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ORIGINAL RESEARCH

Establishment and Validation of Risk Prediction Models for Postoperative Pain After Endoscopic Submucosal Dissection: A Retrospective Clinical Study

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Objective: Postoperative pain is a common complication in endoscopic submucosal dissection (ESD) patients. This study aimed to develop and validate predictive models for postoperative pain associated ESD.

Methods: We retrospectively constructed a development cohort comprising 2162 patients who underwent ESD at our hospital between January 2015 and April 2022. The dataset was randomly divided into a training set (n = 1541) and a validation set (n = 621) in a 7:3 ratio. The bidirectional stepwise regression with Akaike's information criterion (AIC) and multivariate logistic regression analysis were used to screen the predictors of post-ESD pain and construct three nomograms. We evaluated the model's discrimination, precision and clinical benefit through receiver operating characteristic (ROC) curves, calibration plots, Hosmer–Lemeshow (HL) goodness-of-fit test and decision curve analysis (DCA) in internal validation.

Results: The proportion of patients developing postoperative pain in the training and testing data set was 25.6% and 28.5%, respectively. Three nomograms were constructed according to the final logistic regression models. The clinical prediction models for preoperative risks, preoperative and intraoperative risks, and perioperative risks consisted of seven, nine and six independent predictors, respectively, after bidirectional stepwise elimination. The models demonstrated the AUC of 0.794 (95% CI 0.768–0.820), 0.823 (95% CI 0.799–0.847) and 0.817 (95% CI 0.792–0.842) in the training cohort and 0.702 (95% CI 0.655–0.748), 0.705 (95% CI 0.659–0.752) and 0.747 (95% CI 0.703–0.790) in the validation cohort. The calibration plot, HL and DCA demonstrated the model's favorable clinical applicability.

Conclusion: We developed and validated three robust nomogram models, which might identify patients at risk of post-ESD pain and promising for clinical applications.

Keywords: endoscopic submucosal dissection, postoperative pain, nomograms

Introduction

Endoscopic submucosal dissection (ESD) is a new ultra-minimally invasive treatment method for the treatment of gastrointestinal early cancer and precancerous lesions, which can preserve the integrity of the organ structure. In comparison to traditional endoscopic mucosal resection (EMR), ESD is considered superior due to its ability to achieve complete removal of diseased tissue in one piece. Furthermore, several novel techniques derived from ESD have emerged, including endoscopic submucosal excavation (ESE), endoscopic full-thickness resection (EFR) and submucosal tunnel endoscopic resection (STER), which have been widely applied in clinical practice. However, performing ESD, ESE, EFR, and STER procedures necessitates advanced endoscopic skills, meticulous techniques, and longer duration

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which can potentially result in heightened trauma levels; most often conducted under general anesthesia with endotracheal intubation.

The occurrence of pain is a frequently encountered complication following surgery and a significant concern for anesthesiologists. Although ESD is a minimally invasive procedure, it has been reported in the literature that the incidence of moderate and severe pain after ESD can still reach 44.9%–62.8%, and some of them will continue to be long-term pathological pain, reducing patient satisfaction and prolonging hospital stay.[1] Choi et al demonstrated that almost all patients (98%) experienced upper abdominal pain after gastric ESD surgery, regardless of pain severity.[2] Of 156 patients undergoing endoscopic resection of gastric tumor, 66 (42.3%) were treated with intravenous meperidine due to moderate-to-severe postoperative abdominal pain.[3] In a retrospective analysis of 1226 patients treated with gastric ESD, Kim et al found that 461 (36.4%) patients required at least one dose of analgesic after surgery.[4] In addition, a retrospective analysis of 309 patients found that 20% of the patients complained of moderate-to-severe pain after esophageal ESD surgery (VAS > 4) and required analgesic drug treatment.[5]

It can be seen that pain after ESD is relatively common. Some researchers have discussed and analyzed the risk factors of pain after ESD surgery, and found that lesion size, operation duration, lesion site, muscular layer exposure, gender, preoperative surgical history and postoperative fever may be the risk factors after ESD.[4–9] However, existing studies only analyzed the risk factors of postoperative pain in a single surgical site, such as esophagus, stomach, and intestine, and it was not clear how painful the different anatomical sites of the digestive system were and the relationship between multiple variables cannot be visually shown. Moreover, development of medicine has gradually transited from traditional empirical medicine to evidence-based medicine, and the future is developing toward precision medicine. More and more researchers focused on predictive models. Nomograms charted by individualized prediction models to analyze postoperative pain of ESD have remained scarce. In this context, three nomograms using preoperative, preoperative and intraoperative, and perioperative risk factors affecting post-ESD pain intended to be established, in order to identify high-risk patients with acute pain after ESD more directly and take preventive measures timely.

Methods

Patients and Study Design

A retrospective observational study was conducted on a primary cohort of patients who underwent ESD, ESE, EFR or STER between January 2015 and April 2022 at Liaocheng People's Hospital (Shandong, China). Inclusion criteria included the following: (i) Male or female. Age over 18 years; (ii) Underwent ESD or its derivative technologies (ESE, EFR or STER); (iii) ASA I~III. Exclusion criteria were as follows: 1) Routinely use of postoperative analgesic pump after surgery; 2) Patients taking analgesic drugs for non-surgical site pain; 3) Patients taking analgesic drugs before or 48h after surgery; 4) Patients with serious postoperative complications (delayed perforation, bleeding requiring endoscopic hemostasis, transferred to ICU within 24h after surgery, etc); 5) Underwent open or laparoscopic or thoracoscopic surgery the next day after endoscopic treatment; 6) Without complete follow-up information; 7) Other types of surgery were performed at the same time.

Ethics Committee of Liaocheng People's Hospital approved this retrospective analysis. Due to the retrospective nature of our study, patient information was collected from their previous medical records. Furthermore, no interventions were implemented on the patients, and their personal privacy information, such as names, ID numbers, or other identifying fields, was anonymized during data extraction. Additionally, any research results will be shared in the form of summary data or final statistical results on a public platform rather than disclosing the original data if necessary. The Ethics Committee therefore granted approval for the waiver of the informed consent application, in accordance with the principles outlined in the Declaration of Helsinki. We had registered at the Chinese Clinical Trial Registry (Registration number: ChiCTR2300072854, https://www.chictr.org.cn) and recorded at Medical Research Registration and Filing Information System (https://www.medicalresearch.org.cn).

The sample was divided into 2 groups with a ratio of 7:3, all the patients were randomly divided into training set (n = 1541) and testing set (n = 621). The training set was used to develop the prediction models and nomograms, and testing set was used to evaluate their predictive performance.

Data Collection

For each patient, demographic, history, anesthesia and surgery data, and follow-up information were derived from clinical databases and medical records. Demographic data included age, gender, body mass index (BMI), and American Society of Anesthesiologists (ASA) physical status classification system. History of hypertension and diabetes, history of pre-existing pain conditions (which included musculoskeletal pain disorders, peripheral neuropathy, and migraines), smoking or drinking status and operation history were recorded. We collected type of operation, surgical site, operation duration, depth of infiltration (mucosa, submucosa and lamina muscularis propria), muscular injury or not, maximum diameter of the lesion, duration of anesthesia, intraoperative analgesics as anesthesia and surgery data. Postoperative nausea and vomiting (PONV), postoperative fever, usage of analgesics within 48h after surgery, and postoperative hospital stay were also obtained. We categorized age into six subgroups ("18~39 years", "40~49 years", "50~59 years", "60~69", "70~79" and "≥80 years") in our study. Surgical site was classified as esophagus, esophagogastric junction (EGJ), stomach, duodenum, colorectum, multisite (multisite refers to ESD or its derivative technology of surgery in different organ sites), and type of operation was dichotomized into ESD, ESE, EFR, STER and combined operation (two or more surgical procedures). Intraoperative analgesics mainly included fentanyl, sufentanil, oxycodone, nalbuphine, ketoloxic acid and dexamethasone.

