

## 107. 統合失調症患者の周術期での精神症状悪化予測因子に関する研究－ 統合失調症患者の治療機会均等を目指して－

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### 概要

#### Background:

Patients with schizophrenia spectrum disorders (SSDs) have a high risk of physical illnesses requiring surgery. Postoperative delirium (POD) is a common complication in SSDs patients, often requiring psychiatric expertise for management. However, limited epidemiological data on POD in SSDs patients may hinder their acceptance in hospitals without psychiatric wards. This study aimed to investigate the incidence and risk factors for POD in SSDs patients undergoing surgery.

#### Methods:

A retrospective study was conducted at three tertiary hospitals in Japan, including 200 SSDs patients who underwent surgery between April 2017 and March 2022. Patients admitted due to psychiatric crises were excluded. Data on demographics, psychiatric history, surgical details, and POD development were collected. Statistical analysis included chi-squared tests and logistic regression to identify risk factors.

#### Results:

POD occurred in 10.5% (21/200) of SSDs patients, with only one requiring psychiatric ward admission. Most patients had schizophrenia (90.5%), and the mean age was 57.4 years. Significant risk factors for POD included age  $\geq 65$  (adjusted OR: 3.25) and smoking before admission (adjusted OR: 2.97). ICU admission showed a trend toward significance but was not statistically significant. Antipsychotic medication use or dose was not associated with POD.

#### Discussion:

The POD incidence in SSDs patients was comparable to the general population. Most POD cases were managed with psychotropic drug adjustments, suggesting that SSDs patients can be treated at general hospitals if psychiatric expertise is available.

### 背景および目的

Schizophrenia is a serious chronic illness with a high relapse rate and is frequently associated with a wide range of symptoms and disabilities<sup>1</sup>. It affects 1 in every 300 people (0.32%), with a total patient population of approximately 24 million worldwide. Patients with schizophrenia are 2–3 times more likely to die early than the general population<sup>2</sup> because of the high prevalence of various physical illnesses, including cardiovascular, metabolic, and infectious diseases, as well as reduced engagement in health maintenance practices including maintaining healthy eating habits, performing exercise, and avoiding smoking. In addition, disparities in access to treatments for physical illnesses have been associated with higher

mortality rates.<sup>3</sup> Life expectancy for SSDs patients is still short compared to the general population, while the number and percentage of elderly people in SSDs has been increasing as the population ages, resulting in increased frequency of hospitalization for the treatment of physical illnesses in this population.

Additionally, patients with SSDs are at an increased risk of various potentially illnesses, including heart disease; stroke; pancreatic, esophageal, and breast cancer; perforated appendicitis; and cataracts, which may require surgery. Postoperative delirium (POD) is a common disorder that may be accompanied by psychomotor agitation. Such delirium in patients with SSDs can be difficult to treat outside the psychiatric ward<sup>4</sup>. Moreover, patients with SSDs are often prescribed antipsychotics and benzodiazepine receptor agonists (BZRAs) upon admission and have more complex background factors than the general population; therefore, the treatment of delirium in a general ward often requires the expertise of a psychiatrist. However, lack of epidemiological data on POD in patients with SSDs may impede the acceptance of such patients in hospitals without a psychiatrist.

With the continued decline in the number of general hospitals with psychiatric beds in Japan<sup>5</sup>, this problem is becoming increasingly serious, especially in regional cities, which means that hospitals without psychiatrists need to increase their ability to manage POD in patients with SSD. Therefore, this study investigated the frequency of and risk factors for POD in patients with SSDs to improve their access to medical care.

## 方法

### Study setting and data sources

This study included patients from three tertiary care hospitals in urban Japan totaling 2395 beds. All three hospitals perform gastrointestinal, cardiovascular, respiratory, endocrine and breast, plastic, neuro, orthopedic, and pediatric surgeries and include obstetrics and gynecology, ophthalmology, dermatology, urology, and otolaryngology departments. One hospital has a transplant surgery department. All three hospitals also have psychiatric wards and consultation-liaison teams including psychiatrists, nurses, and psychologists who provide psychosocial care to patients with comorbid mental and physical illnesses admitted to the general wards. All three institutions are core hospitals in the region and accept patients with SSDs requiring surgical treatment, regardless of the type of physical illness.

### Selection criteria and outcomes

The study participants were patients with SSDs with psychiatric involvement admitted for surgical treatment at the three study hospitals between April 1, 2017, and March 31, 2022. SSDs included schizophrenia; delusional disorder; short-term psychotic disorder; schizophreniform disorder; schizoaffective disorder; substance-induced or drug-induced psychotic disorder; or psychotic disorder caused by other medical illnesses diagnosed before admission by psychiatrists managing their regular psychiatric treatment based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). The participants were consultation-liaison patients, who were admitted to the general ward for surgery and referred to the consultation-liaison team. Psychiatrists advised the surgeons regarding the management of the patients' psychiatric comorbidities. However, this study excluded patients with SSDs admitted because of worsening psychiatric symptoms, including suicide attempts, owing to unstable mental health before admission.

The main outcome of this study was the proportion of patients who developed POD. We also investigated the number of patients who required admission to the psychiatric ward after developing POD.

