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Risk factors of delayed recovery from general anesthesia in patients undergoing radical biliary surgery
What can we prevent

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Abstract

Delayed recovery (DR) is very commonly seen in the patients undergoing laparoscopic radical biliary surgery, we aimed to investigate the potential risk factors of DR in the patients undergoing radical biliary surgery, to provide evidences into the management of DR.

Patients who underwent radical biliary surgery from January 1, 2018 to August 31, 2020 were identified. The clinical characteristics and treatment details of DR and no-DR patients were compared and analyzed. Multivariable logistic regression analyses were conducted to identify the potential influencing factors for DR in patients with laparoscopic radical biliary surgery.

We included a total of 168 patients with laparoscopic radical biliary surgery, the incidence of postoperative DR was 25%. There were significant differences on the duration of surgery, duration of anesthesia, and use of intraoperative combined sevoflurane inhalation (all $P < .05$), and there were not significant differences on American Society of Anesthesiologists, New York Heart Association, tumor-lymph node- metastasis, and estimated blood loss between DR group and control group (all $P > .05$). Multivariable logistic regression analyses indicated that age ≥ 70 years (odd ratio [OR] 1.454, 95% confidence interval [CI] 1.146–1.904), body mass index $\geq 25 \, kg/m^2$ (OR 1.303, 95% CI 1.102–1.912), alcohol drinking (OR 2.041, 95% CI 1.336–3.085), smoking (OR 1.128, 95% CI 1.007–2.261), duration of surgery ≥ 220 minutes (OR 1.239, 95% CI 1.039–1.735), duration of anesthesia ≥ 230 minutes (OR 1.223, 95% CI 1.013–1.926), intraoperative combined sevoflurane inhalation (OR 1.207, 95% CI 1.008–1.764) were the independent risk factors for DR in patients with radical biliary surgery (all $P < .05$).

It is clinically necessary to take early countermeasures against various risk factors to reduce the occurrence of DR, and to improve the prognosis of patients.

Abbreviations: BMI = body mass index, CI = confidence interval, DR = delayed recovery, OR = odd ratio, TNM = tumor- lymph node- metastasis.

Keywords: biliary surgery, delayed recovery, general anesthesia, laparoscopic, nursing, treatment

1. Introduction

Hilar cholangiocarcinoma accounts for 50% to 70% of all cholangiocarcinomas.[1] The anatomical location of the tumor is special, the surrounding structure is complicated, and because of its invasive growth characteristics, it easily invades the hepatic artery and portal vein.[2] It has been reported that if treated with early radical resection, the 1-year survival rate of patients is 80% and the 5-year survival rate is 39%.[3,4] At present, surgical resection is the first choice for the treatment of hilar cholangiocarcinoma, and the choice of surgical method mainly depends on the extent of local invasion of the cancer.[5] Because of its special anatomical relationship and biological characteristics, the rate of radical surgery is not high, and the prognosis of patients is poor.[6] Therefore, the early diagnosis and treatment is vital to the prognosis of patients.

Delayed recovery (DR) from anesthesia generally refers to that the patient has not recovered 120 minutes after the end of general anesthesia, and cannot respond correctly to external stimuli and language commands.[7] With the continuous development of anesthetics and related monitoring technologies, the incidence of delayed recovery has been declining year by year, but it is still one of the main complications of general anesthesia.[8] It not only increases the perioperative risk, affects the recovery of the patient's physical function, but also increases the economic

burden of the patient, and even causes death.[9] Due to the long operation time and the large amount of anesthetic drugs in laparoscopic radical biliary surgery, the risk of DR after surgery also increases.[10] Therefore, early detection of the risk factors for DR from anesthesia after laparoscopic radical biliary surgery is of crucial importance to reduce its incidence and ensure perioperative safety key. In recent years, most of the researches on high-risk factors for delayed recovery after general anesthesia have been limited to certain anesthetics or certain age groups, and there are few studies on DR after radical biliary tract surgery. In this present study, we analyzed the high-risk factors of DR after laparoscopic radical biliary surgery under general anesthesia, and aimed to provide a theoretical basis for the prevention of DR in patients with laparoscopic radical biliary surgery, thereby providing evidence to the management of DR.

