Am J Transl Res 2023;15(9):5674-5682
www.ajtr.org /ISSN:1943-8141/AJTR0152085

Original Article

Risk factors for hyperactive delirium after laparoscopic radical gastrectomy under general anesthesia in patients with gastric cancer

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Received July 7, 2023; Accepted September 5, 2023; Epub September 15, 2023; Published September 30, 2023

Abstract: Objective: This study aimed to analyze the risk factors for the occurrence of postoperative hyperactive delirium after laparoscopic radical gastrectomy under general anesthesia in patients with gastric cancer. Methods: The clinical data of 280 gastric cancer patients who underwent laparoscopic radical gastrectomy under general anesthesia in First Affiliated Hospital of Gannan Medical University from January 2020 to June 2023 were retrospectively analyzed, and the types and incidence of postoperative delirium were recorded. The factors influencing the occurrence of postoperative hyperactive delirium were analyzed. Results: Multi-factor logistic regression analysis showed that older age, high dosage of anesthetic drug consumption, high American Society of Anesthesiologists (ASA) classification (or ASA grade 3-4), long Post-anesthesia Care Unit (PACU) stay, and long extubation time were independent risk factors for the occurrence of hyperactive delirium after laparoscopic radical gastrectomy ($OR > 1$, $P < 0.05$). The area under the curve of the nomogram was used to predict the occurrence of hyperactive delirium after laparoscopic radical gastrectomy under general anesthesia was 0.903 (95% *CI*: 0.846-0.978). Conclusion: Older age, high dosage of anesthetic drug consumption, high ASA classification (or ASA grade 3-4), long PACU stay, and long extubation time were independent risk factors affecting the occurrence of hyperactive delirium after laparoscopic radical gastrectomy under general anesthesia.

Keywords: Laparoscopic radical gastrectomy, general anesthesia, hyperactive delirium, risk factors

Introduction

Laparoscopic radical gastrectomy is a common procedure for the treatment of gastric cancer, which can achieve the same effect as laparotomy. However, it requires the resection of possible metastatic lymph nodes, primary tumors, and infiltrated tissues during surgery, and patients are prone to increased heart rate due to the stimulation of anesthetic drugs, operating room environment, and other factors, which can easily induce perioperative stress response and increase the risk of postoperative delirium [1-3]. Data have shown that delirium, which is one of the common central nervous system complications, occurs in patients during the general anesthesia recovery period at an incidence ranging from 4% to 57% [4]. Postoperative delirium is mainly manifested as mental disorders such as impairment of consciousness, memory, and disorientation, or accompanied by psycho-behavioral-motor disorders, disturbance of wake-sleep cycle, and reduced ability to engage in social activity [4, 5]. In severe cases, restlessness, hallucinations, delusions, and a state of hypervigilance known as postoperative hyperactive delirium may occur [6]. Without timely intervention, the hyperactive delirium can induce complications such as pulmonary infections and decubitus ulcers, prolonging the postoperative recovery of patients and even increasing the risk of perioperative death. Therefore, exploring the risk factors for the occurrence of postoperative hyperactive delirium and early identification of people at high risk are particularly critical in improving patient prognosis and accelerating the postoperative recovery.

Several theories have been proposed to elucidate the pathogenesis of delirium, including the cortisol theory, neurotransmitter theory, cholin-

