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Original Article

The effectiveness of tumor necrosis factor-α blocker therapy in patients with axial spondyloarthritis who failed conventional treatment: a comparative study focused on improvement in ASAS Health Index

Ah-Ra Choi, M.S.[1,2], Ki-Jeong Park, M.D.[1], Ji-Hyoun Kang, M.D., Ph.D.[1], Yu Jeong Lee, M.S.[1,3], Hyun Hee Jang, M.S.[1], Moon-Ju Kim, Ph.D.[1], Tae-Jong Kim, M.D., Ph.D.[1]

[1]Department of Rheumatology, Chonnam National University Medical School and Hospital, [2]College of Nursing, Chonnam National University, [3]Department of Biomedical Sciences, Graduate School of Chonnam National University, Gwangju, Korea

Objective: The purpose of this study is to evaluate the impact of tumor necrosis factor (TNF)-α blocker therapy on the Assessment of SpondyloArthritis international Society Health Index (ASAS-HI) among patients who have failed conventional nonsteroidal anti-inflammatory drugs.

Methods: A comparative study was conducted involving axial spondyloarthritis (axSpA) patients treated with either TNF-α blocker or conventional therapy. Patient data, including demographics, disease characteristics, and ASAS-HI scores, were collected before and after treatment. Statistical analysis was performed to compare changes in ASAS-HI scores between the TNF-α blocker and the conventional therapy group.

Results: The study population consisted of patients with axSpA, with a mean age of 38.3 years in conventional treatment group and 29.3 years in TNF-α blocker group. Most variables, including C-reactive protein levels, other comorbidities, and disease assessment scores showed no significant difference between groups. Longitudinal analysis within each treatment group from Week 0 to 12 showed no significant change in the conventional treatment group, whereas the TNF-α blocker group experienced a significant reduction in ASAS-HI scores, demonstrating the effectiveness of the treatment. The TNF-α blocker group exhibited a significantly greater improvement in ASAS-HI scores compared to the conventional therapy group. The Bath Ankylosing Spondylitis Functional Index and the Bath Ankylosing Spondylitis Disease Activity Index demonstrated strong positive correlations with ASAS-HI scores, indicating higher disease activity and functional limitation are associated with worse health outcomes in patients.

Conclusion: The research demonstrates that ASAS-HI scores significantly improve with TNF-α blocker therapy in axSpA patients, underscoring ASAS-HI's effectiveness as a tool for evaluating drug responses.

Keywords: Axial spondyloarthritis, Tumor necrosis factor-α blocker, Assessment of SpondyloArthritis international Society Health Index

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease primarily affecting the axial skeleton, often resulting in significant morbidity and impaired quality of life (QoL) for affected individuals. Over the past few decades, the introduction

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Corresponding author: Tae-Jong Kim, https://orcid.org/0000-0002-2871-1635
Department of Rheumatology, Chonnam National University Medical School and Hospital, 42 Jebong-ro, Dong-gu, Gwangju 61469, Korea. **E-mail:** ktj1562@jnu.ac.kr

of biologic agents targeting tumor necrosis factor (TNF)-α has revolutionized the management of axSpA, offering new hope for patients with inadequate responses to conventional therapies [1].

Despite these advancements, there remains a need to comprehensively evaluate the comparative effectiveness of TNF-α blocker therapy versus conventional treatment in improving health outcomes among axSpA patients. Traditionally, clinical assessments and research in axSpA have predominantly focused on objective measures such as disease activity scores, radiographic progression, and laboratory markers. While these metrics provide valuable insights into disease pathology and treatment efficacy, they may not fully capture the holistic burden of axSpA on patients' lives. QoL encompasses a multidimensional construct, including physical, emotional, social, and functional well-being, which are all profoundly affected by axSpA. Recognizing and addressing the impact of axSpA on QoL is paramount for providing comprehensive and patient-centered care. Improving QoL outcomes requires a holistic approach that goes beyond symptom management to address the broader psychosocial and functional aspects of the disease. Furthermore, incorporating patient-reported outcomes and perspectives into clinical research and decision-making processes is essential for ensuring that interventions align with patients' priorities and values.