2. Methods

2.1. Ethical consideration

This present study was approved by the medical ethical committee of our hospital (160,933). We applied a retrospective study design, we had informed the patients that their treatment data might be used for research and the written informed consents had been obtained from all the included patients.

2.2. Patients

Patients who underwent laparoscopic radical biliary surgery treated in our hospital from January 1, 2018 to August 31, 2020 were identified as potential patients. The inclusion criteria for patients were as follows: according to the preoperative computed tomography, magnetic resonance imaging, and color Doppler ultrasound examinations, it was clear that there was hilar space occupation, and the intraoperative or postoperative pathological report confirmed the diagnosis of hilar bile duct cancer.[11] The related characteristics and clinical pathological data were complete. Patients underwent general anesthesia; patients were well informed and signed the written informed consents. The exclusion criteria were: patients with duodenum, pancreas, and ampullary diseases that might require bile duct anastomosis; those patients did not agree to participant in our study.

2.3. Laparoscopic radical biliary surgery

The laparoscopic radical biliary surgery was performed by the same group of surgeons. All patients underwent partial hepatectomy, extrahepatic bile duct resection, regional lymph node dissection, lymph node biopsy, and Roux-en-Y bile duct jejunostomy. The laparoscopic radical biliary surgery was conducted as previous studies[12,13] reported. A biliary drainage catheter was used in all patients, and a grooved drainage tube was routinely placed near the liver section and anastomosis.

2.4. Data collection

We recorded and collected the patient's basic information, medical history, and auxiliary examinations and other indicators before surgery, including sex, age, body mass index (BMI), smoking history, hypertension, diabetes, hyperlipidemia, anemia. And we collected and analyzed the surgery and anesthesia related information, including American Society of Anesthesiologists score, New York Heart Association, tumor (topography) - lymph

node- metastasis (TNM) classification data (TNM Level I: The cancer tissue is limited to the place where the initial formation is initially formed, and there is no sign of diffusion. Level II: Cancer cells have spread to nearby lymph nodes, tissues or organs; Level III: Cancer cells have spread to multiple organs or tissues of the body), duration of surgery, duration of anesthesia, estimated blood loss, the use of intraoperative combined sevoflurane inhalation.

After the operation, all the patients were sent to the anesthesia recovery room, and we evaluated the patient every 15 minutes according to the Steward awakening score.[14,15] The Steward awakening score was divided into 3 dimension including awakeness, unobstructed breathing, extent of physical activity. Steward score <4 points was regarded as not awakened, Steward score ≥4 points was regarded as awakened. According to the Steward awakening score,[16] DR was defined as Steward scores <4 >120 minutes after stoppage of anesthetics. According to the occurrence of DR, the patients included in the study were divided into DR group and control group.

2.5. Statistical analysis

All the collected data were input into and processed with SPSS 22.0 statistical software for data analysis. t Test and Chi-square test were used to analyze the characteristics and treatment details of patients. Besides, we had included in multivariable logistic regression model including all variables that make sense clinically, even if they were insignificant at univariate analyses, to identify the potential influencing factors for DR in patients with laparoscopic radical biliary surgery.[17] $P < .05$ was considered statistically significant in this study, and all of the tests were 2-sided.

3. Results

3.1. Characteristics of included patients

Overall, 180 patients with laparoscopic radical biliary surgery were identified initially, we excluded 12 patients with regards to incomplete medical record. In total, 168 patients with laparoscopic radical biliary surgery were included finally, of whom 42 patients occurred the DR, the incidence of DR in patients with laparoscopic radical biliary surgery was 25%. As showed in Table 1, there were significant differences regarding the age and BMI between DR group and control group (all $P < .05$), and there were not significant differences regarding sex, smoking, hyper-

Table 1

Characteristics of included patients.

