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ORIGINAL SCIENTIFIC REPORT

Preoperative Anxiety as a Predictor of Delirium in Cancer Patients: A Prospective Observational Cohort Study

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Abstract

Background Postoperative delirium is a common and important complication in cancer patients. We need to identify patients at high risk of postoperative delirium such that it can be prevented preoperatively or in early postoperative phase. The aim of this study was to investigate whether preoperative anxiety predicted onset of postoperative delirium in cancer patients, not only in order to identify high-risk groups but also to help develop new preventive approaches.

Methods This was a prospective observational cohort study of cancer patients undergoing tumor resections. Postoperative delirium was assessed using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Preoperative anxiety was evaluated with the Hospital Anxiety and Depression Scale-Anxiety (HADS-A), and we defined HADS-A > 7 as clinical anxiety. We conducted multivariate logistic regression to determine which factors were predictors of delirium.

Results The final analysis included 91 patients, 29 of whom met the criteria for postoperative delirium. In multivariable logistic regression, age (5-year increments; odds ratio (OR) = 1.565, 95% confidence interval (CI) = 1.057–2.317, $p = 0.025$) and HADS-A > 7 (OR = 4.370, 95% CI = 1.051–18.178, $p = 0.043$) predicted delirium onset. These variables explained 74.2% of the variance.

Conclusions Preoperative anxiety strongly predicted postoperative delirium in cancer patients. Our findings suggest that preoperative anxiety may be a new target for prevention of postoperative delirium.

Trial registration number This study was registered at UMIN000018980

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Introduction

Postoperative delirium, which is a clinical syndrome characterized by the acute disruption of attention and cognition [1], is a common complication in cancer patients. Previous studies reported that the prevalence of postoperative delirium [2–6] ranged from 11.5% in a prospective study of head and neck cancer patients [3] to 50% in a retrospective study of esophageal cancer patients [4]. In addition, it was reported that the incidence of delirium was 45 times higher following highly invasive surgeries than after less invasive surgeries [2]. Postoperative delirium is associated with adverse outcomes such as a higher rate of postoperative complications, longer length of hospital stay, functional disability, decline of cognitive function, and high mortality [7–11]. Moreover, because many cancer patients require adjuvant therapy after surgery, prevention of or early recovery from postoperative delirium is especially needed in this population.

Numerous studies have investigated the risk factors of postoperative delirium [2, 3, 12–22]; these include age, cognitive function, physical function, medications, operation time, blood loss, infection, and preoperative psychiatric symptoms [14, 15, 18–23]. The last of these, preoperative psychiatric symptoms, are important because they can be altered by interventions and can be used to identify high-risk groups and to develop prophylactic approaches to postoperative delirium. In particular, previous studies showed that depression predicted postoperative delirium [14, 15, 19, 23]. The mechanism is still unclear, but inflammatory cytokines may be involved. Recent studies suggested that peripheral inflammatory cytokines migrate to the central nervous system and interact with microglia, causing neuroinflammation and the subsequent development of delirium [24–26]. Similarly, it is suggested that inflammatory cytokines contribute to depression [14, 15, 19, 23].

The aforementioned pathway is also involved in anxiety [27, 28], and anxiety could affect delirium. However, preoperative anxiety was not associated with postoperative delirium in cardiac surgery patients in a prospective study by Detroyer et al. [18]. There was also no relation between the two conditions in a retrospective study of hip fracture patients conducted by Van Grootven et al. [22]. However, both studies had several weaknesses, such as a retrospective study design and the fact that the delirium evaluators were not psychiatric experts. Therefore, we planned a prospective study to address these weaknesses. The aim of this study was to investigate whether preoperative anxiety would predict the onset of postoperative delirium in cancer patients. We used a rigorous method to overcome the limitations of previous studies.

