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The assessment of risk factors for postoperative delirium using cubic spline curves in gastroenterological surgery

Yuki Okawa, MD; Kimitaka Tanaka, MD, PhD; Yoshitsugu Nakanishi, MD, PhD; Toshimichi Asano, MD, PhD; Takehiro Noji, MD, PhD; Yuma Ebihara, MD, PhD; Yo Kurashima, MD. PhD; Toru Nakamura, MD, PhD; Soichi Murakami, MD, PhD; Takahiro Tsuchikawa, MD, PhD; Keisuke Okamura, MD, PhD; Toshiaki Shichinohe, MD, PhD; and Satoshi Hirano, MD, PhD

Department of Gastroenterological Surgery II, Hokkaido University Faculty of Medicine, Sapporo, Hokkaido

North 15, West 7, Kita-ku, Sapporo, Hokkaido 060-8648, Japan

CORRESPONDENCE TO:

Kimitaka Tanaka, MD, PhD

Department of Gastroenterological Surgery II, Hokkaido University Faculty of Medicine

North 15, West 7, Kita-ku, Sapporo, Hokkaido 060-8648, Japan

E-mail: kimitaka.t@gmail.com

Tel: +81-11-716-1161 (ext. 5932)

Fax: +81-11-706-7158

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Abstract

Purpose: Delirium is associated with longer hospital stays and increased medical costs and mortality. This study explored the risk factors for postoperative delirium in gastroenterological surgery and investigated the association between qualitative changes in risk factors and the incidence of postoperative delirium.

Methods: A total of 418 patients >18 years old who underwent gastroenterological surgery at our department between April 2018 and September 2019 were included. Risk factors were identified by comparing patients with and without postoperative delirium. Continuous variables were evaluated graphically using cubic spline curves. A logistic regression analysis was performed to assess independent risk factors.

Results: The incidence of postoperative delirium was 6.9%. The cubic spline curve showed that the incidence of postoperative delirium began to increase at 50 years old and increased sharply at 70 years old. A multiple logistic regression analysis of patients >50 years old identified 5 risk factors: age ≥70 years old, preoperative serum albumin ≤3.8 g/dL, psychosis, sedative-hypnotics, and intensive-care unit admission.

Conclusion: The risk of postoperative delirium increases progressively at 50 years old and sharply at 70 years old. Advanced age, preoperative hypoalbuminemia, psychosis, sedative-hypnotics, and intensive-care unit admission are risk factors for postoperative delirium in patients >50 years old undergoing gastroenterological surgery.

KEYWORDS: cubic spline curve, gastroenterological surgery, postoperative delirium, risk factor

Introduction

Delirium is a geriatric syndrome defined as a short-term disturbance of consciousness and cognition. It is associated with increased medical costs, longer hospital stays, and increased mortality [1-3]. The prevalence of delirium in general hospitalized patients is approximately 10%–30% [4]. Delirium is caused by multiple factors, including underlying disease and environmental changes. However, reports on the treatment of delirium are limited [5-7]. Non-pharmacological prevention before delirium is more helpful than pharmacological treatment after delirium. The usefulness of prevention strategies such as consciousness-stimulating activities, physical therapy, minimizing equipment that inhibits activity, and correcting dehydration has been reported [8, 9]. Preoperative screening for patients at high risk for postoperative delirium (POD) is also essential for perioperative prevention.

One systematic review of risk factors for POD in the field of gastroenterological surgery was published in 2016 [10]. It revealed seven risk factors: advanced age, an American Society of Anesthesia (ASA) classification of ≥III, a low body mass index (BMI), low preoperative serum albumin level, intraoperative hypotension, perioperative blood transfusion, and a history of excessive alcohol consumption. Subsequent reports identified various risk factors for POD, including male sex; a preoperative smoking history; preoperative malnutrition; preoperative anemia; preoperative high C-reactive protein (CRP) level; obstructive ventilation disorder; comorbidities, such as cardiovascular disease, cerebrovascular disease, and dementia; and a history of hypnotic and opioid intake [11-30].

Several risk factors have been reported for POD. However, most reports have investigated age-limited populations (i.e. over 65 or 70 years old), including all of the reports included in the 2016 meta-analysis. Which age groups should be investigated for risk factors of POD is unclear, as no reports have shown an association between age and the incidence of POD. In addition, the association between qualitative changes in other risk factors and the incidence of POD has not been clarified.

The present study retrospectively explored risk factors for POD in gastroenterological surgery and investigated the association between qualitative changes in risk factors and the incidence of POD.

Methods

Patients

All patients over 18 years old who underwent gastroenterological surgery under general anesthesia and were managed perioperatively at Hokkaido University Gastroenterological Surgery II between April 2018 and September 2019 were included in this retrospective study. Patients with preoperative delirium and those who did not undergo surgery during their hospital stay were excluded.