If there was a doctor's order for the use of antiemetic drugs within 48h after surgery or a description of PONV in the medical history, we assumed that this patient had PONV. We determined postoperative fever through one of the three aspects: postoperative temperature was more than 37.5°C, application of indomethacin suppository within 48 hours after surgery, or as recorded in the course of medical history. Postoperative hospital stay was defined as the number of days in hospital from the day of surgery to the day of discharge.

Primary Outcome

The primary outcome was the degree of pain within 48h after surgery, and postoperative pain was determined based on whether analgesics were used within 48 hours of surgery. The nursing staff of the ward evaluated the patients' pain with visual analogue scale (VAS) every 4h after surgery. Analgesic drugs were given when the patients' VAS score was greater than 3 points or when the patients themselves requested analgesic drugs.

Sample Size

Sample size calculation was determined by our primary binary outcome. In predictive studies (for example, those used for nomogram development and validation), the number of resulting events will determine the valid sample size. On the basis of some empirical investigations, the sample was defined to have at least 10 outcome events per variable (EPV).[10] Our sample and event numbers exceeded findings using EPV methods to determine sample sizes and, therefore, can be expected to provide robust estimates.

Data Management and Statistical Analysis

We followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement for reporting the development and validation of the prediction model.[11] Statistical analysis was conducted with R software (version 4.3.2; http://www.Rproject.org) and STATA 17.0 for Windows (StataCorp Texas, USA).

As the missing ratio of height data, which was deleted, in clinical records was more than 70%, so BMI was not analyzed in this study. The missing values of other variables that were included in the statistical analysis were less than 5%. Categorized data were presented as numbers and percentages, and continuous non-normal data were expressed using median (IQR). Bivariate analysis was examined using the Wilcoxon rank-sum test for continuous covariates and Pearson's Chi square test or Fisher's exact test for categorical variables. For predictive modeling, three nomograms were constructed using preoperative factors, preoperative and intraoperative factors, and perioperative factors, respectively. Univariate and multivariate logistic regression analyses were utilized to identify potential predictors, employing a bidirectional stepwise regression to determine the final prediction models with Akaike's information criterion (AIC) as the stopping rule. Calibration plots were performed to assess the accuracy of the nomograms. The receiver operating

characteristic (ROC) curves and the areas under the receiver operating characteristic curve (AUC) were used to evaluate the discrimination of the models. Decision curve analyses were conducted to determine the clinical usefulness of nomograms by quantifying the net benefits at different threshold probabilities in validation datasets. All statistical tests were two-sided, and *p*-values <0.05 were considered significant.

Results

Demographic and Clinical Characteristics of Patients Undergoing ESD

From January 2015 to April 2022, 2286 subjects were screened for eligibility at our digestive endoscopy center. After the exclusions, the final analysis included 2162 subjects who were randomly divided into 2 cohorts at the ratio of 7:3, including the training (n = 1541) and validation (n = 621) cohorts. The process for patient selection is shown in Figure 1. Of the 2162 patients, 571 (26.4%) and 418 (19.3%) developed postoperative pain and PONV (Table 1). The proportion of patients developing postoperative pain in the training and testing data sets was 25.6% and 28.5%, respectively. Patients with esophageal, EGJ, stomach, duodenum and colorectal lesions accounted for 967 (44.7%), 210 (9.7%), 698 (32.3%), 16 (0.7%), 194 (9.0%), respectively. ESD, ESE, EFR and STER were performed in 1727 (79.9%), 230 (10.6%), 65 (3.0%), 101 (4.7%) of patients, respectively. The median maximum specimen diameter was 2.5cm (interquartile range, 1.5 to 4.0cm). The operation and anesthesia duration were 64.0 (46.0, 85.0) min and 77.0 (60.0, 99.0) min of total population. The median of postoperative hospital stay was 5.0d (interquartile range, 4.0 to 6.0d). The training and validation cohorts were well balanced, with no significant differences in their baseline variables, except for history of preoperative pain (Table 1).

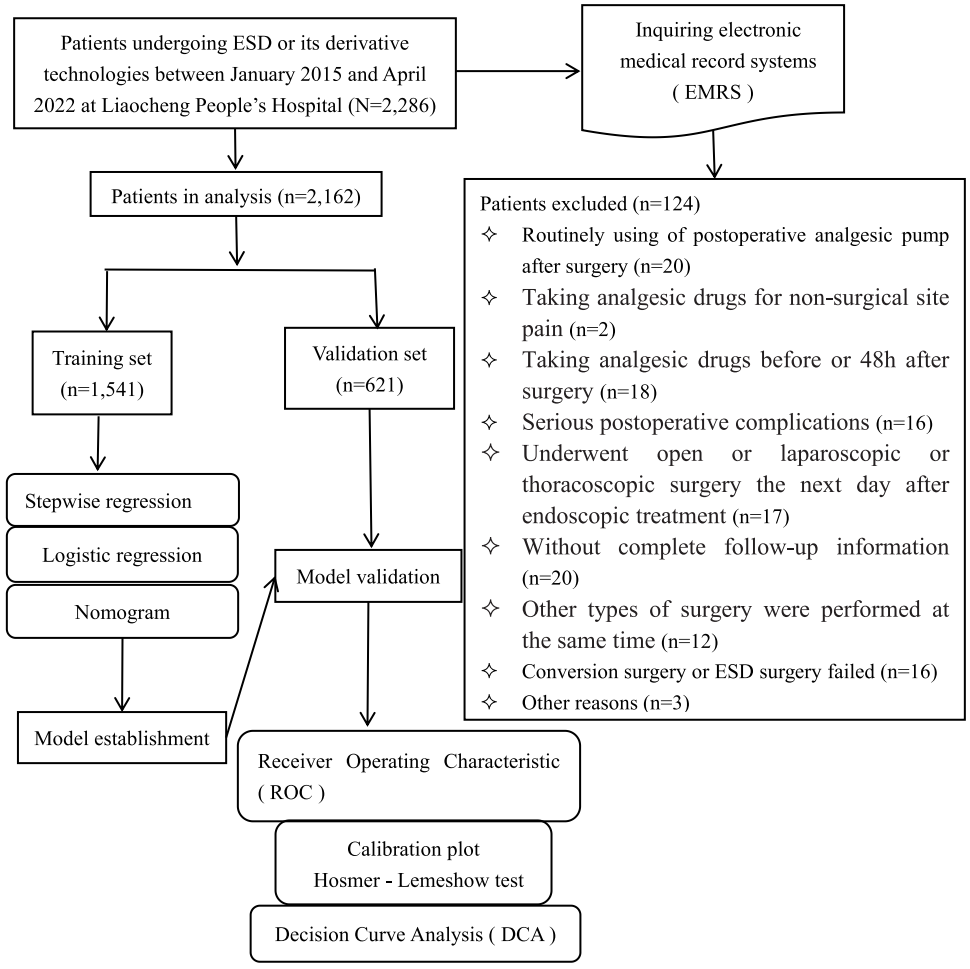

Figure 1 Numbers of participants enrolled, and establishment and validation of models.

