Development and Validation of a Risk Score to Identify Patients at High Risk for Opioid-Related Adverse Drug Events

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ABSTRACT

BACKGROUND: Opioid-related adverse drug events (ORADEs) are common causes of hospitalization and increased health care costs.

OBJECTIVES: To (a) estimate rates of specific adverse drug events (ADEs) among gastrointestinal (GI) surgery patients receiving postoperative opioids; (b) examine the utility of a risk-scoring model in categorizing patients at high risk of experiencing ORADEs; and (c) quantify potential clinical/economic benefits of targeting high-risk GI surgical patients for opioid-sparing regimens in terms of hospitalization cost, length of stay (LOS), and 30-day readmission rates.

METHODS: Using a retrospective design based on an administrative database, patients with an inpatient surgical procedure between January 1, 2010, and December 31, 2010, were included. GI surgical patients aged >18 years followed from admission through 30 days postdischarge were characterized as high or low risk using clinical/demographic characteristics and were evaluated for several outcomes. Using multivariate logistic regression, the ORADE incidence, total hospitalization cost, LOS, and 30-day readmissions were compared for high-risk and low-risk patients.

RESULTS: In 87.8% (n=3,235) of the surgical population, there was a strong concordance between risk assignment and ORADE incidence. Among the remaining 12.2% (n=449) of patients, 5.5% (n=202) were low risk with an ORADE, and 6.7% (n=247) were high risk without an ORADE. Overall, 20.6% (n=344) of high-risk patients experienced ≥1 ORADE (mean cost: $31,988; LOS: 12.1 days) compared with only 5.3% (n=107) of low-risk patients (mean cost: $25,216; LOS: 8.0 days). High-risk patients had higher hospitalization costs and longer LOS than low-risk patients, respectively (mean cost: $19,234 vs. $13,036; mean LOS: 6.8 days vs. 3.3 days). These differences correspond to 47.0% higher costs for high-risk patients and an LOS approximately twice as long compared with low-risk patients.

CONCLUSIONS: Patient clinical/demographic characteristics influence the risk of developing ORADEs. Risk assessment tools can effectively identify high-risk patients, thereby enabling interventions that can reduce ORADEs, decrease hospital costs, and improve postsurgical experiences for patients.

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What is already known about this subject

- Opioid-related adverse drug events (ORADEs) are common causes of hospitalizations and increased health care costs.
- Opioid-sparing or opioid replacement techniques in the management of postsurgical pain consistently prevents ORADEs and reduces resource use such as inpatient hospital length of stay and nursing time.

What this study adds

- Risk assessment tools can effectively identify high-risk patients, thereby enabling interventions aimed at reducing ORADEs, decreasing hospital costs, and improving postsurgical experiences for the intended subsets of high-risk patients.
- Targeted interventions aimed at reducing the incidence of ORADEs in high-risk patients have the potential to improve the postsurgical experience for the patient, reduce costs for hospitals, and may be more cost-efficient than interventions applied to the entire surgical population.

A large majority (approximately 75.0%) of surgical patients in the United States experience postoperative pain following inpatient and outpatient surgical procedures.[1-5] Opioids have demonstrated efficacy for pain relief after surgery and are often the analgesics of choice for postoperative pain. However, opioid use is frequently accompanied by opioid-related adverse drug events (ORADEs) and other negative consequences, including increased mortality.[6,7] Wheeler et al. (2002) found that 29.0% of preventable adverse drug events (ADEs) were associated with analgesic use, the majority of which included opioids.[8] The most common of these ORADEs include gastrointestinal (GI) effects such as constipation, ileus, nausea, and vomiting; central nervous system effects including sedation, euphoria, and delirium; pruritus; urinary retention; and more serious adverse effects such as respiratory depression.[8-10]

Several patient clinical and demographic characteristics have been demonstrated to play a role in increased ORADE risk. Perioperative and intraoperative treatment factors associated with ADE incidence include specific procedure type, longer duration of surgery, use of volatile intraoperative anesthetics, general versus regional anesthesia, and postoperative opioid dose and route of administration.[11] Previously demonstrated patient-specific ADE risk factors include older age, male gender, race/ethnicity, smoking status, obesity, and comorbid diagnoses such as obstructive sleep apnea (OSA), chronic obstructive pulmonary disease (COPD), renal and hepatic function, cardiac dysrhythmia, degenerative joint disease (DJD), and benign prostatic hyperplasia (BPH).[6,12-15] Medication error, which is common with opioid delivery systems, also contributes substantially to the risk of developing an ORADE.[16]

Incidence of ORADEs may result in poorly controlled pain management and accompanying negative impact on patients, such as psychological consequences, extended postanesthesia care unit stay, delayed discharge, and greater likelihood of readmission rates.[14,15,17-20] The frequency of postoperative ORADEs also poses a significant economic burden and strain on resources to hospitals and health care providers. For example, respiratory depression and nausea/vomiting require increased monitoring by the nursing staff and increased utilization of supportive care therapies such as antiemetics.[17] Previous research has found that a significant proportion of surgical patients have unplanned readmissions or are readmitted within 30 days of discharge, with the incidence of pain being the most common reason for readmission.[18] Ultimately, these negative downstream outcomes of ORADEs lead to diminished quality of life for the patient[20] and higher costs.[6,19]