Comprehensive informed consent for the use of patient information for this study was obtained from all participants before surgery. The consent form stated the purpose of the study, and the participant's right to refuse participation at any time was indicated on our website. The Hokkaido University Institutional Review Board (020-0292) approved this study.

Definition and prevention of POD

Patients with suspected POD were evaluated by a psychiatrist. POD was diagnosed using the DSM-5. We did not have a uniform strategy for preventing delirium during the study period. The nurse in charge made a comprehensive assessment of the patient's age, medical history, and cognitive function, and the patients who were considered to be at high risk of POD were examined by a psychiatrist before surgery. When the psychiatrist deemed patients at a high risk of POD, antipsychotics (e.g. risperidone, haloperidol, quetiapine) were prescribed for insomnia and restlessness during perioperative management.

Data collection

Perioperative data were collected from electronic medical records. The information collected included the following: sex, age, body mass index (BMI), preoperative blood data (white blood cell, lymphocyte, anemia, albumin, creatinine, C-reactive protein [CRP]), smoking history, alcohol intake history, forced expiratory volume in 1 second (FEV1.0%), comorbidity (psychotic, hypertension, diabetes, cerebrovascular disorder, cardiovascular disorder, atrial fibrillation, dementia), preoperative medication history (hypnotics, benzodiazepines, opioids, steroids), ASA classification, operation time, intraoperative blood loss, surgical procedure, minimally invasive surgery, postoperative intensive-care unit (ICU) admission, postoperative morbidity, and POD.

Anemia was defined as hemoglobin levels below 13.6 g/dL in males and below 11.5 g/dL in females. Hypnotics were divided into two groups for additional analyses: (1) sedative-hypnotics, for patients who took at least one benzodiazepine or non-benzodiazepine, which have been associated with delirium; and (2) non-sedative-hypnotics, for patients who took only suvorexant or ramelteon, which reportedly prevent delirium. Benzodiazepines included brotizolam, clotiazepam, diazepam, etizolam, flunitrazepam, lorazepam, nitrazepam, and triazolam. Non-benzodiazepines consisted of eszopiclone, rilmazafone, zolpidem, and zopiclone. Postoperative morbidity was categorized according to the Clavien-Dindo classification (CD) [31].

Statistical analyses

All calculations were performed using the R software program, version 3.6.3. Continuous variables are expressed as median, minimum, and maximum. Nominal variables are expressed as frequencies and percentages. Continuous variables were analyzed by a logistic regression analysis to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of POD. Nominal variables were analyzed using the chi-square test or Fisher's exact test.

Statistically significant continuous variables were evaluated graphically using the mgcv package to create cubic spline curves [32]. A cubic spline curve is an interpolation curve, which is a cubic curve connecting all the observed values. The values on the y-axis are the predicted value of the smoothing spline and do not directly indicate the incidence of POD, but spline curves provide a visual prediction of the incidence. The y-axis is labelled s(*factor*, *edf*), where *edf* is the estimated degree of freedom of the smoothing spline.

Receiver operating characteristic (ROC) curves were created to calculate the cut-off values of the risk factors with continuous variables, and the area under the curve (AUC) was calculated. The cut-off values were defined using the Youden Index.

Stepwise selection was performed based on Akaike's information criterion (AIC) that included factors that were statistically significant in the univariate analysis, and a multiple logistic regression analysis was performed. Factors with $p < 0.05$ or 95% CI not containing 0 were considered to indicate a statistically significant difference.

Results

A total of 418 patients were enrolled in this study. The surgical procedures were as follows: pancreatectomy (n = 139), gastrectomy (n = 88), bariatric surgery (n = 39), esophagectomy (n = 32), cholecystectomy (n = 32), hepatectomy (n = 29), small bowel resection (n = 20), gastroenteral bypass (n = 13), extrahepatic bile duct resection (n = 6), appendectomy (n = 6), and others (n = 14).

Table 1 shows the clinical characteristics of POD and non-POD. The incidence rate of POD was 6.9% (n = 29). A univariate analysis identified the following risk factors in all patients: age, preoperative anemia, preoperative serum albumin, preoperative hypnotic intake, preoperative sedative-hypnotic intake, BMI, operation time, blood loss, ICU admission, CD ≥III, and hepatectomy.

Fig. 1 summarizes the distribution of the incidence of POD using cubic spline curves. To show the relationship between the number of patients and the spline curves, the histograms of all patients were added to the spline curves. The five continuous variables identified as risk factors in Table 1 were analyzed (age, preoperative serum albumin, BMI, operation time, and blood loss). Fig. 1a shows that the incidence of POD began to increase at 50 years old and sharply increased at 70 years old. Fig. 1b shows that the spline curve of the albumin level was an upward convex curve that peaked at 3 g/dL. The risk factors of the BMI, operation time, and blood loss were shown to be linearly related to POD (Fig. 1c-e).

