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# Appendectomy and rheumatoid arthritis

## A longitudinal follow-up study using a national sample cohort

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**Abstract**

The present study evaluated the association between appendectomy and rheumatoid arthritis (RA) using a national sample cohort of the Korean population. In this cohort study, the Korean National Health Insurance Service-National Sample Cohort of individuals ≥20 years old was collected from 2002 to 2013. A total of 14,995 appendectomy participants were 1:4 matched with 59,980 control subjects for age, group, sex, income group, region of residence, hypertension, diabetes, and dyslipidemia. We analyzed the occurrence of RA in both the appendectomy and control groups. Appendectomies were identified using operation codes for appendicitis only. RA was defined by International Classification of Disease-10 codes (M05 or M06) and medication histories. Crude and adjusted hazard ratios (HRs) were analyzed using a stratified Cox proportional hazard model. Subgroup analyses were performed on groups stratified by age and sex. The adjusted HR for RA was 1.02 (95% confidence interval = 0.76–1.38) in the appendectomy group ($P = .883$). In all of the subgroup analyses according to age and sex, the adjusted HRs for RA were not higher in the appendectomy group than those in the control group. We could not identify any significant relationship between appendectomy and RA.

**Abbreviations:** CI = confidence interval, DMARD = disease-modifying antirheumatic drug, GALT = gut-associated lymphoid tissue, HR = hazard ratio, ICD-10 = International Classification of Disease-10, NHIS-NSC = National Health Insurance Service-National Sample Cohort, OA = osteoarthritis, RA = rheumatoid arthritis, SD = standard deviation.

**Keywords:** appendectomy, arthritis, cohort studies, gastrointestinal diseases, rheumatoid arthritis, surgery

## 1. Introduction

The first debate regarding the effect of appendectomy on rheumatoid arthritis (RA) was started by Gottlieb et al in 1979.[1] They reported that patients who underwent appendectomy had a 1.7- to 6.6-times increased risk of RA compared with their spouses and siblings.[1] In 1985, Fernandez-Madrid et al showed decreased rheumatoid factor titers and an increased risk of RA after appendectomy.[2] However, other studies reported no relationship[3,4] or even a negative relationship[5–7] between appendectomy and RA.

Previous research has evaluated the association between appendectomy and RA with patient studies or patient-matched studies involving a limited number of participants. Most of these studies were written before 2000, except for 1 study.[5] Recently, a nationwide population-based study involving an Asian population reported a positive association between appendectomy and RA.[8] The study included 4294 appendectomy patients and a 1:3 matched control group with 12,882 subjects. The authors found a positive relationship with a hazard ratio (HR) of 1.76 for appendectomy on RA in Taiwanese females. Therefore, we evaluated whether this association could be validated using a Korean population. Thus, we evaluated the association between appendectomy and RA in a Korean population using a national sample cohort. We extracted data for patients who underwent appendectomy and a 1:4 matched control group and then analyzed the occurrence of RA.

## 2. Materials and methods

### 2.1. Study population and data collection

The Ethics Committee of Hallym University approved the use of the study data (2014-I148). The requirement for written informed consent was waived by the university's institutional review board.

This national cohort study relied on data from the Korean National Health Insurance Service-National Sample Cohort

*Editor: Roberto Cirocchi.*

*The manuscript was edited for proper English language, grammar, punctuation, spelling, and overall style by the highly qualified native English-speaking editors at American Journal Experts (1B65-2FD7-29B8-8EA4-85CP).*

*This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT, and Future Planning (NRF-2016R1C1B1014775 to Il Gyu Kong) and the Hallym University Research Fund (HURF-2015–06 to Il Gyu Kong).*

*The authors have no conflicts of interest to disclose.*

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*How to cite this article: Choi HG, Oh DJ, Kim M, Kim S, Min C, Kong ILG. Appendectomy and rheumatoid arthritis. Medicine 2019;98:40(e17153).*

*Received: 27 February 2019 / Received in final form: 22 July 2019 / Accepted: 20 August 2019*

*http://dx.doi.org/10.1097/MD.0000000000017153*

(NHIS-NSC). The details of the Korean Health Insurance Review and Assessment Service-National Sample Cohort (HIRA-NSC) are described in our previous studies.[9–11]

### 2.2. Participant selection

Among 1,125,691 patients with 114,369,638 medical claim codes, we included individuals who underwent appendectomy. Appendectomies were identified based on operation codes (Q2860-Q2863); only appendectomies performed for appendicitis alone (International Classification of Disease-10 [ICD-10]: K35) were included (n = 22,047).

