


ORIGINAL ARTICLE

Association between psychotropic prescriptions and the total amount of psychotropics ingested during an intentional overdose: A single-center retrospective study

Iori Tanahashi^{1,2}  | Takafumi Shiganami¹ | Takayuki Iwayama^{1,3} | Taisei Wake¹ | Sayaka Kobayashi¹ | Haruo Yoshimasu¹

¹Department of Psychiatry, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan

²The Maruki Memorial Medical and Social Welfare Center, Iruma, Japan

³Department of Psychology, Showa Women's University, Setagaya, Japan

Correspondence

Iori Tanahashi, Department of Psychiatry, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe, Saitama 350-8550, Japan.
Email: ioioiring@gmail.com

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Abstract

Aim: To investigate the association between psychotropic prescriptions and the total amount of psychotropics ingested during a subsequent intentional overdose and to examine factors related to the number of psychotropic prescriptions.

Methods: The initial sample comprised 69 patients who were admitted to the emergency department of a general hospital in Japan following an intentional overdose via psychotropic medications. We performed retrospective hierarchical multiple regression analysis with the total amount of psychotropics ingested at the overdose as a dependent variable and factors related to deliberate self-harm or overdose identified in previous studies as independent variables. We compared two models, one that did not (Step 1) and one that did (Step 2) include the number of different prescribed psychotropic medications as an independent variable in the analysis.

Results: Forty-seven patients were eligible for the analysis. The number of different prescribed psychotropic medications was associated with the total amount of psychotropics ingested at the overdose in Step 2 ($\beta = 0.40, P = .01$). There was a trend toward an association between the past number of deliberate self-harm events and the total amount of psychotropics ingested at the overdose in Step 1 ($\beta = 0.30, P = .05$), but this trend was weakened in Step 2 ($\beta = 0.15, P = .33$).

Conclusion: The number of different prescribed psychotropics appeared to influence the risk of subsequent intentional overdose through increasing the total amount of psychotropics ingested. Cumulative psychotropic prescriptions, particularly those delivered after deliberate self-harm, might be indirectly related to this risk.

KEYWORDS

drug overdose, drug prescriptions, psychotropic drugs, self-injurious behavior, suicide

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1 | INTRODUCTION

Approximately 793,000 people die each year from suicide, and the age-standardized suicide rate in 2016 was 10.5 (per 100 000 people) globally.¹ The suicide rate in Asia is relatively high.^{2,3} In Japan, the age-standardized suicide rate was close to 20 (per 100 000 people) between 1998 and 2010, although national suicide prevention strategies have led to a decreased rate in subsequent years.⁴

For each suicide, more than 20 suicide attempts are documented.⁵ The term deliberate self-harm (DSH), which encompasses intentional overdoses and self-cutting, may or may not include the intention to die because the borderline between suicidal and non-suicidal behaviors is not always clear.⁶ Regardless of an individual's intention to die, a history of DSH is a risk factor for subsequent suicide,⁷ and this risk increases with recurring DSH behaviors.⁸

Poisoning, including overdose, is the most frequent suicide attempt method.^{9,10} A greater total amount of drugs ingested during an overdose is associated with an increased risk of death, particularly when multiple drugs are used together.¹¹ Furthermore, Carter et al reported that an increase in the number of tablets and drugs ingested during a repeated intentional overdose predicted subsequent suicide.¹²

Overdose via psychotropics is common,^{10,13} may cause serious adverse events, and is sometimes fatal.^{14,15} Prescription medications are used in most intentional overdoses of psychotropics^{16,17} and several studies have examined the association between psychotropic prescriptions and overdose. The selection of a suicide method is generally thought to depend on accessibility,^{18,19} and larger medication loads are found in people who have engaged in an intentional overdose.¹⁹ Prescribed psychotropics are easily available as a means of suicide,²⁰ and furthermore, psychotropics are often prescribed after an intentional overdose episode.^{21,22}

Despite the abovementioned risks associated with prescribing psychotropic medications, few studies have quantitatively investigated the association between psychotropic prescriptions and the risk of intentional overdose. Considering that suicide method selection is related to the accessibility of options, we hypothesized that the number of different prescribed psychotropic medications that could be used as a means of overdose would be associated with the total amount of psychotropics ingested at a subsequent intentional overdose.

