









RESEARCH ARTICLE



Costs of psychotropics for outpatients with bipolar disorder in Japan; the MUSUBI 2016 survey

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ABSTRACT

Background: Although the costs of bipolar disorder (BD) treatments are associated with local and universal factors, data from non-Western countries remain limited. The associations between clinical features and costs of outpatient pharmacotherapy have not been well characterized. To estimate the costs of outpatient BD treatments and their associations with clinical features in a Japanese population, we investigated with special reference to the costs of medicines constituted the bulk of the total healthcare expense and were steadily increasing.

Methods: The Multicenter Treatment Survey for Bipolar Disorder (MUSUBI) retrospectively evaluated 3130 patients with BD who visited 176 Japanese psychiatric outpatient clinics in 2016. Clinical features and drug prescriptions were recorded, and the total daily costs of psychotropic drug treatment were calculated. The annual medical costs related to outpatient BD treatments in Japan were estimated based on the corresponding demographics. The associations between daily medical costs and patients' clinical features were analyzed using multiple regression analysis.

Results: The daily costs of psychotropic drugs ranged from zero to JPY3245 (mean, JPY349 equivalent to USD32.5) and were exponentially distributed. The annual costs for outpatients BD treatments were approximately 51.9 billion Japanese yens (519 million US dollars). Subsequent multiple regression analysis revealed that social adjustment, depressive symptoms, age, rapid cycling, psychotic symptoms, and comorbid mental disorders correlated strongly with the daily cost of psychotropic drugs.

Conclusion: The estimated annual costs for outpatient BD treatment in Japan were equivalent to those in OECD countries (except for the US) and higher than those in some Asian countries. The cost of psychotropic treatments was associated with individual characteristics and psychopathological conditions.

KEY MESSAGES

- Psychotropic treatment for an outpatient with bipolar disorder has a daily cost approximately JPY350.
- The annual outpatient treatment cost for bipolar disorder in Japan was estimated to 51.9 billion Japanese yen in 2016.
- Individual characteristics and psychopathological conditions affected the cost of drug treatment.

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Introduction

Bipolar disorder (BD) is a common mental disorder with a long fluctuating course and a range of psychiatric symptoms. The costs associated with treatment

for BD constitute a global burden [1]. Although most BD patients are treated in outpatient clinics [2], outpatient treatment costs have been less studied than those related to inpatients [3]. As pharmacotherapy is the main therapeutic strategy for outpatient

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treatments, the costs of psychotropic drugs are a large component of the total costs of outpatient treatments for BD.

Several studies have focused on the direct and indirect costs related to BD [1,3]. In general, the costs of treatments are likely to reflect socioeconomic and cultural fundamentals in addition to medical demands. Because each country has a unique medical system, global data are required to clarify which specific costs for BD are related to the medical system (local) and which are directly derived from the disease (universal). However, the cost of BD treatment has been reported mostly in Western countries [1,3]. Although data from other countries and regions have more recently become available, the topic has not been sufficiently researched yet. To date, there have been no reports on this issue from Japan. In the Japanese national health system, the proportion of the total costs that is directly attribute to medicines is significant and has been steadily increasing [4]. Thus, it is of interest to rigorously examine the regional differences in BD treatment costs.

Furthermore, in clinical settings, patients with BD tend to receive tailored treatments over a long course of illness. Different treatments can be prescribed to a single patient, owing to fluctuating symptomatology. Few studies have demonstrated an association between comprehensive clinical features and pharmacological costs.

The Members of the Japanese Association of Neuro-Psychiatric Clinic (JAPC) are treating approximately 30% of patients with mood disorders in Japan [2]. The JAPC has collaborated with the Japanese Society of Clinical Psychopharmacology in a nationwide clinical survey, the Multicenter Treatment Survey for Bipolar Disorder (MUSUBI) 2016 to investigate the pathophysiology of BD and evidence-based treatments for the disease [5–9]. The current study aimed to determine the costs of outpatient treatment for BD and their association with clinical features in a Japanese population.

Participants and methods

Patients with BD who visited a nationwide network of psychiatric outpatient clinics (the JAPC member clinics) were surveyed between September and October 2016. The survey was performed using large-scale, multi-institutional, cross-sectional, and consecutive sampling procedures [5–9]. Psychiatric status and pharmacological treatments being received at the term of the survey were assessed by the consultant

psychiatrists, who voluntarily collaborated with the survey.