While opioid analgesics have been a mainstay of postsurgical analgesic regimens, recent treatment guidelines have supported the use of multimodal therapy as a way to decrease opioid usage, thus lowering the risk of ORADEs and their subsequent negative impact on clinical and economic outcomes while successfully managing postoperative pain. Current guidelines from the American Society of Anesthesiologists (ASA) and the American Pain Society (APS) advocate the use of multimodal postoperative pain management strategies.[21-23] The Joint Commission, which issued a Sentinel Alert in August 2012 detailing the risk for opioid-induced oversedation and respiratory depression in certain patient populations, recommends that the best approach to postsurgical pain management in high-risk patients may be to start with a nonopioid medication.[24] However, previous research has demonstrated that clinical guidelines may have limited effectiveness due to poor adherence by health care providers,[25,26] which may be partly attributed to a limited or incomplete preoperative patient assessment.[25] Evidence suggests that decision support systems may increase adherence to guidelines by facilitating characterization of patients according to risk profile, thus providing more information to providers to determine optimal pain management.[27-29] For example, Kooij et al. (2008) found that including a simple risk-scoring system designed to identify patients with a high risk of experiencing postoperative nausea and vomiting (PONV) as part of the routine preoperative screening process significantly improved guideline adherence for prescribing PONV prophylaxis.[27]

Several risk-scoring models, mainly for PONV,[11,30-37] based on a patient's clinical/demographic profile have been developed with the goal of aiding health care providers in identifying high-risk patients and providing an opportunity to determine the safest and most effective pain management strategy. While evaluation of these models has focused primarily on their utility for predicting ADEs, very few have also considered whether the risk scores can transitively predict downstream outcomes such as increased costs and length of stay (LOS).[37,38]

TABLE 1 Gastrointestinal Surgical Procedures

Surgical Procedures	Number of Patients
Total	**3,684**
Laparoscopic cholecystectomy	1,724
Laparoscopic gastric bypass	663
Open colectomy–partial excision of large intestines	482
Other partial gastrectomy	285
Laparoscopic colectomy–partial excision of large intestines	251
Open cholecystectomy	111
Open gastric bypass	68
Ileostomy reversal	55
Open colectomy–total excision of large intestines	40
Laparoscopic colectomy–total excision of large intestines	5

The purpose of this retrospective study was to ascertain rates of specific ORADEs among GI surgery patients who received postoperative opioids and to identify risk factors for these ADEs. A risk-scoring model was developed to identify patients with a high risk for experiencing an ADE based on their clinical and demographic profiles (see Appendix A). The utility of this model was evaluated for predicting not only ORADEs but also hospitalization cost, LOS, and 30-day readmission rates. Finally, the potential clinical and economic benefits of targeting high-risk patients for opioid-sparing pain regimens were quantified as a means of reducing ORADE incidence among GI surgical patients.

Methods

Data Source

This retrospective cohort study utilized data from the Eclipsys Sunrise (EPSI) database, which contains administrative data on patients receiving care within the Memorial Hermann Hospital System. As the largest nonprofit health care system in Texas, the Memorial Hermann Hospital System comprises 11 hospitals and accounts for approximately 3,500 inpatient beds.

Study Design and Sample Selection

Patients aged 18 years or older receiving opioids after undergoing specific GI surgical procedures (Table 1) between January 1, 2010, and December 31, 2010, were eligible for the study. Patients were followed from their admission date through 30 days postdischarge to characterize them according to specific risk factors and to evaluate postoperative pain management, LOS, inpatient costs, adverse events, and 30-day readmissions. Postsurgical opioid pain management was defined by the administration of parenteral or oral opioid analgesics on or after the procedure date and before discharge. Opioid analgesics considered for pain management included morphine, oxycodone, hydrocodone, hydromorphone, fentanyl, meperidine, codeine, methadone, and propoxyphene.

TABLE 2 Opioid-Related Adverse Events

Adverse Event	ICD-9-CM Diagnosis Code
Respiratory	
Bradypnea	786.09 acute
Pulmonary insufficiency following surgery and trauma	518.5 acute
Respiratory complications	997.3 acute
Hypoxemia	799.02
Gastrointestinal	
Constipation	564.09
Constipation–narcotic	E937.9 acute
Postoperative event (following surgery)	997.4 acute
Paralytic ileus	560.1
Nausea/vomiting	787.01 acute
Nausea/vomiting following gastrointestinal surgery	564.3 acute
Genitourinary System	
Urinary retention	788.2 acute
Oliguria	997.5 acute/relatedness

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

Risk Factor Assessment and Identification of ADEs

Risk profiles were derived for patients based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes documented during their admission. Risk factors were selected based on previous research and biologic plausibility.[6,12,13,15] The incidence of ORADEs was similarly ascertained by identifying specific ICD-9-CM diagnosis codes and included GI, respiratory, and genitourinary (GU) diagnoses (Table 2). Patients were then placed into cohorts based on whether they experienced or did not experience any ORADE. Gender-specific multivariate logistic modeling was used to calculate odds ratios (ORs) and accompanying 95% confidence intervals (CIs). Risk factors were selected for final risk models based on statistical and clinical significance and by evaluating likelihood ratios for models that included specific risk factors relative to reduced models that did not.