The Assessment of SpondyloArthritis international Society Health Index (ASAS-HI) serves as a valuable tool for assessing the various dimensions of health-related QoL in axSpA patients, encompassing physical function, pain, sleep, emotional well-being, and fatigue [2]. However, limited research has compared the impact of TNF-α blocker therapy and conventional treatment on ASAS-HI scores in this patient population.

Therefore, the purpose of this study is to evaluate the impact of TNF-α blocker therapy on the ASAS-HI among patients who have failed conventional nonsteroidal anti-inflammatory drug (NSAID) treatments.

MATERIALS AND METHODS

Study design

In this observational cohort study, patients with axSpA receiving treatment at a tertiary healthcare facility between May 2022 and July 2023 were recruited. Based on their treatment approach, participants were categorized into two groups: one receiving TNF-α inhibitor therapy and the other undergoing standard treatment. Consent was secured from all individuals involved, and the research received approval from the Ethics Committee/Institutional Review Board of Chonnam National University Hospital (IRB no. CNUBH-2021-016).

Patients and data collection

The patients with SpA fulfilling the ASAS classification criteria for axSpA were recruited [3]. Those with active SpA, defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of 4 or higher at baseline, and individuals with a Visual Analogue Scale (VAS) score for back pain of 40 mm or higher (on a scale of 0 to 100 mm) at baseline were included. Furthermore, patients were required to have been taking at least two nonsteroidal anti-inflammatory drugs (NSAIDs) at approved dosages for a total duration of 4 weeks or more before stratified and demonstrated an inadequate response or partial response to each NSAID for at least 2 weeks. Exclusion criteria for the study includes patients with: (1) complete ankylosis of the spine, (2) evidence of ongoing infection or malignancy within the last 3 months before screening, (3) previous receipt of immunosuppressive therapy causing immunosuppression, (4) active systemic infections, excluding the common cold, or recurrent infections within the last 2 weeks, or (5) a history of lymphoproliferative disease or malignancy within the last 5 years. Pregnant or breastfeeding women were also excluded from the study. Conventional treatment was based on NSAIDs, with disease-modifying antirheumatic drugs (DMARDs) used as needed, and steroids were not utilized. Baseline demographic data, ASAS-HI, Ankylosing Spondylitis Disease Activity Score (ASDAS) [4], total back pain VAS, BASDAI [5], Bath Ankylosing Spondylitis Functional Index (BASFI) [6], and C-reactive protein (CRP) were collected prior to treatment initiation. The ASAS-HI is comprised of 17 items, each with a binary response option ('I agree' or 'I do not agree'), covering various facets of functionality. The total ASAS-HI score, which can range from 0 to 17, is determined by tallying all 'I agree' responses, with lower scores signifying better health and higher scores denoting poorer health status [2]. Follow-up data, including ASAS-HI scores after treatment, were collected at 12 weeks.

Statistical analysis

Statistical analyses were conducted to compare changes in ASAS-HI scores between the TNF-α blocker and conventional

therapy groups. Paired t-tests were utilized to assess within-group differences in ASAS-HI scores pre- and post-treatment. Patients' characteristics were presented as mean±standard deviation for continuous variables, and number (proportion) for categorical variables. Fisher's exact test and independent t-test were conducted to evaluate the difference of participant's characteristics according to treatment group. A significance level of $p<0.05$ indicated statistical significance in all tests. Statistical analyses were conducted using R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographics

The document contains baseline characteristics of participants in a study comparing conventional treatment and TNF-α blocker therapy, divided into demographics, comorbidities, and disease outcome assessments (Table 1). The study population consisted of patients with axSpA, with a mean age of 38.3 years in conventional treatment group and 29.3 years in TNF-α blocker group (p=0.019). The majority of participants were male, accounting for 19 (86.4%) in conventional treatment group and 21 (95.5%) in TNF-α blocker group (p=0.607). All patients in both groups were positive for human leukocyte antigen (HLA)-B27. Regarding comorbidities, there was a significant difference in hypertension, with 9 cases in the control group and 1 case in the TNF-α blocker group. Hyperlipidemia was more prevalent in the control group with 7 cases compared to 2 cases in the TNF-α blocker group, although there was no statistically significant difference between the two groups. Hypothyroidism, history of pulmonary tuberculosis, and hepatitis B were each observed in one participant from the control group, and there were no statistically significant differences between the two groups in these conditions. Most variables, including CRP levels, other co-