Table 1 Characteristics of Patients in the Training and Validation Cohorts

Characteristics	Total N=2162	Training Set N=1541	Validation Set N=621	*p*
Age, No. (%), Years				0.41
18~39	77 (3.6)	57 (3.7)	20 (3.2)	
40~49	196 (9.1)	132 (8.6)	64 (10.3)	
50~59	630 (29.1)	435 (28.2)	195 (31.4)	
60~69	798 (36.9)	585 (38.0)	213 (34.3)	
70~79	413 (19.1)	297 (19.3)	116 (18.7)	
≥80	48 (2.2)	35 (2.3)	13 (2.1)	
Gender, No. (%)				0.82
Female	970 (44.9)	689 (44.7)	281 (45.2)	
Male	1192 (55.1)	852 (55.3)	340 (54.8)	
Weight, Median (IQR), kg	66.0 (57.0, 74.0)	66.0 (57.0, 73.0)	65.0 (57.0, 74.0)	0.61
Smoking, no. (%)				0.62
Non-Smokers	1450 (67.1)	1037 (67.3)	413 (66.5)	
Present Smokers	573 (26.5)	410 (26.6)	163 (26.2)	
Former Smokers	139 (6.4)	94 (6.1)	45 (7.2)	
Drinking, No. (%)				0.45
Non-Drinkers	1411 (65.3)	1016 (65.9)	395 (63.6)	
Present Drinkers	655 (30.3)	461 (29.9)	194 (31.2)	
Former Drinkers	96 (4.4)	64 (4.2)	32 (5.2)	
History of Surgery, No. (%)				0.50
No	1499 (69.3)	1075 (69.8)	424 (68.3)	
Yes	663 (30.7)	466 (30.2)	197 (31.7)	
Hypertension, No. (%)				0.79
No	1662 (76.9)	1187 (77.0)	475 (76.5)	
Yes	500 (23.1)	354 (23.0)	146 (23.5)	
Diabetes, No. (%)				0.54
No	1871 (86.5)	1338 (86.8)	533 (85.8)	
Yes	291 (13.5)	203 (13.2)	88 (14.2)	
Preoperative Pain, No. (%)				0.04
No	1456 (67.3)	1058 (68.7)	398 (64.1)	
Yes	706 (32.7)	483 (31.3)	223 (35.9)	
ASA, No. (%)				0.27
I	22 (1.0)	16 (1.0)	6 (1.0)	
II	2002 (92.6)	1435 (93.1)	567 (91.3)	
III	138 (6.4)	90 (5.8)	48 (7.7)	
Surgical Site, No. (%)				0.86
Esophagus	967 (44.7)	686 (44.5)	281 (45.2)	
EGJ	210 (9.7)	152 (9.9)	58 (9.3)	
Stomach	698 (32.3)	503 (32.6)	195 (31.4)	
Duodenum	16 (0.7)	13 (0.8)	3 (0.5)	
Colorectum	194 (9.0)	133 (8.6)	61 (9.8)	
Multisite	77 (3.6)	54 (3.5)	23 (3.7)	
Type of Operation, No. (%)				0.47
ESD	1727 (79.9)	1244 (80.7)	483 (77.8)	
ESE	230 (10.6)	162 (10.5)	68 (11.0)	
EFR	65 (3.0)	43 (2.8)	22 (3.5)	
STER	101 (4.7)	67 (4.3)	34 (5.5)	
Combined Operation	39 (1.8)	25 (1.6)	14 (2.3)	

(*Continued*)

Table 1 (Continued).

Characteristics	Total N=2162	Training Set N=1541	Validation Set N=621	*p*
Maximum Specimen Diameter, Median (IQR), cm	2.5 (1.5, 4.0)	2.5 (1.4, 4.0)	2.5 (1.5, 4.0)	0.65
Depth of Infiltration, No. (%)				0.24
Mucous Layer	1645 (76.1)	1184 (76.8)	461 (74.2)	
Submucosa	119 (5.5)	87 (5.6)	32 (5.2)	
Lamina Muscularis Propria	398 (18.4)	270 (17.5)	128 (20.6)	
Muscular Injury, No. (%)				0.59
No	1484 (68.6)	1063 (69)	421 (67.8)	
Yes	678 (31.4)	478 (31.0)	200 (32.2)	
Operation Duration, Median (IQR), Min	64.0 (46.0, 85.0)	64.0 (46.0, 86.0)	63.0 (45.0, 82.0)	0.39
Anesthesia Duration, Median (IQR), Min	77.0 (60.0, 99.0)	78.0 (60.0, 99.0)	77.0 (60.0, 98.0)	0.49
Fentanyl, Median (IQR), mg	0.2 (0.2, 0.2)	0.2 (0.2, 0.2)	0.2 (0.2, 0.2)	0.78
Sufentanil, Median (IQR), μg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.95
Oxycodone, Median (IQR), mg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.86
Nalbuphine, Median (IQR), mg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.86
Ketoloxic Acid, Median (IQR), mg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.97
Dexamethasone, Median (IQR), mg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.84
PONV, no. (%)				0.19
No	1744 (80.7)	1254 (81.4)	490 (78.9)	
Yes	418 (19.3)	287 (18.6)	131 (21.1)	
Postoperative Fever, No. (%)				0.08
No	1895 (87.7)	1363 (88.4)	532 (85.7)	
Yes	267 (12.3)	178 (11.6)	89 (14.3)	
Postoperative Hospital Stay, Median (IQR), d	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)	0.18
Postoperative Pain				0.16
No	1591 (73.6)	1147 (74.4)	444 (71.5)	
Yes	571 (26.4)	394 (25.6)	177 (28.5)	

Abbreviations: ASA, American Society of Anesthesiologists; EGJ, Esophagogastric junction; ESD, Endoscopic submucosal dissection; ESE, Endoscopic submucosal excavation; EFR, Endoscopic full-thickness resection; STER, Submucosal tunnel endoscopic resection; IQR, Interquartile range; PONV, postoperative nausea and vomiting.

Univariate and Multivariate Postoperative Pain Risk Factors

Univariate analysis was performed to compare the candidate predictors between postoperative pain and non-pain groups. The results showed that 15 variables (7 preoperative [demographic and clinical], 6 intraoperative [anesthesia and surgical procedures], and 2 postoperative [in-hospital complications]) were statistically significant ($P<0.05$): smoking, drinking, history of surgery, surgical site, type of operation, preoperative pain, maximum specimen diameter, depth of infiltration, operation duration, anesthesia duration, fentanyl, history of hypertension and diabetes, PONV, postoperative fever (Table 2). These 15 predictors were subsequently subjected to multivariate logistic regression analysis. The results of the multivariate analysis for the preoperative risks (model 1), preoperative and intraoperative risks (model 2), and perioperative risks (model 3) are shown in Table 3.

Establishment of the Nomogram Prediction Models

Three nomograms were constructed according to the final logistic regression models. The final prediction models consisted of seven (smoking, drinking, history of surgery, hypertension and diabetes, surgical site and preoperative pain history), nine (smoking, drinking, history of surgery, hypertension and diabetes, surgical site, depth of infiltration, preoperative pain history and maximum specimen diameter) and six (history of surgery, diabetes and preoperative pain, longer operation duration, surgical site and PONV) independent predictors, respectively, after bidirectional stepwise elimination (Figure 2).