Focusing on the finding that the incidence of POD began to increase at 50 years old, we limited the population to patients over 50 years old and identified the risk factors (Table 2). A univariate analysis identified the following risk factors: age, preoperative serum albumin, psychosis, preoperative hypnotic intake, preoperative sedative-hypnotic intake, operation time, blood loss, and ICU admission; however, three factors identified in the all-age population (preoperative anemia, BMI, hepatectomy) were excluded from the risk factors. Fig. S1 summarizes the distribution of the frequency of POD in patients over 50 years old using cubic spline curves. All four continuous variables (age, preoperative serum albumin, operation time, and blood loss) were similar to those shown in Fig. 1.

To calculate the cut-off values, ROC curves were created for the four risk factors identified among the continuous variables for patients over 50 years old (Fig. S2). The cut-off values were as follows: age, 70 years old; preoperative serum albumin, 3.8 g/dL; BMI, 22.1 kg/m^2; operation time, 543 min; and blood loss, 420 ml. Four risk factors were analyzed as nominal variables using cut-off values (Table 3). These four factors were identified as risk factors for POD by chi-square tests or Fisher's exact test.

Seven factors were used in the multivariate analysis: age, preoperative serum albumin, psychosis, sedative-hypnotics, operation time, blood loss, and ICU admission. For multiple analyses, a stepwise selection method was performed based on the AIC. The operation time and blood loss were excluded, and five factors were selected. In the multiple logistic regression analysis, age over 70 years old, preoperative serum albumin ≤3.8 g/dL, psychosis, sedative-hypnotic intake, and ICU admission were identified as risk factors of POD (Table 3).

Discussion

We identified five risk factors for POD through a multiple logistic regression analysis: advanced age, low preoperative serum albumin levels, psychosis, sedative-hypnotic intake, and ICU admission in patients over 50 years old who underwent gastroenterological surgery. We also visually assessed the association between the incidence of POD and risk factors for continuous variables using cubic spline curves.

In this study, the cubic spline curve showed that the incidence of POD began to increase at 50 years old, and the incidence increased sharply at 70 years old. No delirium was noted in patients under 50 years old. This result suggests that patients ≥50 years old who undergo surgery should be monitored for POD. Most reports on major abdominal surgery, including meta-analyses, have assessed older populations, such as patients over 65 or 70 years old. These studies may therefore not have assessed all patients with POD [10-15]. Furthermore, our results showed that 70 years old, where the incidence began to increase sharply, was consistent with the cut-off value calculated using the ROC curve. Park et al. [16] identified 70 years old as the cut-off value, supporting this result. To our knowledge, our report is the first to clarify the association between aging and the incidence of POD.

In this study, a low preoperative albumin level was identified as a risk factor for POD. Furthermore, the AUC of the ROC curve for albumin was relatively high at 0.73, indicating a high predictive ability for POD. Although the pathophysiological evidence is unclear, low preoperative albumin levels have been reported as a risk factor for POD [10, 14, 16, 17]. However, the spline curve of the albumin level was not linear but an upward convex curve, with a peak at 3 g/dL. We assume this is because few patients with a poor general condition, such as severe hypoalbuminemia, underwent surgery, as shown in the histograms in Fig. 1 and Fig. S1. The further accumulation of cases is needed to clarify the relationship between extreme hypoalbuminemia and POD.

However, Mazzola et al. [33] used the Mini Nutritional Assessment Short Form to classify the preoperative nutritional status of patients undergoing hip fracture surgery. They found that the better the nutritional status, the lower the incidence of POD. Zhao et al. [34] also evaluated the preoperative nutritional status of patients undergoing non-cardiac surgery using the Geriatric Nutritional Risk Index, which is calculated based on serum albumin levels and body weight. They found that more severe malnutrition was associated with POD. As shown by the spline curve for albumin above 3 g/dL, an improvement in preoperative albumin levels may lead to a reduction in POD.

ICU admission has multifactorial involvement in delirium, being associated with environmental changes, sedation, and opioid use [35]. Furthermore, it has been shown that patients with delirium in the ICU have a higher mortality rate than those outside the ICU [36]. Although the ICU admission in this study was for postoperative management of the general condition, and the duration of stay was only a few days, ICU admission was identified as a risk factor for POD, a finding consistent with the report by Kim et al. [37].