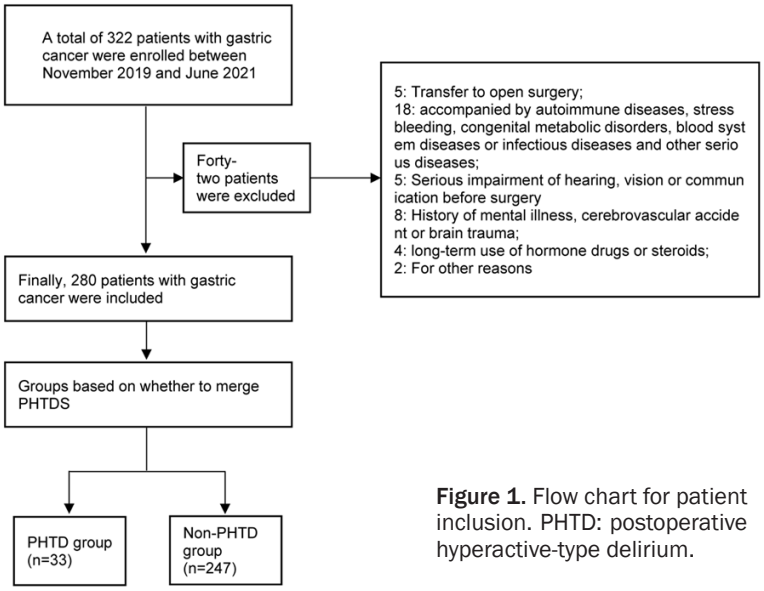

Figure 1. Flow chart for patient inclusion. PHTD: postoperative hyperactive-type delirium.

ergic deficiency theory, and inflammatory mechanism theory, but a consensus on the exact pathogenesis of delirium has not yet been reached [7, 8]. Therefore, exploring the risk factors for delirium has become a focus of current research. Many factors, such as anesthesia mode, type of surgery, and age, are related to the occurrence of delirium. Postoperative hyperactive delirium constitutes about 25% of all delirium cases, with patients experiencing marked agitation, irritability, sudden aggression, hallucinations, and gibberish. This condition delays the recovery of patients due to their lack of emotional stability, so it is of great significance to actively identify the risk factors for postoperative hyperactive delirium. Zhu et al. [9] found that being male, advanced age, and preoperative electrolyte abnormalities were independent risk factors for postoperative hyperactive delirium in elderly orthopedic patients. At present, the incidence of hyperactive delirium after laparoscopic radical gastrectomy and its risk factors have not been reported, and whether the above risk factors also threaten patients after laparoscopic radical gastrectomy under general anesthesia needs further confirmation. Previous studies have primarily employed logistic regression analysis to assess the risk for delirium during the wake-up period, which does not achieve a visual and graphical assessment of risk factors. In this study, on the basis of logistic regression analysis, the risk factors for hyperactive delirium after laparoscopic radical gastrectomy under general anesthesia were analyzed by establishing a nomogram prediction model, so as to achieve a visual and graphical prediction.

Materials and methods

Clinical data

The clinical data of 280 patients with gastric cancer who underwent radical laparoscopic gastrectomy under general anesthesia in the First Affiliated Hospital of Gannan Medical University from January 2020 to June 2023 were retrospectively analyzed. There were 163 males and 117 females, aged 35-80 years, with an average age of (63.48±5.29) years. Patients were eligible if they met the diagnostic criteria of gastric cancer [10] and confirmed by pathology; had a postoperative pathologic diagnosis of complete surgical resection (R0); showed no distant metastasis in preoperative imaging examinations of abdominal CT, abdominal ultrasound and chest X-ray; received no preoperative chemoradiotherapy; were transferred to the post-anesthesia care unit (PACU) after surgery; and had complete clinical data. From January 2020 to June 2023, a total of 322 patients with gastric cancer were admitted, and 42 (13.04%) patients were excluded. The main exclusion reasons were: patients were transferred to laparotomy (n=5); patients were combined with serious diseases such as autoimmune diseases, stress bleeding, inborn metabolic disorders, hematologic diseases, and infectious diseases (n=18); patients had severely impaired hearing, vision, or communication disorders before surgery (n=5); patients had a previous history of psychiatric diseases, cerebrovascular accidents, or traumatic brain injury (n=8); patients had a long-term use of hormonal drugs or steroids (n=4), and other reasons (n=2). The flow diagram is shown in **Figure 1**. This study was approved by the Ethics Committee of First Affiliated Hospital of Gannan Medical University.

