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Causes of Punctal Plug Loss in Sjögren's Syndrome

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Purpose: To evaluate the long-term maintenance rate and associated factors of silicone punctal plugs in patients with Sjögren's syndrome (SS).

Materials and Methods: We retrospectively reviewed the medical records of 163 patients with SS who underwent silicone punctal plug insertion between December 2013 and July 2021 at Severance Hospital. The status of punctal plug insertions was classified into the following three categories by the clinician: maintenance, spontaneous loss, and intended removal. Cox proportional hazards model was used to evaluate the risk factors for spontaneous loss.

Results: The mean maintenance period was 12.8±15.3 (median 7.07) months. The rate of spontaneous loss was 58%, and the rate of punctal plug removal by the clinician was 14%. The number of prior plug insertions was a risk factor for spontaneous loss [hazard ratio (HR) 1.055, p=0.035]. The upper eyelid punctum was at a higher risk than the lower one (p=0.042). Small-sized plugs showed a significantly higher risk for spontaneous loss than large-sized ones (HR 1.287, p=0.035). Flow-controller type plugs were more vulnerable to spontaneous loss than complete occluders [Micro Flow™ vs. EagleFlex® (HR 2.707, p=0.008) and Micro Flow™ vs. Ultraplug™ (HR 3.402, p=0.005)]. The most common reason for removal was tear overflow (5.6%).

Conclusion: In repeated insertion, characteristics of the punctal plug, including the type and size, and location of plug insertion, influenced the spontaneous loss of plugs. The management of punctal plugs, including insertion, maintenance, and removal, requires personalized strategies for versatile situations.

Key Words: Aqueous-deficient dry eye, punctal plug, Sjögren's syndrome.

INTRODUCTION

Sjögren's syndrome (SS) is a representative aqueous-deficient dry eye disease that disrupts the aqueous production of the lacrimal gland. The mainstream treatment of SS is to supply an aqueous component. Punctal plug insertion is a universal treatment for SS that restores the aqueous component and delays the lacrimal drainage of tears.[1]

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For several decades, various types of punctal plugs have been used to ensure an effective and convenient plug application.[2] Silicone punctal plugs are commonly used due to their efficacy, improvement in tear film stability, ocular staining scores, and goblet cell density.[3] However, plug-related complications, such as plug loss (maintenance failure), tear overflow, irritation, and inflammation by the plug, and plug-related infections have been reported. Spontaneous loss of plugs has been considered the most common plug-related complication.[4] Previous studies have reported variable maintenance rates of silicone punctal plugs, ranging from 30% to 70% for 6 months.[5-12] Most studies have compared the maintenance rates between the two punctal plug designs and analyzed the associated factors, including patient age, punctal plug size, and repetitions of plug insertion.[5-7,9,10]

Few studies have reported long-term results of punctal plug maintenance, and most have focused on single punctal plug survival.[11,13] However, SS is a lifelong disease, and most patients show various therapeutic courses over a long follow-up period.

Moreover, considering the maintenance rate of punctal plugs, a patient-focused analysis reflecting the actual clinical situations where the therapeutic confounders exist complexly is also needed. In this study, we concomitantly considered various factors that affect the maintenance of punctal plugs, including their type and size, and other factors for up to 7 years, based on individual patients with SS. This study aimed to analyze the long-term maintenance rate and its associated factors in patients with SS.

MATERIALS AND METHODS

The Institutional Review Board of Severance Hospital Clinical Research Ethics Committee reviewed and approved the study protocol (IRB protocol number: 4-2022-0651). The study complied with the tenets of the Declaration of Helsinki.

Participants

We reviewed the medical records of patients with SS who underwent punctal insertion with a silicone punctal plug between December 2013 and July 2021 at Severance Hospital. Patients who did not show improvement in the ocular surface condition or dry eye-related symptoms after topical eye drop treatment, including artificial tear drop, were included in the study.

The diagnosis of primary SS was based on the American-European Consensus Group 2002 definition and the revised 2016 criteria, including systemic, serological, and immunological examinations, as follows: 1) ocular signs: Shirmer test or Rose Bengal test; 2) salivary gland function; 3) presence of autoantibodies: anti-Ro (SS-A) or anti-La (SS-B); 4) histopathologic findings and subjective criteria; 5) oral symptoms; or 6) ocular symptoms. The participants in this study were registered in the National Health Insurance System as patients with SS.[14,15]

Patients with secondary SS, acute or chronic ocular surface infection or allergy, systemic diseases that can affect dry eye (e.g., Steven–Johnson syndrome, ocular graft-versus-host-disease, and ocular cicatricial pemphigoid), or diseases in the lacrimal drainage system were excluded. Additionally, incomplete medical records were also excluded from the analysis.

