Incidence of Psoriasis in Patients with Inflammatory Bowel Disease: A Nationwide Population-Based Matched Cohort Study

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Keywords

Inflammatory bowel disease · Psoriasis · Incidence

Abstract

Background: Emerging data suggest that inflammatory bowel disease (IBD) and psoriasis are associated, sharing common genetic predispositions and immunological mechanisms. However, concrete data on psoriasis risk in IBD patients compared to the general population are limited. **Objective:** We investigated the risk of developing psoriasis in IBD patients compared to controls without IBD. **Methods:** Using the Korean National Health Insurance Database, patients diagnosed with Crohn's disease (CD) or ulcerative colitis (UC) between 2005 and 2008 were age- and sex-matched 1:4 to non-IBD subjects from 2003 to 2018. IBD patients were defined by combining the International Classification of Diseases 10th revision code and at least one prescription of IBD-

specific medications. Disease phenotypes, including psoriasis severity and psoriatic arthritis, were also identified. We investigated newly diagnosed psoriasis from 2009 to 2018. Incidence rates and risk of psoriasis were assessed with multivariate Cox regression models. Subgroup analyses for age and sex, and sensitivity analysis involving tumor necrosis factor (TNF) inhibitor-naïve patients were performed. **Results:** During nearly a decade of follow-up, 20,152 IBD patients were identified (14,619 [72.54%] UC and 5,533 [27.46%] CD). Among them, 439 patients were newly diagnosed with psoriasis (incidence rate of 217.68 per 100,000 person-years and 228.62 per 100,000 person-years for UC and CD, respectively). The psoriasis risk was higher in IBD patients than in the matched controls (adjusted hazard ratio, aHR, 2.95, 95% confidence interval, CI, 2.60–3.33). Moreover, IBD patients aged <30 years were at an increased risk (aHR 3.35, 95% CI 2.58–4.35), a trend that was unchanged across all psoriasis phenotypes. Sensitivity analysis of TNF inhibitor-naïve pa-

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tients revealed consistent results. **Conclusions:** IBD patients were more likely to develop psoriasis compared to non-IBD subjects, including younger patients at an elevated risk regardless of TNF inhibitor use. This advocates the interplay between IBD and psoriasis; thus, inspection of cutaneous manifestation and dermatological consultation may be helpful in IBD patients at risk.

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Introduction

Inflammatory bowel disease (IBD), typically identified as Crohn's disease (CD) and ulcerative colitis (UC), is an immune-mediated intestinal inflammatory condition which causes relapsing and remitting chronic abdominal pain and/or hematochezia. The global incidence and prevalence of IBD is rapidly increasing with industrialization and changing lifestyles, particularly in Asian countries [1, 2]. Therefore, the association between IBD and other immune-related disorders is being vigorously explored [3]. In particular, psoriasis, previously thought to be a localized cutaneous disease, is now considered an immune-mediated systemic inflammatory disorder with a variety of comorbidities such as IBD [4].

The 2 seemingly different disease entities share a similar pathogenesis which is not fully understood [5]. Multiple genetic susceptibility loci were found to be common between the 2 conditions, while several environmental factors such as stress, smoking, and dietary habits are shared risk factors [6, 7]. Additionally, they both relate to defects in barriers as well as immune mechanisms involv-

ing T-helper cells and subsequent cytokine pathways [5, 8]. Not only do they have overlapping mechanisms, but they are also treated with similar modalities, such as systemic agents and biologics, namely tumor necrosis factor (TNF) inhibitors and interleukin (IL)-12/23 inhibitors.

Previous studies have explored on the epidemiological association between psoriasis and IBD, including a comprehensive meta-analysis which revealed the interaction to be bidirectional [9]. The presence of psoriasis was significantly associated with IBD (odds ratio [OR] 2.0) and vice versa (OR 1.8). Pooled prevalence of psoriasis was 4.2% in the IBD population, and that of IBD was 1.2% in the psoriasis population. In addition, a recent meta-analysis added data on the incidence of IBD in the psoriasis population [10]. In this study, patients with psoriasis had a 2.53-fold increased risk of developing CD and a 1.71-fold increased risk of developing UC, compared with individuals in a control group [11]. Although we can infer that the incidence of psoriasis may also be higher in the IBD population considering bidirectional association and previously reported data on the prevalence [12], there are few studies that report this association. Therefore, we estimated the incidence of psoriasis in patients with IBD compared to controls without IBD and performed additional analysis to clarify demographic characteristics of those at higher risk of developing psoriasis.

Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000514030 for all online suppl. material) (Fig. 1) [12–16].

Fig. 1. Flowchart of Materials and Methods. KNHIS, Korean National Health Insurance Service; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

Table 1. Demographics of the study population

	Total (n = 1,00,760)	IBD (n = 20,152)	Control (n = 80,608)	UC (n = 14,619)	Control (n = 58,476)	CD (n = 5,533)	Control (n = 22,132)
Sex, n (%)							
Male	57,775 (57.3)	11,555 (57.3)	46,220 (57.3)	8,012 (54.8)	32,048 (54.8)	3,543 (64.0)	14,172 (64.0)
Female	42,985 (42.7)	8,597 (42.7)	34,388 (42.7)	6,607 (45.2)	26,428 (45.2)	1,990 (36.0)	7,960 (36.0)
Age (mean ± SD), years	44.06±16.92	44.04±16.97	44.07±16.89	46.68±16.16	46.64±16.27	37.16±16.83	37.16±16.88
Age distribution, n (%)							
<10 years	240 (0.2)	48 (0.2)	192 (0.2)	24 (0.2)	96 (0.2)	24 (0.4)	96 (0.4)
10–19 years	5,240 (5.2)	1,048 (5.2)	4,192 (5.2)	444 (3.0)	1,776 (3.0)	604 (10.9)	2,416 (10.9)
20–29 years	18,315 (18.2)	3,663 (18.2)	14,652 (18.2)	1,941 (13.3)	7,764 (13.3)	1,722 (31.1)	6,888 (31.1)
30–39 years	19,630 (19.5)	3,926 (19.5)	15,704 (19.5)	2,854 (19.5)	11,416 (19.5)	1,072 (19.4)	4,288 (19.4)
40–49 years	19,730 (19.6)	3,946 (19.6)	15,784 (19.6)	3,135 (21.4)	12,540 (21.4)	811 (14.7)	3,244 (14.7)
50–59 years	17,375 (17.2)	3,475 (17.2)	13,900 (17.2)	2,871 (19.6)	11,484 (19.6)	604 (10.9)	2,416 (10.9)
60–69 years	11,650 (11.6)	2,330 (11.6)	9,320 (11.6)	1,930 (13.2)	7,720 (13.2)	400 (7.2)	1,600 (7.2)
70–79 years	6,895 (6.8)	1,379 (6.8)	5,516 (6.8)	1,149 (7.9)	4,596 (7.9)	230 (4.2)	920 (4.2)
≥80 years	1,685 (1.7)	337 (1.7)	1,348 (1.7)	271 (1.9)	1,084 (1.9)	66 (1.2)	264 (1.2)
Types of health insurance program, n (%)							
National health insurance	96,947 (96.2)	19,074 (94.7)	77,873 (96.6)	13,851 (94.7)	56,441 (96.5)	5,223 (94.4)	21,432 (96.8)
Medical aid	3,813 (3.8)	1,078 (5.4)	2,735 (3.4)	768 (5.3)	2,035 (3.5)	310 (5.6)	700 (3.2)

Table 2. Risk of developing psoriasis in patients with inflammatory bowel disease

