of clinical scenarios encompassed by ORADEs, listed in Table 1, which includes pruritus, nausea, vomiting, constipation, bowel dysmotility, altered mental status, disorientation, falls, acute respiratory failure, hypoxemia, atelectasis, aspiration pneumonia and urinary retention, among others. In addition, the reduction in hospital revenue may be attributable to the resultant treatment of ORADEs. Prolongation of the hospital stay increases cost by requiring continued medical monitoring, treatment regimens, and intervention specific to each ORADE. Prolonged LOS further exposes patients to risk of hospital-acquired infections such as pneumonia or UTI, especially in the setting of prolonged mechanical ventilation or urinary catheterization [31,32]. Our results align with evidence from prior studies of endoscopic and surgical procedures which demonstrated an association between ORADEs and inferior patient outcomes, increased likelihood of discharge to facilities other than home, increased mortality, and increased rates of 30-day readmission [4,5,12,14,33,34].

Many elderly patients continue to receive opioids as their primary analgesic in spite of their detrimental side effects, yet approximately 75% of patients endorse continued postoperative pain [5,35,36]. Opioid monotherapy for perioperative analgesia is therefore ineffective and exposes patients to increased risk of harm. In light of the growing awareness of opioids' inherent limitations, new strategies have risen to the forefront. The American Pain Society (APS) and American Society of Anesthesiologists (ASA) guidelines recommend a minimum of two modalities in an algorithmic approach for postoperative pain management, beginning with non-opioid medications such as oral or IV non-steroidal anti-inflammatory drugs, acetaminophen, local anesthetics, and regional blocks, with opioids as a rescue [3,37]. Recent Guidelines for perioperative care in elective colorectal surgery from the Enhanced Recovery After Surgery (ERAS) Society and American Society for Enhanced Recovery (ASER) specifically advocate for multimodal analgesia and minimization of opioids [38]. This approach recognizes the multifaceted nature of pain and nociception, and targets several available mechanisms in order to establish a more robust baseline of analgesia than is possible with opioids alone. As a result, multimodal analgesic strategies, applied pre, intra, and postoperatively effectively lower opioid consumption and lessen the risk of ORADEs.

Enhanced Recovery Pathways (ERPs), in concert with multimodal analgesia, have the potential to reduce ORADEs even further. ERPs were first implemented in colorectal surgery as a mechanism to facilitate recovery of bowel function and, among other strategies, stressed the reduction of opioid consumption in order to limit opioid-induced bowel dysmotility. These programs have since been adopted in a variety of surgical subspecialties. While intended to reduce the medical and economic burdens of surgical complications, they also may potentially decrease risk of ORADEs, further reducing cost [39,40]. Considered broadly, ORADE-reducing ERP protocols may consist of specific order sets designed to curtail ORADE incidence and intervene appropriately when they occur. Both minor and major ORADEs would require a tailored approach, e.g. low-dose naloxone infusion for opioid-induced pruritus versus resuscitation doses of naloxone in the setting of

profound opioid-induced respiratory depression. Along those lines, appropriate postoperative monitoring such as telemetry and pulse oximetry may promote earlier detection of ORADEs, allowing clinicians to intervene before severe sequelae occur. With regard to the impact of ORADEs as illustrated by this study, adoption of ERPs and multimodal analgesic strategies may reduce surgical complications and ORADEs, decrease LOS, and improve hospital revenue.

This study is limited by several factors. Most importantly, while a verifiable association between ORADEs and specific outcomes and diagnoses has been established by several studies [4,5,13], it is not possible to delineate a causal relationship between opioid use as an analgesic and post-surgical ORADEs. The determination of adverse events via ICD codes may overestimate ORADEs and their contribution to LOS and hospital revenue. Adverse events may occur in the absence of opioid administration and, when reported via ICD codes, may be falsely attributed to opioids. In addition, collecting the data via ICD codes may encourage redundancy. A single ORADE may be reported several times with various ICD codes, and this repetition may falsely elevate ORADE rates. Furthermore, the Medicare database does not explicitly describe the medications each patient receives during their hospitalization nor the timing of a medication as it relates to an adverse event. On the contrary, ORADE incidence may be underestimated as hospitals are only able to submit limited numbers of ICD codes and frequently only link severe complications to claims data; common adverse events such as constipation, nausea and vomiting, pruritus and delirium may therefore be underreported. These relatively minor side effects are prevalent and often go unreported, yet they inflict real discomfort to the patient, consequently delaying discharge and decreasing patient satisfaction. Nonetheless, the extensive quantity of hospital networks from which the Medicare database draws, along with the previously validated methodology for identifying ORADEs and the associations derived from the AHRQ CCS categories lends legitimacy to the insights arrived at through our analysis of patients undergoing spine surgery.