Clinical assessments

All of the punctal plug insertion steps were performed by an expert clinician (K.Y.S.). Patients with a tear meniscus height of <200 μm underwent punctal plug insertion.[16] The size of punctal plug was determined by inspecting the puncta, without quantitative measurement. The plug was inserted into the upper or lower punctum using standard techniques.

During the study period, five types of silicone punctal plugs [Supereagle® (Eagle Vision, Memphis, TN, USA); Parasol® (Odyssey Medical, Memphis, TN, USA); EagleFlex® (Eagle Vision); Micro Flow™ (Odyssey Medical); and Ultraplug™ (Angiotech, Vancouver, British Columbia, Canada)] were used.

Three types of silicone punctal plugs (Supereagle®, Parasol®, and Micro Flow™) were available in three different sizes (small, medium, and large) per their recommended punctum size, and the other two types of silicone punctal plugs (EagleFlex® and Ultraplug™) were available in their plug sizes. Ultraplug™ was available in five sizes ranging from 0.4 mm to 0.8 mm, and EagleFlex® was available in six sizes ranging from 0.4 mm to 0.9 mm on a 0.1-mm scale. In this study, we classified the size of the three punctal plugs (Supereagle®, Parasol®, and Micro Flow™) into three categories (small, medium, and large); EagleFlex® into three categories: small (0.4 to 0.6 mm), medium (0.7 to 0.8 mm), and large (0.9 mm); and Ultraplug™ into three categories: small (0.4 to 0.6 mm), medium (0.7 mm), and large (0.8 mm), reflecting the standard size of other silicone punctal plugs.[2]

Spontaneous loss of the punctal plug was defined as an unintentional removal of the punctal plug identified by the clinician during follow-up visits. Plug removal was defined by the clinician as plug removal. Plug maintenance was defined as the presence of a well-positioned plug in the punctum at follow-up visits. The protruding plug, which shows the shaft of the plug, was regarded as a plug extrusion. Plug pushing was considered to deliver additional pressure to reposition the protruded plug until only the plug head was properly placed on the opening of the punctum.

Statistical analysis

Continuous variables were expressed as mean±standard deviation, and categorical variables were expressed as proportions. After testing normal distribution assumption, univariate analyses were conducted using independent sample t-test, Mann-Whitney U test, chi-square test or one-way ANOVA.

Spontaneous loss was considered a dependent binominal variable when we analyzed the maintenance rate and factors associated with punctal plug maintenance. Patient history (age, sex, and ocular surgery history including the eyelid, conjunctiva, punctum, or any other part), presence of eyelid abnormality, history of topical immunomodulatory medication (steroid or tacrolimus), number of prior plug insertions, type (manufacturer) and size of plug, and location of punctal plug insertion (lower or upper eyelid) were considered as independent variables. Cox proportional hazards model was used to evaluate the effect of each factor on the plug maintenance rate. Kaplan–Meier survival analysis was performed to calculate the median survival date. A descriptive analysis was performed for the intended plug removal. A *p* value less than 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS 25.0 (IBM Corp., Armonk, NY, USA) software.

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RESULTS

A total of 163 patients (92% female patients) were enrolled, and 1229 plug insertions were performed (Table 1 and Supplementary Table 1, only online). The mean age was 56.6±12.2 (range 22–85) years. The mean number of punctal plug insertion in a single punctum was 2.3±1.82 times (median: 2, range: 1–13). The mean value of the maintenance duration of a single silicone plug was 12.8±15.3 (median 7.07) months (Table 1 and Fig. 1). A spontaneous loss occurred more frequently than the intended plug removal (58.4% vs. 14.0%) (Fig. 2).