Table 1. Baseline characteristics of enrolled patients

Category	Conventional treatment (n=22)	TNF-α blocker (n=22)	p-value
Demographic			
Age (yr)	38.3±15.4	29.3±7.2	0.019
Male	19 (86.4)	21 (95.5)	0.607
CRP (mg/dL)	3.1±4.5	3.6±9.9	0.833
HLA-B27 positive	22 (100)	22 (100)	>0.999
Comorbidity			
Hypertension	9 (40.9)	1 (4.5)	0.004
Dyslipidemia	7 (31.8)	2 (9.1)	0.132
Other cardiovascular diseases	1 (4.5)	0 (0.0)	>0.999
Diabetes mellitus	2 (9.1)	0 (0.0)	0.488
Hypothyroidism	1 (4.5)	0 (0.0)	>0.999
Other gastrointestinal diseases	1 (4.5)	2 (9.1)	>0.999
History of pulmonary tuberculosis	1 (4.5)	0 (0.0)	>0.999
Hepatitis B	1 (4.5)	0 (0.0)	>0.999
Sleep disturbances	1 (4.5)	0 (0.0)	>0.999
Other oncologic diseases	1 (4.5)	0 (0.0)	>0.999
Outcome assessment			
ASAS-HI	7.9±4.3	7.9±3.7	0.950
ASDAS	3.7±0.7	3.4±0.7	0.296
Total back pain VAS	61.1±10.7	61.1±8.6	>0.999
BASDAI	5.7±1.1	5.2±1.0	0.118
BASFI	3.1±2.3	3.0±2.0	0.918

Values are presented as number (%) or mean±standard deviation. TNF: tumor necrosis factor, CRP: C-reactive protein, HLA: human leukocyte antigen, ASAS-HI: Assessment of SpondyloArthritis international Society Health Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, VAS: Visual Analogue Scale, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index.

morbidities, and disease assessment scores (ASAS-HI, AS-DAS, total back pain VAS, BASDAI, BASFI), showed no significant difference between groups, indicating a well-matched baseline for further comparative analysis of treatment outcomes.

At baseline, the ASAS-HI scores between patients receiving conventional treatment and those receiving TNF-α blocker treatment showed no significant difference (Figure 1A). However, at Week 12, a significant reduction in ASAS-HI scores was observed in the TNF-α blocker group compared to the conventional treatment group, indicating a notable improvement in health status (Figure 1B). Longitudinal analysis within each treatment group from Week 0 to Week 12 showed no significant change in the conventional treatment group (Figure 1C), whereas the TNF-α blocker group experienced a significant reduction in ASAS-HI scores, demonstrating the effectiveness of the treatment (Figure 1D).

Our analysis revealed significant correlations between the ASAS-HI and various indices at weeks 0 and 12 (Table 2). Specifically, the BASFI and the BASDAI demonstrated strong positive correlations with ASAS-HI scores, indicating higher disease activity and functional limitation are associated with worse health outcomes in patients. Additionally, total back pain VAS also showed significant correlations, underscoring the impact of subjective pain perception on health status. In examining sex differences (data not shown), we observed no statistically significant differences in ASAS-HI scores between men and women at baseline and at week 12, suggesting the impact of the disease on health-related QoL is similar across sex.

We also assessed changes in parameters other than ASAS-HI in both groups after 12 weeks. While the TNF blocker group showed significantly more improvement, interestingly, other parameters, excluding BASFI, also demonstrated significant improvement in the conventional group (Table 3). We categorized responders as clinically important improvement according to ASDAS criteria (Delta≥1.1) and subsequently analyzed the correlation of these categories with changes in ASAS-HI. In both cases, there were no significant change in ASAS-HI scores from week 0 to week 12, with lines mostly horizontal indicating stable scores in patients who did not respond to treatment (Figure 2A). In the conventional treatment group, there was no significant change in ASAS-HI scores from week 0 to week

Table 2. Correlation coefficients between ASAS-HI and other indices

Spearman coefficient	Week 0	Week 12
Age (yr)	0.055	0.244
Total back pain VAS	0.367*	0.459**
ASDAS-CRP	0.247	0.441**
BASDAI	0.515**	0.612**
BASFI	0.667**	0.639**

ASAS-HI: Assessment of SpondyloArthritis international Society Health Index, VAS: Visual Analogue Scale, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C-reactive protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index. *p<0.05, **p<0.01.