	Total number	Number of incident cases	Number of person- years	Incident rate (per 10 ⁶ person-years)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	p value
Risk for incident psoriasis							
Non-IBD controls	80,555	601	8,02,531.62	74.89	1 (ref.)	1 (ref.)	
IBD	20,108	439	1,98,924.56	220.69	2.95 (2.61–3.33)	2.95 (2.60–3.33)	<0.0001
UC control	58,430	441	5,82,138.01	75.76	1 (ref.)	1 (ref.)	
UC	14,582	314	1,44,249.68	217.68	2.87 (2.49–3.32)	2.87 (2.49–3.32)	<0.0001
CD control	22,125	160	2,20,393.62	72.60	1 (ref.)	1 (ref.)	
CD	5,526	125	54,674.89	228.62	3.15 (2.49–3.98)	3.15 (2.49–3.98)	<0.0001
Risk for incident mild psoriasis							
Non-IBD controls	80,304	350	8,01,364.61	43.68	1 (ref.)	1 (ref.)	
IBD	19,924	255	1,97,958.32	128.81	2.95 (2.51–3.47)	2.95 (2.51–3.47)	<0.0001
UC control	58,257	268	5,81,299.13	46.10	1 (ref.)	1 (ref.)	
UC	14,457	189	1,43,582.75	131.63	2.85 (2.37–3.44)	2.85 (2.37–3.44)	<0.0001
CD control	22,047	82	2,20,065.48	37.26	1 (ref.)	1 (ref.)	
CD	5,467	66	54,375.58	121.38	3.26 (2.36–4.50)	3.26 (2.36–4.51)	<0.0001
Risk for incident moderate to severe psoriasis							
Non-IBD controls	80,205	251	8,00,926.07	31.34	1 (ref.)	1 (ref.)	
IBD	19,853	184	1,97,710.13	93.07	2.97 (2.46–3.59)	2.97 (2.46–3.59)	<0.0001
UC control	58,162	173	5,80,887.75	29.78	1 (ref.)	1 (ref.)	
UC	14,393	125	1,43,386.02	87.18	2.93 (2.33–3.68)	2.93 (2.33–3.69)	<0.0001
CD control	22,043	78	2,20,038.32	35.45	1 (ref.)	1 (ref.)	
CD	5,460	59	54,324.11	108.61	3.06 (2.18–4.30)	3.06 (2.18–4.30)	<0.0001
Risk for incident psoriatic arthritis							
Non-IBD controls	80,007	53	7,99,999.68	6.63	1 (ref.)	1 (ref.)	
IBD	19,713	44	1,96,923.04	22.34	3.37 (2.26–5.03)	3.38 (2.27–5.05)	<0.0001
UC control	58,035	46	5,80,258.72	7.93	1 (ref.)	1 (ref.)	
UC	14,305	37	1,42,875.08	25.90	3.27 (2.12–5.04)	3.28 (2.13–5.05)	<0.0001
CD control	21,972	7	2,19,740.95	3.19	1 (ref.)	1 (ref.)	
CD	5,408	7	54,047.96	12.95	4.07 (1.43–11.59)	4.09 (1.44–11.66)	0.0084

Results

Characteristics of the Study Population

A total of 20,152 IBD patients were identified between 2005 and 2008 (14, 619 [72.54%] UC patients and 5, 533 [27.46%] CD patients). The baseline characteristics of the study population are displayed in Table 1. The mean fol-

low-up periods for control and IBD patients were 9.96 and 9.89 years, respectively. The health insurance types were not matched for the control, and a larger proportion of IBD patients were medical aid beneficiaries (5.4 vs. 3.4%, $p < 0.001$). This trend remained consistent both for CD and UC participants.

Fig. 2. Subgroup analysis to assess the risk of psoriasis in patients with IBD by age and sex. CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Incidence and Risk of Psoriasis in CD and UC Patients

Overall, 439 patients were newly diagnosed with psoriasis in the IBD group and 601 in the 1:4 matched controls (incidence rate 220.69 vs. 74.89 per 100,000 person-years) (Table 2). The majority of the newly developed cases were plaque type psoriasis (825/1,040 cases, 79.3%). Further adjustment for age and insurance type revealed an increased risk of developing psoriasis in IBD patients (adjusted hazard ratio [aHR] 2.95, 95% confidence interval [CI] 2.60–3.33, $p < 0.001$). The risks were also increased in CD (aHR 3.15, 95% CI 2.49–3.98) and UC (aHR 2.87, 95% CI 2.49–3.32) groups, respectively, when compared with matched controls.

Subclassifying psoriasis according to psoriasis severity showed consistent outcomes of elevated hazard ratios in IBD patients. The risk of incident psoriatic arthritis was also elevated in all IBD patients; both CD and UC subgroups posed increased risks.