Materials and methods

Setting and subjects

This prospective observational cohort study was conducted from October 2015 through April 2016 at the National Cancer Center Hospital (NCCH) in Japan. All study protocols were approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center in Japan, and were conducted in accordance with the Declaration of Helsinki. The study is reported according to the criteria set out in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

The inclusion criteria were (1) a clinical or pathological diagnosis of cancer, (2) scheduled tumor resection, which predicted operation time is 6 h or more, and (3) age greater than 20 years. The exclusion criteria were (1) too physically or psychologically ill as judged by the attending physicians or researchers preoperatively, (2) inability to read or understand the informed consent documents, and (3) surgery lasting less than 6 h due to intraoperative findings.

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Measures

Demographic and clinical characteristics

Demographic data, including age, sex, and socioeconomic variables (educational level, marital status, and current employment) were obtained from face-to-face interviews. Clinical characteristics (primary cancer site, time since diagnosis, and preoperative treatment) and medication lists were obtained from patients' medical charts.

Postoperative delirium

Postoperative delirium was assessed by a trained psychiatrist or psychologist using the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) [29]; this is one of the most rigorous methods to determine whether delirium is present or not. We clinically demonstrated and discuss our findings before this study, with a final determination made once there was satisfactory agreement between the researchers and the principal investigator (K.S). During the course of the study, the researchers assessed a sample of patients simultaneously and independently to check inter-rater reliability of the DSM-5 (20 times for each researcher), and kappa values ranged from 0.85 to 0.95.

Preoperative anxiety

Preoperative anxiety was evaluated using the Hospital Anxiety and Depression Scale-Anxiety (HADS-A) [30, 31], a self-report instrument consisting of 7 items. Symptoms occurring in the previous 2 weeks are scored on a 4-point Likert scale with total scores ranging between 0 and 21. HADS is the most extensively validated scale for screening emotional distress in cancer patients, and the strength of this scale for the assessment of emotional distress in cancer patients is to be able to assess anxiety and depressive symptoms without referring to physical symptoms. Kugaya et al. [30] investigated the reliability and the validity of the Japanese version of HADS in Japanese cancer patients. They showed Cronback's α of HADS-A was 0.77, and the correlations of the scores between test and retest was 0.73. HADS-A also gave high sensitivity and specificity at the cutoff point 7/8. Therefore, we defined a HADS-A score of 8 or more as clinical anxiety in this study.

Other risk factors of POD

Fourteen variables were evaluated as other risk factors of POD. These variables were chosen because previous studies showed them to be risk factors of postoperative delirium [3, 12, 13, 32]. The two preoperative variables were a history of delirium [32] and recent drinking as measured using the CAGE questionnaire [3, 32]. The four medical variables were body mass index (BMI) [33], cognitive function assessed using the Mini Mental State Examination (MMSE) [3, 13, 15, 32], Eastern Cooperative Oncology Group Performance Status (PS) [13–15], and comorbidity evaluated with the Charlson Comorbidity Index (CCI) [14, 15]. The eight surgical variables were the American Society of Anesthesiology (ASA) class [3, 13–16]; duration of surgery [3]; duration of anesthesia [34–36]; type of anesthesia (inhalational or total intravenous) [34–36]; intraoperative blood loss [3]; intraoperative medications; impairment of postoperative physical function measured using the Acute Physiology Age and Chronic Health Examination (APACHE-II) scale [13, 16]; and vocalization ability (whether or not total laryngectomy or tracheotomy were performed), which experts suggested may predict postoperative delirium.

Procedure

We consecutively recruited patients who were admitted to the NCCH to undergo highly invasive surgery. Demographic and medical data, cognitive functioning (MMSE), functional status (PS and ASA), and recent drinking (CAGE) were evaluated on admission by trained research assistants using patient interviews and chart reviews.

We evaluated preoperative anxiety using the HADS-A in the afternoon of the day before surgery. Then we assessed whether delirium, as defined by the DSM-5, appeared during the 5-day postoperative period, as well as its duration. We set the delirium evaluation period to 5 days after surgery because several previous studies suggested that delirium usually appeared between 2 and 3 days postoperatively [2, 4, 6]. In patients who developed postoperative delirium, its severity was assessed using the Delirium Rating Scale Revised-98 (DRS-R-98) [37, 38]. We also evaluated the subtype of postoperative delirium using the Delirium Motor Subtype Scale (DMSS) [39].