Development and Evaluation of Final Risk Scores

Gender-specific risk scores and a final composite risk, which incorporated the 2 gender-specific scores, were calculated by summing the β-coefficients for each risk factor included in each gender-specific model. Patients were then classified as being at high or low risk for experiencing any adverse events. The threshold score for defining high or low risk was determined based on the score with the maximum sum of sensitivity + specificity. The utility of the final risk scores for predicting any ORADE was evaluated using a receiver operator characteristics (ROC) analysis to determine the area under the curve (AUC) for each model and by calculating sensitivity, specificity, and positive predictive value (PPV). Finally, we explored the external validity of the final composite risk score by conducting an ROC analysis after applying the model to a separate surgical population that underwent similar procedures within a large hospital system in the southeastern United States.

Comparison of Outcomes Between High- and Low-Risk Patients

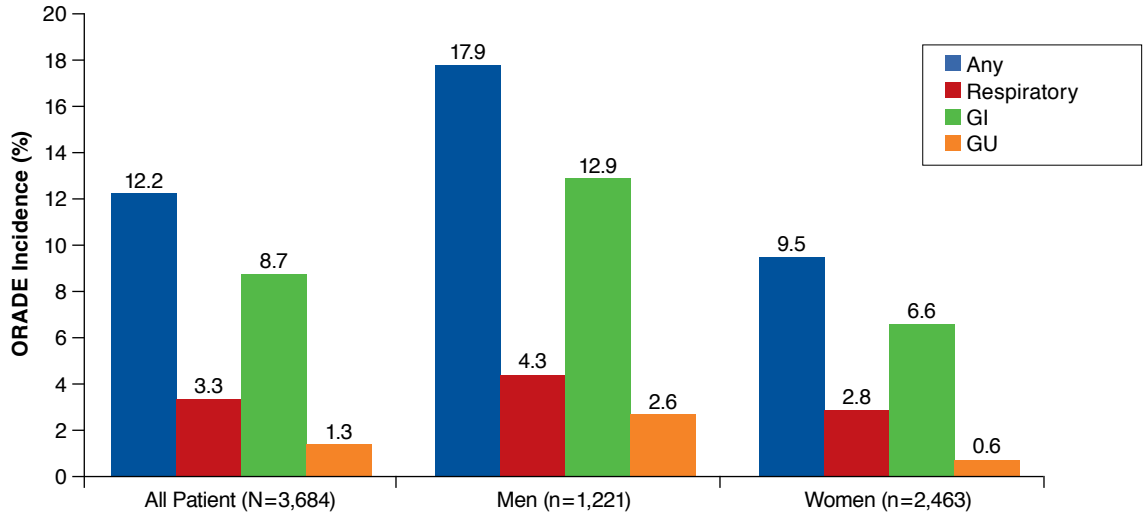
ORADE incidence, total hospitalization costs (based on 2012 region-specific Medicare charge-to-cost ratios), LOS (the time in days from admission to discharge), and 30-day readmissions were compared for high- and low-risk patients. Multivariate logistic regression analysis was used to describe associations between risk and ORADE incidence and 30-day readmissions. Generalized linear modeling with a log-link function and gamma distribution was used for costs, and negative binomial regression modeling was used for LOS. All statistical analyses tested a 2-sided hypothesis of no difference between comparison groups at a significance level of 0.05 and were carried out using SAS statistical software version 9.2 (SAS Institute, Inc., Carey, NC).

Results

A total of 3,684 eligible GI surgical patients were identified. The numbers of patients for specific procedures are presented in Table 1. The most common procedure types performed were cholecystectomies (50.0%; n = 1,835) followed by colectomies (20.1%; n = 778), gastric bypasses (19.8%; n = 731), partial gastrectomies (7.4%; n = 285), and ileostomy reversals (1.5%; n = 55). Female patients made up the large majority of the study population (66.9%; n = 2,463). The mean age at admission was 50.4 years (female: 48.2 years; male: 54.4 years). Figure 1 illustrates the incidence of ORADEs overall and by gender. Overall, 12.2% (n = 449) of patients experienced 1 or more ORADE of any kind; incidence was higher in men (17.9%; n = 219) compared with women (9.5%; n = 234). GI ORADEs were most common, occurring in 8.7% (n = 321) of the total population (12.9% [n = 158] of men vs. 6.6% [n = 163] of women) followed by respiratory ORADEs (3.3% [n = 122]; 4.3% [n = 53] of men vs. 2.8% [n = 69] of women). Very few patients experienced GU ORADEs (1.3% [n = 48]; 2.6% [n = 32] of men; 0.6% [n = 15] of women).

Table 3 shows the distribution of plausible risk factors and the magnitude and statistical significance of their association with ORADE incidence. Ulcerative colitis (OR: 8.28; 95% CI: 2.54, 27.03; $P = 0.001$), BPH (OR: 8.23; 95% CI: 4.36, 15.53; $P < 0.0001$), and cardiac dysrhythmia (OR: 4.20; 95% CI: 2.17, 8.83; $P < 0.0001$) were the strongest risk factors in men. Among women, regional enteritis (OR: 8.13; 95% CI: 2.47, 26.78; $P = 0.001$), cardiac dysrhythmia (OR: 3.12; 95% CI: 1.67, 5.84; $P < 0.0001$), and COPD (OR: 3.04; 95% CI: 1.22, 7.55; $P = 0.017$) had the greatest impact on ORADE risk. Ultimately, age, obesity, COPD, congestive heart failure, cardiac dysrhythmia,

FIGURE 1 Incidence of ORADE Overall and by Gender



GI = gastrointestinal; GU = genitourinary; ORADE = opioid-related adverse drug event.

diverticulitis, and OSA were included in the final male- and female-specific risk score models. Additionally, opioid use prior to surgery, BPH, and ulcerative colitis were included in the male but not female model, while DJD, asthma, diabetes, and regional enteritis were included in the female but not male model.