A total of 3130 patients with BD who visited one of the 176 JAPC member clinics were retrospectively and consecutively investigated with regard to individual characteristics, BD presentation, and prescribed psychotropic medications. BD diagnosis was performed according to the ICD-10 classification of mental and behavioral disorders [10]. Detailed procedures on the demographic characteristics and BD presentation at the time of the survey have been described elsewhere [5,6,9].

Clinical characteristics

Briefly, demographic characteristics included sex, age, years of education, current occupational status, and level of social adjustment assessed though a 4-point scale [11]: excellent (Global Assessment of Functioning [GAF] > 81, good (80 > GAF > 61), insufficient (60 > GAF > 41), and poor (GAF < 40). BD presentation comprised age at onset, duration of follow-up, comorbid mental disorders (e.g. dementia, autisms, or personality disorders), rapid cycling, and psychopathological status (including the presence of euthymia, and five symptoms: depressive state, manic state, psychotic state, substance misuse, and suicidal ideation) on a 4-point scale [7,12].

Prices of psychotropic drugs prescribed

Five classes of psychotropic drugs were prescribed: mood stabilizers, antipsychotics, antidepressants, anxiolytics, and hypnotics. The identity of each prescribed drug and its daily dosage at the time of the survey was recorded. The daily costs associated with each psychotropic drug were calculated in accordance with the 2016 official drug formulary for the Japanese National Health Insurance [13], discriminating between branded and generic medications. The price range for main psychotropic drugs prescribed (per tablet) was as follows: mood stabilizers, JPY5.6 (carbamazepine 100 mg) – JPY232.7 (lamotrigine 100 mg); antipsychotics, JPY5.6 (levomepromazine 25 mg) – JPY489.8 (olanzapine 10 mg); antidepressants, JPY6.5 (amoxapine 10 mg) – JPY282.0 (mirtazapine 30 mg); anxiolytics, JPY5.0 (lorazepam 0.5 mg) – JPY49.7 (tandospirone 20 mg); and hypnotics JPY5.4 (nitrazepam 5 mg) – JPY107.9 (svorexant 20 mg) (Supplementary table) [13]. Psychotropic drugs launched in the middle 2000s or later were considered as ‘new’ to the market at the time of the study.

In cases where there were multiple possible prices for a given medication, the most reasonable (common) combination of tablet types was chosen for the calculations (e.g. for lithium 400mg (200mg \times 2 rather than 100mg \times 4), for duloxetine 60mg (30mg \times 2 rather than 20mg \times 3), and for nitrazepam 10mg (10mg \times 1 rather than 5mg \times 2 or 2mg \times 5). The total cost of daily psychotropic drugs for each patient was ranked by every 100 JPY (converted to 1USD based on 2016 rates).

Annual outpatient costs related to BD treatment were estimated based on the psychopharmacological costs as well as physician and dispensing fees. The psychopharmacological costs comprised the prices of the psychotropic drugs and the costs derived from related blood concentration measurements. Physician fees comprised general administration fees and basic psychotherapy charges. We estimated the national costs of outpatient BD treatments based on populations with BD in JAPC clinics and throughout Japan, using data from the current survey and the MUSUBI pilot study [2].

Reliability for evaluations

The characteristics of psychiatrists who treated and evaluated the patients with BD have been presented elsewhere [9]. Briefly, the current study included 176 consultant psychiatrists with a mean age of 57.5years (standard deviation [SD] 8.7) and an average of 29.8years (SD 8.6) of experience as psychiatrists. The reliability of the BD diagnoses and the validity of psychiatric evaluation procedures have been previously confirmed [12].

Data analysis

Binary or categorical data were compared using the Mann-Whitney *U* test. Relationships with rank-ordered data were analyzed using Spearman's rank-order correlation. Multiple linear regression analysis with backward elimination was used to identify the parameters associated with the daily cost of psychotropic drugs. Statistical significance was set at $p < .05$. All statistical analyses were performed using Statistical Package for Social Sciences 14.0 (SPSS Inc., Chicago, IL, USA).

Ethics

The study was approved by the ethics committees of JAPC and Kyorin University and was conducted in accordance with the Declaration of Helsinki. This

retrospective survey was performed using clinical records and no invasive procedures were performed. The participants were informed of their ability to opt out of the study.