The objectives of this study were to investigate the association between psychotropic prescriptions and the total amount of psychotropics ingested during a subsequent intentional overdose and to examine factors related to the number of psychotropic prescriptions.

2 | METHODS

2.1 | Study design and patient population

This was a single-center retrospective study. The initial patient sample comprised 69 patients who were admitted to the emergency department at Saitama Medical Center for an intentional overdose of

psychotropics and who received a consultation with a psychiatrist between July 2013 and June 2015. Saitama Medical Center is the core general hospital of Kawagoe City, which has a population of 350,000 people, although it has no psychiatric ward. In the emergency department, all intentional overdose inpatients underwent consultations with a psychiatrist. Patients who had been hospitalized at the institution several times owing to intentional overdoses of psychotropics during the study period were enrolled only for the first hospitalization. Patients who acquired psychotropics from sources other than medical institutions were excluded from the sample. The patients' clinical data were extracted from electronic medical charts completed during their hospitalization.

2.2 | Data collection and definitions

Based on previously identified factors related to DSH or overdose, we extracted data regarding demographic factors (age,^{13,17,23} sex^{13,17,23}), past number of DSH events,⁸ psychiatric diagnosis including mood disorders^{9,24} and borderline personality disorder (BPD),²⁴⁻²⁶ recent psychotropic prescriptions received before the overdose (number of different psychotropics,¹² class of psychotropics including benzodiazepines²⁷⁻²⁹), and overdose situation (overdose with combined psychotropic and nonpsychotropic medications,¹¹ concomitant use of alcohol,^{17,30} and other methods used with overdose²⁰). We also extracted the total amount of psychotropics ingested at the overdose.

We defined DSH to include all self-injurious behaviors regardless of the intention to die. Patients were categorized according to the past number of DSH events before the overdose, irrespective of whether they led to hospitalization (as estimated from self-reports, eyewitness reports, and information from medical records), using three categories (none, one, two or more).

We obtained information regarding psychotropic prescriptions from Japanese prescription medicine record books, which provide a detailed record of each prescription issued by pharmacies, or from patient referral documents from a patient's family doctor. The tabulation of different prescribed psychotropic medications included medications that were to be taken as needed. The pharmacist belonging to the ward estimated the psychotropic medications ingested at the overdose based on the empty medicine containers that were left at the scene of the overdose. The total amount of psychotropics ingested at the overdose was defined as the total number of psychotropic tablets, capsules, and packs ingested at the overdose.

Psychotropics were classified into antipsychotics, antidepressants, mood stabilizers, anxiolytics, hypnotics, or others (antiepileptics, antiparkinson drugs, agents used for attention-deficit/hyperactivity disorder). Antiepileptics that had been approved for the treatment of mood disorders in Japan and did not appear to have been used by the patient to treat epilepsy were classified as mood stabilizers. In this study, benzodiazepines included some anxiolytics, hypnotics, and antiepileptics. An experienced psychiatrist in charge of each patient made psychiatric diagnoses during



hospitalization based on the diagnostic criteria of the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision). Patients with comorbidities were not excluded from the study.

2.3 | Statistical analysis

Continuous variables were described as means \pm SD, and categorical variables were described as numbers and percentages in the descriptive analyses.

In this study, we used a hierarchical multiple regression analysis with the total amount of psychotropics ingested at the overdose as a dependent variable. We did not use an ordinary multiple regression analysis, in which the independent variables are entered into the regression model simultaneously, because we wanted to investigate the association between the number of different prescribed psychotropic medications and the total amount of psychotropics ingested at the overdose in addition to factors indirectly associated with this amount, mediated by the number of different prescribed psychotropic medications.

Hierarchical multiple regression analysis is a variable entry method for multiple regression analyses. In this method, the order in which the independent variables are entered into the regression models is determined either theoretically or based on previous research. One of the objectives of this method is to test a hypothesis by comparing the models according to the hierarchical order of entry of the independent variables.

Considering our hypothesis that the number of different prescribed psychotropic medications would be associated with the total amount of psychotropics ingested at the overdose, we added the number of different prescribed psychotropic medications to the model into which the rest of the independent variables had been entered. Then, we compared the β of each independent variable between the two models with and without the number of different prescribed psychotropic medications.