A summary of the final risk models is presented in Figure 2. The AUC for the male-specific, female-specific, and composite risk models were 0.732, 0.702, and 0.734, respectively. The final composite model was successful at accurately identifying 76.3% of patients who experienced ORADEs and 59.0% of patients who did not. Only 20.6% (n = 344) of patients classified as high risk had a corresponding ORADE; however, this value reflects not only the utility of the risk score but is also partly a function of the overall ORADE incidence in the patient population.

A total of 1,670 patients (45.3%) were classified as high risk (75.0% [n = 916] were men and 30.6% [n = 754] were women). Overall, 20.6% (n = 344) of high-risk patients experienced 1 or more ORADEs compared with only 5.3% (n = 107) of low-risk patients. From a relative standpoint, being classified as high risk was significantly associated with a greater than 4-fold increased likelihood of experiencing an ORADE compared with being classified as low risk (OR: 4.62; 95% CI: 3.68, 5.81; $P < 0.0001$; Table 4). In addition to predicting overall ORADEs as designed, the final composite risk score model was effective at predicting specific ORADEs and 30-day readmissions. Furthermore, high-risk patients tended to have higher hospitalization costs and longer LOS than low-risk patients (mean cost: $19,234 vs. $13,036; mean LOS: 6.8 days vs. 3.3 days for high-risk vs. low-risk patients, respectively; Table 4). These differences correspond to 47% higher costs for high-risk patients (cost ratio: 1.47; 95% CI: 1.42, 1.53; $P < 0.0001$) and an LOS approximately twice as long (rate ratio: 2.07; 95% CI: 1.96, 2.17; $P < 0.0001$) compared with low-risk patients.

There was concordance between risk assignment and ORADE incidence in a large majority (87.8%; n = 3,235) of the Memorial Hermann GI surgical population: 64.3% (n = 2,369) of patients were classified as low risk without an ORADE, and 23.5% (n = 866) were high risk with an ORADE. Among the remaining 12.2% (n = 449) of patients, 5.5% (n = 202) were low risk with an ADE, and 6.7% (n = 247) were high risk without an ORADE. Mean costs and LOS differed between these patient cohorts, as illustrated in Figure 3. Low-risk patients without an ADE had the lowest mean cost and LOS ($12,353 and 3.0 days, respectively) followed by high-risk patients without an ADE ($15,925 and 5.4 days), low-risk patients with an ORADE ($25,216 and 8.0 days), and high-risk patients with an ORADE ($31,988 and 12.1 days).

To evaluate external validity, the final risk-scoring model was applied to a test population of different GI surgical patients who underwent procedures within a separate large hospital system located in the southeastern United States. Application of the model to this population yielded an AUC of 0.645 for the test population; this was somewhat lower than the 0.734 AUC observed in the Memorial Hermann population (Figure 4).

Discussion

Results of this study showed that among the overall GI surgical population approximately 12% (n = 449) of patients experienced an ORADE with GI events being the most common. Based on

TABLE 3 Evaluation of Potential ORADE Risk Factors

	Male (n = 1,221)				Female (n = 2,463)			
Risk Factor	**OR**	**95% CI**		***P* Value**	**OR**	**95% CI**		***P* Value**
Age (mean, SD)[a]	1.02	1.01	1.03	0.001	1.03	1.02	1.04	<0.0001
Opioid use prior to surgery[a]	1.42	1.03	1.97	0.032	1.04	0.76	1.42	0.816
Obesity (ICD-9-CM 278)[a]	0.48	0.28	0.81	0.006	1.21	0.85	1.74	0.295
DJD (ICD-9 CM 715)	0.51	0.15	1.71	0.276	1.66	0.98	2.81	0.059
COPD (ICD-9-CM 490, 491, 492)[a]	1.52	0.56	4.13	0.407	3.04	1.22	7.55	0.017
Asthma (ICD-9-CM 493)	0.65	0.22	1.86	0.418	1.44	0.86	2.42	0.170
Pulmonary hypertension (ICD-9-CM 416.18)	-	-	-	-	-	-	-	-
Congestive heart failure (ICD-9-CM 428)[a]	1.79	1.01	3.18	0.047	1.37	0.78	2.41	0.280
BPH (ICD-9-CM 600)[a]	8.23	4.36	15.53	<0.0001	N/A	N/A	N/A	N/A
Coronary atherosclerosis (ICD-9-CM 414)	0.63	0.36	1.11	0.113	1.05	0.58	1.90	0.881
Cardiac dysrhythmia (ICD-9-CM 427)[a]	4.20	2.17	8.13	<0.0001	3.12	1.67	5.84	<0.0001
Hypertension (ICD-9-CM 401)	0.86	0.61	1.21	0.377	0.73	0.54	1.00	0.051
Dementia (ICD-9-CM 290, 294)	0.35	0.11	1.11	0.076	0.72	0.19	2.78	0.638
Depression (ICD-9-CM 296)	3.19	0.77	13.27	0.110	1.34	0.44	4.07	0.601
Diabetes (ICD-9-CM 249, 250)	0.95	0.65	1.40	0.799	1.19	0.84	1.68	0.340
Irritable bowel syndrome (ICD-9-CM 564.1)	-	-	-	-	-	-	-	-
Regional enteritis (ICD-9-CM 555.0, 555.1, 555.9)[a]	-	-	-	-	8.13	2.47	26.78	0.001
Diverticulitis (ICD-9-CM 562)[a]	1.89	1.24	2.87	0.003	1.99	1.29	3.06	0.002
Ulcerative colitis (ICD-9-CM 556)[a]	8.28	2.54	27.03	0.001	1.38	0.25	7.63	0.713
GERD (ICD-9-CM 530.11, 530.81)	0.81	0.49	1.35	0.424	1.13	0.79	1.62	0.506
OSA (ICD-9-CM 327.23, 478.29)[a]	1.96	0.99	3.88	0.049	1.24	0.72	2.12	0.446

