

Original Article

A predictive model for postoperative cognitive dysfunction in elderly patients with gastric cancer: a retrospective study

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Abstract: Objective: To explore the risk factors of postoperative cognitive dysfunction (POCD) in elderly patients with gastric cancer after radical resection and to establish a risk prediction model. Methods: A retrospective analysis of the clinicopathological data of 687 elderly patients who underwent radical gastric cancer surgery from January 2014 to January 2020 in the Third Department of Surgery, Fourth Hospital of Hebei Medical University was conducted. The degree of cognitive impairment was divided into POCD positive group (n=141, 20.52%) and POCD negative group (n=546, 79.48%). The general data of the two groups were compared. Multivariate logistic regression was used to analyze the risk factors for POCD in elderly gastric cancer patients after radical surgery. A risk prediction model was established. The receiver operating characteristic (ROC) curve was used to evaluate the effectiveness of the model. Results: Multivariate logistic regression analysis showed that preoperative ASA classification (OR=4.674, 95% CI: 1.610~12.651, P=0.020), age (OR=3.130, 95% CI: 1.307~8.669, P=0.001), operation time (OR=2.724, 95% CI: 1.232~7.234, P=0.031), preoperative PG-SGA score (OR=4.023, 95% CI: 1.011-10.883, P=0.048), and preoperative hemoglobin (OR=4.158, 95% CI: 2.255~8.227, P=0.001) were independent risk factors for POCD. Intraoperative application of dexmedetomidine (OR=0.172, 95% CI: 0.078~0.314, P=0.002) and maintaining a deeper anesthesia state (OR=0.151, 95% CI: 0.122~0.283, P=0.018) were protective factors. The area under the ROC curve of the POCD risk prediction model for elderly gastric cancer patients after surgery was 0.820 (95% CI: 0.742-0.899) (P<0.01). Conclusion: The occurrence of postoperative POCD in elderly patients with gastric cancer is closely related to a variety of risk factors. By establishing a risk prediction model for the occurrence of POCD, high-risk patients can be effectively identified during the perioperative period, to intervene earlier.

Keywords: Elderly gastric cancer, postoperative cognitive dysfunction, risk factors, risk prediction model

Introduction

Gastric cancer is one of the common malignant tumors of digestive tract in China. It ranks third among all malignant tumors [1]. As the population age increases, elderly patients with gastric cancer establish a slower metabolism and a declined immunity [2]. They are often accompanied with other basic diseases. The reserve function of heart, lung, and brain is poor [3, 4]. The surgical risk and the incidence of postoperative complications are higher than those of non-elderly patients with gastric cancer [5-7]. At present, most studies focus on severe complications of patients, including anastomotic leakage, postoperative bleeding, and postop-

erative intestinal obstruction. Elderly patients with gastric cancer are more likely to have neurological symptoms compared to younger patients. Postoperative cognitive dysfunction is more common.

Postoperative cognitive dysfunction (POCD) refers to the central nervous system complications that occur after anesthesia or surgery with cognitive decline as the main manifestation. It is mainly manifested as the deterioration of mental activity, thinking awareness, personality behavior, and social skills [8-10]. POCD is more common in elderly patients, especially after major abdominal surgery. It can not only cause delays in postoperative recov-

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ery, longer hospital stays, and lower quality of life after surgery, but also increase medical expenses, which will affect long-term quality of life. In severe cases, it may even increase post-operative mortality [11, 12]. POCD generally begins to appear about 2-7 days after surgery. Its occurrence may be closely related to many factors. The clinical diagnosis lacks specific laboratory indicators [13]. It is particularly important to find a predictive model that can better distinguish the occurrence of POCD in elderly patients with gastric cancer after radical resection.

This study retrospectively analyzed the clinicopathological features of elderly patients for the first time, to find the risk factors of POCD in elderly patients with gastric cancer after a radical operation. A predictive model was established. Its predictive value was tested to provide a reference for clinical prevention and treatment of POCD, to reduce the incidence of POCD in elderly patients with gastric cancer after the operation.

Materials and methods

General information

A retrospective analysis of the clinicopathological data of 687 elderly patients with gastric cancer who underwent radical surgery in the Fourth Hospital of Hebei Medical University from January 2014 to January 2020 was conducted.

