

1 **Title**

2 An analysis of factors associated with compliance and dropout of sublingual
3 immunotherapy on Japanese cedar pollinosis patients

4

5 **Short title**

6 Factors linked to SLIT compliance and dropout

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38 The authors declare no conflicts of interest associated with this manuscript.

39

40 **Keywords**

41 Allergic rhinitis, dropout, Japanese cedar pollinosis, medication compliance, sublingual

42 immunotherapy

43

44 **Abbreviations**

45 ATC, Anatomical Therapeutic Chemical; CCI, Charlson Comorbidity Index; CI, confidence interval;

46 JC, Japanese cedar; JCPE, standardized Japanese cedar pollen extract; JMDC, Japan Medical Data

47 Center Co. Ltd.; HR, hazard ratio; NDB, National Database of Health Insurance Claims and Specific

48 Health Checkups of Japan; RCT, randomized clinical trial; SE, standard error; SLIT, sublingual

49 immunotherapy

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Abstract

Background: Sublingual immunotherapy (SLIT) is safe and effective but compliance is problematic. We evaluated dropout and compliance among adults (≥ 20 years of age) and adolescents (< 20 years of age) for Japanese cedar pollen extract (JCPE), an aqueous SLIT approved in 2014 in Japan.

Methods: Administrative claims data on 1,236 Japanese patients, 846 adults (mean age, 43.0 years; 41.8% female) and 249 adolescents (mean age, 14.1 years; 36.6% female), with JCPE prescription between October 2014 and June 2016 were reviewed. Adults and adolescents were divided according to the year they started SLIT (1- and 2-year cohorts) to calculate dropout and compliance and identify associated factors using multivariate Cox and linear regression models.

Results: In 1- and 2-year adult cohorts, dropout rates were 13.5% and 22.1% and compliance rates were 92.8% and 88.8%, respectively. Adolescents had higher dropout and lower compliance. Patients 40-59 years of age had a lower dropout risk than patients 20-29 years of age. Dropout hazard ratios (95% CI) in 1- and 2-year cohorts were 0.26 (0.12-0.58) and 0.40 (0.17-0.93) in patients 40-49 years of age and 0.32 (0.14-0.75) and 0.35 (0.13-0.92) in patients 50-59 years of age, respectively. Younger age contributed to lower compliance in 1- and 2-year adult cohorts ($p=0.001$ and $p=0.02$, respectively). Systemic steroidal medication history and male gender were positively associated with compliance in adults but not in adolescents.

71 **Conclusion:** High dropout rate was associated with younger generations. Compliance in adults, but

72 not in adolescents, was associated with age, systemic steroidal medication history, and gender.

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Introduction

Sublingual immunotherapy (SLIT) is an allergen-specific immunotherapy used to treat a range of environmental allergies and asthma.¹⁻⁴ SLIT has a lower risk of severe adverse events such as systemic allergic reaction as compared with that of subcutaneous immunotherapy (SCIT), thereby allowing more patients to undergo treatment at home.⁵

In contrast, self-management is needed for SLIT administration whereas SCIT is managed by a physician's office. Consequently, SLIT adherence is poorly monitored, resulting in a higher dropout rate and lower compliance as compared to those in SCIT in a real clinical setting.⁶⁻⁹ The rates of dropout within 3 years range between 14% and 93%, but there are large differences among the calculation methods or study designs.⁸⁻¹⁵ Apparently, the dropout rates are lower in randomized controlled trials (RCTs) than in observational studies; in a meta-analysis, the RCT composite dropout rate was reported as 12%.¹⁰

SLIT compliance has also been investigated in observational studies. Reported compliance varied among studies, partly because of differences in the calculation methods. In the Netherlands and Spain, the compliance rates ranged from around 50% to more than 90%.^{9,16} Malet *et al.* reported that the proportion of adult patients with good compliance (> 80%) was 78.1% over 1 year according to real-world data in Spain.¹⁶

In Japan, the first aqueous SLIT drug, standardized Japanese cedar (JC) pollen extract

(Cedartolen®, Torii Pharmaceutical Co., Ltd., Tokyo), was approved and available on the market in October 2014. Japan adopts a universal healthcare system and standardized JC pollen extract (JCPE) is covered by Japanese health insurance. In Japan, JC pollen is the most common pollinosis-causing antigen, affecting more than two million JC pollinosis patients, a number that increases every year.¹⁷⁻¹⁹ Large JC pollen quantities are scattered far from trees in a short annual period, most commonly peaking during April.^{19,20} Typically, SLIT is initiated before the JC pollen season.