The independent variables were entered into the hierarchical multiple regression analysis as follows. First, age and sex were adopted as demographic variables in addition to the number of different prescribed psychotropic medications. Then, the rest of the independent variables that met a criterion of $P < .10$ in the univariate regression analyses were entered into the model. Pearson's correlation analysis was also conducted for the selected independent variables. In Step 1, all of the selected independent variables other than the number of different prescribed psychotropic medications were entered into the model. In Step 2, the number of different prescribed psychotropic medications was added to the Step 1 model.

A case was considered to be an outlier if the standardized residual was three or more, and a sensitivity analysis was conducted accordingly.

Statistical analyses were conducted using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

3 | RESULTS

Among the 69 patients in the initial sample, 47 were eligible for inclusion in the analyses. Figure 1 shows the flow diagram of the study inclusion process. Table 1 shows the results of the descriptive analyses.

Table 2 shows the results of the univariate regression analyses for the factors associated with the total amount of psychotropics ingested at the overdose. BPD ($\beta = 0.28$, $P = .06$) and the past number of DSH events ($\beta = 0.36$, $P = .01$) met the criteria of $P < .10$. Both were subsequently selected as independent variables in the hierarchical multiple regression analysis, in addition to the number of different prescribed psychotropic medications, age, and sex.

The results of Pearson's correlation analysis for the five selected independent variables are shown in Table 3. The past number of DSH events was moderately positively correlated with the number of different prescribed psychotropic medications ($r = .42$, $P < .01$).

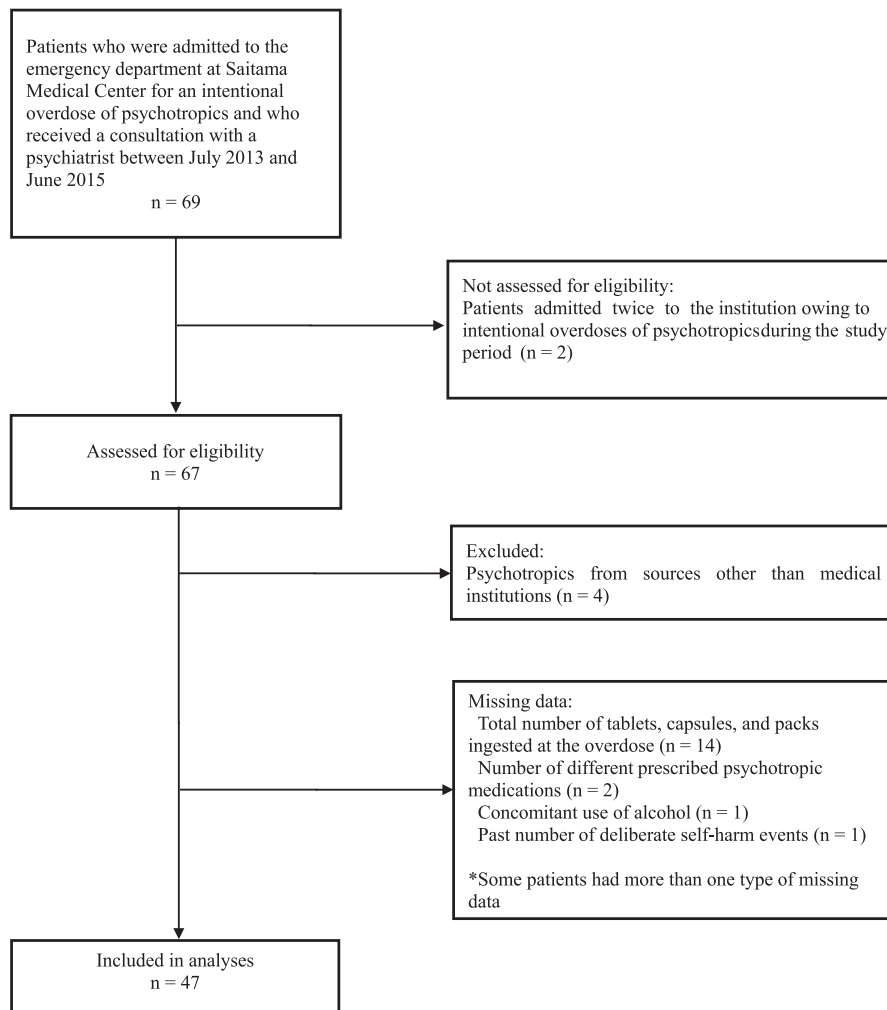
Table 4 shows the results of the hierarchical multiple regression analysis. The number of different prescribed psychotropic medications was associated with the total amount of psychotropics ingested at the overdose in Step 2 ($B = 15.19$, 95% confidence interval (CI) [3.82, 26.55], $\beta = 0.40$, $P = .01$). There was a trend toward an association between the past number of DSH events and the total amount of psychotropics ingested at the overdose in Step 1 ($B = 33.91$, 95% CI [-0.53, 68.34], $\beta = 0.30$, $P = .05$). However, this trend was weakened in Step 2 ($B = 16.91$, 95% CI [-17.65, 51.47], $\beta = 0.15$, $P = .33$).