Inclusion criteria: (1) Patients who were histopathologically confirmed gastric cancer; (2) Patients without distant organ metastasis as shown in preoperative imaging examination; (3) Patients without surgical contraindications, and were able to tolerate radical gastric cancer surgery; (4) Patients without previous anti-tumor drug treatment before surgery.

Exclusion criteria: (1) Patients complicated with preoperative mental and psychological diseases (including depression or Alzheimer's disease); (2) Patients with language and communication disorders, and those with visual and hearing disorders; (3) Patients with the use of preoperative sedatives, psychiatric drugs such as antidepressants; (4) Patients with severe heart, lung, and kidney dysfunction; (5) Patients who were transferred to the intensive care unit after surgery due to coma or severe infection.

This study complies with the principles of the Declaration of Helsinki and related ethical requirements. All patients and their families signed an informed consent form. This trial was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (approval number: 2019012).

Method

POCD diagnosis: The whole group of patients was provided neuropsychological tests on the subjects 1 day before and 7 days after surgery and recorded the Mini Mental State Scale (MMSE) scores to determine whether the patients had postoperative cognitive dysfunction. The patients were divided into a POCD occurrence group and a POCD non-occurring group according to whether they suffer POCD. The specific content of the MMSE test [14, 15] included time and place orientation, language (retelling, naming, and understanding instructions), mental arithmetic, immediate and short-term auditory vocabulary memory, and structural imitation. The full score is 30 points, and it takes 5-10 minutes. Different demarcation points were designated according to the Chinese version of MMSE based on different educational levels: 17 points for the illiterate group, 20 points for the elementary school group, 26 points for the middle school or above group, and cognitive impairment below the threshold. The scoring was done by two technicians who are experts in neuropsychological testing. The final clinical diagnosis was done by doctors who have received formal unified neuropsychological scale training.

Clinicopathological data: The following data were collected from patients: ① General information including gender, age, ECOG score, body mass index (BMI), and education level; ② Preoperative hemoglobin and serum albumin levels; ③ Tumor location and size; ④ Tumor histological type; ⑤ TNM staging; ⑥ Preoperative ASA classification; ⑦ Preoperative morbidity (hypertension, coronary heart disease, diabetes, cerebral infarction, and respiratory diseases); ⑧ Intraoperative operation (including operation method, operation time, whether or not blood transfusion); ⑨ Intraoperative anesthesia (including the depth of anesthesia, preoperative and intraoperative anesthesia related medications).

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Statistical processing

The data was analyzed using SPSS21.0 statistical software. The measured data in accordance with the normal distribution was expressed as $\bar{x}\pm s$, and the count data was expressed as the number of cases (percentage). The measured data between groups were compared by t test and the count data was by χ^2 test. Single factor and multivariate unconditional Logistic regression analysis were used to screen the risk factors for POCD. $P<0.05$ indicated that the difference was statistically significant. The Hosmer-Lemeshow test and receiver operating characteristic (ROC) curve were used to detect the discrimination and goodness of fit of the model.

Results

Comparison of clinical data of enrolled patients

The patients in the whole group were 70-93 years old, with a median age of 77 years old. Among them, 453 (65.94%) were males and 234 (34.06%) were females. There were 141 cases (20.52%) that developed POCD on the seventh day after the operation, and 546 cases (79.48%) that did not develop POCD after the operation. The two groups of patients had statistically significant differences in age, education level, NRS2002 score, PG-SGA score, preoperative hemoglobin level, number of preoperative complications, and ASA classification (all $P<0.05$). There were no statistically significant differences in gender, MMSE score, ECOG score, body mass index, preoperative serum albumin level, pTNM stage, tumor location, tumor size, histological type, surgical method, and preoperative MMSE score (all $P>0.05$) (**Table 1**).

Single factor logistic regression analysis of risk factors for POCD in elderly patients with gastric cancer after radical resection

Elderly patients with gastric cancer are more susceptible to POCD under the circumstances of older age, higher education level, larger preoperative BMI, increased preoperative ASA grade, decreased preoperative hemoglobin level, preoperative or intraoperative anesthesia using atropine, intraoperative blood transfusion, prolonged operation time, and shallow

depth of anesthesia (higher BIS value). The use of phenobarbital sodium and dexmedetomidine were the protective factors of POCD (**Table 2**).