Table 2 Univariable Analysis of the Training Cohort with Perioperative Risks

Variables	Postoperative Pain		Univariable Analysis	
	No (N=1147)	Yes (N=394)	OR (95% CI)	*P*
Age, No. (%), years				
18~39	47 (4.1)	10 (2.5)	Reference	
40~49	103 (9.0)	29 (7.4)	1.32 (0.60–2.94)	0.491
50~59	329 (28.7)	106 (26.9)	1.51 (0.74–3.10)	0.257
60~69	436 (38)	149 (37.8)	1.61 (0.79–3.26)	0.189
70~79	209 (18.2)	88 (22.3)	1.98 (0.96–4.09)	0.066
≥80	23 (2.0)	12 (3.0)	2.45 (0.92–6.51)	0.072
Gender				
Male	647 (56.4)	205 (52.0)	Reference	
Female	500 (43.6)	189 (48.0)	1.19 (0.95–1.50)	0.132
Smoking, No. (%)				
Non-Smokers	781 (68.1)	256 (65)	Reference	
Present Smokers	318 (27.7)	92 (23.4)	0.88 (0.67–1.16)	0.367
Former Smokers	48 (4.2)	46 (11.7)	2.92 (1.91–4.49)	<0.001
Drinking, No. (%)				
Non-Drinkers	741 (64.6)	275 (69.8)	Reference	
Present Drinkers	367 (32.0)	94 (23.9)	0.69 (0.53–0.90)	0.006
Former Drinkers	39 (3.4)	25 (6.3)	1.73 (1.03–2.91)	0.040
History of Surgery, No. (%)				
No	842 (73.4)	233 (59.1)	Reference	
Yes	305 (26.6)	161 (40.9)	1.91 (1.50–2.42)	<0.001
History of Hypertension, No. (%)				
No	944 (82.3)	243 (61.7)	Reference	
Yes	203 (17.7)	151 (38.3)	2.89 (2.24–3.72)	<0.001
History of Diabetes, No. (%)				
No	1074 (93.6)	264 (67.0)	Reference	
Yes	73 (6.4)	130 (33.0)	7.24 (5.28–9.94)	<0.001
Preoperative Pain, No. (%)				
No	849 (74.0)	209 (53.0)	Reference	
Yes	298 (26.0)	185 (47.0)	2.52 (1.99–3.20)	<0.001
ASA, no. (%)				
I	15 (1.3)	1 (0.3)	Reference	
II	1042 (90.8)	393 (99.7)	5.66 (0.74–42.97)	0.094
III	90 (7.8)	0 (0.0)	0.00 (0.00-Inf)	0.972
Surgical Site, No. (%)				
Colorectum	118 (10.3)	15 (3.8)	Reference	
EGJ	133 (11.6)	19 (4.8)	1.12 (0.55–2.31)	0.751
Stomach	419 (36.5)	84 (21.3)	1.58 (0.88–2.83)	0.128
Duodenum	7 (0.6)	6 (1.5)	6.74 (2.00–22.74)	0.002
Esophagus	436 (38.0)	250 (63.5)	4.51 (2.58–7.89)	<0.001
Multisite	34 (3.0)	20 (5.1)	4.63 (2.14–10.00)	<0.001
Type of Operation, No. (%)				
ESD	927 (80.8)	317 (80.5)	Reference	
ESE	132 (11.5)	30 (7.6)	0.66 (0.44–1.01)	0.054
EFR	28 (2.4)	15 (3.8)	1.57 (0.83–2.97)	0.169
STER	48 (4.2)	19 (4.8)	1.16 (0.67–2.00)	0.600
Combined Operation	12 (1.0)	13 (3.3)	3.17 (1.43–7.01)	0.004

(*Continued*)

Table 2 (Continued).

Variables	Postoperative Pain		Univariable Analysis	
	No (N=1147)	Yes (N=394)	OR (95% CI)	*P*
Maximum Specimen Diameter, Median (IQR), cm	2.3 (1.1, 3.5)	3.0 (2.0, 4.5)	1.26 (1.19–1.34)	<0.001
Depth of Infiltration, No. (%)				
Mucous Layer	899 (78.4)	285 (72.3)	Reference	
Submucosa	48 (4.2)	39 (9.9)	2.56 (1.65–3.99)	<0.001
Lamina Muscularis Propria	200 (17.4)	70 (17.8)	1.10 (0.82–1.49)	0.522
Muscular Injury, No. (%)				
No	802 (69.9)	261 (66.2)	Reference	
Yes	345 (30.1)	133 (33.8)	1.18 (0.93–1.51)	0.174
Operation Duration, Median (IQR), Min	60.0 (45.0, 78.0)	75.0 (53.0, 105.0)	1.01 (1.01–1.01)	<0.001
Anesthesia duration, median (IQR), min	72.0 (58.0, 90.0)	90.0 (70.0, 122.0)	1.01 (1.01–1.01)	<0.001
Fentanyl, median (IQR), mg	0.2 (0.2, 0.2)	0.2 (0.2, 0.2)	125.33 (5.95–2641.76)	0.002
Sufentanil, median (IQR), μg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.00 (0.96–1.04)	0.927
Oxycodone, Median (iqr), mg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.02 (0.85–1.23)	0.812
Nalbuphine, Median (iqr), mg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.93 (0.82–1.06)	0.295
Ketoloxic Acid, Median (iqr), mg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.02 (1.00–1.03)	0.066
Dexamethasone, Median (iqr), mg	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.95 (0.84–1.07)	0.410
PONV				
No	984 (85.8)	270 (68.5)	Reference	
Yes	163 (14.2)	124 (31.5)	2.77 (2.12–3.63)	<0.001
Postoperative Fever, No. (%)				
No	1043 (90.9)	320 (81.2)	Reference	
Yes	104 (9.1)	74 (18.8)	2.32 (1.68–3.20)	<0.001

Abbreviations: ASA, American Society of Anesthesiologists; EGJ, Esophagogastric junction; ESD, Endoscopic submucosal dissection; ESE, Endoscopic submucosal excavation; EFR, Endoscopic full-thickness resection; STER, Submucosal tunnel endoscopic resection; IQR, Interquartile range; PONV, postoperative nausea and vomiting.

Table 3 Multivariate Analysis of the Training Cohort Using Preoperative Factors, Preoperative and Intraoperative Factors, and Perioperative Factors Respectively

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Smoking, No. (%)						
Non-Smokers	Reference				Reference	
Present Smokers	1.51 (0.98–2.33)	0.064	1.77 (1.11–2.84)	0.017	1.95 (1.20–3.17)	0.007
Former Smokers	5.28 (2.64–10.55)	<0.001	4.54 (2.15–9.60)	<0.001	4.40 (2.03–9.54)	<0.001
Drinking, No. (%)						
Non-Drinkers	Reference				Reference	
Present Drinkers	0.42 (0.27–0.65)	<0.001	0.39 (0.24–0.63)	<0.001	0.37 (0.23–0.61)	<0.001
Former Drinkers	0.35 (0.16–0.81)	0.013	0.36 (0.15–0.86)	0.021	0.37 (0.15–0.91)	0.030
History of Surgery, No. (%)						
No	Reference				Reference	
Yes	1.99 (1.51–2.62)	<0.001	2.03 (1.52–2.72)	<0.001	1.86 (1.38–2.51)	<0.001
History of Hypertension, No. (%)						
No	Reference				Reference	
Yes	1.62 (1.17–2.25)	0.004	1.68 (1.20–2.37)	0.003	1.79 (1.26–2.55)	0.001
History of Diabetes, No. (%)						
No	Reference				Reference	
Yes	5.46 (3.71–8.02)	<0.001	5.71 (3.80–8.58)	<0.001	5.84 (3.84–8.87)	<0.001

(*Continued*)

Table 3 (Continued).