One patient met the criteria for outliers, and so 46 patients were eligible for the sensitivity analysis. The results of the hierarchical multiple regression analysis for the 46 patients showed a tendency similar to the original analysis (Table S1).

4 | DISCUSSION

The results of Step 2 in the hierarchical multiple regression analysis indicate that among the variables tested, the number of different prescribed psychotropic medications was associated with the total amount of psychotropics ingested during a subsequent intentional overdose. This finding supports the study hypothesis and suggests that the number of different prescribed psychotropic medications was an important factor affecting the risk of overdose.

In this study, we chose the number of different prescribed psychotropic medications to reflect the amount of psychotropics that were available to the patient as a means of overdose. The total amount of psychotropics available to a patient who engages in an intentional overdose is difficult to know and depends not only on the number of different prescribed psychotropic medications, but also factors including patient adherence, prescription intervals, and total daily dose. However, the number of different prescribed psychotropic medications is likely to be somewhat proportional to the total amount of psychotropics prescribed and available as a means of overdose.

FIGURE 1 Flow diagram of study inclusion

In addition to the relationship between suicide method selection and the accessibility of options, the number of different prescribed psychotropic medications may uniquely explain a part of the study results. For instance, specific combinations of psychotropics may synergistically increase suicidality and therefore influence the total amount of psychotropics ingested at an overdose. Indeed, several types of psychotropics, such as antidepressants, benzodiazepines, and antiepileptics, have been found to induce aggressiveness³¹⁻³³ and suicide-related behavior.³⁴⁻³⁶

In the hierarchical multiple regression analysis, the trend showing that the past number of DSH events was associated with the total amount of psychotropics ingested at the overdose had weakened from Step 1 to Step 2. This finding indicates that the past number of DSH events was indirectly associated with the total amount of psychotropics ingested at the overdose, mediated by the number of different prescribed psychotropic medications. This can be interpreted to mean that when DSH occurred in the study sample, different psychotropics were often additionally prescribed and then used by the patient as a means of overdose. Consequently, the total amount of psychotropics ingested at the overdose may have increased. Individuals who repeatedly engage in DSH have high suicidality,^{8,37} making it more likely that they will ingest a higher number

of doses. Thus, the past number of DSH events could be directly related to the total amount of psychotropics ingested at an overdose. However, the hierarchical multiple regression analysis showed that the direct relationship between the past number of DSH events and the total amount of psychotropics ingested at the overdose was relatively small compared with the indirect relationship mediated by the number of different prescribed psychotropic medications.

As there is strong evidence for the efficacy of combination or augmentation psychotropic therapy for treatment-resistant depression,^{38,39} polypharmacy of psychotropics is sometimes used for individuals with severe mental conditions. However, inappropriate prescribing of psychotropics has become a worldwide problem.⁴⁰⁻⁴² For instance, Soerensen et al found that inappropriate prescribing of psychotropics occurred in 59% of psychiatric inpatients.⁴³ Furthermore, evidence regarding the effects of pharmacotherapy for individuals with personality disorders such as BPD is limited.⁴⁴

Nonetheless, there is sufficient evidence that some psychotropics can be effective in suicide prevention, including antipsychotics for the treatment of schizophrenia,⁴⁵ antidepressants for depression,⁴⁶ and lithium for affective disorders.⁴⁷ Despite the great benefits of these medications in terms of suicide prevention, care must be taken when prescribing psychotropics, particularly to patients with