[a]*Included in final male- and/or female-specific risk models.*

BPH = benign prostatic hyperplasia; CI = confidence interval; COPD=chronic obstructive pulmonary disease; DJD = degenerative joint disease; GERD = gastroesophageal reflux disease; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; N/A = not applicable; OR = odds ratio; ORADE = opioid-related adverse drug event; OSA = obstructive sleep apnea; SD = standard deviation.

our final risk score, 45.3% of the population was classified as high risk; this corresponded to 75.0% (n = 916) of males and 30.6% (n = 754) of females. These high-risk patients had a greater than 4-fold ORADE risk, 43.2% increased likelihood of 30-day readmission, 42.2% higher hospitalization costs, and LOS that was 96.1% longer compared with low-risk patients.

Our final risk score model was a composite of a male-specific model that included 10 risk factors and a female-specific model made up of 11 risk factors, for a combined total of 14 factors. The AUC for the final model was 0.734, which exceeds the commonly recognized threshold of 0.70 to be considered diagnostically useful[39] and compares favorably with commonly cited risk-scoring models[30-36] designed to predict PONV (range for AUCs: 0.61-0.70). In addition to having acceptable utility for predicting ORADEs, it is important for a risk score to be practicable in the clinical setting. Minimizing the number of factors included in a risk-scoring system and including primarily factors that are easily and objectively defined is likely to increase ease of administration and the likelihood that a given model will be successfully integrated into the preoperative screening process. The practicability of our model, based on the number of factors considered, fell within the range (4-14 factors) found in existing risk models.

Application of the model to the test population yielded a lower AUC, suggesting a diminished effectiveness for predicting ORADEs in the test population compared with the Memorial Hermann population (AUC: 0.645 vs. 0.734, respectively); however, the observed utility within the test population still exceeded the utility of 3 out of the 6 existing risk-scoring systems referenced in this article. It should be noted that, in addition to the strength of association between component factors of a risk score and ORADE incidence, other parameters such as prevalence and mix of risk factors, ORADE incidence rate, distribution of specific ORADE types, and distribution of specific surgical procedures are likely to influence the utility of a model when applied to different patient populations and should be taken into consideration during model development. In the present study, we observed that the test population tended to be older and have a lower prevalence of ORADE risk factors compared with the Memorial Hermann population.

Identifying ORADE risk can help target common causes of hospitalization thus ultimately impacting large costs to society. ORADEs were found to be associated with greater costs, increased LOS, and higher rates of 30-day readmission. Greater overall cost and LOS are inter-related and are consequences of increased personnel time, intensity of pain management, and direct costs of treating ORADEs, including costs related to

FIGURE 2 Final Risk Model

Overall GI Surgical Population

Male Patients		
Risk Factor	**Component Score**	**OR**
Age	0.0128	1.013
Prior opioid use	0.3176	1.374
Obesity	-0.8129	0.444
COPD	0.2925	1.34
CHF	0.4806	1.617
BPH	1.9851	7.28
Cardiac dysrhythmia	1.4024	4.065
Diverticulitis	0.6633	1.941
Ulcerative colitis	2.0049	7.426
OSA	0.6139	1.848
-	-	-
AUC		**0.732**
Sensitivity		**68.4%**
Specificity		**66.4%**
PPV		**30.7%**

Female Patients		
Risk Factor	**Component Score**	**OR**
Age	0.0253	1.026
Obesity	0.1422	1.153
DJD	0.4957	1.642
COPD	1.1957	3.306
Asthma	0.411	1.508
CHF	0.3605	1.434
Cardiac dysrhythmia	1.1335	3.106
Diabetes	0.1303	1.139
Regional enteritis	2.1388	8.489
Diverticulitis	0.6724	1.959
OSA	0.2276	1.256
AUC		**0.702**
Sensitivity		**61.8%**
Specificity		**71.4%**
PPV		**18.4%**

Overall GI Surgical Population	
Risk Factor	**Component Score**
Male gender	1.2528
Gender-specific risk score	∑ Component score
High-risk threshold	≥ 1.7204
AUC	**0.734**
Sensitivity	**76.3%**
Specificity	**59.0%**
PPV	**20.6%**

AUC = area under the curve; BPH = benign prostatic hyperplasia; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; DJD = degenerative joint disease; GI = gastrointestinal; OR = odds ratio; ORADE = opioid-related adverse drug event; OSA = obstructive sleep apnea; PPV = positive predictive value.

laboratory, diagnostic, antidote, and symptom control medications. Incidence of ORADEs in this study was found to increase LOS by 80%, costs by 86%, and 30-day readmission rates by 71%. Furthermore, patients with ORADEs were much more likely to be outliers with respect to costs and LOS, making it more difficult to accurately anticipate and allocate necessary postsurgical resources.