RA was defined according to previous studies reporting the prevalence and incidence of RA in Korea.[12,13] RA was identified by ICD-10 codes (M05 or M06) and a prescription for a biologic agent or any disease-modifying antirheumatic drug (DMARD) (n = 7783). DMARDs were prescribed to 99.1% of RA participants.

In the cohort, the participants who underwent appendectomy were matched 1:4 with participants (control subjects) who did not undergo appendectomy between 2002 and 2013. The control group was selected from the general population (n = 1,103,644). The participants were matched based on age, group, sex, income group, region of residence, and prior medical history (hypertension, diabetes, and/or dyslipidemia). To prevent selection bias when selecting the matched participants, the control group participants were sorted using a random number order and then selected from top to bottom. Each appendectomy patient and the matched control participants were assumed to have received any necessary medical treatment during concurrent time periods (based on the relevant index date). Therefore, the patients in the control group who died before the index date were excluded. In both the appendectomy and control groups, participants with a history of RA before the index date were excluded. In the appendectomy group, 91 participants were excluded. Patients who underwent appendectomy for whom we could not identify a sufficient number of matched participants were also excluded (n = 19). We excluded participants who were younger than 20 years old (n = 6,942). Ultimately, 1:4 matching resulted in the inclusion of 14,995 appendectomy recipients and 59,980 control participants (Fig. 1). However, the participants were not matched with respect to ischemic heart disease, cerebral stroke, or a history of depression because strict matching based on these characteristics increased the drop-out rate for subjects due to a lack of control participants.

### 2.3. Variables

The following age groups were defined using 5-year intervals: 20 to 24, 25 to 29, 30 to 34 . . . , and 85+ years. A total of 14 age groups were designated. The income groups were initially divided into 41 classes (1 health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were recategorized into 5 classes (class 1 [lowest