Methods

Surgical methods: Tracheal intubation was performed under general anesthesia, and each patient was placed in a supine position with

legs apart, with the surgeon and two assistants on the left side, between the legs, and on the right side of the patient, respectively. Next, the Trocar was placed, and the pneumoperitoneum was established. The intra-abdominal pressure was maintained at 12-15 mmHg. Then, laparoscopic radical gastrectomy was performed according to the requirements in Japanese gastric cancer treatment guidelines 2018 (14th edition).

Delirium assessment: The patient case data and medical records were sorted out, and the number of delirium cases and delirium subtypes were counted by a professionally trained anesthesiologist who was unaware of any grouping information. Then, the occurrence of delirium in the patients within 7 days after surgery was recorded. The first assessment for delirium started on the morning of postoperative day 1 to avoid patient agitation during postoperative anesthesia awakening period, which could affect the accurate assessment of delirium status. CAM-ICU [11] was utilized as the diagnostic criteria for the assessment of delirium: 1) sudden onset, fluctuating course; 2) inattention; 3) disorganized thinking; 4) altered levels of consciousness. The patients with symptoms 1), 2), plus either 3) or 4) were diagnosed as having delirium. There were three subtypes of delirium, hypoactive, hyperactive, and mixed. Hypoactive delirium is characterized by difficulty in awakening, decreased alertness, weakness, hypersomnia, and reduced motor activity. Hyperactive delirium, on the contrary, is characterized by restlessness, agitation, hallucinations, delusions, hyperalertness, and heightened vigilance of the surrounding environment. Mixed delirium is characterized by the alternating presence of both hyperactive and hypoactive signs and symptoms.

Data collection: 1) General data were collected, including age, gender, body mass index (BMI), disease duration, tumor diameter, years of education, tumor site, degree of differentiation, American Society of Anesthesiologists (ASA) classification, underlying disease, and smoking status. 2) Preoperative assessment included Self-rating Anxiety Scale (SAS), Self-rating Depression Scale (SDS), Mini-Mental State Exam (MMSE) [12], blood glucose, systolic blood pressure (SBP), and diastolic blood pressure (DBP). The SAS scale contains 20 items scoring 1-4, with 50 as the cut-off value. The SDS scale also contains 20 items scoring 1-4, with 53 as the cut-off value. MMSE is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language, with a maximum score of 30. Cognitive impairment was defined if the score was 24 points or less in patients with junior high school or higher educational level, 20 points or less in patients who only went to elementary school, and 17 points or less in illiteracy. 3) Intraoperative and postoperative data were recorded, including operative time, intraoperative bleeding volume, amount of IV fluids, anesthetic drug consumption, awakening time, extubation time, PACU stay, and Visual Analogue Scale (VAS) scores after awakening. In VAS scale, a score from 0 to 10 is used to represent pain levels, with 0 indicating no pain and 10 signifying severe unbearable pain.

Statistical analysis

Statistical processing was performed using SPSS 24.0 and R3.5.2. All measurement data were performed with normality test. Normally distributed measurement data were expressed as mean ± SD. In case of homogeneity of variance, the independent sample t-test was employed for comparisons between the two groups, and the paired sample t-test was utilized for within-group comparisons. In case of heterogeneity of variance, the corrected t test (t'test) was employed. The measurement data of skewed distribution were described using the median (M) and interquartile range (IQR) and analyzed utilizing the Mann-Whitney U test. Count data were expressed as n or %, with χ^2 or kruskal-wallis rank sum test used for comparison between groups. Risk factors for postoperative hyperactive delirium were analyzed using dichotomous logistic regression and nomogram analysis. The receiver operator characteristic (ROC) curve was drawn to analyze the prediction value, with an area under the curve (AUC) value greater than 0.9 indicating high prediction performance, 0.71-0.9 indicating a certain level of prediction performance, 0.5-0.7 indicating low prediction performance, and less than 0.5 indicating no predictive value. Two-sided test was utilized, with a significance level of α=0.05, wherein $P < 0.05$ indicated statistically significant difference.