The cost of hospitalization is, however, only a part of the total costs. Beyond the negative consequences evaluated in this study, ORADEs also may result in the risk for medication and device-related errors, which are also significant cost drivers and impact patient safety. In a retrospective evaluation of voluntarily reported medication errors in the intensive care unit, opioid analgesics ranked among the top 3 drugs related to medication errors.[40] Additionally, ORADEs can have a significant impact on patient recovery after surgery.[41]

Since the APS advocates the use of multimodal postoperative pain management strategies, considering alternative approaches to managing postsurgical pain—such as the use of other pain medications in combination with opioids (opioid-sparing) or by replacing opioids with other analgesics (opioid replacement)—may reduce ORADE incidence in high-risk patients.[21] Opioid replacement or alternative treatment options include nonsteroidal anti-inflammatory drugs, acetaminophen, bupivacaine, devices to extend delivery of bupivacaine, elastomeric pain pumps, or delivery technologies that distribute bupivacaine over time. These medications may be delivered intravenously, orally, or locally into the surgical site, thereby having a potential opioid-sparing benefit. Current literature suggests that using opioid-sparing or opioid replacement techniques in the management of postsurgical pain consistently prevents ORADEs and reduces resource use such as inpatient hospital LOS and nursing time.[42]

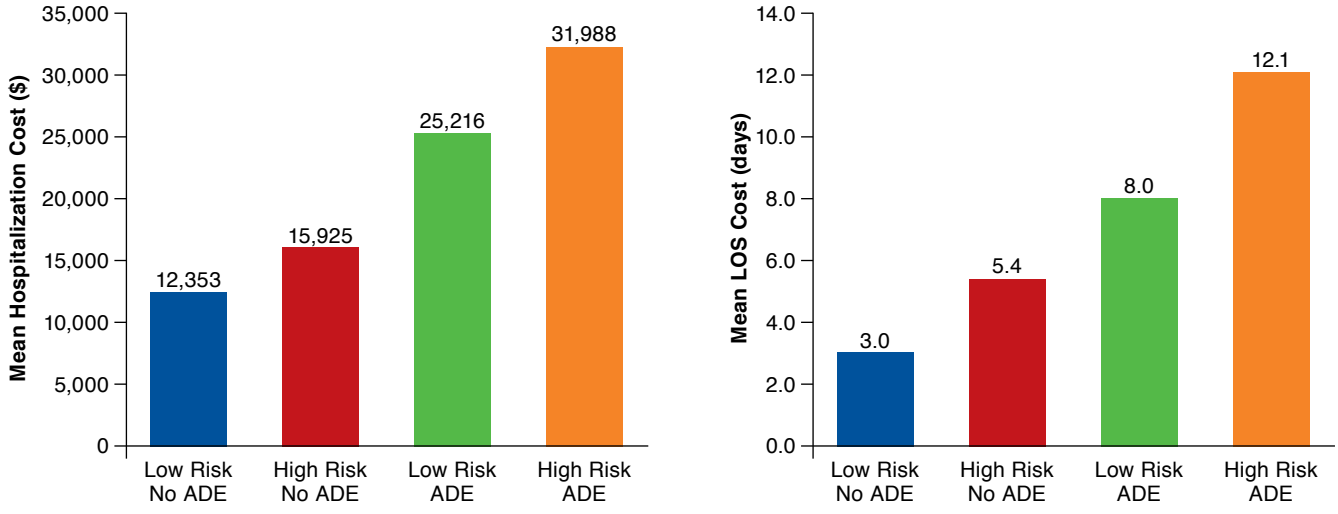
TABLE 4 Outcomes by High- Versus Low-Risk Patients

	Incidence (%)						
	Overall (N = 3,684)	Low Risk (n = 2,014)	High Risk (n = 1,670)	OR	95% CI		*P* Value
Any ORADE	12.2	5.3	20.6	4.62	3.68	5.81	<0.0001
Respiratory ORADE	3.3	1.0	6.0	6.05	3.76	9.72	<0.0001
GI ORADE	8.7	4.2	14.3	3.73	2.89	4.83	<0.0001
GU ORADE	1.3	2.5	0.2	12.96	4.64	36.23	<0.0001
30-day readmission	6.4	4.7	8.4	1.87	1.43	2.45	<0.0001
	Mean						
	Overall (N = 3,684)	Low Risk (n = 2,014)	High Risk (n = 1,670)	Cost/Rate Ratio[a]	95% CI		*P* Value
Total hospitalization cost	$15,846	$13,036	$19,234	1.47	1.42	1.53	<0.0001
LOS (days)	4.9	3.3	6.8	2.07	1.96	2.17	<0.0001

[a]*Note: High Risk: Low Risk*

CI = confidence interval; GI = gastrointestinal; GU = genitourinary; LOS = length of stay; OR = odds ratio; ORADE = opioid-related adverse drug event.