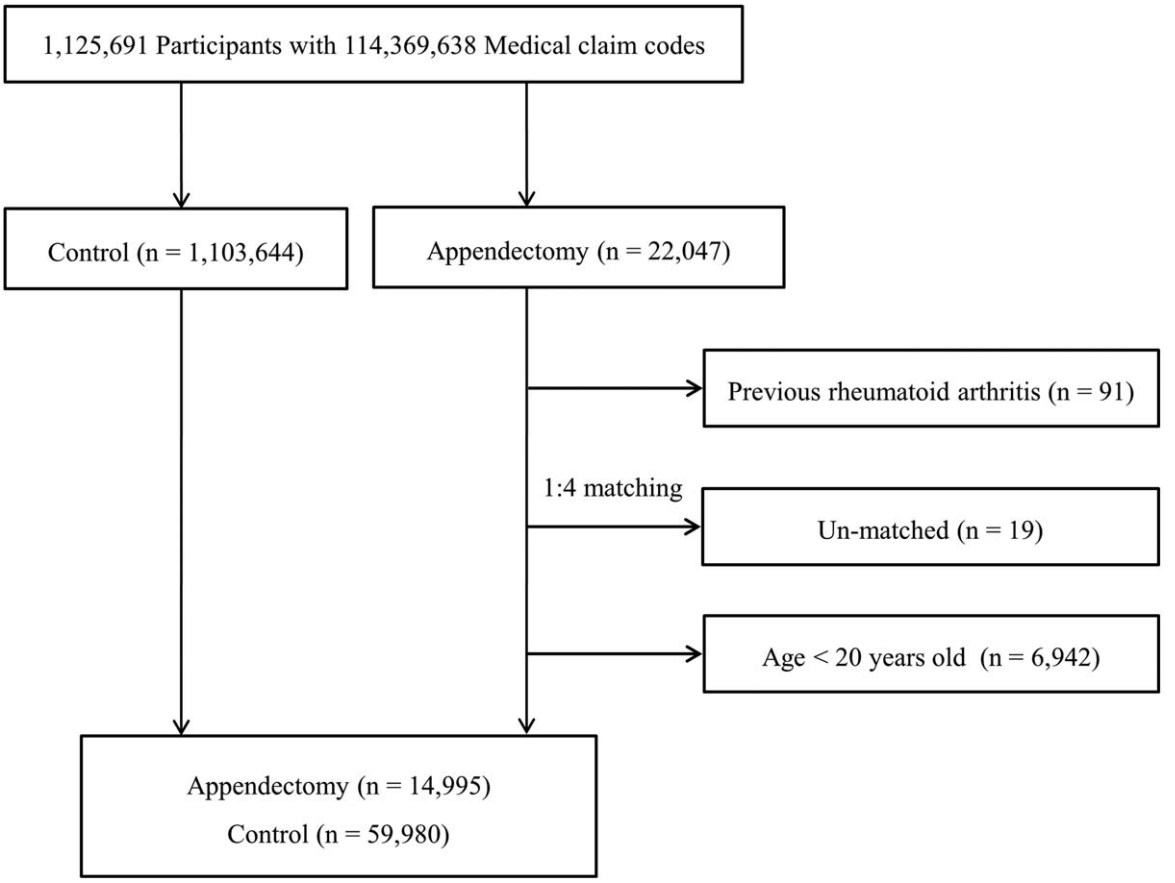


**Figure 1.** Schematic illustration of the participant selection process used in the present study. Among a total of 1,125,691 individuals, 14,995 appendectomy patients were matched with 59,980 control participants by age, group, sex, income group, region of residence, and prior medical history.

income]-class 5 [highest income]). Region of residence was initially divided into 16 areas based on administrative districts. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The participants' prior medical histories were evaluated using ICD-10 codes. To ensure an accurate diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were regarded as present if a participant was treated ≥ 2 times. Ischemic heart disease (I24 and I25) and cerebral stroke (I60-I66) were regarded as present if a participant was treated ≥1 time. Depression was defined based on ICD-10 codes from F31 (bipolar affective disorder) to F39 (unspecified mood disorder) recorded by a psychiatrist from 2002 to 2013. Among patients with such codes, we selected the participants who were treated ≥2 times. We included psoriasis (B02), systemic lupus erythematosus (M32), systemic sclerosis (M34), Sjogren syndrome (M350), dermatopolymyositis (M33), and polyarteritis nodosa and related conditions (M30) treated ≥1 time as the "autoimmune disease" variables.

### 2.4. Statistical analyses

Chi-square tests were used to compare the general characteristics between the appendectomy and control groups.

Stratified Cox proportional hazard models were used to assess HRs for appendectomy with respect to RA. In this analysis, crude (simple) and adjusted (for ischemic heart disease, cerebral stroke, depression, and autoimmune disease) models were used, and 95% confidence intervals (CIs) were calculated. Age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia were stratified. Kaplan–Meier analysis and the log-rank test were used.

For the subgroup analyses, we divided the participants by age (<40 years old, and ≥40 years old) and sex (men and women).

Two-tailed analyses were conducted, and *P*-values less than .05 were regarded as indicative of significance. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY).

## 3. Results

The mean follow-up was 68.5 months (standard deviation [SD] = 40.6) in the appendectomy group and 68.5 months (SD = 40.6) in the control group. The time interval between the index date and the occurrence of RA was 43.7 months (SD = 34.4) in the appendectomy group and 42.8 months (SD = 33.4) in the control group.

The rate of RA was not higher in the appendectomy group (0.4% [55/14,995]) than that in the control group (0.4% [210/59,980], $P = .758$; Table 1). The 2 groups of participants were identical with respect to general characteristics (age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories) due to matching ($P = 1.000$). The rates of ischemic heart disease, cerebral stroke, and depression and autoimmune disease were higher in the appendectomy group than those in the control group ($P < .05$ for each comparison).