Table 1. Occurrence of postoperative delirium in the 280 included patients

Type	Number of cases (n)	Percentage (%)
Hypoactive	59	21.07
Hyperactive	33	11.79
Mixed	10	3.57
Total	102	36.43

Results

Incidence of delirium

Among the 280 included subjects, a total of 102 cases developed delirium after surgery, and the incidence of hypoactive, hyperactive, and mixed types was 21.07%, 11.79%, and 3.57%, respectively (**Table 1**). The patients with hyperactive delirium were included in a PHTD group (n=33), and the other patients were included in a non-PHTD group (n=247).

Comparison of baseline data

There were no statistically significant differences in gender, BMI, disease duration, tumor diameter, years of education, tumor site, and tissue differentiation between the PHTD group and the non-PHTD group (all $P > 0.05$). The PHTD group was associated with older age and higher ASA classification (both $P < 0.001$) (**Table 2**).

Comparison of preoperative factors

There were no statistically significant differences observed between the PHTD group and the non-PHTD group in preoperative scores for SAS, SDS, and MMSE, blood glucose levels, SBP, DBP, smoking status, and prevalence of hypertension, coronary artery disease, and diabetes mellitus (all $P > 0.05$) (**Table 3**).

Intraoperative and postoperative factors

The PHTD group demonstrated higher anesthetic drug consumption, longer extubation time, longer PACU stay, and higher VAS score after awakening than the non-PHTD group (all $P < 0.001$). While no statistically significant differences were found in operative time, intraoperative bleeding, fluid amount, and awakening time between the two groups (all $P > 0.05$) (**Tables 4** and **5**).

Multivariant analysis of factors affecting the incidence of postoperative hyperactive delirium

The indicators with significant differences in **Tables 2**-**5** (age, ASA classification, anesthetic drug dosage, PACU stay, extubation time, etc.) were used as independent variables and assigned values (**Table 6**), and the occurrence of postoperative hyperactive delirium was used as the dependent variable (1= occurrence, 0= non-occurrence). Multivariant logistic regression analysis with independent variables $\alpha_{in}=0.05$ and $\alpha_{out}=0.10$ was performed to screen variables by stepwise regression, and the results showed that older age, high dosage of anesthetic drug consumption, high ASA classification (or ASA grade 3-4), long PACU stay, and long extubation time were independent risk factors for the occurrence of hyperactive delirium after laparoscopic radical gastrectomy under general anesthesia (*OR* > 1, *P*=0.001, 0.025, < 0.001, 0.031, 0.009, respectively) (**Table 7**).

Nomogram prediction model for the risk of postoperative hyperactive delirium

With the occurrence of postoperative hyperactive delirium as the dependent variable, and age, ASA classification, anesthetic drug consumption, extubation time, and PACU stay as predictor variables, nomogram analysis was performed by applying R language modeling. The results are shown in **Table 8**.

ROC curve of the nomogram

With the occurrence of postoperative hyperactive delirium as the dependent variable, and the total risk score as the independent variable, the ROC curve was plotted and found that the AUC of the nomogram to predict the occurrence of hyperactive delirium after radical laparoscopic gastrectomy was 0.903 (95% *CI:* 0.846-0.978) (**Figure 2**).

Discussion

During the laparoscopic radical gastrectomy under general anesthesia, patients' respiratory and circulatory systems are in a state of suppression, which will impair brain function to a certain extent and increase the risk of postoperative hyperactive delirium [12, 13]. Although

Table 2. Comparison of baseline data ($\bar{X}$±SD, n)

Group	Number of cases	Male/female	Age (years)	BMI (kg/m^2)	Duration of disease (years)	Tumor diameter (cm)	Years of education (years)	Tumor site	Tissue differentiation	ASA classification
								A/B/C	D/E/F	I/II/III
Non-PHTD group	247	145/102	61.03±4.18	23.95±2.24	2.75±0.48	4.39±1.28	8.59±2.47	111/84/52	120/85/42	102/113/32
PHTD group	33	18/15	69.28±5.43	24.03±2.73	2.82±0.39	4.67±1.39	9.02±2.37	17/11/5	15/11/7	2/23/8
$t/Z/\chi^2$		0.207	10.251	0.188	0.803	1.168	0.944	0.777	0.484	3.816
P		0.649	0.000	0.851	0.423	0.244	0.346	0.678	0.628	0.000

Note: PHTD: postoperative hyperactive-type delirium, BMI: body mass index, ASA: American Society of Anesthesiologists, A: cardia, B: gastric sinus, C: lateral lesser curvature of gastric body, D: hypofractionated adenocarcinoma, E: moderately differentiated adenocarcinoma, F: highly differentiated adenocarcinoma.