### Clinical data collection

During this study, psychiatrists with sufficient knowledge and experience in consultation-liaison psychiatry conducted chart reviews of all care records as well as records related to prescriptions and laboratories. Before conducting the reviews, the reviewers collected the following patient data: sex, age, smoking status, type and dose of psychotropic medication, Charlson Comorbidity Index, and psychiatric diagnosis based on DSM-5. Among psychotropic medication, the amount of chlorpromazine equivalent of antipsychotic drugs used was calculated. The living environment before hospitalization was classified as either home or outside home (psychiatric hospital or support facility).

The presence or absence of POD was determined based on DSM-5 criteria through chart review and data on the use of physical restraints, intensive care unit admission, anesthesia (general or local), emergency or planned surgery, and operative time were also collected. Long-duration surgery was defined as a surgery with a surgical time of  $\geq 180$  min, as the risk of worsening perioperative psychiatric symptoms increases beyond this cutoff. Additionally, as changes in surface morphology during surgery may affect psychological reactions, we also investigated whether the patients had undergone tracheostomy, amputation, mastectomy without reconstruction, gastrostomy, colostomy, nephrostomy, or eye resection. After identifying patients who met the criteria for developing POD during an independent review, several reviewers made a final decision on existence of delirium. In cases where it was difficult to distinguish between a worsening of SSD symptoms or the reviewers disagreed on the classification, reviewers reached consensus through discussion. The missing values were treated as normal for blood tests and none for smoking history.

### Statistical analysis

Continuous variables are presented as mean with standard deviation or medians with interquartile ranges (IQRs). Categorical variables are presented as number and percentage. We performed the chi-squared test to compare categorical variables when the expected value of each cell was  $>5$ ; otherwise, we applied Fisher's exact to assess the relationship between delirium and background factors. In conducting multivariate analysis, we selected variables based on the number of patients who developed POD from those used in the univariate analysis that were considered to be clinically closely related to the development of POD. For all statistical analyses, a two-tailed p-value of 0.05 was considered statistically significant. All analyses were performed using JMP, version 18 (SAS Institute, Cary, NC, USA).

## 結果および考察

### Results

Among 208 patients with SSDs who underwent surgery at the study sites during the study period, we included 200 patients after excluding 8 patients admitted for suicide attempts. Of these patients, 181 (90.5%) had schizophrenia, 9 (4.5%) had schizoaffective disorders, and 5 (2.5%) had delusional disorders. The mean age of the patients was 57.4 years (SD, 14.4 years), with 35.5% (71/200) of the patients aged  $\geq 65$  years and 61% (122/200) being female. The median chlorpromazine equivalent of the administered antipsychotic was 400 mg (IQR, 200–714 mg), and approximately half of patients were using BZRAs (98/200). The median operative time was 133 min (IQR, 92–208 min). Surgical duration was  $>180$  min in 76 patients (38%). A total of 121 (60.5%) patients were hospitalized from their homes.

In this study, 10.5% (21/200) of the patients experienced POD, in particular, 16.9% (12/71) of patients aged 65 years or older developed postoperative delirium. Only one of the POD patients required admission to the psychiatric ward. Univariate analysis of the factors contributing to delirium development revealed significant differences for hospitalization from outside of home (crude OR, 3.5; 95% CI, 1.34–9.13;  $p < 0.01$ ), age  $\geq 65$  years (crude OR, 2.7; 95% CI, 1.08–6.80;  $p = 0.03$ ) and Alb  $< 3.5$  (crude OR, 2.88; 95% CI, 1.14–2.23;  $p = 0.03$ ) as risk factors. Intensive care unit admission (crude OR, 2.4; 95% CI, 0.96–5.99;  $p = 0.06$ ), Smoking before admission (crude OR, 2.36; 95% CI, 0.91–6.12;  $p = 0.09$ ), and Hb  $< 12$  (crude OR, 2.23; 95% CI, 0.89–5.57;  $p = 0.09$ ), were not significantly related to the development of POD, although the p-values for the association indicated a trend toward significance. We observed no significant differences in the Charlson Comorbidity Index scores, surgery for malignancy, surgery duration of  $>180$  min, changes in surface morphology during surgery, emergency surgery, use of two or more antipsychotic medications, or antipsychotic medication dose.

As the number of patients with POD was 21, the number of factors to be included in the multivariate analysis was determined to be 3, and logistic regression analysis was performed using the three variables of age, smoking history before hospitalization, and ICU admission.

The results of analysis showed that Age  $> 65$  (adjusted OR, 3.25; 95% CI, 1.23–7.88;  $p = 0.02$ ) and Smoking before admission (adjusted OR, 2.97; 95% CI, 1.03–8.43;  $p = 0.04$ ) significantly increased the risk of developing POD. While a

similar trend was also observed among patients used the ICU, the difference was not significant (adjusted OR, 2.00; 95% CI, 0.77–5.27;  $p = 0.15$ ).