Results

Characteristics of the outpatients with BD

The characteristics of the participants in this study have been reported elsewhere [5,9]. This study included 3130 patients with BD (1420 men and 1710 women) with a mean age of 49.6years (SD 7.4years). The mean number of years of education was 13.6years. The employment rate (including school attendance) was 65.7%. Patients had attended these clinics for a mean of 7.3years (SD 4.2years). Social functioning was excellent in 1008 patients, good in 1410, insufficient in 605, and poor in 88. At the time of the survey, 1292 patients presented with euthymia, 1267 with depressive, 268 with manic, and 303 with mixed states. The total score for psychiatric symptoms ranged from 0 to 8 (mean: 1.1, SD: 0.7, median: 1). The number of valid answers for each item differed across patients and questions.

Psychotropic drug prescriptions and daily costs

The total number of psychotropic drugs prescribed for each patient ranged from 0 to 12 (mean 3.6, SD 1.8), comprising 0–5 mood stabilizer (mean 1.1, SD 0.7), 0–4 antidepressants (mean 0.5, SD 0.7), 0–4 antipsychotics (mean 0.7, SD 0.7), 0–3 anxiolytics (mean 0.4, SD 0.6), and 0–5 hypnotics (mean 0.9, SD 0.8).

The daily costs of prescribed psychotropic drugs ranged from zero to JPY3245 (mean JPY349, SD JPY351.8, median JPY201–300, mood 1–100). The distribution of the daily costs is shown in Figure 1. The daily cost was significantly correlated with the number of psychotropic drugs prescribed ($r = 0.583$, $p < .001$).

Estimated costs of outpatient BD treatments in Japan

For outpatients with BD, the total cost of psychotropic drugs was JPY350 per day, corresponding to JPY10500 per month and JPY126000 per year. Serum concentrations of lithium, valproate, and carbamazepine, are measured once every two years in JAPC clinics at a cost of JPY4000 approximately. Thus, the annual drug administration cost for these drugs was estimated at JPY128000.

After considering the physician's consulting fees (JPY5000 per month, including a basic psychotherapy

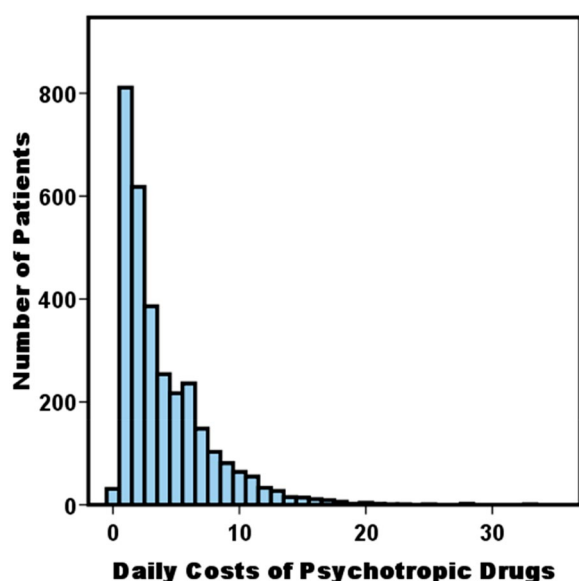


Figure 1. Distribution of daily costs of psychotropic drugs. The X axis shows the daily costs of psychotropic drugs, ranked by every JPY100 (USD1 in 2016). The Y axis shows the number of patients. The total number of patients was 3130; 800 patients were 25.6% of total, 600 patients were 19.2%, 400 patients were 12.8%, and 200 patients were 6.4%. The daily costs of psychotropic drugs ranged JPY0-JPY3245 (mean, 349, median 201–300, mode 1–100). The distribution was exponential. Seventy-four percent of the patients were treated with five drugs or less.

fee) and dispensing fees (JPY4000 per month), the annual medical costs for an outpatient receiving BD treatments were estimated to be approximately JPY236000 (USD2360), not including fees for additional examinations or special psychotherapy.

As each JAPC member clinic treats a mean of 40 patients with BD every month [2], annual medical costs for BD treatment in each clinic were estimated to be 9.44 million Japanese yens (JPY236000×40). The total annual costs for BD treatment in the 1650 member clinics from the JAPC network was approximately 15.58 billion Japanese yens (9.44 million × 1650, corresponding to 156 million US dollars). Since the JAPC member clinics treat approximately 30% of all patients with BD in Japan [2], the annual medical costs for outpatients with BD in Japan was estimated to be approximately 51.93 billion Japanese yens (15.58 millions × 100/30, corresponding to 519 million US dollars).