Multivariate logistic regression analysis to determine independent risk factors affecting the onset of POCD

Multivariate logistic regression analysis showed that the higher preoperative ASA grade (OR=4.674, 95% CI: 1.610-12.651, $P=0.020$), the older age (OR=3.130, 95% CI: 1.307~8.669, $P=0.001$), the longer operation time (OR=2.724, 95% CI: 1.232~7.234, $P=0.031$), the higher preoperative PG-SGA score (OR=4.023, 95% CI: 1.011-10.883, $P=0.048$), and preoperative anemia (OR=4.158, 95% CI: 2.255~8.227, $P=0.001$) were independent risk factors for POCD. Intraoperative application of dexmedetomidine (OR=0.172, 95% CI: 0.078~0.314, $P=0.002$) and maintaining a deep anesthesia state (OR=0.151, 95% CI: 0.122~0.283, $P=0.018$) during the operation were protective factors (**Table 3**).

Establishment and verification of risk prediction scoring model

A risk prediction equation was established based on the results of multi-factor Logistic regression: $\text{logit}(p) = -7.638 + 1.672 \times X_1 + 1.454 \times X_2 + 1.673 \times X_3 + 1.585 \times X_4 - 1.722 \times X_5 - 1.884 \times X_6 + 1.212 \times X_7$. Hosmer-Lemeshow test was used to detect the goodness of fit of the regression equation ($P=0.794$). Each factor X is a binomial assignment (0 or 1), among which X_1 - X_7 are ASA classification (level III was assigned to 1), age (≥ 80 years was assigned to 1), preoperative PG-SGA score (≥ 4 was assigned to 1), Preoperative hemoglobin (≤ 110 g/L was assigned to 1), dexmedetomidine (not used during surgery was assigned to 1), depth of anesthesia (BIS >40 was assigned to 1), operation time (≥ 4 h was assigned to 1). The area under the ROC curve of established model to predict postoperative POCD in elderly patients with gastric cancer was 0.820 (95% CI: 0.742-0.899) ($P<0.01$) (**Figure 1**). According to the regression coefficient of the multi-factor Logistic regression equation, the risk factors of postoperative POCD were scored (**Table 4**), and the parameter model was established. Using the established risk prediction scoring model analysis,

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Table 1. Comparison of basic clinical data of the two groups of patients

Clinical date	POCD (N=141)	non-POCD (N=546)	χ^2/t value	<i>P</i> value
Gender			0.163	0.686
Male	95	358		
Female	46	188		
Age (years old)	82.5±5.3	75.1±4.1	9.478	0.001
ECOG score (points)			1.504	0.220
0~2	111	454		
>2	30	92		
BMI (Kg/m ²)	22.9±4.1	24.1±3.8	1.424	0.416
NRS2002 score	4.1±1.1	3.5±0.9	5.278	0.019
PG-SGA score	5.8±2.2	4.6±1.9	6.252	0.002
Education level			17.311	0.000
illiteracy	26	93		
primary school	48	286		
Junior high school and above	67	167		
Preoperative hemoglobin (g/L)	99.2±8.2	117.1±9.7	12.464	0.000
Preoperative albumin (g/L)	39.8±3.2	41.1±4.1	2.243	0.086
Number of concomitant diseases			19.042	0.000
0~1	34	242		
≥2	107	304		
Preoperative MMSE score				
illiteracy	21.1±2.2	20.9±3.1	0.624	0.516
primary school	23.9±3.0	23.5±4.2	0.536	0.227
Junior high school and above	29.2±4.4	28.9±3.4	0.712	0.353
ASA rating			14.881	0.001
Class I	38	214		
Class II	45	194		
Class III	58	138		
Tumor location			2.804	0.246
Cardia-Fundus of Stomach	64	212		
Stomach-Antrum	68	281		
Whole stomach	9	53		
Tumor size (cm)			0.495	0.482
<5	48	169		
≥5	93	377		
TNM staging			5.871	0.053
I	16	35		
II	36	181		
III	89	330		
Tumor histological type			1.012	0.314
High-moderate differentiation	79	280		
Low-undifferentiated	62	266		
Surgical approach			0.760	0.383
Open surgery	100	407		
Laparoscopic surgery	41	139		

the probability of postoperative POCD in elderly gastric cancer patients with a score ≥4 points

was 42.55%, and the probability of a patient with a score less than 4 points was 5.24%.