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Preoperative Pain, No. (%)						
No	Reference				Reference	
Yes	2.72 (2.07–3.57)	<0.001	2.92 (2.19–3.91)	<0.001	2.95 (2.19–3.98)	<0.001
Surgical Site, No. (%)						
Colorectum	Reference				Reference	
EGJ	1.06 (0.49–2.30)	0.879	0.72 (0.27–1.93)	0.517	0.65 (0.24–1.75)	0.395
Stomach	1.60 (0.85–3.00)	0.143	1.14 (0.48–2.70)	0.772	1.08 (0.46–2.56)	0.862
Duodenum	6.19 (1.61–23.72)	0.008	6.16 (1.24–30.57)	0.026	6.92 (1.35–35.50)	0.020
Esophagus	4.68 (2.56–8.55)	<0.001	4.46 (1.94–10.22)	<0.001	4.35 (1.91–9.91)	<0.001
Multisite	4.38 (1.88–10.21)	<0.001	1.93 (0.60–6.22)	0.272	1.98 (0.60–6.51)	0.260
Type of Operation, No. (%)						
ESD	Reference				Reference	
ESE	NA	NA	0.66 (0.35–1.25)	0.205	0.58 (0.30–1.14)	0.113
EFR	NA	NA	1.55 (0.60–4.00)	0.364	1.26 (0.46–3.45)	0.650
STER	NA	NA	0.43 (0.18–1.02)	0.055	0.37 (0.15–0.91)	0.029
Combined Operation	NA	NA	2.18 (0.69–6.87)	0.184	1.65 (0.49–5.52)	0.417
Maximum Specimen Diameter, Median (IQR), cm	NA	NA	1.18 (1.08–1.28)	<0.001	1.17 (1.07–1.27)	<0.001
Depth of Infiltration, No. (%)						
Mucous Layer	Reference				Reference	
Submucosa	NA	NA	8.25 (4.55–14.98)	<0.001	8.88 (4.81–16.37)	<0.001
Lamina Muscularis Propria	NA	NA	3.28 (1.74–6.18)	<0.001	3.82 (1.98–7.36)	<0.001
Operation Duration, Median (IQR), Min	NA	NA	1.01 (1.00–1.01)	0.063	1.01 (1.00–1.01)	0.047
Anesthesia Duration, Median (IQR), min	NA	NA	1.00 (1.00–1.01)	0.225	1.00 (1.00–1.01)	0.340
Fentanyl, Median (IQR), mg	NA	NA	17.62 (0.18–1731.3)	0.220	11.03(0.11–1059.83)	0.303
PONV, no. (%)						
No	Reference		Reference		Reference	
Yes	NA	NA	NA	NA	2.96 (2.10–4.17)	<0.001
Postoperative Fever, No. (%)						
No	Reference		Reference		Reference	
Yes	NA	NA	NA	NA	2.12 (1.41–3.19)	<0.001

Notes: Model 1, Preoperative model; Model 2, Preoperative and intraoperative model; Model 3, Perioperative model.
Abbreviations: EGJ, Esophagogastric junction; ESD, Endoscopic submucosal dissection; ESE, Endoscopic submucosal excavation; EFR, Endoscopic full-thickness resection; STER, Submucosal tunnel endoscopic resection; IQR, Interquartile range; PONV, postoperative nausea and vomiting.

Validation of the Nomogram Prediction Models

The models demonstrated the AUC of 0.794 (95% CI 0.768–0.820), 0.823 (95% CI 0.799–0.847) and 0.817 (95% CI 0.792–0.842) in the training cohort and 0.702 (95% CI 0.655–0.748), 0.705 (95% CI 0.659–0.752) and 0.747 (95% CI 0.703–0.790) in the validation cohort (Figure 3). The Hosmer–Lemeshow goodness-of-fit test also indicated good fits of the prediction nomograms (χ^2=11.764, P=0.162; χ^2=8.628, P=0.375; χ^2=3.639, P=0.888). The calibration plot suggested good calibration ability of the nomograms (Figure 4), demonstrating good agreement between the forecasted probabilities and actual observations. Figure 5 presents the DCA curves used to assess the clinical utility of the nomograms, demonstrating a threshold probability range of 10%~70%.

Discussion

The nomogram is a simple, convenient and user-friendly tool for clinical evaluation and is gradually being widely used in clinical practice.[12] We developed and internally validated three nomograms with perioperatively known patients and surgery factors associated with increased acute pain after ESD. The reasons for three prediction models are as follows. As previously reported in the literature, risk factors associated with acute postoperative pain encompass various aspects, including demographic and sociological factors, psychological variables, preoperative pain and opioid usage, as well as

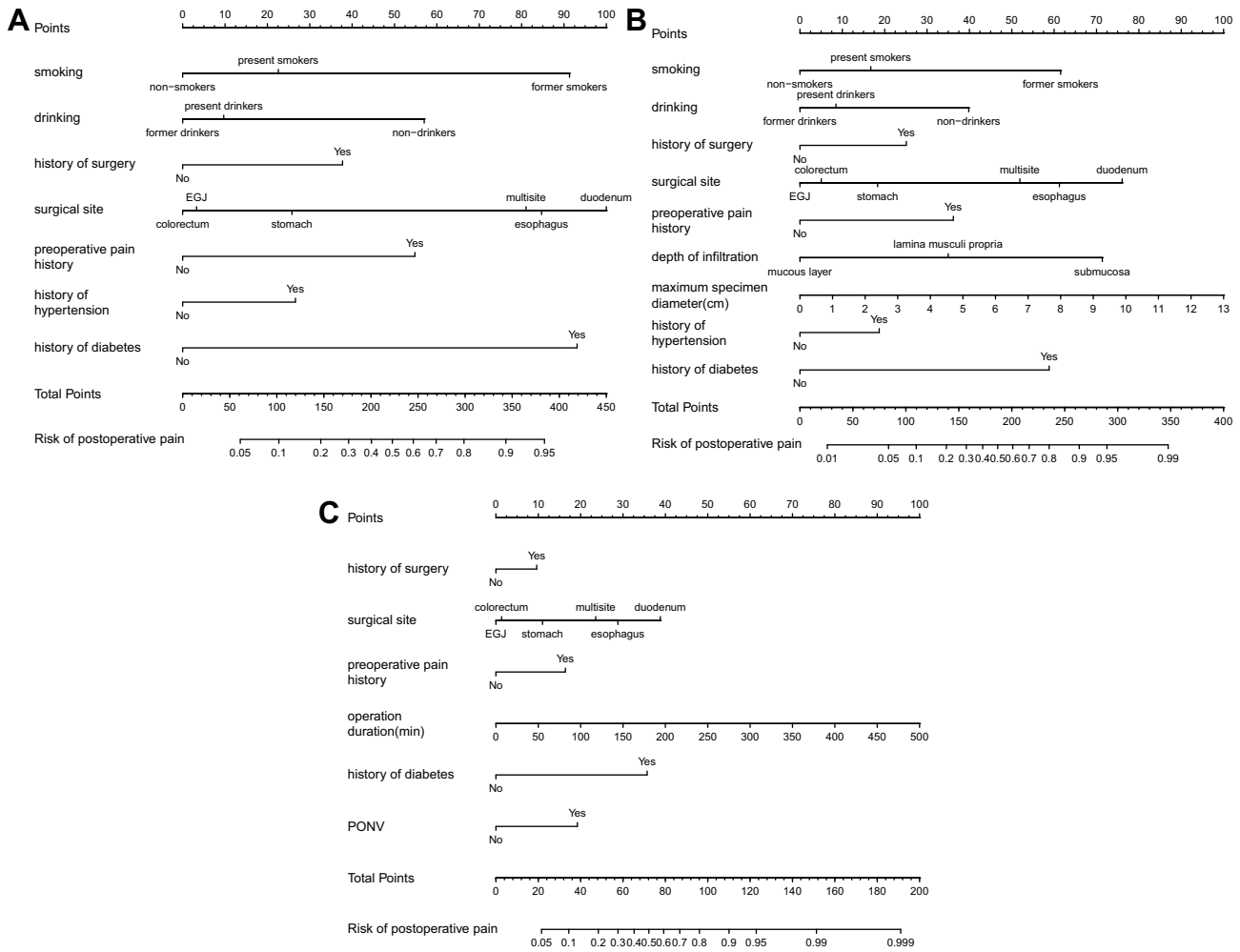

Figure 2 Nomograms to predict pain within 48h after surgery following ESD. To use the nomogram, find the position of each variable on the corresponding axis, draw a straight line to the points axis for the number of points, add the points from all of the variables, and draw a straight line from the total points axis to determine the postoperative pain probabilities at the lower line of the nomogram. (**A**) Preoperative nomogram. (**B**) Preoperative and intraoperative nomogram; (**C**) Perioperative nomogram. EGJ: esophagogastric junction.