FIGURE 3 Mean Hospitalization Cost and LOS by Risk x ORADE Status

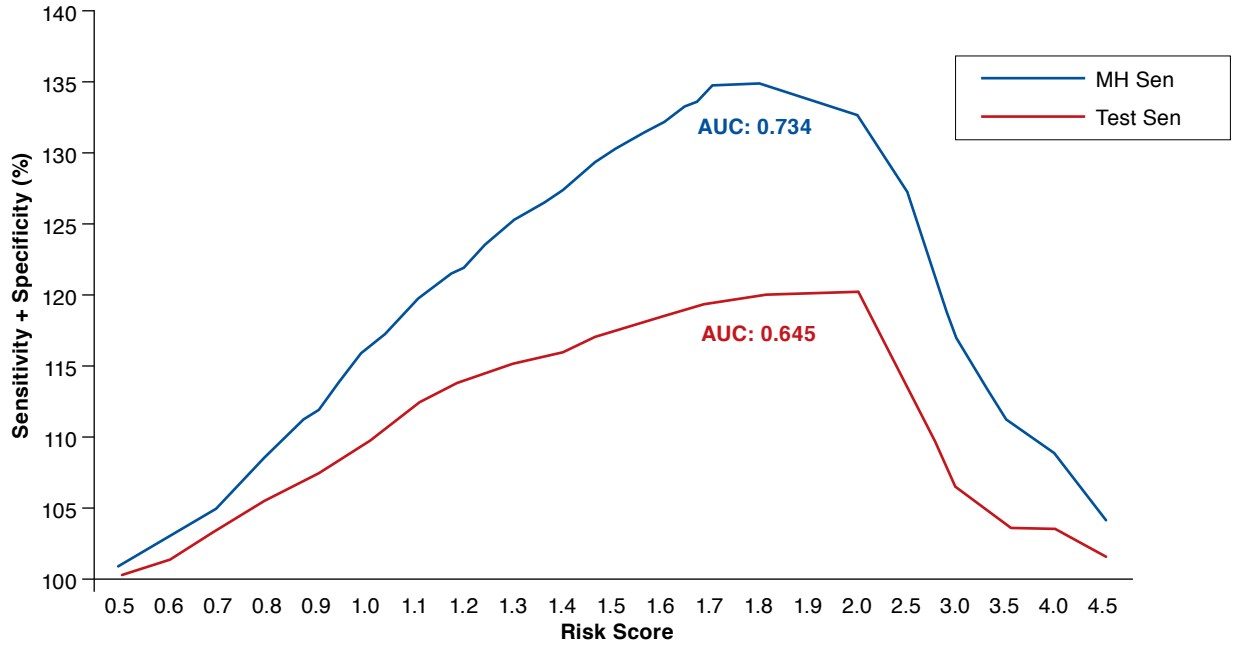


ADE = adverse drug event; LOS = length of stay; ORADE = opioid-related adverse drug event.

Limitations

While this study is novel and innovative, it is preliminary and contains several limitations. A key limitation is that the majority of the study population is women, which is perhaps explained by the relative distribution of bariatric surgery in men versus women.[43] This study repurposed administrative data from Memorial Hermann's EPSI database. Since administrative data were used to identify ORADEs and relied on documentation of specific ICD-9-CM codes, the true incidence of ORADEs in this population may be greater than what was observed. Similarly, undercoding of comorbidities may have led to underestimation of the prevalence of certain specific conditions and subsequent misclassification of patients by exposure. This study also lacked detailed clinical data such as opioid dosage/morphine equivalency and clinically defined patient characteristics such as body mass index, body surface area, and medical history. The inability to control for these factors makes it impossible to rule out some degree of residual confounding in the observed associations between risk factors and outcomes of ORADEs. Furthermore, a true temporal

FIGURE 4 AUC: Memorial Hermann Versus Test Population



AUC = area under the curve; MH Sen = Memorial Hermann population sensitivity; Test Sen = test population sensitivity.

relationship between opioid use and occurrence of ORADEs could not be established, since the ICD-9-CM diagnosis codes were not linked to a specific hospitalization day. Therefore, we cannot draw definitive conclusions regarding a causal link between opioid use and ORADEs. Additionally, applying common ORADE risk factors to patients who had GI surgical procedures based upon literature focused on PONV literature may challenge the validity and clinical utility of the approach. This study did not include insurance status from EPSI and whether having Medicare or commercial insurance made a difference in the comparison of outcomes between high- and low-risk patients. Finally, the participating hospital system is confined primarily to the Houston metropolitan area, which may limit the generalizability of our results to the broader U.S. population.

Conclusions

To our knowledge, this is the first study to evaluate the utility of a risk score for predicting other outcomes in GI surgical patients and to evaluate the benefits of application. This study contributes to the literature in terms of identifying risk factors for ORADEs and quantifying clinical and economic outcomes associated with ORADEs. Targeted interventions aimed at reducing the incidence of ORADEs in high-risk patients have the potential to improve the postsurgical experience for the patient and reduce costs for hospitals and may be more cost-efficient than interventions applied to the entire surgical population.