Table 3. Comparison of preoperative factors ($\bar{X}$±SD, n)

Group	Number of cases	SAS score (points)	SDS score (points)	MMSE score (points)	Blood glucose level (mmol/L)	SBP (mmHg)	DBP (mmHg)	Hypertension	Coronary heart disease	Diabetes	Smoking
Non-PHTD group	247	42.02±3.62	46.67±4.32	27.65±1.29	5.98±0.54	129.65±12.02	96.35±5.48	94	48	53	45
PHTD group	33	43.12±4.57	45.75±5.21	27.89±1.35	5.82±0.49	131.06±10.65	97.65±4.36	13	5	7	6
t/χ^2		1.586	1.120	0.998	1.615	0.641	1.308	0.022	0.348	0.001	0.000
P		0.114	0.264	0.319	0.107	0.522	0.192	0.882	0.555	0.974	0.996

PHTD: postoperative hyperactive-type delirium, SAS: Self-rating Anxiety Scale, SDS: Self-rating Depression Scale, MMSE: Mini-Mental State Exam, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Table 4. Comparison of intraoperative factors ($\bar{X}$±SD)

Group	Number of cases	Operative time (min)	Intraoperative bleeding volume (mL)	Amount of fluid (mL)	Amount of anesthetic drug (mL)
Non-PHTD group	247	242.65±29.65	242.36±65.62	2623.65±262.32	322.45±49.51
PHTD group	33	239.98±30.05	241.65±66.29	2609.74±273.02	412.65±52.44
t		0.485	0.058	0.285	9.762
P		0.628	0.954	0.776	0.000

PHTD: postoperative hyperactive-type delirium.

Table 5. Comparison of postoperative factors ($\bar{X}$±SD)

Group	Number of cases	Time to wake up (min)	Extubation time (min)	PACU stay (h)	VAS score after awakening (score)
Non-PHTD group	247	8.02±1.24	10.33±2.24	30.25±4.15	3.65±0.68
PHTD group	33	8.21±1.09	12.98±3.65	37.52±5.58	4.28±0.38
t		0.838	5.850	9.016	5.209
P		0.403	0.000	0.000	0.000

PHTD: postoperative hyperactive-type delirium, PACU: post-anesthesia care unit, VAS: Visual Analogue Scale.

Table 6. Assignment of each variable in multivariate Logistic analysis

Independent variable	Variable description	Assignment		
		0	1	2
Age	Categorical variable	< 60 years	60-70 years	> 70 years
ASA classification	Categorical variable	Grade I	Grade II	Grade III
Anesthetic drug consumption	Categorical variable	< 360 mL	360-372 mL	> 372 mL
Extubation time	Continuous variable	-	-	-
PACU stay	Categorical variable	< 31 h	31-35 h	> 35 h
VAS scores after awakening	Continuous variable	-	-	-

ASA: American Society of Anesthesiologists, PACU: post-anesthesia care unit, VAS: Visual Analogue Scale.