Variables	DR group (n = 42)	Control group (n = 126)	t/χ^2	P
Male/female	31/11	90/36	1.203	.094
Age, yr	73.03 ± 9.11	67.35 ± 10.12	10.406	.041
BMI, kg/m²	27.45 ± 3.21	24.13 ± 3.44	7.524	.028
Alcohol drinking	28 (66.67%)	89 (68.99%)	1.180	.097
Smoking	15 (35.71%)	52 (41.27%)	1.094	.101
Hypertension	29 (69.05%)	88 (69.84%)	1.182	.055
Diabetes	18 (42.85%)	50 (39.68%)	1.225	.073
Hyperlipidemia	11 (26.19%)	37 (29.37%)	1.136	.072
Anemia	9 (21.43%)	29 (23.02%)	1.085	.086

BMI = body mass index.

Table 2

Comparison of treatment details of 2 groups.

Variables	DR group (n = 42)	Control group (n = 126)	t/χ^2	p
ASA			1.143	.093
Level II	35 (83.33%)	99 (78.57%)		
Level III	7 (16.67%)	27 (21.43%)		
NYHA			1.104	.088
Level I	30 (71.43%)	87 (69.05%)		
Level II	10 (23.81%)	31 (24.60%)		
Level III	2 (4.76%)	8 (66.35%)		
TNM			1.028	.156
Level I	12 (28.57%)	39 (30.95%)		
Level II	16 (38.09%)	51 (40.47%)		
Level III	14 (33.33%)	36 (28.57%)		
Duration of surgery, min	238.07 ± 28.25	210.53 ± 32.11	32.063	.031
Duration of anesthesia, min	245.18 ± 21.22	205.12 ± 23.93	31.034	.018
Intraoperative combined sevoflurane inhalation	31 (73.81%)	50 (39.68%)	1.406	.011

TNM Level I: The cancer tissue is limited to the place where the initial formation is initially formed, and there is no sign of diffusion. Level II: Cancer cells have spread to nearby lymph nodes, tissues, or organs; Level III: Cancer cells have spread to multiple organs or tissues of the body.
ASA = American Society of Anesthesiologists, NYHA = New York Heart Association, TNM = tumor- lymph node- metastasis.

tension, diabetes, hyperlipidemia, and anemia between DR group and control group (all $P > .05$).

3.2. Treatment details comparison of 2 groups

As presented in Table 2, there were significant differences regarding the duration of surgery, duration of anesthesia, and use of intraoperative combined sevoflurane inhalation (all $P < .05$), and there were no significant differences regarding American Society of Anesthesiologists, New York Heart Association, TNM, and estimated blood loss between DR group and control group (all $P > .05$).

3.3. Logistic regression analysis on the risk factors for DR

Table 3 demonstrates the assessment of variables of multivariable logistic regression. As Table 4 presented, multivariable logistic

Table 3

Assessment of variables of multivariable logistic regression.

Factors	Variables	Assignment
DR	Y	Yes = 1, no = 2
Gender	X_1	Male = 1, female = 2
Age, yr	X_2	≥70 = 1, <70 = 2
BMI, kg/m²	X_3	≥25 = 1, <25 = 2
Alcohol drinking	X_4	Yes = 1, no = 2
Smoking	X_5	Yes = 1, no = 2
Hypertension	X_6	Yes = 1, no = 2
Diabetes	X_7	Yes = 1, no = 2
Hyperlipidemia	X_8	Yes = 1, no = 2
Anemia	X_9	Yes = 1, no = 2
ASA	X_{10}	Level III = 1, level II = 2
NYHA	X_{11}	Level III = 1, level II = 2, level I = 3
TNM	X_{12}	Level III = 1, level II = 2, level I = 3
Duration of surgery, min	X_{13}	≥220 = 1, <220 = 2
Duration of anesthesia, min	X_{14}	≥230 = 1, <230 = 2
Intraoperative combined sevoflurane inhalation	X_{15}	Yes = 1, no = 2