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Table 2. Univariate unconditional logistic regression analysis of POCD in elderly patients with gastric cancer after radical resection

Independent variable (assignment)	SE	Wald	P	OR	95% CI
ASA classification (level)	0.214	5.231	0.001	1.685	1.115~2.859
age (years old)	0.121	9.573	0.005	1.534	0.893~2.422
BMI (kg/m ²)	0.188	8.153	0.005	1.597	1.323~2.681
Education level (example)	0.086	4.463	0.000	2.282	1.721~3.218
NRS2002 score before operation	0.286	17.216	0.029	2.148	1.622~2.768
Preoperative PG-SGA score	0.362	5.769	0.006	2.440	1.824~2.962
Preoperative hemoglobin (g/L)	0.581	4.415	0.034	0.687	0.423~0.968
Preoperative albumin (g/L)	0.379	6.721	0.002	1.880	1.547~2.539
Number of concomitant diseases before operation (a)	0.590	7.455	0.009	1.627	1.321~2.362
Phenobarbital Sodium (Example)	0.712	4.691	0.021	0.525	0.323~0.728
Atropine (example)	0.643	6.231	0.001	2.067	1.821~2.462
Dexmedetomidine (example)	0.781	11.409	0.027	0.687	0.455~0.997
Depth of Anesthesia (BIS)	0.378	9.781	0.001	1.861	1.514~2.715
Operation time (min)	0.553	12.891	0.000	1.739	1.389~2.555
Whether blood transfusion during the operation	0.678	5.098	0.042	0.511	0.358~0.867

Table 3. Multivariate unconditional logistic regression analysis of POCD in elderly patients with gastric cancer after radical resection

Clinical factors	SE	Wald	P value	OR	95% CI
ASA classification	1.309	5.401	0.020	4.674	1.610~12.651
age	0.081	11.020	0.001	3.130	1.307~8.669
PG-SGA score	0.806	3.317	0.048	4.023	1.011~10.883
hemoglobin (g/L)	0.911	10.750	0.001	4.158	2.255~8.227
Dexmedetomidine	1.421	6.578	0.002	0.172	0.078~0.314
(BIS)	0.096	8.042	0.018	0.151	0.122~0.283
Operation time	0.013	5.735	0.031	2.724	1.232~7.234

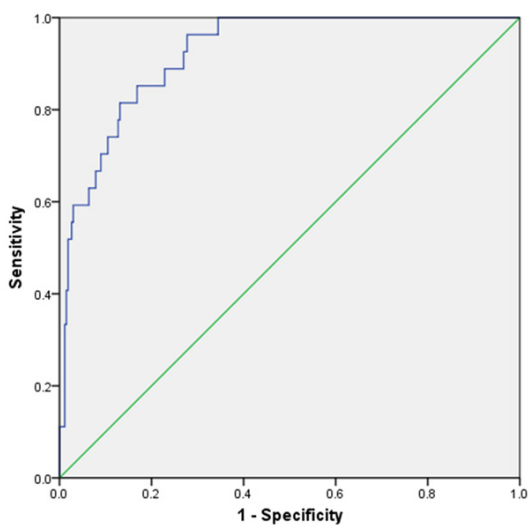


Figure 1. Receiver operating characteristic curve of POCD risk prediction model for elderly patients with gastric cancer after surgery.

Table 4. The risk factors score of POCD after radical gastrectomy for gastric cancer

clinical pathological factors	b	score
ASA classification	1.672	1
Age	1.454	1
PG-SGA score	1.673	1
Hemoglobin (g/L)	1.585	1
Dexmedetomidine	-1.722	-1
(BIS)	-1.884	-1
Operation time	1.212	1

Discussion

Gastric cancer is one of the common malignant tumors of the digestive tract in China. Its incidence ranks third among all malignant tumors. Its tumor-related mortality ranks second [16]. According to authoritative epidemiological re-

search reports, with the emergence of the problem of an aging society in China, the incidence of elderly patients with gastric cancer has shown an upward trend each year. The incidence and mortality rates are 21% and 30% respectively [17]. Previous related studies [18] have shown that, compared with the best conservative treatment, radical surgery in elderly patients with gastric cancer can effectively improve survival and improve patient prognosis. Elderly patients with gastric cancer often suffer from related complications after the operation due to the slow metabolism and declined immunity, accompanied with underlying diseases [19]. POCD is a complication related to cognitive dysfunction that occurs after surgery. It is a relatively common complication in elderly patients. The incidence is significantly higher than that of non-elderly patients with gastric cancer. The results of this study show that the incidence of POCD in elderly patients with gastric cancer (≥ 70 years old) on the seventh day after radical gastric cancer surgery under total intravenous anesthesia was 20.47%, which was slightly lower than the 25.8% released by the International POCD Research Collaboration Group [20]. The reasons for the difference are mainly related to the sample size, the different diagnostic criteria of POCD, the age of the research subjects, the method of anesthesia, and the depth of anesthesia.