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 22. Descriptive statistics were used to describe baseline characteristics and outcome measures. We considered BMI, MMSE score, duration of operation, duration of anesthesia, amount of blood loss, and APACHE-II scores to be continuous variables, while other factors were nominal categorical variables. We dealt with age as a categorical variable (5-year increments) because this seemed more clinically meaningful than treating it as a continuous variable. We used the χ^2 test for dichotomous

or nominal variables, the Mann–Whitney U test for ordinal or non-normally distributed continuous variables, and Student's t test for normally distributed continuous variables to compare the delirium group and non-delirium group. P values < 0.05 were considered statistically significant.

Variables with $p < 0.25$ in univariable analyses were included in a multivariate logistic regression model to determine which were predictors of delirium. The HADS-A score was added to the multivariate model as a variable of interest. Multicollinearity was tested, excluding variables with a Pearson correlation of 0.6 or greater. In addition, since it would be more clinically meaningful if we could predict the onset of postoperative delirium using only preoperative variables, we also created a model that included only these variables to further clarify the preventive factors for postoperative delirium.

Results

Sample

Of 135 consecutive patients who were eligible, 118 (87.4%) were enrolled (Fig. 1). Nine were excluded after surgery because the operations were changed to less invasive surgeries, such as intestinal bypass surgery and exploratory laparotomy. Eighteen of the 109 patients who received follow-up dropped out, for reasons shown in Fig. 1. The final analysis included 91 patients. There was no significant difference in age, sex, primary cancer site, or preoperative treatment between patients who refused to participate and those who were enrolled.

Outcomes of postoperative delirium

Twenty-nine (31.9%) patients met the criteria for postoperative delirium. In the patients with delirium, the mean of the peak day DRS-R-98 score for patients with delirium was 8.4 (SD = 4.2) and the mean duration of delirium was 2.3 (SD = 1.8) days. The subtype classification is shown in Table 1.

Clinical outcomes in patients with and without delirium

Table 2 shows data on patient demographics and preoperative medical characteristics. Subjects averaged 66.0 years of age (range 39–84), and the majority were male (68.1%). The mean MMSE score was 27.6 (SD = 2.3), and only five patients had a history of delirium. Overall, the patients' general condition was good; most had PS 2 or less (98.9%) and ASA 2 or less (89.0%). Patients with delirium were older (mean 70.0, SD = 8.9 vs. mean 64.2, SD = 10.1, $p = 0.009$) and had a lower preoperative MMSE score (mean 26.8, SD = 2.8 vs. mean 27.9, SD = 1.9, $p = 0.024$). There was no patients who used steroids before surgery in both groups (not shown in Table 2).

The mean operation time was 8.2 (SD = 1.7) hours in the delirium group and 7.7 (SD = 1.6) hours in the non-delirium group ($p = 0.131$). The APACHE-II score immediately after surgery was significantly higher in the delirium group than the non-delirium group ($p = 0.025$) (Table 3).