ASA = American Society of Anesthesiologists, BMI = body mass index, DR = delayed recovery, NYHA = New York Heart Association, TNM = tumor- lymph node- metastasis.

regression analysis showed that age ≥70 years (odd ratio [OR] 1.454, 95% confidence interval [CI] 1.146–1.904), BMI ≥25 kg/m² (OR 1.303, 95% CI 1.102–1.912), alcohol drinking (OR 2.041, 95% CI 1.336–3.085), smoking (OR 1.128, 95% CI 1.007–2.261), duration of surgery ≥220 minutes (OR 1.239, 95% CI 1.039–1.735), duration of anesthesia ≥230 minutes (OR 1.223, 95% CI 1.013–1.926), intraoperative combined sevoflurane inhalation (OR 1.207, 95% CI 1.008–1.764) were the independent risk factors for DR in patients with radical biliary surgery (all $P < .05$).

4. Discussions

Previous studies[18,19] indicate that the incidence of DR in patients with laparoscopic radical biliary surgery is high, and it has adverse effects on the short-term and long-term prognosis of patients. In this study, the incidence of DR in patients with laparoscopic radical biliary surgery was 25%, which was consistent with previous reports. Taking into account the potential correlation between DR and related complications, early identification, diagnosis and intervention of high-risk patients for DR have clinically significance to the prognosis of patients.[20–22] The results of this present study indicate that age ≥70 years, BMI ≥25 kg/m², alcohol drinking, smoking, duration of surgery ≥220 minutes, duration of anesthesia ≥230 minutes, and intraoperative combined sevoflurane inhalation were the independent risk factors for DR in patients with radical biliary surgery (all $P < .05$).

The time for patients with general anesthesia to recover from anesthesia mainly depends on the metabolic rate of analgesic drugs.[23] In recent years, the comprehensive evaluation of patients before surgery and the continuous development of anesthetic drugs and monitoring technology have reduced the occurrence of anesthesia DR.[24] The rate gradually declines, and most patients can wake up quickly after surgery, but the phenomenon of delayed wake-up still occurs, which brings a huge challenge to medical staff related to anesthesia.[25] The basic patient factors include age, sex, genetic factors, and preoperative combined underlying diseases.[26] Some authors[27,28] hypothesize that there is a clear relationship between age and the

Table 4

Logistic regression analysis on the risk factors for DR in patients who underwent radical biliary surgery.

Variables	β	SE	OR	95% CI	P
Age ≥70 yr	0.185	0.202	1.454	1.146~1.904)	.048
BMI ≥25 kg/m²	0.122	0.319	1.303	1.102~1.912	.037
Alcohol drinking	0.119	0.121	2.041	1.336~3.085	.042
Smoking	0.176	0.114	1.128	1.007~2.261	.018
Duration of surgery ≥220 min	0.105	0.103	1.239	1.039~1.735	.011
Duration of anesthesia ≥230 min	0.173	0.110	1.223	1.013~1.926	.015
Intraoperative combined sevoflurane inhalation	0.118	0.106	1.207	1.008~1.764	.043

BMI = body mass index, CI = confidence interval, DR = delayed recovery, OR = odd ratio.

occurrence of DR. The elderly are more likely to experience DR after surgery. The reason may be that the function of the body's central nervous system decreases with age. The clearance rate and plasma protein binding rate of drugs are reduced, and the free plasma concentration of the drug is higher, so the metabolism of anesthetic drugs is slower.

Smoking patients generally have varying degrees of pulmonary ventilatory dysfunction. Smoking can induce small airway remodeling, and the reduction of lung function is the case mechanism leading to hypoxemia.[29] Smoking can also increase HbCO in the blood, causing the dissociation curve of oxidized hemoglobin to shift to the left, and the tighter combination of Hb and oxygen makes it more difficult for tissues to use oxygen, which leads to DR.[30] Drinking alcohol is a risk factor for DR. After ethanol enters liver cells, it is oxidized to acetaldehyde through 2 pathways of liver alcohol dehydrogenase, hydrogen peroxide decomposition enzyme, and liver microsomal alcohol oxidase. A large amount of acetaldehyde has obvious effects on liver cells. Its toxic effects directly and indirectly lead to liver cell degeneration, necrosis and fibrosis, and can develop into cirrhosis or even liver cancer in severe cases.[31] Most anesthetics and analgesics are decomposed by the liver and increase the burden on the liver, which leads to prolonged and enhanced antagonistic effects of anesthetics and muscle relaxants,[32] which easily leads to postoperative DR.