In a randomized clinical trial (RCT) of JCPE treatment conducted in Japan, dropout rates in the first and the second year were reported to be 2.4% and 8.7%, respectively.²¹ This dropout rate is low and similar to that reported in a systematic SLIT review, showing approximately 14% patient dropout in the first year.¹⁰ However, such low rates might be different from the real-world situation because observational studies are thought to more accurately reflect the actual clinical situation in comparison with RCTs.

Patient dropout and SLIT compliance are affected by factors such as patient characteristics (e.g. age), therapy-related factors (e.g. effectiveness), and the healthcare environment in each country (e.g. hospital visiting frequency, financial burden, insurance coverage).¹⁶ The SLIT compliance between adults and children is controversial. Some studies found better compliance in adults than in children, but the others found the opposite.^{8,10,15,16} Typically, children younger than 12 years of age have a good compliance, which might be due to the influence of their caregivers, but

compliance in adolescents is the same or less than in adults. It is reported that adolescents and adults have similar reasons for dropout and low SLIT compliance.⁸¹⁶ Generally, insurance coverage has a strong influence on compliance in a real-world setting.²²⁻²⁴ The low dropout and favorable compliance of JCPE in Japan, compared with similar studies in other countries, are therefore likely to be attributable to the availability to all patients of the Japanese universal health insurance system. However, JCPE is a remedy that needs to be used throughout the entire year including during asymptomatic periods, for at least 3 to 5 years, which may worsen dropout and compliance rates. Therefore, actual patient dropout rates and SLIT compliance with JCPE immunotherapy are not clear in the real world.

To develop countermeasures for appropriate SLIT in seasonally allergic patients, it is important to investigate the actual situation independently of patient health insurance status. Japan is ideal for such a study because of its universal insurance system where patient copayment is constant. Therefore, we investigated SLIT patient dropout and a SLIT compliance in a real-world setting using claims data from throughout Japan.

Methods

Study design and data source

This study was a retrospective cohort study conducted using data from the largest commercial claims database in Japan created by Japan Medical Data Center Co. Ltd. (JMDC).²⁵ Since 2005, this database has accumulated more than 3 million individual claims of enrollees and their family members associated with the health insurance of the Japanese universal health care system. Although there is the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) launched by the Japanese government in 2009, it is not commonly used because of the stringent criteria for obtaining access, whereas the JMDC is user-friendly and well-organized. Thus, JMDC has been used for various types of epidemiological studies.²⁶ This database is sourced from the Japanese union-managed health insurance system and mainly includes salaried workers of medium to large scale companies and their dependents. All data were completely anonymized and de-identified. The main elements in the database are patient demographic information, medical claim date, pharmacy claims, and reimbursement cost. Clinical diagnoses present in the database are coded under the International Classification of Diseases, 10th Revision (ICD-10) classification,²⁷ with drug prescription information coded according to the Anatomical Therapeutic Chemical (ATC) classification.²⁸ The data period was from January 1, 2012, to June 30, 2016.

143 This study was approved by the Ethics Committee of Kyoto University School of
144 Medicine (Approval number, R0938). Because all data were anonymized, the informed consent of
145 patients was not required based on Japanese ethical guidelines for medical and health research
146 involving human subjects.

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148 **Exposure**

149 JCPE is prescribed in three dosage forms – a 200 U/mL spray bottle, a 2,000 U/mL spray bottle and
150 2,000 U/mL pack (1 mL) to be taken once a day. JCPE must be prescribed by a suitably trained
151 physician. Patients are treated over 2 phases—an induction phase with sequentially increased doses
152 administered over a 2-week period and a maintenance phase. For the 2-week induction phase, a 200
153 U/mL bottle and a 2,000 U/mL bottle are prescribed. Then, the maintenance phase starts and 2,000
154 U/mL packs are prescribed. Patients take one pack (1 mL) once per day during the maintenance
155 phase.

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157 **Eligible Patients**

158 Patients with data from at least one complete prescription of JCPE (ATC code “V01AA05”) from
159 October 2014 to June 2016 were considered for the study. Exclusion criteria were the lack of

prescription data for the initial 200 U/mL bottle (induction phase) or the initial 2000 U/mL pack (maintenance phase).