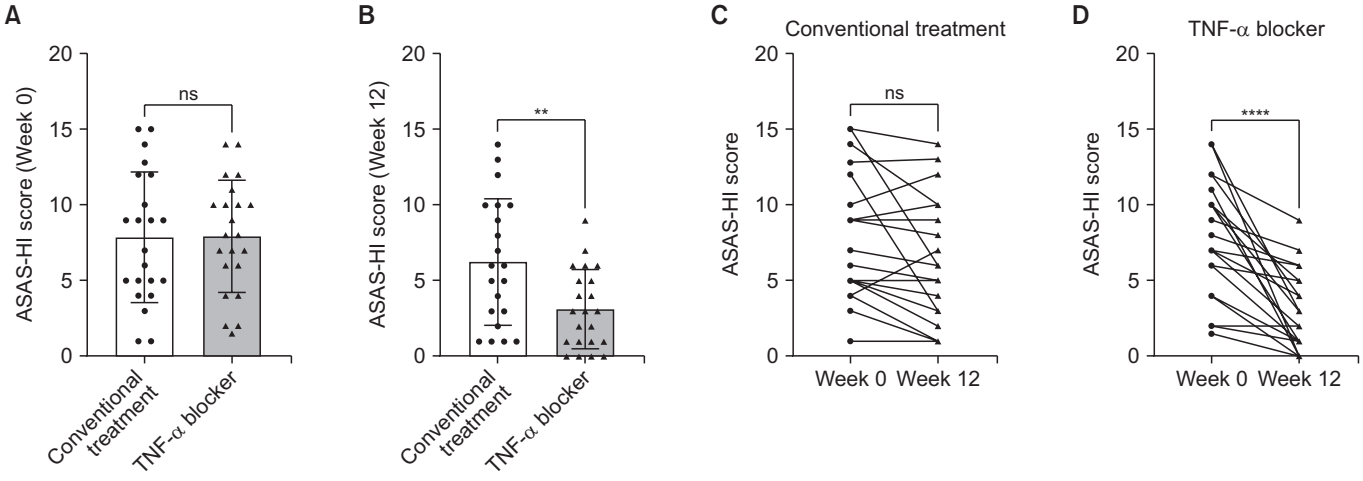

Figure 1. Comparison of ASAS-HI changes from baseline to Week 12 between groups. (A) Illustrates the baseline ASAS-HI scores for both groups, while (B) shows the scores at Week 12, highlighting the changes over time. Further dissect these comparisons by (C) focusing on the conventional treatment group and (D) on the TNF-α blocker group, both from baseline to Week 12. ASAS-HI: Assessment of SpondyloArthritis international Society Health Index, TNF: tumor necrosis factor, ns: no significant. **p<0.01, ****p<0.0001.

Table 3. Comparative efficacy of TNF-α blocker versus conventional treatment

Outcome assessment	Conventional treatment		p-value	TNF-α blocker		p-value
	0 week	12 weeks		0 week	12 weeks	
ASAS-HI	7.9±4.3	6.2±4.3	0.286	7.9±3.7	3.1±2.6	<0.0001
ASDAS-CRP	3.7±0.7	2.8±0.9	0.0003	3.4±0.7	1.2±0.5	<0.0001
Total back pain VAS	61.1±10.7	43.3±15.1	0.0005	61.1±8.6	8.9±8.7	<0.0001
BASDAI	5.7±1.1	4.5±1.4	0.0011	5.2±1.0	1.4±1.0	<0.0001
BASFI	3.1±2.3	2.7±2.2	0.329	3.0±2.0	0.9±1.3	<0.0001

Values are presented as mean±standard deviation. TNF: tumor necrosis factor, ASAS-HI: Assessment of SpondyloArthritis international Society Health Index, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C-reactive protein, VAS: Visual Analogue Scale, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index.