5. Conclusion

Our study demonstrates that potential ORADEs (both major and minor) in spine surgery are common and are associated with longer hospitalizations and decreased hospital revenue in the elderly population. Therefore, better perioperative pain management strategies that reduce ORADEs may improve patient care and increase hospital revenue.

Areas of interest for future research should emphasize prospective cohort studies that specify the medications and timing of administration in relation to adverse events. This will allow a more definitive causal relationship to be established between opioid medications and ORADEs in spine surgery. Our data may be used as a starting point from which to design quality improvement and cost reduction efforts focused on improving patient outcomes in at-risk populations, such as the elderly, following spine surgery.

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References

[1] S.J. Armaghani, D.S. Lee, J.E. Bible, D.N. Shau, H. Kay, C. Zhang, M.J. McGirt, C.J. Devin, Increased preoperative narcotic use and its association with postoperative complications and length of hospital stay in patients undergoing spine surgery, Clin. Spine Surg. 29 (2016) E93–E98, https://doi.org/10.1097/BSD.0000000000000109.

[2] A.J. Pugely, C.T. Martin, Y. Gao, S. Mendoza-Lattes, Causes and risk factors for 30-Day unplanned readmissions after lumbar spine surgery, Spine (Phila. Pa. 1976) 39 (2014) 761–768, https://doi.org/10.1097/BRS.0000000000000270.

[3] American society of anesthesiologists task force on acute pain management, practice guidelines for acute pain management in the perioperative setting: an updated report by the american society of anesthesiologists task force on acute pain management, Anesthesiology 116 (2012) 248–273, https://doi.org/10.1097/ALN.0b013e31823c1030.

[4] H.S. Minkowitz, S.K. Gruschkus, M. Shah, A. Raju, Adverse drug events among patients receiving postsurgical opioids in a large health system: risk factors and outcomes, Am. J. Heal. Pharm. 71 (2014) 1556–1565, https://doi.org/10.2146/ajhp130031.

[5] E.R. Kessler, M. Shah, S.K. Gruschkus, A. Raju, Cost and quality implications of opioid-based postsurgical pain control using administrative claims data from a large health system: opioid-related adverse events and their impact on clinical and economic outcomes, Pharmacother. J. Hum. Pharmacol. Drug Ther. 33 (2013) 383–391, https://doi.org/10.1002/phar.1223.

[6] S.J. Herzig, M.B. Rothberg, M. Cheung, L.H. Ngo, E.R. Marcantonio, Opioid utilization and opioid-related adverse events in nonsurgical patients in US hospitals, J. Hosp. Med. 9 (2014) 73–81, https://doi.org/10.1002/jhm.2102.

[7] M. Wheeler, G.M. Oderda, M.A. Ashburn, A.G. Lipman, Adverse events associated with postoperative opioid analgesia: a systematic review, J. Pain 3 (2002) 159–180 (accessed July 6, 2019), http://www.ncbi.nlm.nih.gov/pubmed/14622770.

[8] U. Department of Health, H. Services, O. of Disease Prevention, H. Promotion, Natio nal Ac tio n Plan for Advers e Drug Event Prevention, n.d. https://health.gov/hcq/pdfs/ade-action-plan-508c.pdf (accessed July 6, 2019).

[9] J.A. Eckstrand, A.S. Habib, A. Williamson, M.M. Horvath, K.G. Gattis, H. Cozart, J. Ferranti, Computerized surveillance of opioid-related adverse drug events in perioperative care: a cross-sectional study, Patient Saf. Surg. 3 (2009) 18, https://doi.org/10.1186/1754-9493-3-18.

[10] F.J. Overdyk, O. Dowling, J. Marino, J. Qiu, H.-L. Chien, M. Erslon, N. Morrison, B. Harrison, A. Dahan, T.J. Gan, Association of opioids and sedatives with increased risk of in-hospital cardiopulmonary arrest from an administrative database, PLoS One 11 (2016) e0150214, , https://doi.org/10.1371/journal.pone.0150214.