Study cohort

All eligible patients were analyzed for age and SLIT initiation date distribution. The analysis of patient dropout and compliance, which was the focus of the study, was performed separately for adults (age, ≥ 20 years) and adolescents (age, < 20 years), because of reported differences in SLIT compliance between adults and children.⁸¹⁶

The patients were divided into three cohorts according to the initial date of the induction phase. (1) SLIT2014, from October 2014 to April 2015; (2) SLIT2015, from May 2015 to April 2016; and (3) SLIT2016, from May 2016 to June 2016. SLIT2015 (1-year of SLIT) and SLIT2014 (2-year of SLIT) were used for the patient dropout and compliance analysis, whereas SLIT2016 was not used because of the short observation period.

Definition of dropout and SLIT compliance

Dropout was defined as a gap of more than 56 days between the last prescription date of the 2,000 U/mL pack and the last recorded observation date. This definition was derived from a two-fold prescription period. Typically, JCPE users should have a monthly visit to the clinical office to obtain

the 2,000 U/mL pack prescription containing 28 individual units that last for 28 days. We defined the proportion of days covered (PDC) as a surrogate for SLIT compliance, which is the ratio between the number of days that the patient remained in the maintenance phase and the number of 2,000 U/mL packs prescribed. The number of days in the maintenance phase was calculated by determining the number of days between the first and the last 2,000 U/mL pack prescription date and the number of 2,000 U/mL packs prescribed at the last date.

Study Outcomes and follow-up

Study outcomes were dropout rate and SLIT compliance during the SLIT treatment phase. These outcomes were observed in each eligible patient from the initiation date of the treatment to June 30, 2016.

Investigated variables

The factors we examined were sex, age, a concurrence of asthma, Charlson Comorbidity Index (CCI), and history of systemic steroid usage during cedar pollen season.²⁹ Asthma concurrence was defined as any patient diagnosed with asthma (ICD-10 code J45 and J46) and prescribed inhalant glucocorticoids (ATC code “R03BA”). Patients were defined as having a history of systemic steroid use if they were prescribed systemic corticosteroids (ATC code “H02A” and “H02B”) during the JC

pollen season before commencing SLIT. CCI was calculated using ICD-10 codes with associated weighting corresponding to the severity of the comorbid condition of interest. We used the patient data starting from January 2012 to calculate these factors.

Statistical methods

Patient distribution and characteristics

Patient age and date of initiation of the JCPE induction phase were specified and distributions calculated using data from the entire SLIT eligible cohort (including adults and children). Patient characteristics and investigated variables were described for the SLIT adult and adolescent cohorts and each of the selected subgroups (SLIT2014, SLIT2015, and SLIT2016). All variables were assessed using descriptive statistics.

Factors related to dropout

Kaplan-Meier curves of the time to dropout during the maintenance phase were plotted for cohorts associated with variables that were investigated in the study. The mean duration of the maintenance phase and the dropout rate were calculated. To investigate the association between dropout and the investigated variables, univariate and multivariate Cox regression models were developed using each variable (sex, age, concurrence of asthma, CCI, and history of systemic steroid usage; age was

excluded from the adolescents' analysis). The models were fitted separately using the SLIT2014 and SLIT2015 cohorts to investigate differences in dropout rates during the first year of SLIT (1-year SLIT) and the second year of SLIT (2-year SLIT). The hazard ratio (HR) and 95% confidence interval (CI) were calculated for each variable.

Factors related to SLIT compliance

Mean SLIT compliance was calculated for each cohort. The factors associated with compliance were investigated using linear regression. In this model, the objective variable was SLIT compliance rate, with the explanatory variable adjusted to all investigated variables (sex, age, concurrence of asthma, CCI, and history of systemic steroid usage). The standard partial regression coefficient (β'), the regression coefficient (β) with standard error (SE), and 95% CI were calculated for each variable.

SAS9.4 (SAS Institute Inc., Cary, NC) was used for statistical analysis. A two-sided p-value of ≤ 0.05 was deemed to represent statistical significance.