The adjusted HR for RA was 1.06 (95% CI = 0.76–1.38) in the appendectomy group ($P = .883$; Table 2). Kaplan–Meier curves did not show differences between the appendectomy and control groups ($P = .774$; Fig. 2). In all of the subgroup analyses according to age and sex, the adjusted HRs for RA were not higher in the appendectomy group than those in the control group (Table 3).

**Table 1**

**General characteristics of the participants.**

| Characteristics | Total participants | | |
|---|---|---|---|
| | Appendectomy (n, %) | Control group (n, %) | *P*-value |
| Age (yr old) | | | 1.000 |
| 20–24 | 1815 (12.1) | 7260 (12.1) | |
| 25–29 | 2018 (13.5) | 8072 (13.5) | |
| 30–34 | 2045 (13.6) | 8180 (13.6) | |
| 35–39 | 1832 (12.2) | 7328 (12.2) | |
| 40–44 | 1617 (10.8) | 6468 (10.8) | |
| 45–49 | 1321 (8.8) | 5284 (8.8) | |
| 50–54 | 1181 (7.9) | 4724 (7.9) | |
| 55–59 | 886 (5.9) | 3544 (5.9) | |
| 60–64 | 701 (4.7) | 2804 (4.7) | |
| 65–69 | 603 (4.0) | 2412 (4.0) | |
| 70–74 | 460 (3.1) | 1840 (3.1) | |
| 75–79 | 283 (1.9) | 1132 (1.9) | |
| 80–84 | 171 (1.1) | 684 (1.1) | |
| 85+ | 62 (0.4) | 248 (0.4) | |
| Sex | | | 1.000 |
| Male | 7594 (50.6) | 30,376 (50.6) | |
| Female | 7401 (49.4) | 29,604 (49.4) | |
| Income | | | 1.000 |
| 1 (lowest) | 2188 (14.6) | 8752 (14.6) | |
| 2 | 2529 (16.9) | 10,116 (16.9) | |
| 3 | 3027 (20.2) | 12,108 (20.2) | |
| 4 | 3424 (22.8) | 13,696 (22.8) | |
| 5 (highest) | 3827 (25.5) | 15,308 (25.5) | |
| Region of residence | | | 1.000 |
| Urban | 6754 (45.0) | 27,016 (45.0) | |
| Rural | 8241 (55.0) | 32,964 (55.0) | |
| Hypertension | 3225 (21.5) | 12,900 (21.5) | 1.000 |
| Diabetes | 1648 (11.0) | 6592 (11.0) | 1.000 |
| Dyslipidemia | 2780 (18.5) | 11,120 (18.5) | 1.000 |
| Ischemic heart disease | 613 (4.1) | 1970 (3.3) | <.001* |
| Cerebral stroke | 919 (6.1) | 3203 (5.3) | <.001* |
| Depression | 1261 (8.4) | 4285 (7.1) | <.001* |
| Autoimmune disease | 1930 (12.9) | 6645 (11.1) | <.001* |
| Rheumatoid arthritis | 55 (0.4) | 210 (0.4) | .758 |

* Chi-square test.
Significance at $P < .05$.

**Table 2**

**Crude and adjusted hazard ratios (95% confidence interval) of appendectomy for rheumatoid arthritis.**

| Characteristics | Rheumatoid arthritis | | | |
|---|---|---|---|---|
| | Crude† | *P*-value | Adjusted†,‡ | *P*-value |
| Appendectomy | 1.06 (0.78–1.42) | .722 | 1.02 (0.76–1.38) | .883 |
| Control | 1.00 | | 1.00 | |

Cox-proportional hazard regression model, significance at $P < 0.05$.
† Stratified model for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, and depression histories.
‡ Adjusted model for ischemic heart disease, cerebral stroke, depression, and autoimmune disease histories.