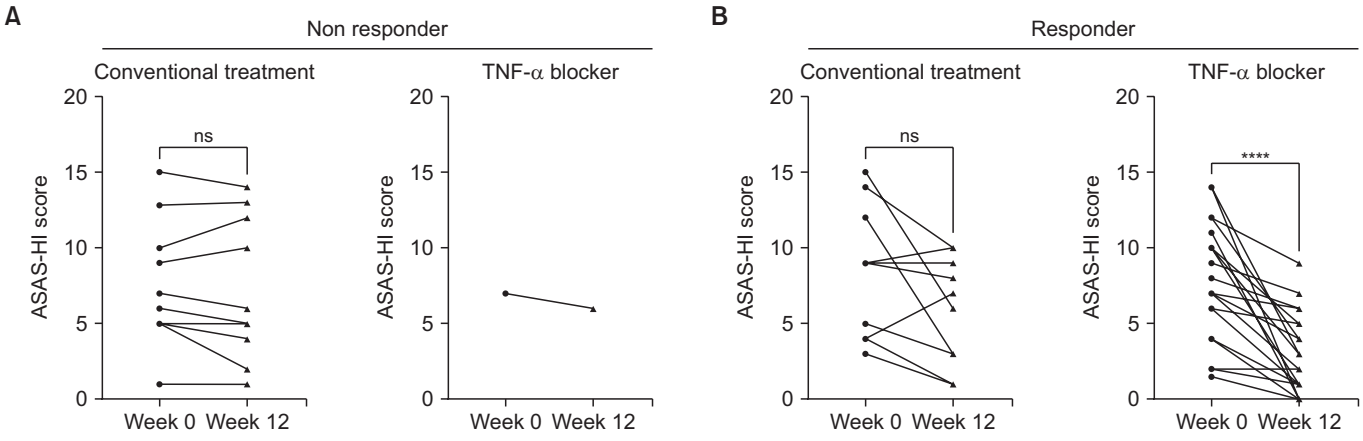

Figure 2. Assessing ASAS-HI score dynamics from baseline to Week 12 across treatment responder and non-responder. (A) For non-responders, ASAS-HI scores remained unchanged from week 0 to week 12, as depicted by the mostly flat lines. (B) In the conventional treatment group, there is no significant change in ASAS-HI scores from week 0 to week 12. However, in the TNF-α blocker group, there is a significant decrease in ASAS-HI scores from week 0 to week 12. Responder defined as clinically important improvement according to ASDAS criteria (Delta≥1.1), ASAS-HI: Assessment of SpondyloArthritis international Society Health Index, TNF: tumor necrosis factor, ASDAS: Ankylosing Spondylitis Disease Activity Score, ns: no significant. ****p<0.0001.

12. However, in the TNF-α blocker group, there is a significant decrease in ASAS-HI scores from week 0 to week 12, indicating a substantial improvement in the health index among patients who responded to TNF-α blocker treatment (Figure 2B).

During this observation period, neither group experienced adverse events severe enough to warrant drug or injection discontinuation. Additionally, the conventional treatment group did not report any unusual or adverse occurrences. In the TNF-α blocker group, there were a few isolated cases of side effects including injection site reactions (n=2), mild liver function elevation (n=1), and COVID-19 infection (n=1). The adverse effects were all graded mild while monitoring these cases.

DISCUSSION

To our knowledge, no study in Korea has yet analyzed the response to the ASAS-HI as the primary outcome in groups receiving TNF blockers and conventional treatments. This real-world clinical data shows significant improvements in the ASDAS, total back pain, and BASDAI within the conventional treatment group. Even within the responder subset of the conventional treatment group, there was no improvement in ASAS-HI. This suggests that assessing treatment response based solely on disease activity may not fully capture the overall disease state. The ASAS-HI more fully reflects actual changes in patient function and health status in everyday life, capturing QoL improvements not easily measured by traditional inflammatory markers or disease activity scores, and without needing blood tests for inflammation markers like CRP. It assesses not just functional status but the broader impact of the disease, including pain, fatigue, and daily activity limitations, offering a more comprehensive understanding of treatment's overall effect on patient

health.