Psychosis attributed to attributed to schizophrenia, anxiety disorders, and depression have been identified as risk factors for delirium [38]. The effects of psychological factors on delirium have not been clearly studied, but a strong correlation has been found between subjective emotional factors (e.g. pain and anxiety) and delirium. Benzodiazepine or non-benzodiazepine intake was also identified as a risk factor. Benzodiazepines and non-benzodiazepines, which are classified as hypnotics, have a strong pharmacological association with delirium and may be involved in the etiology of delirium through the overstimulation of the cortical GABA system [39,40]. In contrast, suvorexant and ramelteon, hypnotics with other functional mechanisms, have been shown to prevent delirium [41, 42]. No clinical trials have examined hypnotic adjustment, but Ogawa et al. [43] reported that a systematic management program that included avoiding prescribing benzodiazepines for insomnia and encouraging the prescription of antipsychotics as the first-line treatment for restlessness reduced delirium. Thus, the preoperative adjustment of hypnotic intake may reduce the incidence of POD.

Several limitations associated with the present study warrant mention. First, this was a single-center study from an academic hospital, so some degree of case bias may exist. As the proportion of patients with acute abdominal disease in the academic hospital is lower than that in the general hospital, the general condition of surgical patients is relatively stable. To validate the results of this study, validation studies need to be conducted in multi-center settings. Second, in the present study, POD was not routinely assessed using a diagnostic tool, such as the confusion assessment method. Therefore, delirium with minimal symptoms, especially hypoactive delirium, may not have been diagnosed in all cases. Third, as this was a retrospective study, the diagnosis of POD was based on electronic medical record data. Therefore, we were able to confirm the timing of the diagnosis of POD, but we could not obtain the exact timing of the POD onset. The difference between the timing of the delirium diagnosis and the delirium onset may have ranged from several hours to several days. Postoperative outcomes, such as complications and the duration of hospital stay, are expected to depend on the onset timing of POD. However, due to the retrospective nature of this study, we were unable to accurately assess the onset timing of POD. Consequently, a prospective study is needed to evaluate hypoactive delirium and the onset timing of POD.

In conclusion, using spline curves, the risk of POD was found to increase progressively at 50 and 70 years old. An advanced age, low preoperative serum albumin levels, psychosis, sedative-hypnotic intake, and ICU admission were identified as risk factors for POD in patients over 50 years old who underwent gastroenterological surgery. Nutritional improvement and the adjustment of hypnotic intake before surgery might help prevent POD.

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Table 1. Clinical characteristics of POD and non-POD patients

	POD n = 29		Non-POD n = 389		P-value	OR	95% CI
Age (years)	73	(54-91)	66	(18-89)	<0.001	1.09	(1.05-1.14)
Male	19	(65.5)	223	(57.3)	0.5	1.41	(0.64-3.12)
White blood cell (/μL)	5500	(2800-13100)	5600	(2300-18000)	0.81	1	(0.99-1.0002)
Lymphocytes (/μL)	1459	(275-3039)	1504	(190-4108)	0.91	1	(0.99-1.0006)
Preoperative anemia	20	(69)	180	(46.3)	0.03	2.58	(1.15-5.81)
Preoperative serum albumin (g/dL)	3.7	(2.9-4.3)	4.2	(1.3-5.1)	<0.001	0.42	(0.25-0.71)
Serum creatinine (mg/dL)	0.74	(0.55-15.16)	0.71	(0.32-9.94)	0.05	1.27	(1-1.62)
CRP (mg/L)	0.2	(0.02-7.48)	0.09	(0.02-23.45)	0.79	0.98	(0.82-1.16)
History of alcohol excess	9	(31)	90	(23.1)	0.46	1.5	(0.66-3.4)
Current smoker	5	(17.2)	83	(21.3)	0.88	0.82	(0.3-2.23)
FEV1.0% (%)	71.6	(43-98)	74	(27.8-95.6)	0.11	0.97	(0.93-1.01)
Comorbidities							
Atrial fibrillation*	1	(3.4)	16	(4.1)	1	0.83	(0.04-5.33)
Psychosis*	3	(10.3)	16	(4.1)	0.14	2.68	(0.63-9.78)
Hypertension	15	(51.7)	166	(42.7)	0.45	1.44	(0.68-3.06)
Diabetes	7	(24.1)	88	(22.6)	1	1.09	(0.45-2.63)
Cerebrovascular disease*	3	(10.3)	28	(7.2)	0.46	1.49	(0.36-5.3)
Cardiovascular disease	4	(13.8)	58	(14.9)	1	0.91	(0.31-2.72)
Preoperative medication							
Hypnotics	17	(58.6%)	87	(22.4%)	<0.001	4.92	(2.26-10.69)
Sedative-hypnotics	15	(51.7%)	81	(20.8%)	<0.001	4.07	(1.89-8.78)
Non-sedative-hypnotics*	2	(6.9%)	7	(1.8%)	0.12	4.02	(0.58-19.87)
Opioids*	0	(0)	7	(1.8)	1	0	(0-7.87)
Steroids*	0	(0)	19	(4.9)	0.38	0	(0-2.58)