Subgroup Analyses Regarding Psoriasis

Further subgroup analyses were performed upon stratification by sex and age (Fig. 2). In terms of age, the risk of developing psoriasis was consistently greater in all age groups, including those younger than 30 years. With regard to gender differences, both male and female patients with IBD demonstrated an increased risk of psoriasis. Further analyses conducted on disease severity revealed consistent findings (online suppl. Fig. 1 and 2). Subgroup analyses with psoriatic arthritis by age and sex also revealed an increased risk of developing in both female CD and UC patients (online suppl. Table 1).

Sensitivity Analysis

Acknowledging the increasing evidence of paradoxical psoriasiform reactions secondary to TNF inhibitors [16], we performed further sensitivity analysis in TNF inhibitor-naïve patients to provide robustness to our conclusion. The outcomes in the sensitivity analysis generally agreed with the main results (Table 3). Regardless

Table 3. Sensitivity analysis: risk of psoriasis in TNF inhibitor-naïve patients with IBD

	Total number	Number of incident cases	Number of person-years	Incident rate (per 10 ⁶ person-years)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	p value
Risk for incident psoriasis							
Non-IBD controls	70,969	385	7,06,927.15	76.1	1 (ref.)	1 (ref.)	
IBD	17,713	538	1,75,160.33	219.8	2.89 (2.53–3.29)	2.89 (2.53–3.29)	<0.0001
UC control	54,571	412	5,43,533.29	75.8	1 (ref.)	1 (ref.)	
UC	13,617	295	1,34,657.67	219.1	2.89 (2.49–3.35)	2.89 (2.49–3.35)	<0.0001
CD control	16,398	126	1,63,393.86	77.1	1 (ref.)	1 (ref.)	
CD	4,096	90	40,502.66	222.2	2.88 (2.20–3.78)	2.88 (2.20–3.78)	<0.0001
Risk for incident mild psoriasis							
Non-IBD controls	70,737	306	7,05,858.62	43.4	1 (ref.)	1 (ref.)	
IBD	17,553	225	1,74,351.39	129.0	2.98 (2.51–3.53)	2.98 (2.51–3.53)	<0.0001
UC control	54,404	245	5,42,820.12	45.1	1 (ref.)	1 (ref.)	
UC	13,503	181	1,34,074.00	135.0	2.99 (2.47–3.62)	2.99 (2.47–3.62)	<0.0001
CD control	16,333	61	1,63,038.51	37.4	1 (ref.)	1 (ref.)	
CD	4,050	44	40,277.39	109.2	2.92 (1.98–4.30)	2.92 (1.98–4.31)	<0.0001
Risk for incident moderate to severe psoriasis							
Non-IBD controls	70,663	232	7,05,571.49	32.9	1 (ref.)	1 (ref.)	
IBD	17,488	160	1,74,136.42	91.9	2.79 (2.28–3.42)	2.79 (2.28–3.42)	<0.0001
UC control	54,326	167	5,42,451.55	30.8	1 (ref.)	1 (ref.)	
UC	13,436	114	1,33,840.17	85.2	2.77 (2.18–3.51)	2.77 (2.18–3.51)	<0.0001
CD control	16,337	65	1,63,119.93	39.8	1 (ref.)	1 (ref.)	
CD	4,052	46	40,296.25	114.2	2.87 (1.96–4.18)	2.87 (1.96–4.18)	<0.0001
Risk for incident psoriatic arthritis							
Non-IBD controls	70,486	55	7,04,735.85	7.8	1 (ref.)	1 (ref.)	
IBD	17,371	43	1,73,499.21	24.8	3.18 (2.13–4.73)	3.19 (2.14–4.75)	<0.0001
UC control	54,204	45	5,41,930.97	8.3	1 (ref.)	1 (ref.)	
UC	13,359	37	1,33,412.49	27.7	3.34 (2.16–5.16)	3.35 (2.17–5.17)	<0.0001
CD control	16,282	10	1,62,804.88	6.1	1 (ref.)	1 (ref.)	
CD	4,012	6	40,086.72	15.0	2.44 (0.89–6.70)	2.45 (0.89–6.78)	0.0822

of age and sex, IBD patients were at an increased risk of developing psoriasis, across all psoriasis phenotypes (online suppl. Table 2).