Results

Patient characteristics

A total of 1,236 patients were prescribed JCPE during the study period. We excluded 50 patients with no initial data in the induction phase and 91 patients who withdrew from treatment before commencing the maintenance phase (Figure 1). The patient's age at the induction phase showed a bimodal distribution. The first peak was around 12 years old and the second around 30 years old (Figure 2A). After excluding patients, 1095 patients were eligible for the study (Figure 1). There were 271 adults and 50 adolescents in SLIT2014 cohort, 505 adults and 175 adolescents in SLIT2015 cohort, and 70 adults and 24 adolescents in SLIT2016 cohort. There were no missing data in this study.

Most patients initiated the induction phase after May when JC pollen season was concluding (Figure 2B). The mean age of eligible adult patients was 43.0 years and 41.8% were female. Most patients were 30 to 59 years of age. The systemic steroid prescription rate was 34% during the JC pollen season. The proportion of patients with asthma was 3.8% (Table 1). Most of the medical institutions responsible for patient treatment (94.7%) were clinics. These characteristics were similar in each cohort. The mean age of eligible adolescent patients was 14.1 years and 36.6% were female. The mean CCI was 1.4, the systemic steroid prescription rate was 47.8% during the JC pollen

season, and the proportion of patients with asthma was 8.4% (Table 2). Adolescents had a lower CCI and a higher proportion of steroid history and asthma complications than adults.

Dropout

In patients in the 1-year SLIT cohort, the mean duration of the maintenance phase and dropout rate were 343.7 days and 13.5%, respectively, whereas, in the 2-year SLIT cohort, these parameters were 501.5 days and 22.1%, respectively. Using multivariate Cox regression models for each age group in the 1-year SLIT cohort (Table 3 and Figure 3A), hazard ratios (HR) relative to patients in their 20s (95% CI; P value) were 0.69 (0.34-1.37; 0.29) for patients in their 30s, 0.26 (0.12-0.58; 0.001) for those in their 40s, 0.32 (0.14-0.75; 0.008) for patients in their 50s, and 0.18 (0.04-0.82; 0.027) for patients aged 60 years or older. Other investigated factors did not show statistically significant relationships with patient dropout. During the 2-year SLIT, HRs relative to patients in their 20s for patients in their 40s and 50s were also statistically significant using multivariate Cox regression models for each age group. The HR (95% CI; P value) were 0.66 (0.30-1.47; 0.31) for patients in their 30s, 0.40 (0.17-0.93; 0.03) for those in their 40s, 0.35 (0.13-0.92; 0.03) for patients in their 50s and 0.60 (0.19-1.88; 0.38) for those of 60 or more years of age. In contrast to the 1-year SLIT cohort, the HRs for patients of 60 or more years of age were not statistically significant. Systemic

steroid history showed statistically low HR in univariate analysis but no statistical significance in multivariate analysis (Table 3 and Figure 3B).

SLIT compliance

SLIT compliance in adults was 92.8% in all patients in the 1-year SLIT cohort and 88.8% in the 2-year SLIT cohort. For the 1-year cohort, age was the only statistically significant factor associated with compliance ($P = 0.001$) (Table 4). In this model, increasing age was associated with a greater rate of SLIT compliance during one year of SLIT. In the 2-year SLIT cohort, sex, age, and systemic steroid history were statistically significant factors associated with compliance ($P = 0.03, 0.02$ and 0.04 , respectively) (Table 4). Compliance increased in males with age and having a systemic steroid history increased compliance during 2 years of SLIT.

Dropout and SLIT compliance in adolescents

In adolescents in the 1-year SLIT, the mean duration of the maintenance phase and dropout rate were 284.7 days and 22.3%, respectively, whereas, in the 2-year SLIT, these parameters were 493.0 days and 36.0%, respectively. Univariate and multivariate Cox regression analysis did not identify a statistically significant association between patient dropout and any of the monitored parameters.

279 SLIT compliance was 90.5% in the 1-year SLIT cohort and 85.1% in the 2-year SLIT cohort. There

280 were no statistically significant factors associated with compliance.

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Discussion

In this study, we investigated patient dropout and SLIT compliance in a retrospective cohort study of SLIT by JCPE for the treatment of JC pollinosis. The goal of the study was to determine contributing factors in a real-world clinical setting. Dropout rates lower than those previously reported, as well as high compliance, were observed in the present study. Patient age, systemic steroid use history, and sex were factors associated with low dropout rates and high SLIT compliance.