Costs of psychotropic drugs according to clinical features

The variation in the daily costs according to specific clinical features are shown in Table 1.

Among the general characteristics of patients with BD, age, years of education, occupational status, and social adjustment were significantly correlated with the daily cost of psychotropic drugs.

Regarding BD presentation, age at onset, years of attendance to JAPC clinics, rapid cycling phenomena, and comorbid mental diseases showed statistically significant correlations with the daily medication cost. Regarding present psychiatric status, the presence of euthymia and the severity of psychopathology (depression, psychosis, suicidal ideation, and total score) were significantly correlated with the daily costs.

The clinical variables that showed statistically significant associations with daily costs were entered into the initial model for multiple regression analysis. After implementing step-wise elimination procedures, the final model showed that seven variables (social adjustment, depressive symptoms, age, rapid cycling, psychotic symptoms, and comorbid mental disorders) best correlated with the daily cost of psychotropic drugs ($R=0.335$, adjusted $R^2=0.109$, $F=30.172$, $p=.000$; Table 2), although the correlations was not statistically significant for comorbid mental disorders. Social maladjustment, presence of rapid cycling, and severe depressive symptoms were closely associated with increased medication costs (adjusted beta > 0.1); and younger age and severe psychotic symptoms were also significantly associated with increased costs.

Discussion

The current study demonstrated that an outpatient with BD in Japan is treated with 3.6 psychotropic drugs on average, which have an associated cost of approximately JPY350 per day. This is the first nationwide survey to show the direct medical costs of outpatient BD treatments in Japan.

At the time of the survey, the majority of patients were well-managed with low medical costs. As many patients maintained euthymia, the medical costs of BD treatments were kept reasonably low. The costs of treating patients with symptomatic BD would be much higher. Frequent use of conventional psychotropic drugs, such as lithium, valproate, and carbamazepine as mood stabilizers; sulpiride, haloperidol and levomepromazine as typical antipsychotics; tricyclics and tetracyclics as antidepressants; and benzodiazepines as anxiolytics or hypnotics reduced the costs of BD treatment in the JAPC clinics [5,6]. While the use of these drugs has been often discouraged owing to their lower tolerability, the psychotropic effects and the

Table 1. Relationship between clinical features and daily cost of psychotropic drugs.

	Percent of total patients (n=3130)	Mean daily costs of psychotropic drugs (JPY)	Statistic	p
Individual characteristics				
Sex (men/women)	45.5/54.5	343/352	$z = -0.663$.507
Age at time of survey			$r = -0.163$	<.001
Education level (junior high s/high s/college/university/postgraduate)	5.0/44.4/8.7/33.9/3.2	299/353/352/349/398	$r = 0.044$.017
Occupation (nil/exist)	34.3/65.4	380/332	$z = -1.63$.090
Social adjustment (excellent/good/insufficient/poor)	32.2/45.0/19.3/2.8	246/372/444/484	$r = 0.263$	<.001
Bipolar Disorder characteristics				
Age of onset			$r = -0.107$	<.001
Clinic follow-up years			$r = -0.043$.017
Comorbid mental disorders (nil/exist)	80.4/19.3	339/387	$z = -3.34$.001
Rapid cycling (nil/exist)	87.5/10.5	329/497	$z = -7.46$	<.001
Present mental status				
Euthymia (yes/no)	38.4/61.6	278/392	$z = -10.48$	<.001
Depressive (nil/mild/severe/very severe)	49.8/36.2/13.4/0.6	284/381/497/455	$r = 0.238$	<.001
Manic (nil/mild/severe/very severe)	81.7/15.9/2.4/0.03	353/316/397/450	$r = -0.024$.172
Psychotic (nil/mild/severe/very severe)	92.4/7.1/0.4/0.03	340/457/557/450	$r = 0.090$	<.001
Substance misuse (nil/mild/severe/very severe)	94.6/4.8/0.6/NA	347/368/385/NA	$r = 0.018$.313
Suicidal idea (nil/mild/severe/very severe)	89.2/9.6/1.1/0.1	333/461/561/1300	$r = 0.147$	<.001
Total of the 5 symptoms			$r = 0.214$	<.001

Statistics: z, Mann-Whitney U test, r, Spearman rank correlation coefficient.