In patients with higher BMI, there are dual factors of increased total dose of anesthetic drugs and slower metabolism. Therefore, the risk of DR is significantly higher than that of patients with normal BMI.[33] However, there are fewer studies on the specific cut-off value of BMI. Some authors[34–36] believe that awakening after anesthesia is usually related to the genetic modifications of the drug receptor or target. For example, the polymorphic changes of the gamma-aminobutyric acid receptor may make the anesthetic drug propofol in the body, and the rate of metabolism slows down accordingly. Studies[37,38] have shown that patients with preoperative heart disease, hypertension, and diabetes are prone to delayed recovery even if they undergo surgery unrelated to the comorbidities, but the specific mechanism is still unclear. In the perioperative factors of DR from anesthesia, the main factors are the dosage of anesthetic drugs, the patient's body temperature and duration of surgery, and the amount of intraoperative fluid infusion.[39] Patients who are lighter or have liver and kidney function abnormalities who are not carefully evaluated before surgery, may be given overdosed anesthetic drugs, which may lead to high drug concentration in the body and DR.[40] If the operation time is very long and the evaluation of the end of the operation is biased, the anesthesia duration will be too long accordingly,[41] which is also an important factor for occurrence of DR from anesthesia. It must be noted that patients with lower body temperature who enter the recovery room after surgery are more likely to develop DR.[42] Drops in body temperature may decrease the activity of enzymes related to drug metabolism, which may cause drugs to accumulate in the body and patients experience DR.[43]

Several limitations in this present study must be considered. Firstly, here is a high correlation between the amount of intraoperative fluid infusion and the delay in awakening after anesthesia.[44,45] Larger volumes of intraoperative fluid infusion increases the chance of delayed awakening after surgery.[46] However, this mechanism is unclear. In this present study, due to the lack of related data, we cannot include those factors into further analysis, future studies with larger sample size and more comprehensive factors are needed. Secondly, we chosen the cutoffs because our study was a retrospective design with small sample size, it would be better if we could build a model with time to recovery from anesthesia stop as a continuous variable, duration of surgery and duration of anesthesia used as continuous variables to evaluate the influence on DR, which will provide more reliable evidence into the clinical management of DR. Therefore, prospective studies on this topic are needed in the future.

5. Conclusions

In conclusions, we have found that age ≥70 years, BMI ≥25 kg/m², alcohol drinking, smoking, duration of surgery ≥220 minutes, duration of anesthesia ≥230 minutes, and intraoperative combined sevoflurane inhalation were the independent risk factors for DR in patients with radical biliary surgery. Among the relevant factors analyzed in this study, patients' age and BMI are high-risk factors that cannot be corrected immediately, but operation and anesthesia duration, intraoperative anesthetic drug use are factors that can be improved. On the one hand, clinicians should ensure patient safety and surgery under the premise of curative effect, accurately assess the patient's dosage of anesthetics, and minimize the operation time and the use time of anesthetics; on the other hand, it's necessary to accurately identify high-risk patients with delayed awakening, corresponding nursing strategies should be formulated on the basis of routine care, and the training of nursing staff should be strengthened. For patients with older age, higher BMI, and longer surgery and anesthesia time, it is necessary to closely monitor the patient's vital signs to reduce the risk of DR.

Author contributions

Guohui Zhang, Yingzi Ling designed research; Guohui Zhang, Bingbing Pan, Dan Tan conducted research; Guohui Zhang

analyzed data; Guohui Zhang and Yingzi Ling had primary responsibility for final content. All authors read and approved the final manuscript.

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