TABLE 1 Patient characteristics and psychiatric diagnoses

Variables	Patients (n = 47)
Age in years, mean (SD)	38.5 (17.3)
Sex (Female), n (%)	36 (76.6%)
Past number of deliberate self-harm events, n (%)	
None	9 (19.1%)
One	13 (27.7%)
Two or more	25 (53.2%)
Overdose with combined psychotropic and nonpsychotropic medications, n (%)	21 (44.7%)
Concomitant use of alcohol, n (%)	13 (27.7%)
Other methods used with overdose, n (%)	6 (12.8%)
Number of different prescribed psychotropic medications, mean (SD)	4.4 (2.4)
Class of prescribed psychotropic	
Antipsychotics	
Prescription, n (%)	22 (46.8%)
Number of different prescribed medications, mean (SD)	1.7 (0.8)
Antidepressants	
Prescription, n (%)	27 (57.4%)
Number of different prescribed medications, mean (SD)	1.3 (0.8)
Mood stabilizers	
Prescription, n (%)	12 (25.5%)
Number of different prescribed medications, mean (SD)	1.2 (0.4)
Anxiolytics	
Prescription, n (%)	29 (61.7%)
Number of different prescribed medications, mean (SD)	1.3 (0.6)
Hypnotics	
Prescription, n (%)	39 (83.0%)
Number of different prescribed medications, mean (SD)	1.7 (0.9)
Other psychotropics [†]	
Prescription, n (%)	11 (23.4%)
Number of different prescribed medications, mean (SD)	1.5 (0.9)
Prescription of benzodiazepines, n (%)	39 (83.0%)
Total number of tablets, capsules, and packs ingested at the overdose, mean (SD)	100.4 (90.5)
Psychiatric diagnosis (DSM-IV-TR), n (%)	
Mood disorders	22 (46.8%)
Major depressive disorder	8 (17.0%)
Other depressive disorder	9 (19.1%)
Bipolar I disorder	1 (2.1%)
Bipolar II disorder	4 (8.5%)
Borderline personality disorder	13 (27.7%)

TABLE 1 (Continued)

Variables	Patients (n = 47)
Adjustment disorder	6 (12.8%)
Substance related disorder	4 (8.5%)
Schizophrenia	2 (4.3%)
Eating disorders	2 (4.3%)
Narcissistic personality disorder	2 (4.3%)
Diagnosis deferred	5 (10.6%)
Other [‡]	5 (10.6%)

Note: DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision.

[†]"Other psychotropics" include antiepileptics, antiparkinson drugs, and agents used for attention-deficit/hyperactivity disorder.

[‡]"Other" includes mental retardation, attention-deficit/hyperactivity disorder, conduct disorder, and somatoform disorders (one patient each).

TABLE 2 Univariate regression analyses for factors associated with the total number of tablets, capsules, and packs ingested at the overdose

Independent variables	β	P value
Age	-.22	.13
Sex	-.15	.31
Mood disorders	.10	.52
BPD	.28	.06
Prescription of benzodiazepines	.02	.91
Overdose with combined psychotropic and nonpsychotropic medications	.22	.13
Concomitant use of alcohol	-.02	.91
Other methods used with overdose	.19	.20
Past number of DSH events	.36	.01
Number of different prescribed psychotropic medications	.51	<.001

Note: Bold letters indicate $P < .10$.

Abbreviations: BPD, borderline personality disorder; DSH, deliberate self-harm.

a history of DSH, because the risk of suicide by overdosing with prescribed psychotropics may increase.

Nonpharmacotherapeutical approaches for suicide prevention may carry a lower risk in some cases. Some forms of psychotherapy after suicide attempts and intentional overdoses have been found to be effective for suicide prevention.^{48,49} However, in primary care, it is more difficult for patients to access psychotherapy compared with pharmacotherapy.⁵⁰ Indeed, previous studies have indicated that improving the accessibility of psychotherapy should be a priority.^{51,52}

Techniques for measuring polypharmacy of psychotropics are also important. In general, restricting access to a means of suicide

TABLE 3 Pearson's correlations among the five selected independent variables

	1	2	3	4	5	
1. Age	-	0.10	-0.40	**	-0.18	-0.22
2. Sex		-	0.12		-0.05	-0.12
3. BPD			-	0.34	*	0.25
4. Past number of DSH events				-	0.42	**
5. Number of different prescribed psychotropic medications					-	

Abbreviations: BPD, borderline personality disorder; DSH, deliberate self-harm.