The influence of axSpA on QoL significantly affects multiple dimensions. While current patient-reported outcomes (PROs) can describe disease activity, physical functionality, and health-related quality of life (HRQoL), they fall short in accurately assessing the complete health and disability levels in axSpA patients. Despite the use of various PROs for measuring activity, function, and HRQoL, these measures are inadequate for systematically estimating the health status of patients with axSpA. To create a questionnaire that is both comprehensive and specific to the disease, capable of accurately reflecting the overall health condition of patients, the ASAS developed the ASAS-HI. This tool is aimed at evaluating overall health and functioning in axSpA [7,8]. The notion of overall health and functioning has been incorporated into the 2021 revision of the ASAS-Outcome Measures in Rheumatology core domain set, identifying the ASAS-HI as the chosen instrument for self-reporting [9,10].

Despite the ASAS-HI being a relatively recent outcome measure, it is emerging as a significant instrument in axSpA studies. Notably, the ASAS-HI was selected as the primary outcome measure for the inaugural trial employing a Treat-to-Target strategy in axSpA, known as the Tight Control in Spondyloarthritis (TICOSPA) study [11]. Prior research has demonstrated a notable link between the ASAS-HI and various PROs, such as the BASDAI, BASFI, EuroQol Visual Analogue Scale (EQ-VAS) and the ASDAS [2,12,13]. The current study also revealed similar findings, reinforcing the idea that known PROs in axSpA share characteristics with the items on the ASAS-HI questionnaire, and that ASAS-HI provides a comprehensive evaluation of health status.

In real-world scenarios, the ASAS-HI demonstrates a strong correlation with existing measures and effectively distinguishes health states among patients with radiographic axSpA and non-radiographic axSpA. It is deemed a dependable tool for evaluating patient health and functionality in daily clinical practice [14]. The study underlines the significant influence of disease activity and physical function on ASAS-HI scores, establishing its validity as a measure of overall functioning and health in axSpA patients [15]. An observational study in a real-life cohort further supports the utility of the new ASAS-HI questionnaire in practical settings, suggesting its ease of integration into routine care and its potential to assist rheumatologists in assessing their patients' health functioning [16].

Our study has certain limitations that warrant acknowledgment. Numerous studies have indicated that advanced spinal structural damage is linked to poor PROs in individuals with axSpA. Specifically, two earlier studies identified a positive correlation between the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) and the BASFI [17,18]. Moreover, spinal mobility, as measured by the Bath Ankylosing Spondylitis Metrology Index (BASMI), was found to be significantly correlated with mSASSS [19]. However, this study did not observe the mSASSS and BASMI. The study was conducted as a short-term observational study, therefore, it was not possible to assess the long-term impact of several factors identified to be associated with the ASAS-HI. Further research is warranted to confirm these findings in larger cohorts and to explore the long-term impact of TNF-α.

CONCLUSION

The research demonstrates that ASAS-HI scores significantly improve with TNF-α blocker therapy in axSpA patients, underscoring ASAS-HI's effectiveness as a tool for evaluating drug responses. The use of ASAS-HI presented in this study emphasizes a patient-centered approach in evaluating treatment response, along with a deeper understanding of patients' health status. Therefore, ASAS-HI can contribute to a broader evaluation of the treatment's impact when used in conjunction with existing parameters.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

T.J.K., A.R.C., J.H.K., and K.J.P. designed the study and contributed to the acquisition and analysis of data. T.J.K., A.R.C., J.H.K, Y.J.L. H.H.J., and M.J.K. performed data curation and visualization. T.J.K., A.R.C., J.H.K, Y.J.L., H.H.J., and M.J.K. drafted the manuscript. All authors approved the final manuscript.

ORCID

Ah-Ra Choi, https://orcid.org/0000-0001-8154-7857
Ki-Jeong Park, https://orcid.org/0000-0002-9742-0743
Ji-Hyoun Kang, https://orcid.org/0000-0003-1113-2001
Yu Jeong Lee, https://orcid.org/0000-0003-1282-4210
Hyun Hee Jang, https://orcid.org/0000-0002-4611-3196
Moon-Ju Kim, https://orcid.org/0000-0002-8018-6903
Tae-Jong Kim, https://orcid.org/0000-0002-2871-1635

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