[11] G.M. Oderda, R.S. Evans, J. Lloyd, A. Lipman, C. Chen, M. Ashburn, J. Burke, M. Samore, Cost of opioid-related adverse drug events in surgical patients, J. Pain Symptom Manage. 25 (2003) 276–283 (Accessed July 6, 2019), http://www.ncbi.nlm.nih.gov/pubmed/12614962.

[12] G.M. Oderda, Q. Said, R.S. Evans, G.J. Stoddard, J. Lloyd, K. Jackson, D. Rublee, M.H. Samore, Opioid-related adverse drug events in surgical hospitalizations: impact on costs and length of stay, Ann. Pharmacother. 41 (2007) 400–407, https://doi.org/10.1345/aph.1H386.

[13] H.S. Minkowitz, R. Scranton, S.K. Gruschkus, K. Nipper-Johnson, L. Menditto, A. Dandappanavar, Development and validation of a risk score to identify patients at high risk for opioid-related adverse drug events, J. Manag. Care Pharm. 20 (2014) 948–958, https://doi.org/10.18553/jmcp.2014.20.9.948.

[14] G.M. Oderda, T.J. Gan, B.H. Johnson, S.B. Robinson, Effect of opioid-related adverse events on outcomes in selected surgical patients, J. Pain Palliat. Care Pharmacother. 27 (2013) 62–70, https://doi.org/10.3109/15360288.2012.751956.

[15] J. Friedly, C. Standaert, L. Chan, Epidemiology of spine care: the back pain dilemma, Phys. Med. Rehabil. Clin. N. Am. 21 (2010) 659–677, https://doi.org/10.1016/j.pmr.2010.08.002.

[16] R.A. Deyo, S.K. Mirza, B.I. Martin, W. Kreuter, D.C. Goodman, J.G. Jarvik, Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults, JAMA 303 (2010) 1259, https://doi.org/10.1001/JAMA.2010.338.

[17] C.J. Devin, M.J. McGirt, Best evidence in multimodal pain management in spine surgery and means of assessing postoperative pain and functional outcomes, J. Clin. Neurosci. 22 (2015) 930–938, https://doi.org/10.1016/j.jocn.2015.01.003.

[18] H.J. Gerbershagen, S. Aduckathil, A.J.M. van Wijck, L.M. Peelen, C.J. Kalkman, W. Meissner, Pain intensity on the first day after surgery, Anesthesiology 118 (2013) 934–944, https://doi.org/10.1097/ALN.0b013e31828866b3.

[19] Overview, (2019) (accessed July 6, 2019), https://www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/LimitedDataSets/.

[20] H. Crews, P.J. Pronovost, P.R. Helft, J.M. Austin, Improving the quality of data for inpatient claims-based measures used in public reporting and pay-for-Performance programs, Jt. Comm. J. Qual. Patient Saf. 43 (2017) 671–675, https://doi.org/10.1016/j.jcjq.2017.08.003.

[21] Find and compare information about Hospitals | Hospital Compare, (n.d.). https://www.medicare.gov/hospitalcompare/search.html (accessed July 6, 2019).

[22] C. McAdam-Marx, C.L. Roland, J. Cleveland, G.M. Oderda, Costs of opioid abuse and misuse determined from a medicaid database, J. Pain Palliat. Care Pharmacother. 24 (2010) 5–18, https://doi.org/10.3109/15360280903544877.

[23] A.B. Stone, M.R. Jones, N. Rao, R.D. Urman, A dashboard for monitoring opioid-related adverse drug events following surgery using a national administrative database, Am. J. Med. Qual. (2018), https://doi.org/10.1177/1062860618782646.

[24] G. Oderda, Challenges in the management of acute postsurgical pain, Pharmacotherapy 32 (2012) 6S–11S, https://doi.org/10.1002/j.1875-9114.2012.01177.x.

[25] S. Haroutounian, Postoperative opioids, endocrine changes, and immunosuppression, Pain Rep. 3 (2018) e640, https://doi.org/10.1097/PR9.0000000000000640.

[26] A. Chen, M.A. Ashburn, Cardiac effects of opioid therapy, Pain Med. 16 (2015) S27–S31, https://doi.org/10.1111/pme.12915.