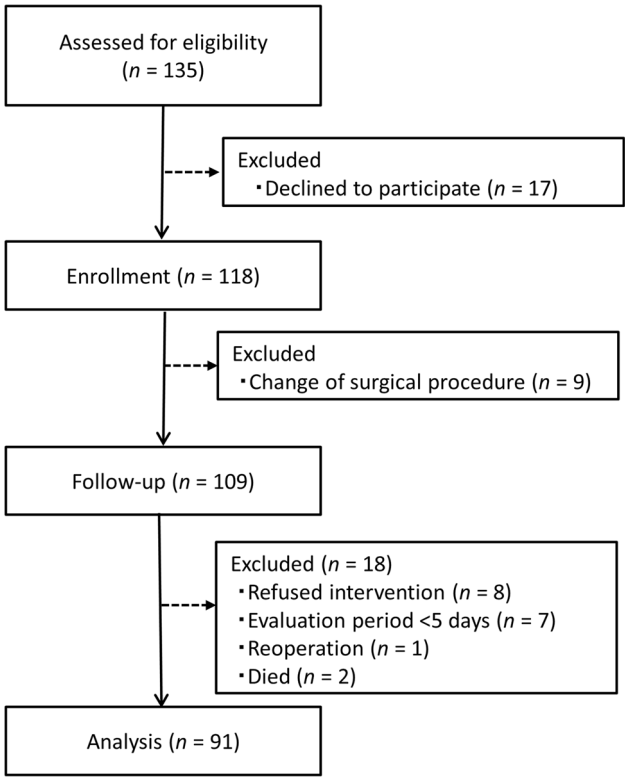

Fig. 1 Flow diagram outlining derivation of the final sample

Table 1 Postoperative delirium outcomes

	n	%
DRS-R-98, mean (SD)	8.4 (4.2)	
Duration of delirium, mean (SD), days	2.3 (1.8)	
Subtypes of delirium		
Hyperactive	7	24.1
Hypoactive	6	20.7
Mixed	0	0.0
No subtype	16	55.2

SD, standard deviation; DRS-R-98, Delirium Rating Scale-R-98

Table 2 Demographic and preoperative medical characteristics

Characteristics	Total population (n = 91)		Delirium (n = 29)		Non-delirium (n = 62)		p value[a]
	n	%	n	%	n	%	
Age							
Mean (SD), years	66.0 (10.0)		70.0 (8.9)		64.2 (10.1)		0.009
Sex							
Male	62	68.1	18	62.1	44	71.0	0.396
BMI							
Mean (SD), kg/m^2	21.7 (3.2)		21.7 (3.2)		22.5 (5.5)		0.438
Education							
College graduate or higher	52	57.1	15	51.7	37	59.7	0.475
Marital status							
Married/has a partner	76	83.5	22	75.9	54	87.1	0.347
Current employment							0.578
Self-employed	17		4		13		
Employee (full time/part time)	28		8		20		
Retiree	9		4		5		
Unemployed	28		11		17		
Others	9		2		7		
History of delirium	5	5.5	2	6.9	3	4.8	0.688
MMSE							
Mean (SD)	27.6 (2.3)		26.8 (2.8)		27.9 (1.9)		0.024
CAGE questionnaire score (≥2 "yes" responses)	13	14.3	3	10.3	10	16.1	0.462
Primary cancer site							0.538
Esophageal	37	40.7	11	37.9	26	41.9	
Hepatobiliary and pancreas	34	37.4	11	37.9	23	37.1	
Head and neck	17	18.7	7	24.1	10	16.1	
Others	3	3.3	0	0.0	3	4.8	
Time since diagnosis							
Mean (SD), months	3.4 (2.1)		3.6 (2.2)		3.3 (2.2)		0.523
Preoperative treatment							
Chemotherapy	35	38.5	12	41.4	23	37.1	0.696
Radiotherapy	7	7.7	2	6.9	5	8.1	0.846
ECOG PS							0.476
1	68	74.7	20	69.0	48	77.4	
2	22	24.2	9	31.0	13	21.0	
3	1	1.1	0	0.0	1	1.6	
4	0	0.0	0	0.0	0	0.0	
ASA							0.355
1	9	9.9	1	3.4	8	12.9	
2	72	79.1	25	86.2	47	75.8	
3	10	11.0	3	10.3	7	11.3	
4	0	0.0	0	0.0	0	0.0	
CCI							
Mean (SD)	1.4 (0.6)		1.4 (0.6)		1.4 (0.6)		0.867
Benzodiazepine use	5	5.5	1	3.4	4	6.5	0.558
Opioid use	3	3.3	1	3.4	2	3.2	0.956

SD, standard deviation; BMI, body mass index; MMSE, Mini Mental State Examination; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ASA, American Society of Anesthesiologists class; CCI, Charlson comorbidity index

[a] p values of age, BMI, time since diagnosis, and CCI were obtained via t test, and others were obtained via χ^2 test