Table 2. Variables associated with costs of psychotropics in the outpatients clinics.

Final (7th) step	Unstandardized coefficients		Standardized beta	t	P
	B	SE			
Age	-0.022	0.005	-0.087	-4.782	<.001
Rapid cycling	1.232	0.206	0.109	-5.987	<.001
Depressive symptoms	0.529	0.107	0.109	4.945	<.001
Psychotic symptoms	0.623	0.226	0.051	2.777	.006
Social adjustment	0.537	0.102	0.120	5.288	<.001
Comorbid mental disorders	-0.301	0.167	-0.033	-1.804	.071
(constant)	4.131	0.263		15.707	<.001

Multiple regression analysis.

adherence of the patients to the treatment appeared to be satisfactory, since most patients had been treated at the clinic for long periods under stable conditions [7]. Novel psychotropic drugs recommended by recent treatment guidelines, such as lamotrigine as a mood stabilizer, atypical antipsychotics, new antidepressants and non-benzodiazepine hypnotics are likely to increase treatment costs considerably [14].

Estimated annual costs of outpatient BD treatments in Japan

Annual treatment costs for an outpatient with BD in Japan were estimated to be approximately JPY236000 (USD2360). Direct costs for BD treatments in Western countries have been reported to range from USD4521 to USD21523 in the US for the 1999–2008 period [1]

and approximately GBP3911 (USD6258) in the UK during the 2010–2011 period [15]. Additional studies have examined more specific issues such as the costs of treating comorbid somatic conditions [16] and that of specific drugs [17]. Recent studies have also reported medical costs in non-Western countries, expanding our knowledge of global medicine and public health, with USD3200 reported as an annual cost in Taiwan during 2008 [18], USD134 in India during 2014 [19], and USD1284 in Indonesia during the 2016–2018 period [20].

The annual costs associated with psychotropic drugs in Japan (approximately JPY126000, or USD1260) were roughly equivalent to those for BD-II treatments in Australia during 2010 (AUD1405, or USD1293) [21], BD treatments in Spain during 2007 (EUR1280 or USD1792) [22], and BD treatment in Italy during the 2008–2009 period (EUR1145 or USD1603) [23]. Since the 2000s, many novel psychotropic drugs for BD treatment have been introduced, and treatment guidelines have been revised accordingly [4]. The increased use of newly developed drugs, which are more expensive than traditional drugs, is likely to inflate the direct costs of BD outpatient treatment, while the total costs (including inpatient and indirect costs) need to be considered comprehensively. Khan et al. [24] demonstrated a steady increase in the cost of medications in the US. Another consideration is that metabolic diseases and subsequent comorbid problems may also increase owing to the prescription of new psychotropic drugs [16]. Furthermore, indirect costs can be 2–5 times higher than direct treatment costs [4,25].

Associations between medication costs and patient clinical features

The costs of psychotropic drugs are distributed exponentially, suggesting multiple associations with various clinical factors such as individual vulnerability, long duration of illness, complicated and intractable symptoms, and the introductions of new drugs. Polypharmacy leads to higher costs and is likely to be an indicator of poor social functioning as well as of longer disease duration [9].

Characteristics of patients

Patient age was inversely associated with the cost of psychotropic drugs, which may be due to the multiple compounded conditions. Psychopathological symptoms tend to stabilize with aging [26]. Patients with a long remission period were likely to have been prescribed conventional psychotropic drugs because their symptoms subsided and a longer remission was associated with fewer prescribed psychotropic drugs and lower dosage. In addition, job-related stress which often aggravates psychopathological symptoms, decreases after retirement [27]. The dosage of prescribed psychotropic drugs can be reduced in the elderly to avoid adverse physical effects, [28]. The ability to afford copayment (ranging from 10% to 30% according to age and income) is likely to be reduced due to decreased income or increased medical costs associated with poor physical condition [28].

The level of social functioning showed the strongest association with the costs of psychotropic drugs. These findings are in line with studies showing that social functioning is a key factor in the cost of treatment [29]. The level of social adjustment can be regulated to varying degrees, based on individual capacity, personality, severity of illness, and socioeconomic conditions. As social functioning can either be a cause or result of pharmacotherapy, it is impossible to characterize a causal association through a cross-sectional survey. In addition, social functioning can be associated with demographic factors, such as age, sex, and occupation [30].