* $P < .05$, ** $P < .01$.

TABLE 4 Hierarchical multiple regression analysis to predict the total number of tablets, capsules, and packs ingested at the overdose (n = 47)

Step	B	95%CI	β	P value
1. $F = 2.36$, Adjusted $R^2 = .11$				
Age	-0.57	[-2.17, 1.04]	-.11	.48
Sex	-23.48	[-83.50, 36.55]	-.11	.43
BPD	24.88	[-39.50, 89.26]	.12	.44
Past number of DSH events	33.91	[-0.53, 68.34]	.30	.05
2. $F = 3.62^{**}$, Adjusted $R^2 = .22$, $\Delta R^2 = .12$				
Age	-0.33	[-1.84, 1.18]	-.06	.66
Sex	-16.42	[-72.69, 39.86]	-.08	.56
BPD	19.19	[-41.06, 79.43]	.10	.52
Past number of DSH events	16.91	[-17.65, 51.47]	.15	.33
Number of different prescribed psychotropic medications	15.19	[3.82, 26.55]	.40	.01*

Note: Sex: female = 0, male = 1; BPD: absence = 0, presence = 1; past number of DSH events: none = 1, one = 2, two or more = 3.

Abbreviations: BPD, borderline personality disorder; DSH, deliberate self-harm.

* $P < .05$, ** $P < .01$.

is an effective strategy for suicide prevention,¹⁸ including suicide by overdose. Legal restrictions on prescriptions have reduced the use of pharmaceutical drugs,⁵³ deaths by suicide, suicide attempts, and the total number of drugs ingested at overdose.⁵⁴ Special education for medical staff may be effective in reducing polypharmacy of psychotropics. Ungvari et al reported that an educational program changed prescription behaviors in a rehabilitation facility for chronic psychiatry patients.⁵⁵

This study has several limitations. First, we did not assess the severity of mental conditions in the patients, which could influence the number of psychotropic prescriptions and the total amount of psychotropics ingested during an intentional overdose. Further studies that examine the severity of mental conditions are needed to confirm the results of this study. Second, although data from 47 patients were eligible for statistical analyses, a larger sample size is needed to obtain a more statistically stable model. Third, the data were from a single Japanese general hospital, so there might be a selection bias caused by the study location. Furthermore, medical insurance systems and laws regulating psychotropics vary by country, and these factors may affect prescription behaviors. Further multi-center and multi-country

studies are needed to address this. Fourth, empty medicine containers discovered at the scene of the overdose were used to measure of the total amount of psychotropics ingested. However, in many clinical settings, the method for measuring this information may be inaccurate. Blood drug levels are necessary to determine the precise intake. Fifth, because the study was retrospective, follow-up assessments were not conducted. Prospective studies could investigate psychotropic prescriptions before and after each DSH, as well as measuring the levels of prescribed psychotropics ingested at overdose events.

5 | CONCLUSIONS

The data suggest that the number of different prescribed psychotropic medications is an important factor affecting the risk of intentional overdose and that the number of previous DSH events might be indirectly related to this risk because additional psychotropics are often prescribed after DSH events.

Thus, psychotropics must be prescribed carefully, particularly to patients with a history of DSH. Precise diagnostic methods and



evidence-based pharmacotherapy are important for reducing the risk of suicide, and psychotherapy should be proposed as an alternative to pharmacotherapy when appropriate.

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CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Iori Tanahashi contributed to the design of the study and drafting of the manuscript. Iori Tanahashi and Takafumi Shiganami collected the data. Iori Tanahashi and Takayuki Iwayama conducted the statistical analysis. Taisei Wake, Sayaka Kobayashi, and Haruo Yoshimasu participated in the interpretation of data for the study. All authors contributed to the critical revision of the manuscript and approved the final version of the manuscript to be published.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEW BOARD

This study was approved by the ethics committee at Saitama Medical Center.

INFORMED CONSENT

The requirement to obtain informed consent was waived in this study because the data were retrospectively extracted from electronic medical charts.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

Not applicable.

ANIMAL STUDIES

Not applicable.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy and ethical restrictions. The raw data belonged to the present study cannot be made publicly available, because the disclosure of personal data was not included in the research protocol of the present study.

ORCID

Iori Tanahashi  <https://orcid.org/0000-0003-1657-2102>

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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