Discussion

To the best of our knowledge, this is the first study comparing the incidence of psoriasis in patients with IBD with a non-IBD population. We discovered a more than 2-fold increase in the risk of developing psoriasis and psoriatic arthritis in the IBD population compared with age- and sex-matched non-IBD subjects. This trend remained unaffected in various analyses including multivariate analysis, subgroup analyses by age and sex, and sensitivity analysis in TNF inhibitor-naïve IBD patients.

This association between psoriasis and IBD may be ascribed to the fact that they share a common pathogenesis. First, there are common genetic susceptibility loci [17]. Genome-wide association studies consisting of more than 4,500 patients and 10,000 controls identified 7 non-HLA susceptibility loci shared between CD and psoriasis (9p24 near JAK2, 10q22 at ZMIZ1, 11q13 near PRDX5,

16p13 near SOCS1, 19p13 near FUT2, 17q21 at STAT3, 22q11 at YDJC) and also confirmed 4 already established common risk loci (IL23R, IL12B, REL, and TYK2) [8]. Regarding the Th17 cell pathway with a pivotal role in the pathogenesis of psoriasis and IBD, CD and psoriasis appear to share more risk loci points (IL12B, JAK2, STAT3, CCR6, and TNFSF15) than UC [18, 19]. Moreover, the high risk of developing psoriasis in the younger IBD population may be partially due to shared genetic polymorphisms and traits. Considering that various extraintestinal manifestations are also more common in the younger IBD patients, they may have distinguished disease phenotypes and underlying mechanisms.

Second, gut dysbiosis is commonly observed in both IBD and psoriasis [20]. Gut microbiota play a crucial role in skin homeostasis by affecting epidermal differentiation signaling pathways [21]. Certain types of bacteria, including *Parabacteroides* and *Coprobacillus*, are lost in abundance in both psoriasis and IBD [22]. Theoretically, a decrease in these beneficial bacteria phyla may drive alteration in immune tolerance and inflammation. For example, *Faecalibacterium prausnitzii*, a colonizer known to be beneficial, acts as a source for butyrate, which has anti-

oxidative and anti-inflammatory functions by triggering regulatory T cells [23]. Levels of this species drop particularly in psoriasis patients as well as IBD patients [22, 24]. It can be postulated that these metabolites can also act directly on distant organs, such as skin, via systemic circulation as DNA of the gut microbiome can be isolated from the blood of patients with psoriasis [25].

Third, psoriasis and IBD share similar immunological mechanisms. TNF- α plays a role in the pathogenesis of CD, UC, and psoriasis. Meanwhile, CD has been associated with the Th1 immune response, while UC has a Th2 cytokine profile. Recent studies demonstrate that Th17 cells also have an important role in IBD, particularly CD [19]. Similarly to CD, the role of Th1 and Th17 cells has been regarded as prominent in the immunopathogenesis of psoriasis [26]. Along with genetic concordance, the common immunological aberration may also explain the strong link between psoriasis and IBD as shown in the present study.

Stratified analysis according to age and sex revealed unaffected results of increased psoriasis risk. Especially, it can be inferred that those at a young age (<30 years) are also at a particular risk for the development of all psoriasis subtypes in IBD patients. The recent literature suggests an increased risk of myocardial infarction in patients with IBD, especially in the younger population [27, 28]. Similarly, the risk of myocardial infarction is also associated with psoriasis; the association is strongest in the young and diminished with age [29]. Both young-age psoriasis and IBD are thought to be more debilitating and aggressive, maybe involving higher inflammation and lower immune-regulatory levels. It implies that cautious monitoring and active risk factor reduction may be warranted, especially for young IBD patients, as they are at an increased risk for not only psoriasis, but also for other shared comorbidities.

Previous studies have reported paradoxical psoriasiform reactions secondary to TNF inhibitors [3]. A recent publication involving Korean claims data also demonstrated an increased risk of psoriasiform diseases in IBD patients treated with TNF inhibitors [16]. Although the underlying mechanism is not fully disclosed, the current hypothesis supports intermingling of complex mechanisms, including cytokine and T-cell imbalance, as a result of TNF- α inhibition [8, 30, 31]. This paradoxical phenomenon may have exaggerated the incidence of psoriasis in IBD patients. Thus, we performed sensitivity analysis to overcome this limitation and found that the risk of developing psoriasis was not affected. This supports the idea that even with paradoxical psoriasis lesions, IBD itself is still an independent risk factor for the development of psoriasis.