Characteristics of BD

The cost of psychotropic drugs is higher in patients with rapid cycling phenomena due to the presence of intractable symptoms [7,31]. Since drugs that were prescribed previously cannot control the phases effectively in these patients, new and more costly drugs are

likely to be introduced. Patients whose BD symptoms responsive to lithium treatment tend to have a preferable socioeconomic status [32]. Switching from traditional mood stabilizers (i.e. lithium, valproate, or carbamazepine) to lamotrigine increases the cost of treatment approximately twentyfold (e.g. JPY18 for lithium 400mg vs. JPY466 for lamotrigine 200mg).

Furthermore, psychopathology can play a significant role in cost determination. Among the psychopathological symptoms considered, depressive and psychotic symptoms showed statistically significant associations with medication costs. In the long course of BD, a depressive state can be the dominant presentation, and this is a painful phase in most patients [4]. Depressive states tend to induce further symptoms, including anxiety, irritations, insomnia, and various somatic complaints; and these symptoms often require additional pharmacological treatments. Many studies have shown the relatively high costs of treatment for depressive states [21,25]. In contrast, patients in a hypomanic state may have fewer complaints under exhilarating moods. Several guidelines on BD treatments recommend the use of newer and more expensive antidepressants rather than traditional antidepressants for preventing manic episodes. A psychotic state is often difficult to treat and can have serious consequences. However, psychotic symptoms occur infrequently compared to other symptoms. To control intractable psychotic symptoms that are resistant to conventional drugs, newer antipsychotic drugs associated with higher costs are needed.

Limitations

This study has several limitations that should be considered. First, official market prices for drugs changed every two years (every year at present) based on Japanese health insurance regulations; thus, the costs of psychotropic drugs recorded during the 2016 survey may have changed as a result. However, the principles of drug price setting in Japan have not changed substantially during the implementation period of the current study, and the market prices of novel drugs has been maintained for approximately ten years. Second, while the large sample size and nationwide distribution of the participating clinics are the strengths of this study, our findings may not be representative of the entire population with BD. For example, the number of severely intractable patients in outpatient clinics may be lower than in hospitals. The costs for inpatients receiving treatment for BD are necessarily high, although patients admitted to psychiatric wards

account for 3%–5% of the population with BD in Japan. Third, the current study analyzed the costs of five classes of psychotropic drugs but did not include all the psychotropic drug available for f BD-related states. For example, drugs normally used to treat dementia, developmental disorders, or alcohol abuse, which are sometimes prescribed to treat BD but were not included in the current study. Drugs used to treat the adverse effects of psychotropics were not included either. Fourth, the factors associated with drug costs in this study accounted for approximately 10% of the total variances, suggesting that unevaluated factors strongly affected the costs. Additional factors need to be examined in future studies. Fifth, the estimated annual costs may vary with prescription changes. However, as patient conditions change unpredictably (better, worse, or unchanged), treatment costs can be expected to show the same unpredictable variations. Thus, daily costs based on large datasets may be used as an approximate estimate of the annual costs.

Conclusion

The current study estimated an individual daily cost of approximately JPY350 for outpatient treatment of BD, and an annual costs of 51.9 billion Japanese yens in the entire country. Medication costs were associated with individual characteristics and psychopathological symptoms. Further prospective studies will reveal the cost-effectiveness of current treatment practices. Our findings will guide and inform future research, medical and public health guidelines, and policy considerations relevant to BD treatment.

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Author contributions

NA prepared the original draft of the article. NA, TA, KE, EG, SH, EK, YK, KM, HU, and YW conducted data collection and curation. NA, MK, TK, AN, TT, KW, NYF, and RY performed data analysis and supervising. All authors participated in designing the study, interpreting data, and reviewing the manuscript.

Ethical approval

The study was approved by the JAPC and Kyorin University's ethics committees and was conducted in accordance with the Declaration of Helsinki. This retrospective survey was performed using clinical records and no invasive procedures

were performed. The patients were informed of their ability to opt out of the study if any personal identifiable information was abstracted.

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Data availability statement

Anonymized data not published within this article will be made available by request from any qualified investigators if approved by our institutional ethical committees.

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