In the one-year SLIT cohort of adults, dropout rate and mean SLIT compliance were 13.5% and 92.8%, respectively, while in the two-year SLIT cohort, the dropout rate was 22.1% and the mean SLIT compliance 88.8%. The dropout rates are lower and the SLIT compliance rates are higher than those reported in previous studies from other countries.^{8,9,14–16} The major determinants associated with high dropout rates and low compliance during SLIT are known to be lack of efficacy, patient's perception of efficacy, cost of treatment, and convenience of administration.^{16,30} In addition, the convenience of access to treatment was reported as one of the positive factors for a low dropout rate of SLIT.⁹ Therefore, a major reason for low dropout rates in Japan may be due to the accessibility of clinics or/and the low medical costs for patients in a universal health insurance system.

The patient's age was associated with SLIT dropout in adults, and the dropout rates in adolescents were higher than those in adults. Young adult patients (<30 years of age) were found to be more likely to drop out from the JCPE SLIT regime. Dropout rates of patients in their 40s and 50s

300 were relatively low compared with the rates for those in their 20s. This may be associated with lower
301 average income and a higher likelihood of undergoing changes in the locality and (therefore changes
302 in attending physician) by patients in their 20s compared with patients in their 40s or 50s. As in the
303 case of dropout, lower average income might be a major reason for low compliance because the
304 compliance rate is related to patient age and was seen to improve with age in the first year. The
305 dropout hazard rate in patients aged 60 years or older was lower than that of patients in their 20s in
306 the first year, but there was no difference in the second year. As the SLIT duration became longer,
307 elderly patients might have had problems due to medication cost or a less stable housing situation,
308 like patients in their 20s, or they might have been more likely to consider that the medication lacked
309 efficacy. In this study, dropout rates were higher in adolescents than in adults. Although previous
310 studies reported differences in SLIT compliance between adults and children, the results in children
311 were inconsistent.^{8,16} High compliance was observed in children younger than 12 years of age, which
312 might be due to the dose management by caregivers. It is also possible that frequent check-ups with
313 a specialist during the short periods led to better compliance.⁸ However, adolescents of 15 or more
314 years of age had high dropout rates because of the complexity of SLIT and the long treatment period.
315 The same reasons were reported for adults.¹⁶ In this study, we found low compliance in pediatric
316 patients; most of them were 12 years of age or older. Our result on adolescents' compliance was
317 similar to that of previous studies.^{8,16} In Japan, adolescents between 12 and 20 years of age would

experience a drastic change of their environment within a short period due to an advance in their education level every three years by advancing through junior high school, high school, and university. This environment could make it difficult to continue SLIT.

Interestingly, systemic steroid history improved SLIT compliance in the second year in adults, indicating that patients with more severe allergic rhinitis have better compliance even with long-term treatment because systemic steroid treatment is only used in severe cases according to the Japanese guideline for allergic rhinitis.³¹ Thus, patients with severe disease may tend to continue SLIT.

Indeed, more patients suffering severe symptoms are selected for SLIT than other therapies.^{32,33}

However, steroid history was not associated with SLIT compliance in adolescent patients. This difference might depend on the patient's background such as a higher steroid use history in adolescents. Further studies are needed to the efficacy of SLIT in more severe cases.

The strength of the present study is that it is based on real-world data. Accordingly, the results are a better reflection of the actual situation than RCTs or other prospective study designs. Furthermore, because the JMDC database is sourced from a union-managed health insurance system, we were able to identify all insurance-covered medical records for each patient, even if they visited multiple hospitals and/or changed the health care provider. Therefore, we were able to evaluate the dropouts using all insurance-covered medical records in the JMDC database.

There are four major limitations of this study. Firstly, JMDC data were taken from the employed population, so the representation of patients aged 65 years and older is low compared to the general Japanese population. However, JC pollinosis is not an age-related disease, so the influence of this limitation on our findings might be very small. Secondly, because the JMDC database does not include the address data of the patients, we could not take into consideration the degree of scattering of the cedar pollen that may vary between the home addresses of patients in the cohort. Thirdly, we may underestimate dropout rates and SLIT compliance. We could not directly measure the SLIT compliance even if the prescription was regularly recorded. And lastly, there may have been other, yet unknown factors that influence dropout or compliance.