This study has some limitations. First, the disease phenotypes of IBD were not considered, which is an inevitable drawback of using claims data. The South Korean reimbursement system does not allow for a “top-down approach” in treating IBD with biologics, that is, only severe, steroid-refractory patients are prescribed with biologic agents. Thus, we could consider the internal validation analysis group with TNF inhibitor-naïve subjects as those with mild disease forms. This may add nuance to the unchanged risks of psoriasis even in patients with mild IBD. Second, only Korean residents were included in the study population, yielding a largely homogenous ethnic group. The statistical power of the calculated incidence rate and risks may vary among different ethnicities. Future studies involving various ethnic backgrounds could provide further concrete evidence in generalization. Third, a chance of misclassification cannot be excluded due to inbuilt limitation of using the claims data. However, the operational diagnosis used in the present study demonstrated considerable sensitivity and specificity in the separate validation studies. Fourth, a chance of misclassification cannot be excluded due to inbuilt limitation of using the claims data. However, the operational diagnosis used in the present study demonstrated considerable sensitivity and specificity in the separate validation studies. Lastly, IBD and psoriasis have common treatment modalities, such as cyclosporine, methotrexate and TNF- α inhibitors. The database system cannot differentiate which drug is for which disease. However, oral cyclosporine and methotrexate have rapidly lost their position as IBD-specific medication in Korea since the introduction of biologics and reimbursement of infliximab and adalimumab in 2006 and 2007, respectively. In contrast, oral cyclosporine and methotrexate are continuously commonly used in psoriasis. Thus, it can be inferred that IBD patients between 2005 and 2008 had these drugs for IBD, because we excluded the patients with a psoriasis history prior to 2009. Meanwhile, IBD patients with the newly diagnosed psoriasis between 2009 and 2018 would have taken the drugs for psoriasis. Moreover, for TNF- α inhibitors, we have performed sensitivity analysis to minimize the bias.

In spite of the limitations, we were able to estimate the incidence and risk of psoriasis in established IBD patients with a nationwide database. Since IBD is a rare disease, especially in Asian countries, investigating the incidence of psoriasis in IBD is challenging. We could overcome the problem utilizing a large cohort and the most updated and well-established operational definition of IBD with high specificity and sensitivity [14]. We also believe that the data on incidence provide more robust evidence for

the causal relationship of psoriasis in IBD patients, compared to the prevalence data.

In conclusion, this nationwide control-matched cohort study demonstrated that IBD patients are more susceptible to developing psoriasis. The incidence of psoriasis in IBD was 220.7 per 100,000 person-years, while that of non-IBD controls was 74.9 per 100,000 person-years. The risk was also elevated in younger IBD patients regardless of disease severity and TNF inhibitor use. In addition to various shared pathogenic mechanisms and paradoxical psoriasis-form reactions, this association between IBD and psoriasis may support the interplay between the 2 diseases.

Key Message

IBD patients were more likely to develop psoriasis, including the young, regardless of tumor necrosis factor inhibitor use.

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Statement of Ethics

The study was exempted by the Institutional Review Board of Seoul Metropolitan Government-Seoul National University Boramae Medical Center (IRB No. 07-2019-24).

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.M.M. was involved in analysis and interpretation of data, and drafting and critical revision of the manuscript. J.Y.L. was involved in the acquisition of data, analysis and interpretation of data, and critical revision of the manuscript. S.-J.K. and H.P. were involved in the study concept and design, interpretation of data, drafting of the manuscript, funding acquisition, critical revision of the manuscript for important intellectual content, and study supervision. S.K. was involved in acquisition and analysis of data, and critical revision of the manuscript. H.S. and H.J.L. were involved in interpretation of data and critical revision of the manuscript. J.P.I. was involved in interpretation, critical revision of the manuscript, and funding acquisition. J.S.K. was involved in interpretation, critical revision of the manuscript, and study supervision.

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