ASA-PS classification ≥III*	4	(13.8)	73	(18.8)	0.63	0.69	(0.21-2.09)
BMI (kg/m^2)	21.7	(16.4-26.1)	23.1	(11.4-54.5)	0.02	0.88	(0.8-0.98)
Operation time (min)	457	(80-904)	307.5	(28-997)	<0.001	1.003	(1.001-1.005)
Blood loss (mL)	570	(0-6155)	70	(0-5620)	<0.001	1.0006	(1.0003-1.0009)
Minimally invasive surgery	10	(34.5)	205	(52.7)	0.09	0.47	(0.21-1.04)
Admission to ICU	15	(51.7)	86	(22.1)	<0.001	3.77	(1.75-8.13)
CD ≥III	12	(41.4)	84	(21.6)	0.03	2.56	(1.18-5.58)
Surgical methods							
Pancreatectomy	13	(44.8)	126	(32.4)	0.24	1.7	(0.79-3.63)
Gastrectomy*	4	(13.8)	84	(21.6)	0.48	0.58	(0.18-1.74)
Bariatric surgery*	0	(0)	39	(10)	0.09	0	(0-1.28)
Esophagectomy*	3	(10.3)	29	(7.5)	0.48	1.43	(0.35-5.07)
Cholecystectomy*	0	(0)	32	(8.2)	0.15	0	(0-1.63)
Hepatectomy*	5	(17.2)	24	(6.2)	0.04	3.16	(1.06-9.08)
Small bowel resection*	2	(6.9)	18	(4.6)	0.64	1.52	(0.24-6.79)
Gastroenteral bypass*	0	(0)	13	(3.3)	1	0	(0-4.15)
Extrahepatic bile duct resection*	1	(3.4)	5	(1.3)	0.35	2.73	(0.11-21.33)
Appendectomy*	0	(0)	6	(1.5)	1	0	(0-10)
Others*	1	(3.4)	13	(3.3)	1	1.03	(0.05-7.08)

Data are expressed as the number (%) or median (minimum value - maximum value).

*Fisher’s exact test

POD, postoperative delirium; OR, odds ratio; CI, confidence interval; CRP, C-reactive protein; FEV1.0%, forced expiratory volume in 1 second percent; ASA-PS, American Society of Anesthesiologists physical status; BMI, body mass index; ICU, intensive-care unit; CD, Clavien-Dindo classification

Table 2. Clinical characteristics of POD and non-POD patients over 50 years old

	POD n = 29		Non-POD n = 308		P-value	OR	95% CI
Age (years)	73	(54-91)	69	(50-89)	<0.001	1.08	(1.03-1.14)
Male	19	(65.5)	183	(59.4)	0.66	1.3	(0.58-2.88)
White blood cell (/μL)	5500	(2800-13100)	5600	(2300-18000)	0.46	1.0001	(0.99-1.0002)
Lymphocytes (/μL)	1459	(275-3039)	1462	(406-4108)	0.72	1.0001	(0.99-1.0008)
Preoperative anemia	20	(69)	163	(52.9)	0.14	1.98	(0.87-4.48)
Preoperative serum albumin (g/dL)	3.7	(2.9-4.3)	4.1	(1.7-5.1)	<0.001	0.38	(0.21-0.69)
Serum creatinine (mg/dL)	0.74	(0.55-15.16)	0.725	(0.32-9.94)	0.08	1.24	(0.97-1.57)
CRP (mg/L)	0.2	(0.02-7.48)	0.09	(0.02-23.45)	0.93	0.99	(0.83-1.18)
History of alcohol excess	9	(31)	82	(26.6)	0.77	1.24	(0.54-2.83)
Current smoker*	5	(17.2)	64	(20.8)	1	0.85	(0.3-2.39)
FEV1.0% (%)	71.6	(43-98)	72.5	(41.3-94.8)	0.44	0.98	(0.94-1.03)
Comorbidities							
Atrial fibrillation*	1	(3.4)	14	(4.5)	1	0.75	(0.03-5.01)
Psychosis*	3	(10.3)	4	(1.3)	0.02	8.65	(1.62-41.79)
Hypertension	15	(51.7)	143	(46.4)	0.73	1.24	(0.58-2.65)
Diabetes	7	(24.1)	68	(22.1)	0.98	1.12	(0.46-2.74)
Cerebrovascular disease*	3	(10.3)	25	(8.1)	0.72	1.31	(0.32-4.78)
Cardiovascular disease*	4	(13.8)	58	(18.8)	0.62	0.69	(0.21-2.13)
Preoperative medication							
Hypnotics	17	(58.6%)	70	(22.7%)	<0.001	4.82	(2.2-10.57)
Sedative-hypnotics	15	(51.7%)	64	(20.8%)	<0.001	4.08	(1.88-8.9)
Non-sedative-hypnotics*	2	(6.9%)	6	(1.9%)	0.14	3.7	(0.52-20.76)
Opioids*	0	(0)	7	(2.3)	1	0	(0-6.2)
Steroids*	0	(0)	16	(5.2)	0.38	0	(0-2.5)