Regarding the maintenance period of five different types of plugs with one-way ANOVA, Parasol® (24.9±22.7 months) showed significant difference with Supereagle® (37.3±35.9 months, $p<0.001$) and EagleFlex® (46.6±55.8 months, $p=0.049$). On the other hand, Micro Flow™ (23.8±22.5 months) and Ultraplug™ (52.3±62.1 months) did not show a significant difference. For reinsertion rate of five different types of plugs, all pairwise comparisons between plug types, except for the comparison between EagleFlex® (12.7%) and Ultraplug™ (46.2%, $p=0.586$), showed significant differences in univariate analysis ($p<0.001$) (Supplementary Table 2, only online).

Table 1. Demographics and Details of Silicone Punctal Plug Application

Variables	Value
Age (yr)	56.6±12.2 (range 22–85)
Sex	
Male	13 (8.0)
Female	150 (92.0)
Location of punctum	
Upper lid	245 (44.3)
Lower lid	296 (55.7)
Plug size	
Small	456 (37.1)
Medium	547 (44.6)
Large	212 (17.2)
Unknown	14 (1.1)
Plug size	
Supereagle®	570 (46.4)
Parasol®	311 (25.3)
EagleFlex®	238 (19.3)
Micro Flow™	33 (2.7)
Ultraplug™	23 (1.9)
Unknown	54 (4.4)

Data are presented as mean±standard deviation or n (%).

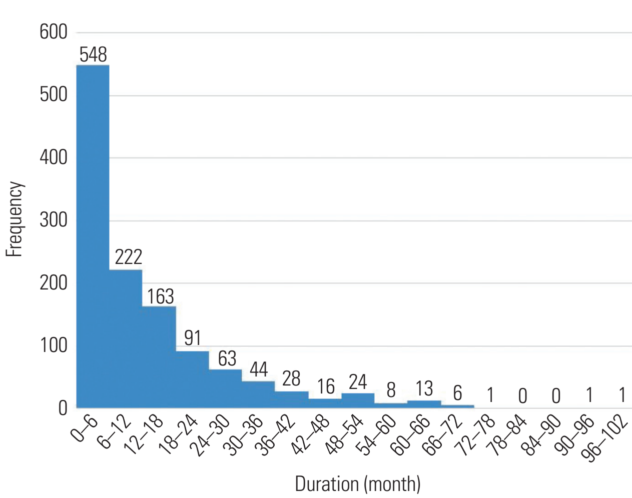

Fig. 1. Distribution of duration of punctal plug. Frequency of each 6-month interval is noted as the number above the histogram.

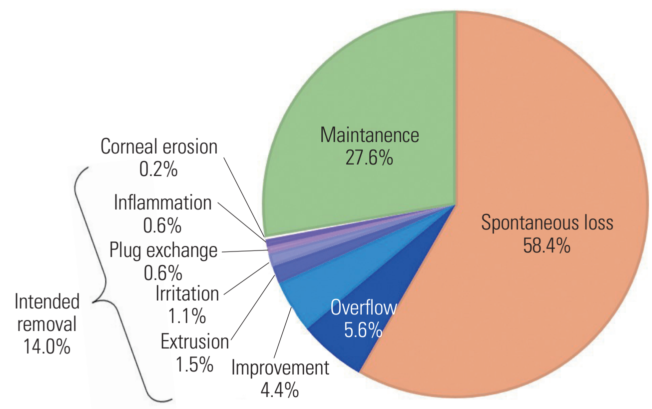

Fig. 2. A circle chart for the final condition of punctal plugs. Final condition was classified as follows: 1) spontaneous loss, 2) intended removal by physician, and 3) maintenance in place. In case of intended removal, details of reason for removal were also classified.