Conclusions

We found a low dropout rate and high compliance of SLIT compared to previous reports from other countries. Systemic steroid use is associated with better compliance, suggesting that SLIT may be effective even in patients with severe disease. Age was a factor related to both dropout and compliance; younger patients tended to have high dropout rates and low compliance. Further studies are needed to elucidate the reasons for the strong influence of age on dropout and compliance to take steps that will improve SLIT efficacy.

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Tables

Table 1. Participant demographics and baseline characteristics in the adult population (age, ≥ 20 years)

Characteristics	Adult all N=846	SLIT 2014 N=271	SLIT 2015 N=505	SLIT 2016 N=70
No. of female patients (%)	354 (41.8)	119 (43.9)	201 (39.8)	34 (48.6)
Mean age in years (SD)	43.0 (10.4)	43.5 (10.2)	43.1 (10.4)	40.9 (10.3)
No. of patents in each age group (%)				
20s	75 (8.9)	21 (7.8)	46 (9.1)	8 (11.4)
30s	259 (30.6)	77 (28.4)	156 (30.9)	26 (37.1)
40s	279 (33.0)	98 (36.2)	160 (31.7)	21 (30.0)
50s	176 (20.8)	54 (19.9)	111 (22.0)	11 (15.7)
≥ 60	57 (6.7)	21 (7.8)	32 (6.3)	4 (5.7)
CCI (median)	2.5 (2.0)	2.5 (2.0)	2.6 (2.0)	2.1 (2.0)
Systemic steroid history (%)	321 (37.9)	92 (34.0)	199 (39.4)	30 (42.9)
Asthma (%)	32 (3.8)	9 (3.3)	21 (4.2)	2 (2.9)
Management body, no. of patients (%)				
Clinic	772 (94.7)	241 (94.9)	465 (94.5)	66 (95.7)
University hospital	15 (1.8)	5 (2.0)	9 (1.8)	1 (1.5)
Public hospital	4 (0.5)	2 (0.8)	2 (0.4)	0 (0.0)

SD, standard deviation, CCI, Charlson comorbidity index.

Table 2. Participant demographics and baseline characteristics in the adolescent population (age, < 20 years)

	Adolescent	SLIT 2014	SLIT 2015	SLIT 2016
Characteristics	all N=249	N=50	N=175	N=24
No. of female patients (%)	91 (36.6)	11 (22.0)	70 (40.0)	10 (41.7)
Mean age in years (SD)	14.1 (1.9)	14.1 (2.1)	14.1 (1.9)	13.9 (2.0)
CCI (median)	1.4 (1.2)	1.6 (1.3)	1.4 (1.1)	1.0 (1.0)
Systemic steroid history (%)	119 (47.8)	16 (32.0)	87 (49.7)	16 (66.7)
Asthma (%)	21 (8.4)	3 (6.0)	16 (9.1)	2 (8.3)
Management body, no. of patients (%)				
Clinic	220 (90.9)	41 (89.1)	155 (90.1)	24 (100.0)
Public hospital	10 (4.1)	1 (2.2)	9 (5.2)	0 (0.0)
Other	12 (5.0)	4 (8.7)	8 (4.7)	0 (0.0)

SD, standard deviation, CCI, Charlson comorbidity index.