Table 3 Surgical variables

Characteristics	Delirium (n = 29)		Non-delirium (n = 62)		p value[a]
	n	%	n	%	
Duration of surgery					
Mean (SD), hours	8.2 (1.7)		7.7 (1.6)		0.131
Duration of anesthesia					
Mean (SD), hours	9.4 (1.8)		8.9 (1.6)		0.162
Type of anesthesia					0.299
Inhalational anesthesia	27	93.1	53	85.5	
Total intravenous anesthesia	2	6.9	9	14.5	
Blood loss					
Median (min–max), ml	676.0 (113–3980)		511.5 (84–3107)		0.141
Benzodiazepine use	4	13.8	12	19.4	0.516
Steroid use	16	55.2	36	58.1	0.795
Dexmedetomidine use	5	17.2	5	8.1	0.192
APACHE-II score, mean (SD)	7.9 (3.1)		6.6 (2.4)		0.025
Postoperative speech disability	9	31.0	11	17.7	0.154

SD, standard deviation; APACHE-II, the Acute Physiology Age and Chronic Health Examination

[a]p values of duration of surgery, duration of anesthesia, and APACHE-II score were obtained via t test, and others were obtained via χ^2 test

Table 4 Preoperative anxiety outcomes

Characteristics	Delirium (n = 29) Mean (SD)	Non-delirium (n = 62) Mean (SD)	p value[a]
HADS-anxiety, mean (SD)	5.3 (3.5)	4.3 (3.0)	0.158
HADS-anxiety > 7	7 (24.1%)	7 (11.3)	0.113

SD, standard deviation; HADS, Hospital Anxiety and Depression Scale

[a]p values were obtained via t test and χ^2 test

Outcomes of preoperative anxiety

In the patients with postoperative delirium, the mean HADS-A score was 5.3 (SD = 3.5) and seven patients (24.1%) had clinical anxiety. In patients without postoperative delirium, the mean HADS-A score was 4.3 (SD = 3.0) and seven patients (11.3%) had clinical anxiety. There was no significant difference in either HADS-A score or incidence of clinical anxiety between the two groups (Table 4).

Multivariate logistic analysis

The following variables were included in the multivariate logistic regression model: age (as a categorical variable with 5-year increments), MMSE, duration of surgery, blood loss, intraoperative dexmedetomidine use, APACHE-II score, postoperative speech disability, and clinical anxiety (HADS-A > 7). Duration of anesthesia was not included in the model because of high multicollinearity with duration of surgery. Only age (odds ratio (OR) = 1.565, 95% confidence interval (CI) = 1.057–2.317, p = 0.025) and HADS-A > 7 (OR = 4.370, 95% CI = 1.051–18.178, p = 0.043) predicted delirium onset. These variables explained 74.2% of the variance (Table 5).

In addition, we included only preoperative variables, namely age, history of delirium, MMSE, CAGE, ASA, and HADS-A > 7 in the multivariate logistic regression model. Only age (OR = 1.398, 95% CI = 1.015–1.925, p = 0.040) and HADS-A > 7 (OR = 5.399, 95% CI = 1.332–21.876, p = 0.018) predicted delirium onset, even in that model. These variables explained 71.4% of the variance (Table 6).

Discussion

In this study, the incidence of postoperative delirium was 31.9%, confirming that this is a common complication of highly invasive surgery in cancer patients, as previous studies suggested [2–6]. Multivariate analysis showed that age and preoperative anxiety predicted the development of

Table 5 Multivariate analysis of risk factors for the incidence of postoperative delirium

	Odds ratio (95% confidence interval)	*p* value
Age (5-year increments)[a]	1.565 (1.057–2.317)	0.025
MMSE[b]	0.896 (0.699–1.149)	0.387
Duration of surgery[b]	1.002 (0.995–1.009)	0.529
Blood loss[b]	1.000 (0.999–1.001)	0.784
Intraoperative DEX use[a]	1.945 (0.311–12.148)	0.477
APACHE-II score[b]	1.029 (0.825–1.284)	0.797
Postoperative speech disability[a]	0.954 (0.238–3.796)	0.942
HADS-A > 7[a]	4.370 (1.051–18.178)	0.043

MMSE, Mini Mental State Examination; DEX, dexmedetomidine; APACHE-II, the Acute Physiology Age and Chronic Health Examination; HADS-A, Hospital Anxiety and Depression Scale-Anxiety