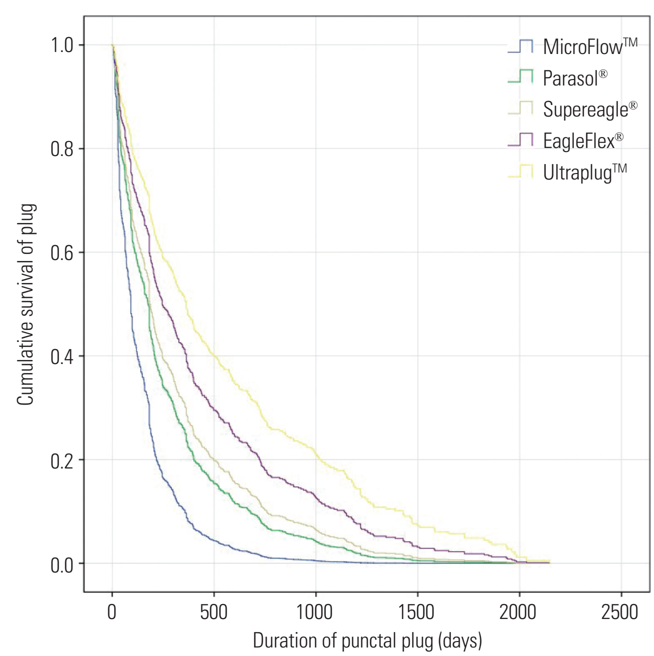

Fig. 3. A cumulative survival curve of silicone punctal plugs according to its types. The x-axis shows the duration of punctal plugs at daily intervals, and the y-axis demonstrates the proportion of remained punctal plugs in place. MicroFlow™ (blue line) showed a significantly higher rate of plug loss compared to EagleFlex® [purple line, HR 0.388 (95% CI 0.187–0.808); $p=0.011$] and Ultraplug™ [yellow line, HR 0.293 (95% CI 0.123–0.695); $p=0.005$]. HR, hazard ratio; CI, confidence interval.

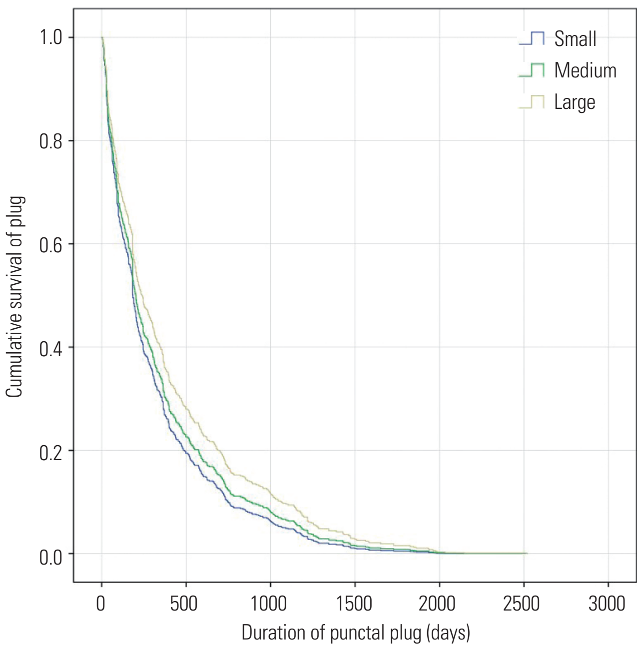

Fig. 4. A cumulative survival curve of silicone punctal plugs according to their sizes. The x-axis shows the duration of punctal plugs at daily intervals, and the y-axis demonstrates the proportion of remained punctal plugs in place. Small-sized punctal plugs (blue line) shows a significantly higher rate of plug loss than large-sized punctal plugs [olive line, HR 0.781 (95% CI 0.616–0.990); *p*=0.041]. HR, hazard ratio; CI, confidence interval.

Repetitive plug insertion increased the risk of spontaneous loss {hazard ratio (HR) 1.055 [95% confidence interval (CI) 1.004–1.110]; *p*=0.035}. For the punctal plug types, Micro Flow™ had the highest risk compared to the other four types. EagleFlex® and Ultraplug™ showed significant differences from Micro Flow™ [HR 2.707 (95% CI 1.303–5.622) and 3.402 (95% CI 1.435–8.065); *p*=0.008 and 0.005, respectively] (Fig. 3). The small punctal plug had a significantly higher risk than the large punctal plug [HR 1.287 (95% CI 1.018–1.626); *p*=0.035] (Fig. 4). Punctal plug insertion in the upper eyelid punctum was at a higher risk than in the lower eyelid punctum [HR 1.186 (95% CI 1.003–1.310); *p*=0.042] (Table 2).

Intended punctal plug removal occurred in cases of: 1) epiphora (overflow of tear in the absence of corneal erosion) (40.0%), 2) improvement of dryness or aqueous deficiency (31.4%), 3) extrusion of the plug by the surgeon (10.7%), 4) irritation (foreign body sensation) (7.9%), 5) exchange to another plug (4.3%), 6) inflammation due to plug (4.3%), and 7) corneal erosion due to plug (1.4%) (Fig. 2).