ASA-PS classification ≥III*	4	(13.8)	41	(13.3)	1	1.04	(0.32-3.04)
BMI (kg/m^2)	21.7	(16.4-26.1)	22.75	(11.4-52.2)	0.05	0.9	(0.8-1)
Operation time (min)	457	(80-904)	342	(42-997)	0.02	1.002	(1.0004-1.004)
Blood loss (mL)	570	(0-6155)	122.5	(0-5620)	<0.001	1.0006	(1.0002-1.0009)
Minimally invasive surgery	10	(34.5)	152	(49.4)	0.18	0.54	(0.24-1.2)
Admission to ICU	15	(51.7)	73	(23.7)	<0.001	3.45	(1.59-7.48)
CD ≥III	17	(58.6)	236	(76.6)	0.06	2.31	(1.06-5.07)
Surgical methods							
Pancreatectomy	13	(44.8)	105	(34.1)	0.34	1.57	(0.73-3.39)
Gastrectomy*	4	(13.8)	78	(25.3)	0.26	0.47	(0.15-1.43)
Bariatric surgery*	0	(0)	9	(2.9)	1	0	(0-5.47)
Esophagectomy*	3	(10.3)	26	(8.4)	0.73	1.25	(0.3-4.5404)
Cholecystectomy*	0	(0)	28	(9.1)	0.15	0	(0-1.49)
Hepatectomy*	5	(17.2)	24	(7.8)	0.09	2.46	(0.83-7.09)
Small bowel resection*	2	(6.9)	13	(4.2)	0.38	1.68	(0.26-7.2)
Gastroenteral bypass*	0	(0)	10	(3.2)	1	0	(0-4.68)
Extrahepatic bile duct resection*	1	(3.4)	2	(0.6)	0.24	5.41	(0.18-71.06)
Appendectomy*	0	(0)	2	(0.6)	1	0	(0-37.31)
Others*	1	(3.4)	11	(3.6)	1	0.96	(0.04-7.1)

Data are expressed as the number (%) or median (minimum value - maximum value).

*Fisher's exact test

POD, postoperative delirium; OR, odds ratio; CI, confidence interval; CRP, C-reactive protein; FEV1.0%, forced expiratory volume in 1 second percent; ASA-PS, American Society of Anesthesiologists physical status; BMI, body mass index; ICU, intensive-care unit; CD, Clavien-Dindo classification

Table 3. Results of a multiple logistic regression analysis in patients over 50 years old

	POD		Non-POD		Univariate analysis			Multivariate analysis		
	n = 29		n = 308		P-value	OR	95% CI	P-value	OR	95% CI
Age ≥70 years	23	(79.3)	145	(47.1)	<0.001	4.31	(1.71-10.89)	0.02	3.33	(1.23-9.04)
Preoperative serum albumin ≤3.8 g/dl	17	(58.6)	70	(22.7)	<0.001	4.78	(2.18-10.48)	<0.001	4.23	(1.8-9.93)
Psychosis	3	(10.3)	4	(1.3)	0.02*	8.59	(1.61-41.51)	0.01	11.1	(1.63-75.41)
Sedative-hypnotics	15	(51.7)	64	(20.8)	<0.001	4.05	(1.86-8.83)	0.02	2.84	(1.19-6.76)
Operation time ≥543 min	12	(41.4)	62	(20.1)	0.02	2.78	(1.26-6.12)			
Blood loss ≥420 mL	17	(58.6)	100	(32.5)	0.01	2.92	(1.34-6.34)			
Admission to ICU	15	(51.7)	73	(23.7)	<0.001	3.42	(1.58-7.42)	0.01	3.2	(1.36-7.54)

Data are expressed as the number (%).

*Fisher's exact test

POD, postoperative delirium; OR, odds ratio; CI, confidence interval; BMI, body mass index; ICU, intensive-care unit

Figure legends

Fig. 1. Histograms for risk factors and cubic spline curves for risk factors and the incidence of postoperative delirium in all patients

(a) Age, (b) Serum albumin, (c) Body mass index, (d) Operation time, (e) Blood loss. The x-axis of the graph represents the explanatory variable. The values on the left side y-axis are the predicted value of the smoothing spline. The right side y-axis is the frequency of the histogram. The 95% confidence intervals are represented as dashed lines. The incidence of delirium is plotted as a circle. BMI, body mass index.