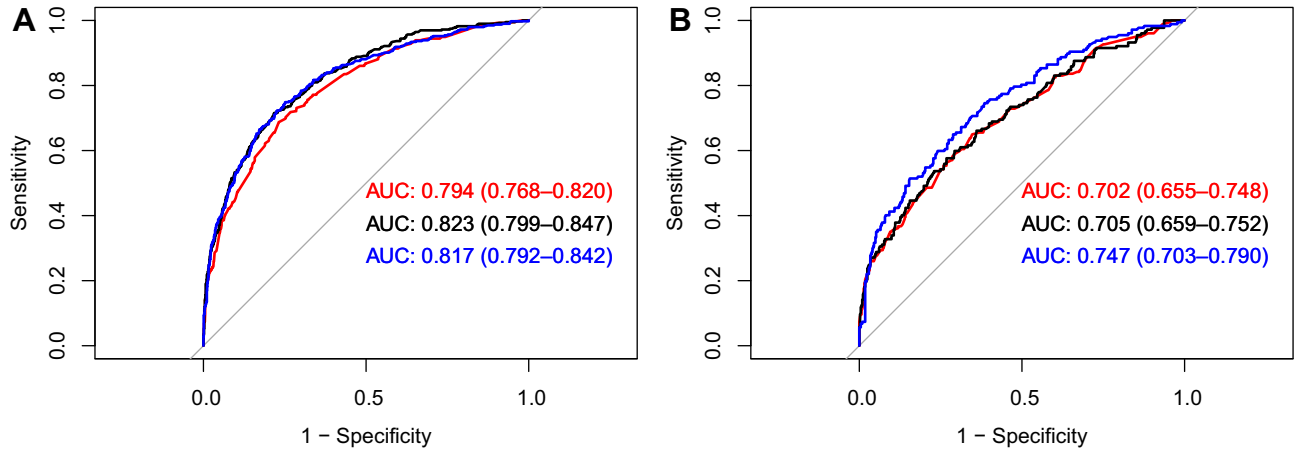

Figure 3 Receiver operating characteristic (ROC) curves of the nomograms in the training (**A**) and validation data sets (**B**). Red line represented the preoperative model, black line represented the preoperative and intraoperative model, and blue line represented the perioperative model. The discrimination was quantified by calculating the area under the ROC curve (AUC). A larger AUC indicated adequate discrimination between patients who will have serious postoperative pain and those who will not. An AUC of 0.5 indicated no discrimination, and an AUC of 1.0 represented excellent discrimination.

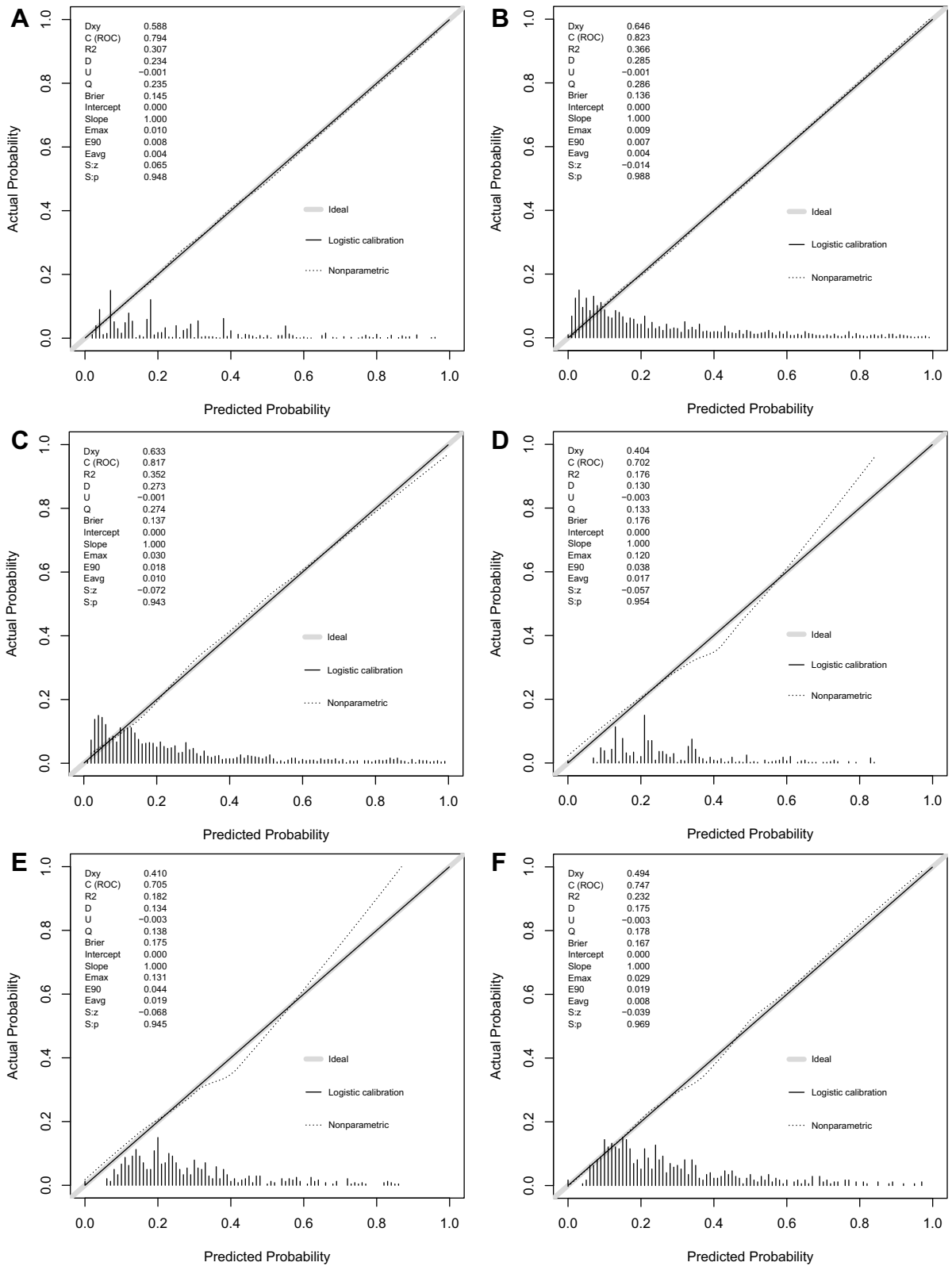

Figure 4 Calibration curves for the nomograms of preoperative, preoperative and intraoperative, and perioperative models in the training cohorts (**A**–**C**) as well as in the validation cohorts (**D**–**F**). The y-axis represented the actual rate of postoperative pain and x-axis represented the predicted probability of postoperative pain. For a nomogram with better calibration, the scatter points should be arranged along a 45°diagonal line. The Hosmer-Lemeshow (HL) goodness-of-fit test was often used to compare whether significant differences existed between the prediction probability and the actual occurrence, with $P > 0.05$ indicating no statistically significant difference, and the calibration of the model was good. HL: χ^2=4.059, P = 0.852 (**A**); HL: χ^2=2.882, P = 0.942 (**B**); HL: χ^2=7.918, P = 0.442 (**C**). HL: χ^2=11.764, P = 0.162 (**D**); HL: χ^2=8.628, P = 0.375 (**E**); HL: χ^2=3.639, P = 0.888 (**F**).