466 Table 3. Risk factors associated with dropout during the 1-year and 2-year SLIT maintenance period

Factors	1-year SLIT (SLIT2015)							2-year SLIT (SLIT2014)					
	No. of patients	% of dropouts	Univariate analysis		Multivariate analysis		P-value	No. of patients	% of dropouts	Univariate analysis		Multivariate analysis	
			HR (95% CI)	P-value	HR (95% CI)	P-value				HR (95% CI)	P-value	HR (95% CI)	P-value
All	505	13.5						271	22.1				
Sex													
Male	304	12.8	1		1			152	26.3	1		1	
Female	201	14.4	1.16 (0.72, 1.88)	0.54	1.23 (0.75, 2.01)	0.42		119	16.8	0.59 (0.34, 1.00)	0.052	0.64 (0.37, 1.12)	0.12
Age	505	13.5	0.96 (0.93, 0.98)	0.0003	-	-		271	22.1	0.96 (0.94, 0.99)	0.0068	-	-
Age group													
20s	46	23.9	1		1			21	42.9	1		1	
30s	156	19.2	0.70 (0.35, 1.40)	0.31	0.69 (0.34, 1.37)	0.29		77	27.3	0.62 (0.28, 1.35)	0.23	0.66 (0.30, 1.47)	0.31
40s	160	8.8	0.29 (0.13, 0.65)	0.0025	0.26 (0.12, 0.58)	0.001		98	17.4	0.35 (0.16, 0.78)	0.01	0.40 (0.17, 0.93)	0.03
50s	111	9.9	0.35 (0.15, 0.80)	0.013	0.32 (0.14, 0.75)	0.008		54	14.8	0.31 (0.12, 0.80)	0.02	0.35 (0.13, 0.92)	0.03
≥60 years	32	6.3	0.21 (0.05, 0.94)	0.041	0.18 (0.04, 0.82)	0.027		21	23.8	0.59 (0.20, 1.78)	0.35	0.60 (0.19, 1.88)	0.38
CCI													
<2.0	193	13.5	1		1			102	25.5	1		1	
≥2.0	312	13.5	1.00 (0.61, 1.63)	0.99	1.27 (0.76, 2.12)	0.37		169	20.1	0.75 (0.45, 1.26)	0.28	0.97 (0.56, 1.68)	0.90
Systemic steroid history													
No	306	11.8	1		1			179	26.3	1		1	
Yes	199	16.1	1.42 (0.88, 2.29)	0.15	1.49 (0.92, 2.42)	0.10		92	14.1	0.50 (0.27, 0.92)	0.02	0.55 (0.29, 1.02)	0.056
Asthma													
No	484	13.6	1		1			262	22.1	1		1	
Yes	21	9.5	0.64 (0.16, 2.63)	0.54	0.65 (0.16, 2.70)	0.55		9	22.2	1.04 (0.25, 4.25)	0.96	1.16 (0.27, 4.90)	0.84

467 SLIT, sublingual immunotherapy; CI, confidence interval, HR, hazard ratio; CCI, Charlson comorbidity index.

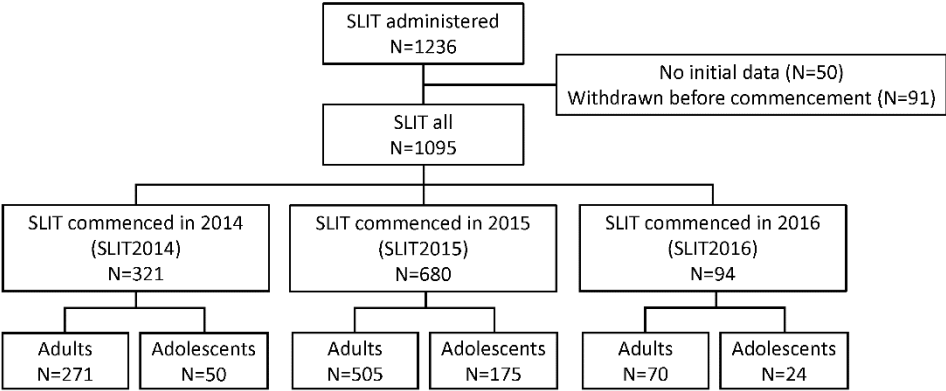
468 Table 4. Risk factors associated with compliance during maintenance period

Factors	1-year SLIT (SLIT2015)				2-year SLIT (SLIT2014)			
	β'	β	SE (95% CI)	p-value	β'	β	SE (95% CI)	P-value
Intercept		0	84.39 2.44 (79.59, 89.18)	<.0001		0	77.09 6.31 (64.67, 89.51)	<.0001
Sex (Female)		0.01	0.26 1.15 (-2, 2.52)	0.82		-0.14	-6.6 2.93 (-12.37, -0.82)	0.03
Age		0.15	0.19 0.06 (0.08, 0.3)	0.001		0.15	0.35 0.15 (0.06, 0.64)	0.02
CCI		0.01	0.06 0.26 (-0.46, 0.58)	0.82		-0.09	-1.09 0.74 (-2.54, 0.36)	0.14
Systemic steroid history		0.01	0.26 1.16 (-2.01, 2.53)	0.82		0.12	6.2 3.07 (0.16, 12.24)	0.04
Asthma		0.02	1.43 2.82 (-4.12, 6.98)	0.61		0.02	2.01 8.07 (-13.88, 17.91)	0.8

469 SLIT, sublingual immunotherapy; β' , standard partial regression coefficient; β , regression coefficient; SE, standard error; CI, confidence interval, CCI, Charlson comorbidity index.