## Discussion

The incidence of POD in patients with SSDs in the present study was approximately 10%, and multivariate analysis showed that age >65 and history of smoking before admission were associated with the development of POD in patients with SSDs. In addition, although the evaluation using multivariate analysis was not possible due to the limitation of the sample size, univariate analysis showed that hospitalization from outside of home and low albumin levels were also associated with the development of POD.

## Comparisons with previous studies

In this study, the incidence of delirium occurred in 16.9% of patients aged 65 years and older and 7.0% in those 18–65 years. In previous study<sup>5</sup>, the incidence of POD was 6.3% in those 65 years and older and 2.3% in those 18–65 years, and this study, POD occurred about 3 times more than in previous study. Among problematic behaviors from a medical safety perspective in patients with SSD who had undergone surgery, Tsuji et al. reported bizarre behavior in 52.4% (11/21) of psychiatric inpatients (15 of whom had schizophrenia), and Farasatpour et al. reported that 19.6% (11/56) and 21.4% (12/56) of patients with schizophrenia verbally and physically attacked their caregivers, respectively.<sup>6,7</sup> Cooke et al. observed disruptive behavior in 29% (16/55) of patients with schizophrenia who underwent surgery for acute appendicitis.<sup>8</sup> However, these previous studies did not clarify whether these behaviors that interfered with physical treatment during the perioperative period were caused by POD, worsening of psychiatric symptoms due to SSD, or the patients' own personality traits. In this study, we were able to accurately show the frequency of POD in patients with SSD by conducting a more detailed evaluation of the psychiatric symptoms that patients with SSD presented with postoperatively, by conducting a study over a longer period of time at more facilities than in previous studies.

In our previous study of SSD patients conducted at the same facility as the present study, the frequency of worsening of psychiatric symptoms other than postoperative delirium and insomnia was 11.1%<sup>9</sup>. When combined with the results of the present study, the frequency of deterioration of the mental status of SSD patients due to POD or worsening of psychiatric symptoms due to SSD is estimated to be approximately 20%, which is similar to the frequency reported in previous studies. Compared with the previous studies, the present study focused on patients with SSDs who developed POD, and was conducted at more sites and over a longer period to ensure a larger number of eligible patients.

## Clinical significance

With regard to risk factors for POD, the same as in the general population, age, low albumin levels, ICU use, and pre-admission smoking were considered risk factors for POD in patients with SSD. On the other hand, there was no association between the occurrence of POD and the dosage of antipsychotic medication or the use of BZRAs. The use of BZRAs is generally thought to be a risk factor for postoperative delirium, though there is a report that the incidence of delirium in patients who had used BZRAs continuously during the perioperative period was not higher than in patients who had not used them at all.<sup>10</sup> In patients with SSD, they have been taking antipsychotics that may work therapeutically against delirium, which may have offset the risk of POD from the use of BZRAs.

Among the patients with SSD who developed POD, only one patient required transfer to a psychiatric ward, which was 0.05% of the total. In other words, most cases of POD in patients with SSDs could be managed by adjusting psychotropic medications, thus we believe that most cases of perioperative management of patient with SSD can be performed without problems at general hospitals with a psychiatric liaison consultation service, even if they do not have a psychiatric ward.

Healthcare providers may harbor negative views of patients with SSDs, which can prevent appropriate physical treatment for these patients. These views are presumably caused by a lack of medical resources (e.g., full-time psychiatrists engaged in consultation-liaison services and psychiatric wards able to provide perioperative management), resulting in an inadequate response when patients' psychiatric symptoms worsen during the perioperative period. As physical treatment for inpatients

with SSDs is expected to increase with population aging, the need has increased for psychiatrists to manage consultation-liaison services and psychiatric wards able to provide perioperative management in general hospitals. Additionally, hospitals should be selected based on the patient's age and place of residence before hospitalization and the use of limited medical resources in the community, thus contributing to improved access to medical care for patients with SSDs.

#### Strengths and limitations

Owing to the retrospective study design, unmeasured items could not be evaluated. Specifically, the severity of the psychiatric symptoms at the time of admission could not be evaluated using a unified scale. Additionally, the severity of cognitive impairment due to SSDs could not be assessed. Therefore, we collected information on the place of residence prior to hospitalization and antipsychotic medication dosage as indicators of psychiatric symptom severity.

Moreover, as all of the participants in this study received psychiatric interventions, it was not possible to evaluate the frequency of postoperative delirium in SSD patients who did not receive psychiatric intervention. The incidence of POD in SSD patients who did not receive psychiatric intervention during the perioperative period may be lower than that in the patients in this study, therefore the incidence of POD in SSD patients in this study might be overestimated. In order to calculate the incidence more accurately, it is necessary to conduct a survey of all SSD patients who underwent surgery with or without psychiatric intervention.

Finally, the small sample size did not allow us to include a sufficient number of variables in multivariate analysis. As the results, we could only assess the effects of a limited number of variables. However, our study involved a large sample size than previous studies, and we calculated the exact frequency of POD in SSD patients and evaluated the predictive factors. Future research is warranted to investigate a wider range of factors associated with the development of POD in patients with SSDs to determine its risk and assist with the selection of hospitals for patients with SSDs requiring physical treatment. Additionally, research is needed to determine whether hospitals without psychiatrists can manage patients with POD.

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