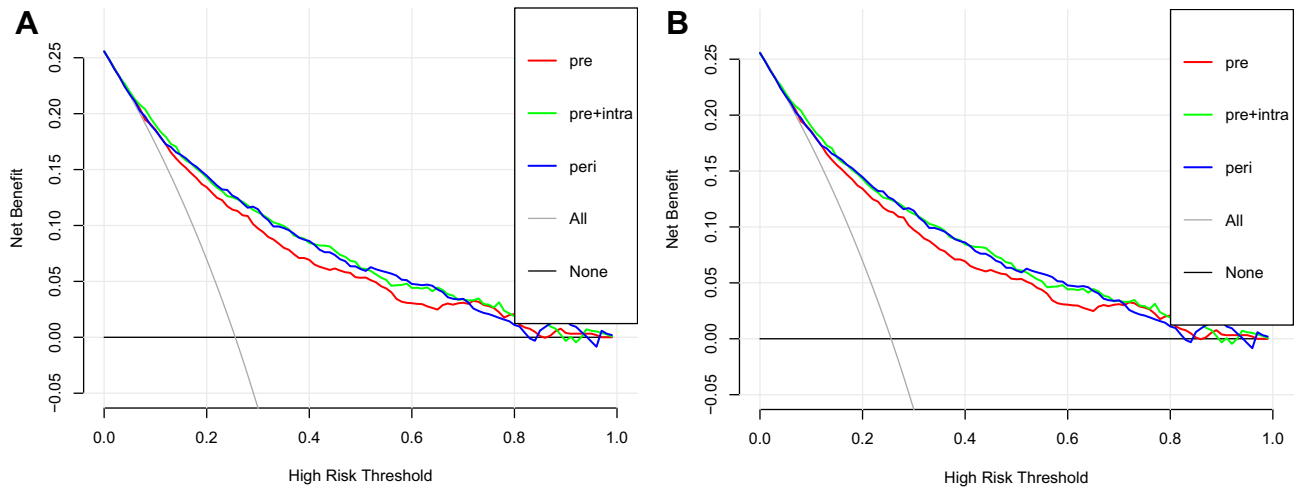

Figure 5 Decision curves for the nomograms of preoperative, preoperative and intraoperative, and perioperative risk factors in the training cohorts (**A**) as well as in the validation cohorts (**B**). Red line represented the preoperative model, black line represented the preoperative and intraoperative model, and blue line represented the perioperative model. The x-axis displayed the threshold probability and y-axis displayed standardized net benefit. The oblique grey line showed that all patients received the intervention, and the grey horizontal line showed that no patient received the intervention.

surgical and anesthesia-related elements. These factors collectively span the entire perioperative process, encompassing preoperative, intraoperative, and postoperative stages.[13] Preoperative model, which incorporated 7 easily available preoperative variables, can be used to screen the high-risk group of pain before ESD and reduce the postoperative pain through preventive analgesia. Preoperative and intraoperative model, comprising 9 independent predictors, can guide anesthesiologists in conducting a comprehensive assessment of individual patient and surgery-related risk factors. This enables them to administer analgesics or implement multimodal analgesia during or after the surgery, irrespective of prophylactic analgesia administration, with the aim of minimizing postoperative pain. The perioperative model is primarily utilized for comprehensive assessment of all preoperative, intraoperative, and postoperative risk factors, encompassing 6 key variables, with a primary focus on remedial analgesia. If the anesthesiologist did not take active analgesia measures before or/and during the ESD surgery for patients with high risk of postoperative pain, the APS team or ward bed doctor could give timely analgesia treatment based on the judgment of these risk factors. Three nomograms performed well, with the AUC of 0.794, 0.823 and 0.817 in the training cohort and 0.702, 0.705 and 0.747 on internal validation. The calibration curves demonstrated the agreements between prediction and actual observation.

Prior studies have found that surgical duration was an independent risk factor for post-ESD pain,[4,6,14,15] which is similarly to our perioperative model. However, longer procedure time is determined by several factors, including location and size of the lesion, the endoscopist's skill, submucosal fibrosis, and patient cooperation during the procedure. Thus, some researchers suggested that both specimen size or area and long treatment duration were risk factors for post-ESD pain,[6,15] but, on the contrary, study of Zhao et al was not.[5] Jung et al only showed that large specimen size was a risk factor, while surgical duration was not.[16] The same was true for our preoperative and intraoperative model. In addition to above reasons, the variables and patients included may also lead to different outcomes because of the difference importance and contribution of each variable to the outcome. Whereas Pyo et al found that longer procedure time was associated with less postoperative pain, this may be due to the delicate dissection of the tumor with minimal submucosal injury which reduced postoperative pain even though longer time.[17] Most studies that investigated influencing factors of pain after ESD did not include the endoscopist as a risk variable, so as our research. Only one study showed that there was no significant difference between the postoperative electrocoagulation syndrome (PECS) and non-PECS group of operator.[18] Studies have reported that postoperative pain after ESD is related to postoperative electrocoagulation syndrome (PECS).[14,16] Effect of the endoscopist's technique on postoperative pain needs to be further discussed, because even if the same endoscopist performs the operation, the technical level will gradually improve over time. The mechanism of long operation time leading to postoperative pain may be that the longer time can result in a large amount of gas instillation and a severe electrical burn that may induce more pain, as suggested in previous studies.[19]

As mentioned above, specimen size was another important factor affecting postoperative pain, so as our present study. Pain occurred more often with wide resection areas, most likely because the wide area meant that more electric cauterization was required.[20] Additionally, ESD procedure of large size could create big artificial ulcers where edema and inflammation smolder for several days.[1,21] They were both likely induce postoperative pain. However, Sakai et al showed that specimen size was not associated with the incidence of postoperative pain,[7] because that pain severity caused by artificial ulcers could not be assessed by a single factor (such as location, size, and procedure time).[7] Otherwise, though ESD of large size seems to entail an increased frequency of electrocoagulation with hot biopsy forceps and tissue necrosis extends into the submucosa, causing pain of varying degrees,[8] we found that there was no correlation between muscular injury and postoperative pain.

Previous studies have found that there were no correlations between the depth of invasion and postoperative pain[4,5,7] or PECS.[6,15,22] Unlike previous studies, our model 2 showed that pain of the lesion located in the submucosa and lamina muscularis propria was more severe than that in the mucosa. The mechanisms of that caused pain were not well understood. This might be because the submucosa and lamina muscularis propria were rich in nerve plexus, and there might be nerve cutting injury or electrical burn during surgery, which might cause pain. In addition, the artificial ulcer surface exposed the nerves directly to chemicals such as stomach acid, the irritation of which caused pain.