[a]Categorical variables

[b]Continuous variables

Table 6 Multivariate analysis of preoperative risk factors for the incidence of postoperative delirium

	Odds ratio (95% confidence interval)	*p* value
Age (5-year increments)[a]	1.398 (1.015–1.925)	0.040
BMI[b]	0.957 (0.848–1.081)	0.483
History of delirium[a]	1.021 (0.122–8.565)	0.985
MMSE[b]	0.844 (0.666–1.071)	0.163
CAGE[a]	0.537 (0.112–2.574)	0.437
ASA[a]	1.377 (0.458–4.137)	0.569
HADS-A > 7[a]	5.399 (1.332–21.876)	0.018

BMI, Body Mass Index; MMSE, Mini Mental State Examination; ASA, American Society of Anesthesiology; HADS-A, Hospital Anxiety and Depression Scale-Anxiety

[a]Categorical variables

[b]Continuous variables

postoperative delirium, with an unexpectedly high odds ratio of 4.370 in multivariate analysis. The model that contained only preoperative variables showed a similar result.

This study showed that preoperative anxiety strongly predicted postoperative delirium in cancer patients. We evaluated anxiety on the day before surgery because it would be highest at that point due to the proximity to the operation. However, since it takes time to alleviate anxiety, only if it is detected early can it be considered truly modifiable and a candidate for intervention. In addition, the pathogenesis of both delirium and anxiety has been shown to involve inflammatory cytokines [24–28]. Because chronic, preexisting anxiety and anxiety related to an upcoming surgery are thought to differ in terms of molecular mechanisms and reversibility, we should have compared anxiety levels well in advance of surgery (ideally before cancer diagnosis) and on the day before surgery.

There are three main strengths to this study. First, this study is the first to propose and then prove the clear hypothesis that preoperative anxiety would affect postoperative delirium in cancer patients [18, 22]. Second, we identified and then measured the risk factors for postoperative delirium reported in previous studies [3, 12–16, 33–36] and used univariate analysis to compare them between the delirium group and the non-delirium group. Third, the quality of this study was high, in that we took into account the opinions of both anesthesiologists and surgeons when we chose the target surgeries in order to focus on highly invasive surgeries. In addition, trained psychiatrists or clinical psychologists assessed postoperative delirium on a daily basis using an international standardized criterion (DSM-5), and we could identify hypoactive delirium that is generally overlooked.

This study has several limitations. First, several risk factors that were previously correlated with postoperative delirium, such as history of delirium [32], CAGE [3, 32], ASA [3, 13–16], duration of surgery [3], and APACHE-II score [13, 16], showed no association in this study. This may be due to the small sample size or to other unidentified reasons. We should consider keeping these factors in the model and performing further studies with larger sample

sizes to validate our model. Second, we should have assessed other factors that were previously shown to affect the incidence of postoperative delirium, including calcium blockers [40], antihistamines [40], and preoperative nutrition status [12]. Third, this study included only patients with esophageal, hepatobiliary/pancreatic, and head and neck cancers, which could limit the generalizability of our results to other cancer patients. Fourth, approximately 10% of enrolled patients could not be followed up due to changes in their surgical procedures, which further reduced our sample size. Finally, our study could not clearly explain why preoperative anxiety predicted postoperative delirium because it was an observational cohort study.

Despite these drawbacks, our results provide useful information for predicting postoperative delirium in cancer patients. Specifically, the fact that preoperative anxiety was a predictive factor for postoperative delirium impacts cancer patients because it may allow us to identify those at high risk of postoperative delirium. To clarify this point, we would like to longitudinally evaluate anxiety in our next study, although it will be a challenge to identify a population in which to assess anxiety before cancer is diagnosed. Our findings also suggest that control of preoperative anxiety may be a new target for prevention of postoperative delirium, if inflammatory cytokines contribute to both psychiatric conditions. Further research with larger and more representative study populations, preferably randomized controlled trials, should assess pathophysiological factors such as inflammatory cytokines or other biological markers to examine the association between preoperative anxiety and postoperative delirium in cancer patients.

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Compliance with ethical standards

Conflict of interest The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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