Table 2. Results of the Cox Regression Analysis to Evaluate the Risk Factors of Spontaneous Loss of Silicone Punctal Plug

Variables	Spontaneous loss vs. Maintenance		
	HR	95% CI	*p* value
Age	1.006	0.998–1.013	0.134
Sex	0.721	0.494–1.053	0.090
Lid operation history	0.885	0.585–1.339	0.563
Punctal electrocauterization history	1.323	0.883–1.981	0.198
Conjunctival electrocauterization history	1.522	0.941–2.460	0.087
Other ocular operation history	1.837	0.390–8.658	0.442
History of steroid medication	1.096	0.906–1.327	0.345
History of tacrolimus medication	0.852	0.630–1.151	0.296
Presence of lid scrubbing	0.920	0.769–1.100	0.358
Presence of lid abnormality	0.905	0.667–1.227	0.519
History of lid abnormality correction	0.812	0.397–1.660	0.568
Insertion location (upper vs. lower)	1.186	1.003–1.310	0.042*
Number of prior plug insertions	1.055	1.004–1.110	0.035*
Plug size (small vs. large)	1.287	1.018–1.626	0.035*
Plug size (medium vs. large)	1.168	0.936–1.457	0.170
Plug type (Micro Flow™ vs. Parasol®)	1.674	0.807–3.473	0.166
Plug type (Micro Flow™ vs. Supereagle®)	1.941	0.949–3.971	0.069
Plug type (Micro Flow™ vs. EagleFlex®)	2.707	1.303–5.622	0.008*
Plug type (Micro Flow™ vs. Ultraplug™)	3.402	1.435–8.065	0.005*
Plug pushing	0.634	0.325–1.239	0.183

HR, hazard ratio; CI, confidence interval.
*$p<0.05$.

DISCUSSION

We investigated the long-term progress of punctal plug insertion in patients with SS, considering various conditions around the plug application, to identify the associated factors. Therefore, a spontaneous loss was a more common reason for punctal plug failure than intentional removal by the clinician. Along with small-sized plugs, a "flow-controller" type design of silicone plug, repetitive plug insertion, and plug insertion in the upper eyelid punctum were analyzed as risk factors for spontaneous loss of plug.

In our study, most patients with SS (82%) required repetitive plug insertion throughout the follow-up period. Univariate analysis for the proportion of spontaneous loss between the first plug and the later plugs did not show significant differences (67.7% vs. 65.0%; *p*=0.362), possibly since this analysis only considered the final state of punctal plug without maintenance duration. We found that repetitive insertion of punctal plug is a risk factor of its spontaneous loss using the Cox proportional hazard model. Balaram, et al.[5] and Tai, et al.[17] reported that the initial punctal plug showed a higher maintenance rate compared to the punctal plug refitted after spontaneous loss of the initial plug. Kaido, et al.[6] reported an increased punctum size after plug loss. In contrast, Boldin, et al.[8] analyzed the punctal and proximal canalicular stenoses after silicone punctal plug treatment. The development of granulomas or fibrovascular bands around the punctum also suggests that plug insertion may lead to tissue injury around the punctum.[18,19] Plug insertion imposes mechanical stress, which can lead to microscopic tissue changes around the punctum and make the punctum more prone to the loss of the punctal plug, regard-

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less of whether the eyelid punctum widens or narrows after plug insertion.

The plug size is a major risk factor for plug maintenance. Our study showed that larger-sized punctal plugs stayed longer. The balance between the expanding pressure of the punctal plug towards the inner canal and the restoring force of the punctal tissue towards the inserted plug holds the plug in place.[6] However, a larger plug was also related to the occurrence of punctal granuloma,[18] which was experienced in one case with a medium-sized Parasol® plug. A larger size is considered to reinforce the plug to endure in the punctum; however, this reinforcement force sometimes damages the tissue around the punctum. From this point of view, we assume that not just the plug size, but also the contact of punctal plug and punctum tissue, is crucial for maintaining the plug in place. Punctal plug augmentation and selection of an appropriate plug size may also be important. In our experience, referring to the size of the previous plug, in the case of a repetitive plug, may help in selecting the proper plug size.