This study conducted univariate and multivariate logistic regression analysis for the risk factors that may affect the occurrence of POCD. The results found that the higher preoperative ASA grade, older age, longer operation time, higher preoperative PG-SGA score, and pre-existed anemia were independent risk factors for POCD. Intraoperative application of dexmedetomidine and maintenance of a deep anesthetic state during surgery were protective factors, which are consistent with the results of related studies in many countries [21-24]. The older the patient, the greater the risk of POCD after surgery. The analysis may be related to the following factors [25-27]: ① The function of the central nervous system in elderly patients gradually declines with age, mainly manifested by the decreases in nerve cells, the number of synapses, and the number of neurotransmitters and neurons, which leads to a decrease in the functional activity of the central nervous

system; ② In elderly patients, due to cerebrovascular sclerosis, cerebral blood flow, and the ability to control cerebral hemodynamics are reduced, which leads to decreased brain function and metabolism rate; ③ Elderly patients have poor reserve function of heart, lung, and kidney organs, especially the decline in liver and kidney function which leads to the weakening of the body's drug detoxification ability, slower metabolism, and excretion of drugs from the body; ④ Due to long-term drug consumption in elderly patients, the muscle content in the body decreases, and the proportion of fat tissue in body mass increases, resulting in the distribution of fat-soluble drugs and the prolongation of the half-life, which increases the action time of anesthetics in the body. The general condition and nutritional status of the patient before surgery are also risk factors for the occurrence of POCD. The reason may be that the patient does not correct the general status in time before surgery. This can lead to intraoperative hypovolemic hypotension, which causes the brain to be in a state of hypoperfusion. Continuous insufficient blood supply to the brain causes ischemic damage to brain tissue, which in turn affects brain function [28, 29]. Surgical trauma stimulation, excessive operation time, and shallow depth of anesthesia will aggravate the damage caused by insufficient blood supply to the brain. This can cause neuronal degeneration and axonal rupture in the brain and induce intracellular mitochondrial transport and functional impairment, affecting memory and cognitive function [30].

Once POCD occurs in elderly patients with gastric cancer after surgery, it will cause serious consequences. If it is not handled properly, it will increase the risk of postoperative death and increase hospitalization costs, resulting in a decline in the quality of life after surgery and affecting the long-term survival of the patient. A simple and effective scoring model can be established for the prediction of POCD in elderly patients with gastric cancer in advance. This will be of guiding significance for patients with high risk to carry out active intervention before surgery. We conducted a multi-factor analysis on the risk factors that may be related to the occurrence of POCD in elderly patients and established the Logistic risk prediction equation. The Hosmer-Lemeshow test was used to detect the goodness of fit and the ROC curve to

prove that the model fit well, indicating that the prediction equation has good clinical practical value. Analysis based on the prediction equation found that the probability of POCD in elderly patients with scores ≥ 4 points was 42.55%, and the probability of POCD in patients with scores < 4 points was 5.24%.

With the improvement of anesthesia and surgical techniques, elderly patients are included as surgical objects. The clinical incidence of postoperative POCD is gradually increasing, and is still an unavoidable problem after radical gastric cancer surgery in elderly patients. The prediction of POCD during the perioperative period in elderly patients who underwent surgery has positive clinical guiding significance. For high-risk patients in the perioperative period, the following targeted interventions can be done: preoperative assessments, improvement of general conditions, correction of nutritional status, prediction of surgical difficulty and risk in advance, reduction of surgical time, and appropriate intraoperative amounts the use of dexmedetomidine will have important clinical significance in reducing the incidence of POCD in elderly patients with gastric cancer.

Our research still has some limitations. This study is a single-center retrospective study with a limited number of cases and certain limitations. We only investigated the clinicopathological features of the patients, without imaging examination and molecular mechanism research. It is necessary to carry out a multi-center prospective study, combined with imaging examinations and new molecules to predict the occurrence of POCD in patients.

Disclosure of conflict of interest

None.

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