Future studies should focus on developing more detailed and precise risk assessment tools to further differentiate high-risk segments of the surgical population. Additional research examining genetic and underinvestigated clinical patient characteristics with different risk and ORADE profiles involving outpatients and children should improve predictive systems. Developing models with further granular procedures, incorporating other clinical parameters, and evaluating effectiveness of alternatives would increase generalizability, especially if data from multiple systems could be combined in pooled analyses.

Application of well-validated practical clinical nomograms has the potential to target high-risk segments of the patient population that may benefit from alternatives. In addition to the implications related to patient safety and quality of life, increasing health care providers' ability to determine the most appropriate pain management strategy for a given patient may translate to increased efficiency within a hospital and decreased economic burden to the overall health care system.

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DISCLOSURES

This research and manuscript were funded by Pacira Pharmaceuticals. Minkowitz has performed other clinical research funded by Pacira. Scranton is employed by Pacira. At the time of this research, Gruschkus was employed by Xcenda, a consulting company that received funding from Pacira.

Nipper-Johnson has previously worked as a contract employee for Pacira to present this research project. Menditto is a paid consultant for Pacira. Dandappanavar is employed by Xcenda, a consulting company that received funding from Pacira to support development of this manuscript.

Study concept and design were contributed by Minkowitz, Scranton, and Gruschkus, with assistance from Nipper-Johnson and Menditto. Data were collected primarily by Gruschkus and Nipper-Johnson, with assistance from Scranton and Minkowitz, and interpretation was performed by Gruschkus, Minkowitz, and Scranton, with input from Nipper-Johnson and Menditto. The manuscript was written by Menditto and Dandappanavar, with assistance from Scranton, Gruschkus, and Nipper-Johnson, and revised primarily by Dandappanavar, with assistance from Menditto and Scranton.

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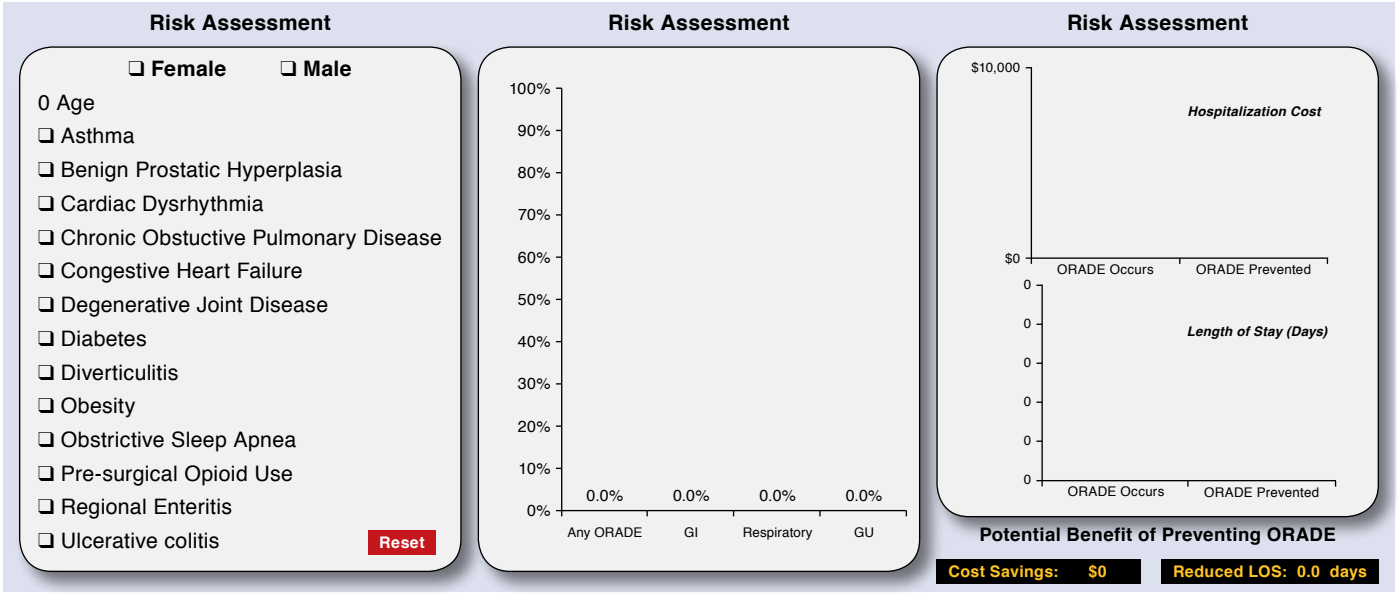
APPENDIX ORADE Risk and Predicted Outcomes Calculator for GI Surgical Patients Receiving Postoperative Opioids

Purpose

1. The primary purpose of this risk model is to provide an estimate of the probability that a given patient receiving a gastrointestinal (GI) soft tissue procedure will experience an opioid-related adverse drug event (ORADE) based on his or her clinical and demographic profiles.
2. A secondary goal is to quantify the potential cost savings and reduction in hospital length of stay for that patient if an ORADE was successfully avoided.

Instructions

1. Make sure that the risk assessment panel has been fully reset by clicking on the Reset button.
2. Complete risk assessment based on the patient's clinical and demographic characteristics at admission date.



GI = gastrointestinal; GU = gastrourinary; LOS = length of stay; ORADE = opioid-related adverse drug event.