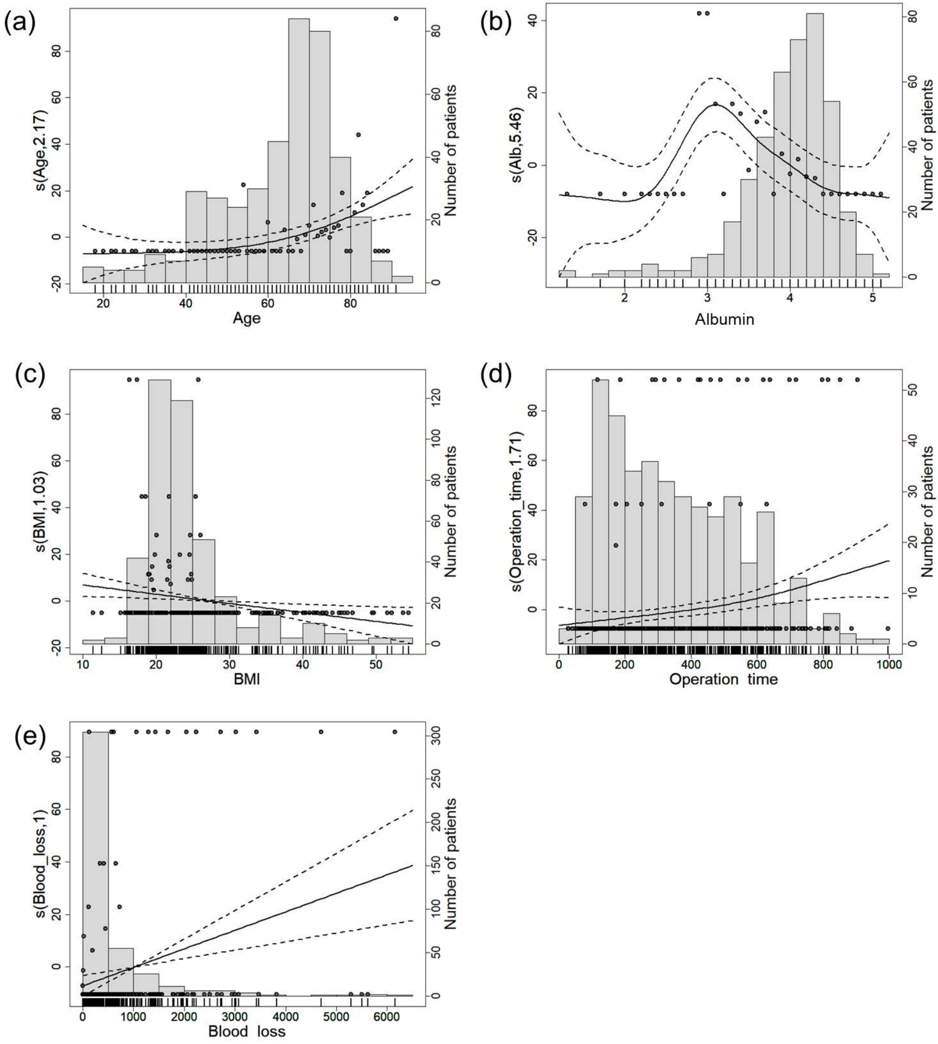
Fig. S1. Histograms for risk factors and cubic spline curves for risk factors and the incidence of postoperative delirium in patients over the age of 50 years

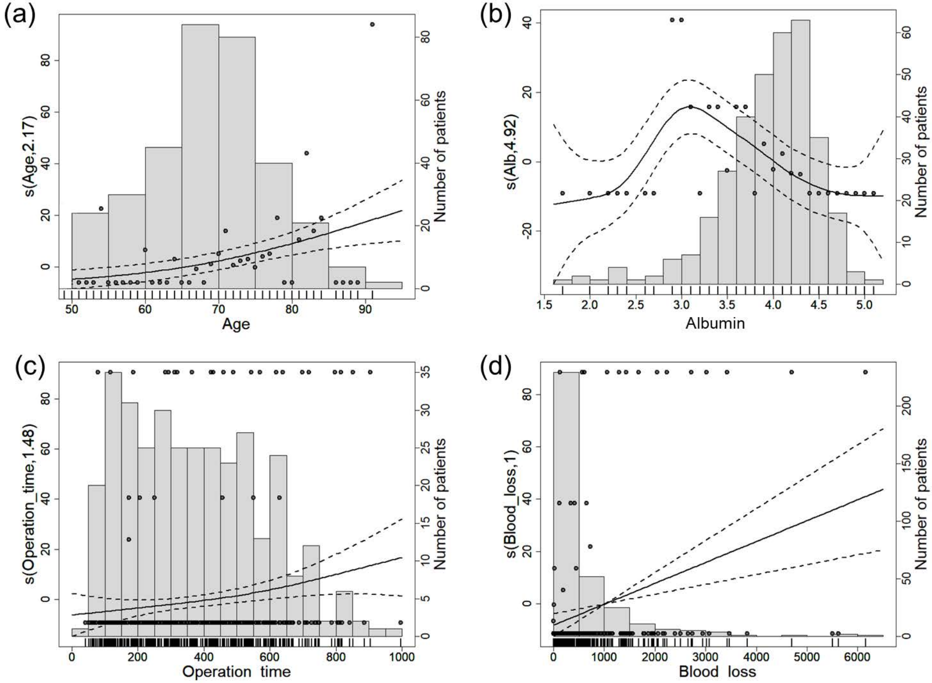
(a) Age, (b) Serum albumin, (c) Operation time, (d) Blood loss. The x-axis of the graph represents the explanatory variable. The values on the left side y-axis are the predicted value of the smoothing spline. The right side y-axis is the frequency of the histogram. The 95% confidence intervals are represented as dashed lines. The incidence of delirium is plotted as a circle.