[27] S. Dublin, R.L. Walker, M.L. Jackson, J.C. Nelson, N.S. Weiss, M. Korff, L.A. Jackson, Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study, J. Am. Geriatr. Soc. 59 (2011)

1899–1907, https://doi.org/10.1111/j.1532-5415.2011.03586.x.
[28] M.R. Jones, K.P. Ehrhardt, J.G. Ripoll, B. Sharma, I.W. Padnos, R.J. Kaye, A.D. Kaye, Pain in the elderly, Curr. Pain Headache Rep. 20 (2016), https://doi.org/10.1007/s11916-016-0551-2.
[29] M. Kahan, A. Mailis-Gagnon, L. Wilson, A. Srivastava, National Opioid Use Guideline Group, Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 1: general population, Can. Fam. Phys. 57 (2011) 1257–1266 e407-18http://www.ncbi.nlm.nih.gov/pubmed/22084455 (accessed July 6, 2019).
[30] O.H.G. Wilder-Smith, Opioid use in the elderly, Eur. J. Pain 9 (2005) 137–140, https://doi.org/10.1016/j.ejpain.2004.07.011.
[31] D.S. Aaronson, A.K. Wu, S.D. Blaschko, J.W. McAninch, M. Garcia, National incidence and impact of noninfectious urethral catheter related complications on the surgical care improvement project, J. Urol. 185 (2011) 1756–1760, https://doi.org/10.1016/j.juro.2010.12.041.
[32] H.L. Wald, A. Ma, D.W. Bratzler, A.M. Kramer, Indwelling urinary catheter use in the postoperative period, Arch. Surg. 143 (2008) 551, https://doi.org/10.1001/archsurg.143.6.551.
[33] S. Shafi, A.W. Collinsworth, L.A. Copeland, G.O. Ogola, T. Qiu, M. Kouznetsova, I.-C. Liao, N. Mears, A.T. Pham, G.J. Wan, A.L. Masica, Association of opioid-related adverse drug events with clinical and cost outcomes among surgical patients in a large integrated health care delivery system, JAMA Surg. 153 (2018) 757, https://doi.org/10.1001/jamasurg.2018.1039.
[34] F. Overdyk, A. Dahan, M. Roozekrans, R. van der Schrier, L. Aarts, M. Niesters, Opioid-induced respiratory depression in the acute care setting: a compendium of case reports, Pain Manag. 4 (2014) 317–325, https://doi.org/10.2217/pmt.14.19.
[35] H. Owen, V. McMillan, D. Rogowski, Postoperative pain therapy: a survey of patients' expectations and their experiences, Pain 41 (1990) 303–307 (accessed July 6, 2019), http://www.ncbi.nlm.nih.gov/pubmed/1697058.
[36] C.A. Warfield, C.H. Kahn, Acute pain management, Anesthesiology 83 (1995) 1090–1094, https://doi.org/10.1097/00000542-199511000-00023.
[37] D.B. Gordon, J.L. Dahl, C. Miaskowski, B. McCarberg, K.H. Todd, J.A. Paice, A.G. Lipman, M. Bookbinder, S.H. Sanders, D.C. Turk, D.B. Carr, American pain society recommendations for improving the quality of acute and Cancer pain management, Arch. Intern. Med. 165 (2005) 1574, https://doi.org/10.1001/archinte.165.14.1574.
[38] M. Melnyk, R.G. Casey, P. Black, A.J. Koupparis, Enhanced recovery after surgery (ERAS) protocols: Time to change practice? Can. Urol. Assoc. J. 5 (2011) 342–348, https://doi.org/10.5489/cuaj.11002.
[39] C. Eskicioglu, S.S. Forbes, M.-A. Aarts, A. Okrainec, R.S. McLeod, Enhanced Recovery after Surgery (ERAS) Programs for Patients Having Colorectal Surgery: A Meta-analysis of Randomized Trials, J. Gastrointest. Surg. 13 (2009) 2321–2329, https://doi.org/10.1007/s11605-009-0927-2.
[40] K. Lassen, M. Soop, J. Nygren, P.B.W. Cox, P.O. Hendry, C. Spies, M.F. von Meyenfeldt, K.C.H. Fearon, A. Revhaug, S. Norderval, O. Ljungqvist, D.N. Lobo, C.H.C. Dejong, Enhanced recovery after surgery (ERAS) group, consensus review of optimal perioperative care in colorectal surgery, Arch. Surg. 144 (2009) 961, https://doi.org/10.1001/archsurg.2009.170.