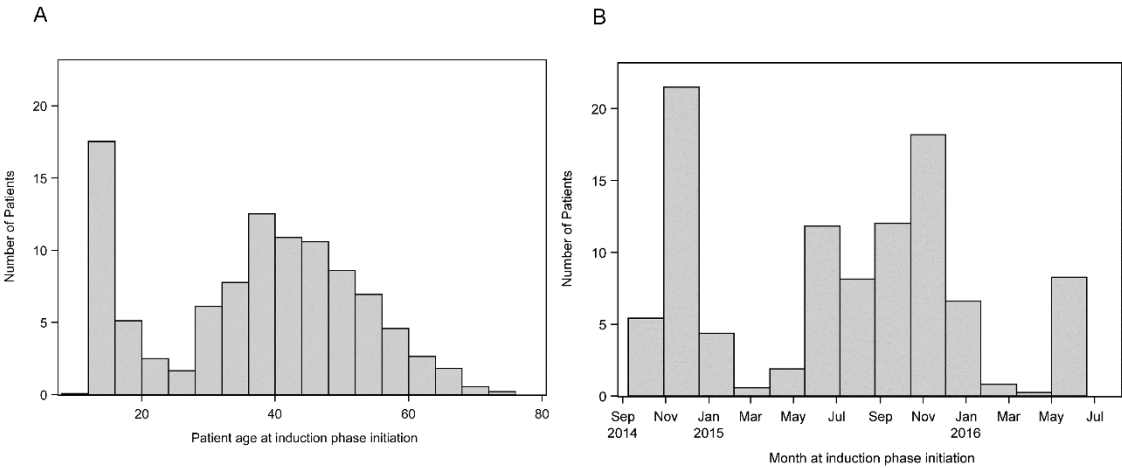
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471 **Figure and Figure Legends**



472
473 Figure 1. Flowchart of the patient selection process.

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476 Figure 2. Distribution of patients who started the standardized Japanese cedar pollen extract (JCPE)

induction phase. A) Age distribution of JCPE patients selected for the study (SLIT all, 1095 patients). B) Distribution of the initiation date of the JCPE induction phase (SLIT adults, 846 patients).

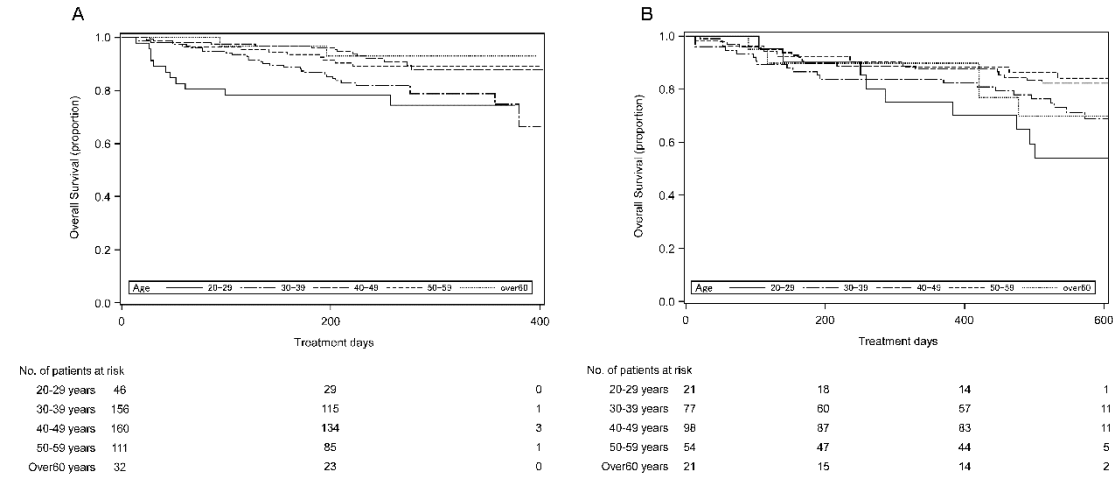


Figure 3. Kaplan-Meier curves of the time to dropout during the maintenance phase with age groups for the 1-year SLIT cohort (A) and the 2-year SLIT cohort (B).