## 4. Discussion

We could not find any positive or negative association between appendectomy and RA despite the large number of participants

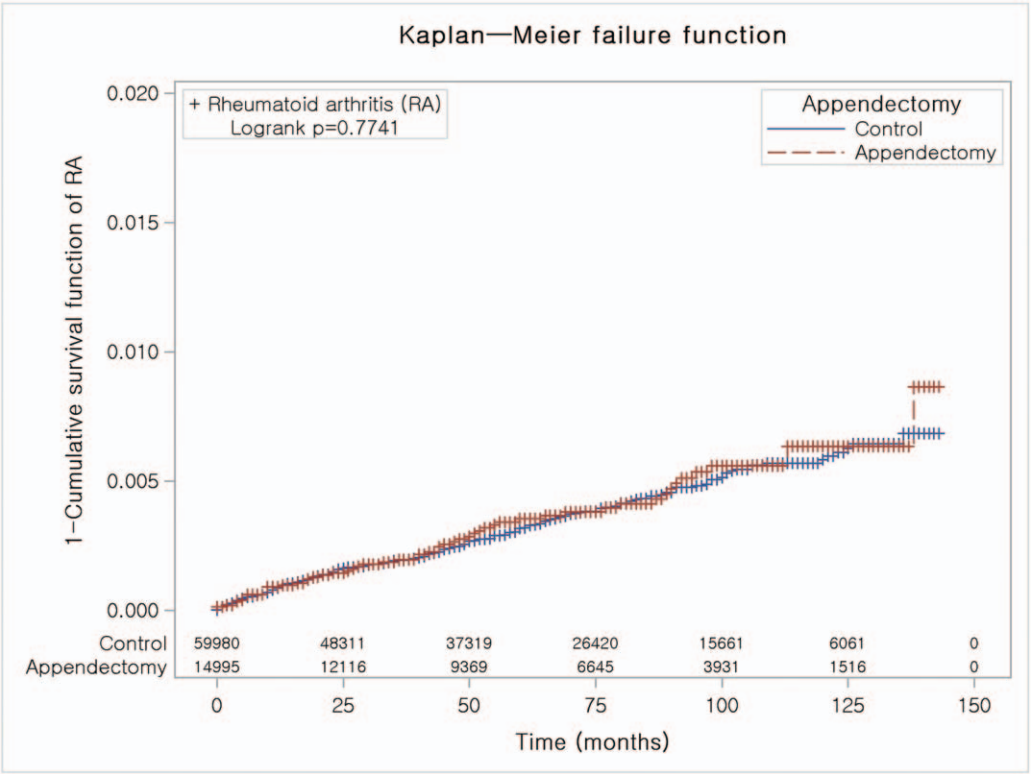


**Figure 2.** Kaplan–Meier curve for the rheumatoid arthritis risk of the appendectomy group and the control group.

(n = 74,975). In the subgroup analyses, the lack of an association between appendectomy and RA was consistent.

As stated above, 3 studies reported a positive association between appendectomy and RA,[1,2,8] while the pathophysiological association between them has not been clearly defined. Extensive evidence indicates that RA is an autoimmune disease mediated by immune cells, including T cells, B cells, dendritic cells, and fibroblasts.[14–16] RA is partly mediated by autoantibody production due to failure of the immune system to induce self-tolerance, and trials investigating the therapeutic application of oral tolerance agents to treat RA are ongoing.[17,18] Gut-associated lymphoid tissue (GALT) produces regulatory T cells from dendritic cells and can elicit immune tolerance by promoting regulatory T cell generation or inducing T-cell deletion/anergy.[19,20] As a part of the GALT in the human immune system, the appendix may have a role in the induction of self-tolerance to autoantigens, and removal of the appendix can potentially predispose individuals to RA.

**Table 3**

**Subgroup analyses of crude and adjusted hazard ratios (95% confidence interval) of appendectomy for rheumatoid arthritis according to age and sex.**

| | Rheumatoid arthritis | | | |
|---|---|---|---|---|
| **Characteristics** | **Crude**[†] | ***P*-value** | **Adjusted**[†,‡] | ***P*-value** |
| Age <40 yr old (n = 38,550) | | | | |
| Appendectomy | 1.16 (0.67–2.03) | .600 | 1.16 (0.66–2.02) | .613 |
| Control | 1.00 | | 1.00 | |
| Age ≥40 yr old (n = 36,425) | | | | |
| Appendectomy | 1.02 (0.72–1.45) | .923 | 0.98 (0.69–1.40) | .915 |
| Control | 1.00 | | 1.00 | |
| Men (n = 37,970) | | | | |
| Appendectomy | 0.88 (0.48–1.61) | .684 | 0.87 (0.48–1.59) | .656 |
| Control | 1.00 | | 1.00 | |
| Women (n = 37,005) | | | | |
| Appendectomy | 1.12 (0.80–1.58) | .505 | 1.07 (0.76–1.52) | .691 |
| Control | 1.00 | | 1.00 | |

Cox-proportional hazard regression model, significance at $P < .05$.