Degree of pain was closely related to the surgical site. Luo et al found that patients undergoing esophageal ESD had significantly more severe pain than that gastric ESD during their pre-experiment.[23] This was similar to our findings. The reasons for this may be that the esophagus does not have serosa membrane, and exposure of bare muscle fibers may have an effect on the propagation of inflammatory substances through muscularis propria, and it may be more susceptible to PECS compared with other regions of the digestive tract. Additionally, our study also found that pain intensity of duodenal ESD is greater than esophageal. Though ESD is widely performed as a standard endoscopic treatment in most of the gastrointestinal organs, endoscopic resection of duodenum lesion is considered more challenging than in other parts of the gastrointestinal tract.[24] Pain after duodenal ESD was rarely reported in the literature. Some specific anatomical features of the duodenum can be given as reasons why the duodenal ESD experienced more serious pain.[25,26] First, the narrow, crooked, and deeply located lumen makes it difficult to achieve good endoscopic control and to keep an adequate visual field for ESD in many cases. In addition, as the proper muscle layer is extremely thin, compression of endoscopic devices and burning effect can often cause perforation during the procedure. Even if there was no significant perforation during surgery, gas might diffuse into the retroperitoneal space through the exposed posterior wall thin muscularis propria. In previous reports, the cause of pain after ESD was attributed to transmural burn or air leak.[8,20,27] Lastly, direct exposure to bile and pancreatic juice after surgery.[28]

Our models found that patients with history of surgery or/and previous pain were more likely to experience post-ESD pain. This is consistent with the study of Zhao et al.[5] Pain memory, inflammatory response, and repair processes after nerve injuries incurred during previous surgeries may render patients' peripheral and central nervous systems more sensitive to pain.[29–32] In addition, patients with a history of surgery or preoperative pain may be more prone to post-operative pain anxiety before surgery. Preoperative fear of pain can increase the surgical stress response along with anxiety, increasing postoperative pain and the amount of analgesia consumption.[33,34] Therefore, for such patients, preemptive analgesia preoperatively is necessary in order to prevent or reduce the memory of the nociceptive stimuli in the central nervous system.

Diabetes mellitus and hypertension were common preoperative complications. Our study found that preoperative combination of diabetes and hypertension were high-risk factors for postoperative pain in ESD, which had not been reported in previous ESD studies. However, literatures were clear that pain was a common adverse outcome of diabetes.[35–37] They reported that diabetes changed nociceptive physiology resulting in increased hypersensitivity to pain and a weaker response to morphine, particularly for neuropathic pain. Ekstrom et al[37] showed that patients had higher pain scores both preoperatively and postoperatively as compared to non-diabetic patients. Tuomas et al[36] found that previously diagnosed diabetes was strongly associated with persistent pain in the operated joint 1–2 years after primary hip or knee replacement. They thought that diabetic patients have unique physiology and heightened pain, which argues the need for more tailored postoperative pain management. Whereas the mechanism of hypertension to promote postoperative pain is unclear, only one literature found that hypertension was an independent risk factor related to the

development of PPCS after colonoscopic polypectomy.[20] The author thought that patients with hypertension are more likely to have endothelial dysfunction and atherosclerosis, which may be contributing factors.

Kim et al[4] found that the proportion of alcohol consumers was significantly higher in the no pain group after gastric ESD. Our two models also showed that non-drinkers were more likely to experience postoperative pain than those who did. Researchers reported that associations between alcohol consumption and pain may be curvilinear in nature. Though excessive drinking and alcohol use disorder appear to be associated with greater pain severity, moderate alcohol use was associated with positive pain-related outcomes.[38] We did not collect data on the amount and duration of drinking, however, in clinical experience, most patients drink socially. Additionally, we also found that former drinkers were less likely to experience postoperative pain than present drinkers.

We found that current and former smokers showed an increased pain intensity compared to patients who had never smoked, which was not shown in previous studies of ESD surgery. Similarly to our study, studies showed that cigarette smoking was associated with increased postoperative pain intensity and more analgesics.[39–41] Shen et al reported that abstinent smokers showed decreased pain tolerance and needed more opioids after surgery than nonsmokers.[42] Woodside also reported that patients who never smoked used significantly less narcotic than former smokers or current smokers, but there was no difference between current and former smokers.[43] However, Chiang et al found that the male current-smokers required more morphine than nonsmokers and past-smokers during the 72h after surgery.[41] However, our study investigated that former smokers appeared to be more likely to experience postoperative pain than current smokers. The potential mechanisms of smoking and acute postoperative pain are complex, and the effect of tobacco withdrawal on pain-related outcomes was yet to be thoroughly investigated. Some studies thought that smoking cessation may help improve small airway function and reduce postoperative complications.[44,45] However, most studies in a systematic review showed that cigarette withdrawal in the acute phase might lead to decreased pain tolerance as well as increased pain intensity.[46] Zhao et al[47] reported that preoperative smoking cessation at least 3 weeks before surgery led to better postoperative pain outcomes than smoking cessation within 3 weeks of surgery. Other researchers also have shown that nicotine withdrawal in nicotine-dependent patients appears to result in hyperalgesia or lower pain threshold after surgical procedures.[41] However, our retrospective study did not collect data on smoking volume, smoking years, and cessation time. More studies on the initiation timepoint for the change in pain perception after smoking cessation should be conducted.

As we all know, PONV is a common complication experienced by patients after surgery and is often described as one of the most unpleasant experiences. Our perioperative model showed that PONV was a risk factor for postoperative pain. A study reviewed that postoperative pain was a potential promoter of PONV and pain management can be a crucial factor in preventing PONV.[48] The physiological basis of the association between postoperative pain and PONV is not fully understood. In addition, the PONV in our retrospective study was determined through the application of postoperative antiemetic drugs or medical records, and we did not pay attention to the time of application of analgesic drugs and antiemetic drugs, so the correlation between PONV and postoperative pain was still unclear. In the following study, PONV in ESD patients will be discussed and the relationship between PONV and postoperative pain will be further analyzed.

The nomogram is a valuable innovation for the individualized prediction of postoperative symptoms. Its use will improve clinical decision-making for clinicians and patients, allowing for greater net benefits. Patients with more severe pain should receive early preventive intervention. In contrast, excessive intervention for patients with a lower risk of postoperative pain should be avoided.[10] Three nomograms that can provide individualized risks estimate of a patient's likelihood of experiencing moderate or greater acute pain following ESD were constructed in present study. The scoring systems of nomograms were simple and comprehensible which achieved good predictive accuracy and favorable stability.

However, there were still some limitations in our present study. First, the definition of pain was somewhat ambiguous and was only defined as a need for painkillers regardless of numeric intensity score, but this may accurately reflect the demand for painkillers in actual clinical practice. Second, the risk factors of post-ESD pain are complex and factors, such as preoperative anxiety, depression and insomnia which are potential predictors of postoperative pain[49,50] and may affect the results of the nomogram, were not included in the analysis. Third, because intraoperative drugs are

single and uniform in our center, it is difficult to discuss the effect of anesthesia drugs on postoperative pain. Further multimodal drug analgesia regimens and RCT studies are needed to explore the effect of anesthesia drugs on postoperative pain.

Conclusion

In conclusion, our study constructed three predictive models which were presented as nomograms to quantify the risks of postoperative pain in ESD surgery patients. The nomograms showed powerful predictive abilities and could help clinicians proactively manage and decrease postoperative pain with preventive analgesia or multimodal analgesia or adjustment of modifiable risk factors. We anticipate that our predictive models will assist more anesthesiologists and endoscopists in conscientiously identifying perioperative pain risk factors and prioritizing postoperative pain management for ESD patients. Additionally, we anticipate that further validation of our model by a larger central study cohort will provide more comprehensive guidance for clinical practice.

Data Sharing Statement

Reasonable requests for access to the datasets used and/or analysed during this study can be made to the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

None of the authors have any financial disclosure or a potential conflict of interest for this work.

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