Table 7. Multifactorial analysis of factors affecting the occurrence of postoperative hyperactive delirium

Indicator	*B*	*S.E.*	Wald χ^2	*P*	*OR*	95% *CI*	
						Lower limit	Upper limit
Constant	-52.658	15.987	12.025	0.000	0.000	-	-0.000
Age	0.586	0.324	7.956	0.001	1.598	1.154	3.652
ASA classification	1.035	0.215	20.652	0.000	3.975	1.654	5.021
Anesthetic drug consumption	0.169	0.587	5.986	0.025	1.325	1.035	2.564
Extraction time	0.524	0.198	6.245	0.009	1.409	1.098	3.246
PACU stay	0.065	0.019	4.896	0.031	1.168	1.006	1.986
VAS scores after awakening	21.751	7.855	0.125	0.798	0.004	0.002	0.013

ASA: American Society of Anesthesiologists, PACU: post-anesthesia care unit, VAS: Visual Analogue Scale.

the mechanism of postoperative hyperactive delirium has not been clarified in clinical practice, through the analysis of risk factors, the controllable factors can be identified and regulated, providing directions for the formulation of prevention and treatment measures.

In this study, a total of 102 among 280 patients developed delirium after surgery, with an incidence of 36.43%, and the incidence of hypoactive, hyperactive, and mixed types was 21.07%, 11.79% and 3.57%, respectively. Our results are similar to those of previous studies [14, 15].

Table 8. Nomogram prediction model for the occurrence of postoperative hyperactive delirium

Age (years)	Score	ASA classification	Score	Anesthetic drug consumption (mg)	Score	Extubation time (min)	Score	PACU stay (h)	Score	Total score	Risk rate (%)
35	0	Grade III	0	200	0	4	0	18	0	91	0.001
40	10	Grade II	14	250	5	6	3	20	2	98	0.010
45	20	Grade I	27	300	9	8	6	22	5	103	0.050
50	30			350	14	12	8	24	7	105	0.100
55	40			400	18	14	11	26	9	108	0.200
60	50			450	23	16	14	28	11	109	0.300
65	60			500	27	18	17	30	14	111	0.400
70	70			550	32	20	19	34	16	112	0.500
75	80					22	22	36	18	113	0.600
80	90						25	38	21	114	0.700
85	100							40	23	116	0.800
								42	25	119	0.900
								44	27	121	0.950
										126	0.990

ASA: American Society of Anesthesiologists, PACU: post-anesthesia care unit, VAS: Visual Analogue Scale.

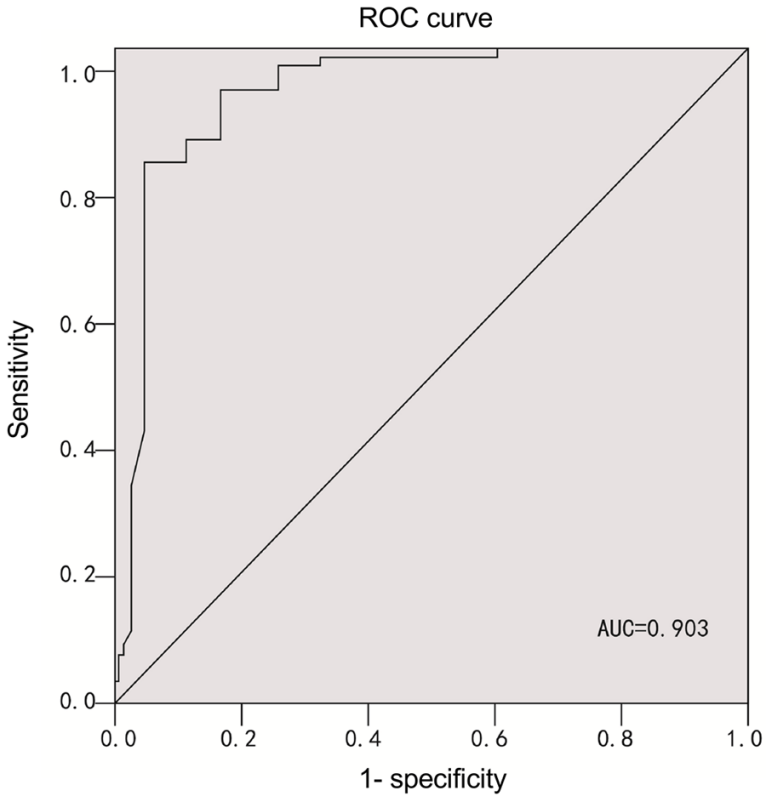

Figure 2. ROC curve of the columnar graph of postoperative hyperactive delirium. ROC: receiver operator characteristic, AUC: area under the curve.