[†] Stratified model for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, and depression histories.

[‡] Adjusted model for ischemic heart disease, cerebral stroke, depression, and autoimmune disease histories.

Moreover, some reports link the appendix to various immunologic functions in human intestinal health in relation to the gut microbiota.[21–23] As a component of GALT, the appendix functions as a lymphoid organ and a reservoir of microorganism in the gut.[24,25] In human disease, especially ulcerative colitis (UC), large population-based studies have reported a low appendectomy rate in UC patients and a decreased incidence of UC after appendectomy.[26–28] In this context, removal of lymphoid tissue may alter immune function and affect the course of RA since RA is a systemic autoimmune inflammatory disease.[29]

However, Moens et al found no significant difference in appendectomy between 1194 osteoarthritis (OA) and 1524 RA patients.[4] Linos et al reached the same conclusion with 229 RA participants and 458 matched control subjects.[3] Eftekharian et al demonstrated an inverse relationship in 116 RA and 117 control patients who underwent appendectomy.[5] Ter Borg et al reported higher appendectomy rates in a fibromyalgia group than those in an RA group.[6] Patel et al reported an appendectomy rate of 18.5% in RA patients and a rate of 32.2% in OA patients.[7] We think that removal of the appendix may not be sufficient to affect the systemic immune responses.

The advantages of this study are consistent with those of our prior studies using the NHIS-NSC.[30–32] The data that we have analyzed correspond to a very large, representative, nationwide Korean population. We used relatively reliable inclusion criteria in that operation codes were strictly supervised by the NHIS, and the definition of RA was validated in previous studies.[12,13] All medical clinics or hospital visits were recorded by the NHIS without exception since it is the only national health insurance system. We adjusted for age, sex, income, region of residence, and prior medical history to avoid confounding effects.

However, our study has several limitations. Because we used health insurance claim codes, participants who did not visit a medical institution for RA may not have been included in this study. Even though we used the verified method following the previous study, some RA patients might be included or excluded due to the inaccurate diagnosis according to clinicians. We did not analyze the relationship between RA and appendectomy according to the severity of RA among the participants. Some participants with mild symptoms of RA or appendicitis may have been excluded. Although HIRA-NSC includes more than 1 million patients, only 74,975 patients were included in this study because the number of appendectomy recipients was smaller than 15,000. A larger number of patients from a larger cohort could have resulted in more statistical power in the analyses. The mean follow-up was 68.5 months in both appendectomy and control groups, and RA can occur after this follow-up, a study with a longer follow-up period would provide stronger results. Other possible confounders, such as obesity, smoking, alcohol use, dietary habits, other diseases which were not adjusted, and medication histories were not included. This study only included a Korean population, and the results cannot be generalized to the other ethnic groups, such as Chinese or Caucasian populations.

## 5. Conclusion

We could not identify any significant relationship between appendectomy and RA. Given that appendectomy is one of the most common operative procedures, this study may have clinical significance by providing evidence of no association between appendectomy and RA from the analysis of extensive population-based data.

## Author contributions

**Conceptualization:** Hyo Geun Choi, Miyoung Kim, Il Gyu Kong.
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**Formal analysis:** Hyo Geun Choi, Chanyang Min, Il Gyu Kong.
**Funding acquisition:** Il Gyu Kong.
**Investigation:** Dong Jun Oh, Miyoung Kim, Sunmi Kim, Il Gyu Kong.
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**Validation:** Hyo Geun Choi, Miyoung Kim, Sunmi Kim, Il Gyu Kong.
**Visualization:** Il Gyu Kong.
**Writing – original draft:** Hyo Geun Choi, Il Gyu Kong.
**Writing – review & editing:** Hyo Geun Choi, Dong Jun Oh, Miyoung Kim, Sunmi Kim, Il Gyu Kong.

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