Fig. S2. Receiver operating characteristic curves of risk factors for continuous variables in patients over the age of 50 years

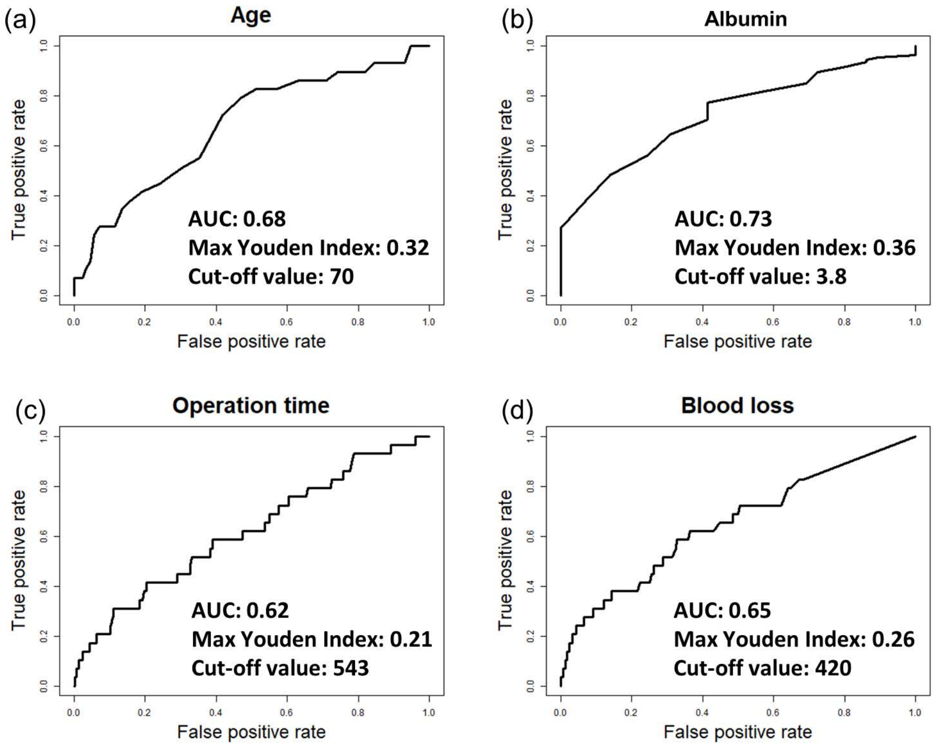
(a) Age, (b) Serum albumin, (c) Operation time, (d) Blood loss. The cut-off values are defined using the

Youden Index. AUC, area under curve.


(a)
s(Age,2.17)
Age
Number of patients
(b)
s(Alb,5.46)
Albumin
Number of patients
(c)
s(BMI,1.03)
BMI
Number of patients
(d)
s(Operation_time,1.71)
Operation time
Number of patients
(e)
s(Blood_loss,1)
Blood loss
Number of patients



(a)
s(Age,2.17)
Number of patients
Age
(b)
s(Alb,4.92)
Number of patients
Albumin
(c)
s(Operation_time,1.48)
Number of patients
Operation time
(d)
s(Blood_loss,1)
Number of patients
Blood loss


(a)
Age
AUC: 0.68
Max Youden Index: 0.32
Cut-off value: 70
True positive rate
False positive rate
(b)
Albumin
AUC: 0.73
Max Youden Index: 0.36
Cut-off value: 3.8
True positive rate
False positive rate
(c)
Operation time
AUC: 0.62
Max Youden Index: 0.21
Cut-off value: 543
True positive rate
False positive rate
(d)
Blood loss
AUC: 0.65
Max Youden Index: 0.26
Cut-off value: 420
True positive rate
False positive rate