Plug design may influence the plug duration. We noted a lower maintenance rate of Micro Flow™ than that of EagleFlex® and Ultraplug™. The punctal plugs in this study, except for Micro Flow™, are complete occluders that are usually designed to apply force horizontally for good maintenance in the punctum. In contrast, Micro Flow™ has a hollow lumen in its straight shaft, which allows tear drainage.[2] In our study, seven plug exchanges were performed for patients who complained of epiphora after punctal plug insertion, and plug exchange into Micro Flow™ helped them get better. The hollow lumen in the shaft has its strength by reducing the overflow of the tear, but it makes the plug structure more flexible, which is vulnerable to plug loss. Before punctal plug insertion, clinicians should check for the presence of punctal stenosis or symptoms that the patient complains of, in order to properly select the type of punctal plug, flow-controller, or good retainer.

Plug insertion location was identified as a factor associated with spontaneous loss of the punctal plug. Balaram, et al.[5] and Sakamoto, et al.[7] reported that punctal plugs inserted into the upper punctum were lost more than those inserted into the lower punctum. Boldin, et al.[8] and Tai, et al.[17] showed that spontaneous loss of the punctal plug was not related to the location of the plug insertion. Our data showed that plug insertion into the upper punctum was associated with the spontaneous loss of the punctal plug. Mechanical stress caused by eyelid blinking or scrubbing may cause punctal plug loss. However, eyelid scrubbing and other structural problems of the eyelid did not lead to significant differences in plug maintenance. It is still debated whether one side of the punctum is more prone to spontaneous loss of the punctal plug, suggesting further studies using a more controlled method.

In light of our findings, we suggest considering the use of larger punctal plugs, if they can be comfortably tolerated by patients, and punctal plugs of a complete occluder type as a potentially more durable option.

One strength of our study is that it included a large number of patients with SS and detailed information about the plug application status over a long period. Unlike evaluating a single plug use per punctum, we identified repetitive and multiple plugs use for one punctum over several years. We also performed a comprehensive evaluation of plug application and identified the associated factors that significantly influence plug maintenance.

Although our research has its strength by following the long-term progress of punctal plugs in patients with SS, this study also has had several limitations. First, due to the retrospective nature of the study, each of the patients had their own visiting date, without a scheduled study date, and we also did not know the exact date of loss of the punctal plug. In contrast to plug maintenance or removal, spontaneous loss was considered when the previously placed plug was not in place during the follow-up visit, and the duration of plug was defined from the insertion date to the date when the clinician checked the loss of the plug. Second, since the measurement of punctum size and detailed information about the size and design of punctal plug were not available, our result did not fully demonstrate the effect of plug size on its maintenance. In addition, the effect of repeated insertions of punctal plug on the size of punctum and the microscopic structural changes around punctum needs to be examined further, as mentioned in previous studies.[6,8,18,19] Third, MicroFlow™ and Ultraplug™ had relatively small sample sizes than other plugs. Although our data implies significant differences in maintenance duration between the flow-controller type and the complete occluder type, further evaluation with statistically more powered, larger data is needed to compare maintenance along the axes of structural design of punctal plugs. We suggest further studies about the maintenance of punctal plugs, including the effect of plug design in punctum, quantitative analysis between punctum size and plug size, and structural change of punctum after repeated insertions of punctal plug.

In conclusion, punctal plugs are needed for lifelong and timely management throughout the disease course of patients with SS, and can be applied simply and repetitively. For more efficient application of the punctal plug, a customized plugging strategy regarding the patient and plug factors is needed.

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AUTHOR CONTRIBUTIONS

Conceptualization: Na Eun Kim, Hyunmin Ahn, and Kyoung Yul Seo.

Data curation: Na Eun Kim and Hyunmin Ahn. Formal analysis: Na Eun Kim and Hyunmin Ahn. Funding acquisition: Kyoung Yul Seo. Investigation: Na Eun Kim and Hyunmin Ahn. Methodology: Na Eun Kim, Hyunmin Ahn, and Kyoung Yul Seo. Project administration: Kyoung Yul Seo. Resources: Hyunmin Ahn and Kyoung Yul Seo. Software: Na Eun Kim, Hyunmin Ahn, and Kyoung Yul Seo. Supervision Ikhyun Jun, Tae-im Kim, and Kyoung Yul Seo. Validation: Ikhyun Jun, Tae-im Kim, and Kyoung Yul Seo. Visualization: Na Eun Kim and Hyunmin Ahn. Writing—original draft: Na Eun Kim and Hyunmin Ahn. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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