In this study, a nomogram prediction model was established based on the results of multivariant logistic regression analysis, and the results showed that older age, high dosage of anesthetic drug consumption, ASA classification (or ASA grade 3-4), long PACU stay, and long extubation time were independent risk factors for the occurrence of hyperactive delirium after laparoscopic radical gastrectomy. The specific reasons were as follows: (1) Age. Norkiene et al. [16] reported that age over 70 years was an independent risk factor for the occurrence of delirium after orthopedics, and the risk was positively correlated with age. It has been found that abnormal changes in the levels of central neurotransmitter factors, such as dopamine, acetylcholine, and 5-hydroxytryptamine, can induce delirium [17]. Elderly patients usually experience degenerative brain function and reduced compensatory function of brain tissue, thus the content of central neurotransmitters in the brain is unbalanced, so they are prone to have postoperative hyperactive delirium. Elderly patients have reduced

adaptive ability and compensatory function of organs, increased abnormal excitatory conduction, and increased sensitivity to stressors, so intraoperative infection or surgical stimulation can lead to increased levels of inflammatory factors, which can damage brain tissue and the function of blood-brain barrier. Moreover, elderly individuals often exhibit reduced tolerance to anesthetic drugs and incisional pain. When coupled with low sleep quality, they are more susceptible to hyperactive delirium during the recovery period [18, 19]. (2) ASA classification. ASA classification ≥ 2 often indicates that patients have impaired cardiopulmonary function, cardiopulmonary compensation, and systemic diseases, which are associated with higher risk of postoperative hyperactive delirium. (3) Anesthetic drug consumption. Excessive administration of anesthetic drugs (e.g., propofol) can lead to alterations in neurotransmitters, such as catecholamines and dopamine, in the central nervous system through the mimetic effect of γ-aminobutyric acid, and diminish the capacity of the central cholinergic system, thus promoting the occurrence of postoperative hyperactive delirium [20, 21]. (4) Extubation time and PACU stay. Endotracheal extubation is not indicated since the respiratory function of most patients has not yet recovered, and the prolonged recovery of respiratory function can impair the patients' brain function, thus indirectly leading to the occurrence of postoperative hyperactive delirium [22]. During the PACU awakening period, patients may experience stress reactions, such as shouting and agitation, due to the stimulation of urinary catheters, tracheal tubes, and other drainage tubes, thus inducing postoperative hyperactive delirium.

Nomogram is a graphical statistical prediction model built by incorporating the risk factors from Logistic multifactor analysis. A nomogram can predict the risk of occurrence of a structural event individually, precisely, and visually [23]. In this study, a nomogram prediction model was constructed, and the results revealed that the risk rate for each factor ranged 0.001-0.999, the total risk score ranged 123-182, and the incidence of postoperative hyperactive delirium was directly proportional to the total risk score. ROC curves revealed that the AUC of the nomogram was 0.878 *(95%* CI: 0.820-0.936), which showed that nomogram could improve the predictive value for the occurrence of postoperative hyperactive delirium.

In conclusion, older age, high ASA classification, high dosage of anesthetic drug consumption, long extubation time, and long PACU stay were independent risk factors for the occurrence of hyperactive delirium after laparoscopic radical gastrectomy, and the nomogram could visually predict the occurrence of postoperative hyperactive delirium. However, there are still some limitations. Firstly, this is a retrospective single-center study, so the data may have selection bias. Secondly, the inclusion factors may not be comprehensive. Thirdly, the effects of general anesthesia and local anesthesia on postoperative hyperactive delirium were not compared. Fourthly, no follow-up data were available to assess further outcome measures, and no data on delirium treatment were collected. Lastly, the nomogram model still needs to be verified in a larger sample size to clarify the extrapolation of the model. Improvements in these aspects are the key directions for future research.

Disclosure of conflict of interest

None.

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