Retrospective Study

Influence of Handgrip Strength and Psoas Muscle Index on Analgesic Efficacy of Epidural Steroid Injection in Patients With Degenerative Lumbar Spinal Disease

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Free full manuscript: www.painphysicianjournal.com **Background:** Handgrip strength (HGS) and psoas muscle index (PMI) are widely used protocols for screening or diagnosing sarcopenia by measuring muscle strength and mass. Epidural steroid injection (ESI) is a common intervention for the treatment of spinal pain; however, the influence of pre-procedural sarcopenic status on therapeutic effects after ESI has not been investigated.

Objectives: In the present study, whether pre-procedural HGS or PMI predicts analgesic efficacy of ESI in elderly patients with degenerative lumbar spinal disease was investigated.

Study Design: This was a retrospective observational study.

Setting: The study included patients from the outpatient department for interventional pain management at a university hospital.

Methods: Following institutional review board (IRB) approval, patients \geq 65 years of age who underwent fluoroscopy-guided lumbar ESI from 2016 to 2017 in our clinic were enrolled in the present study. Good analgesia was defined as \geq 50% reduction in pain score at 4 weeks after injection. Patient characteristics, pain-related factors, clinical factors, HGS, and PMI measurements were collected and analyzed using multivariate analysis to identify the predictors of good analgesia after lumbar ESI. In addition, a receiver operating characteristic curve (ROC) analysis was performed, and area under the curve (AUC) values with 95% confidence interval (CI) were calculated for the HGS.

Results: A total of 259 patients satisfied the study protocol requirements. HGS was significantly higher in the good analgesia group $(23.12 \pm 7.54 \text{ vs} 16.55 \pm 6.66 \text{ kg}, P < 0.001)$. However, the PMI did not differ between the 2 groups $(5.25 \pm 1.55 \text{ vs} 5.08 \pm 1.69 \text{ cm}^2/\text{m}^2, P = 0.406)$. Multivariate analysis revealed higher HGS (odds ratio, OR = 1.142, 95% CI = 1.094-1.193, P < 0.001) and low-grade foraminal stenosis (OR = 0.403, 95% CI = 0.199-0.814, P = 0.011) were significantly associated with good analgesia after injection. The AUC values with 95% CI for HGS were 0.819 (0.718-0.920) in men and 0.800 (0.732-0.869) in women. In addition, HGS cutoff values for predicting good analgesic outcomes were 26.5 kg in men and 16.5 kg in women.

Limitations: This study was conducted in a single center, and sample size was relatively small. The lack of physical performance evaluation did not fully meet the current criteria for sarcopenia. In addition, post-procedural clinical data associated with disability or quality of life could not be collected.

Conclusion: In the present study, pre-procedural HGS was an independent predictor of analgesic efficacy after ESI in elderly patients with degenerative lumbar spinal disease. However, the PMI was not associated with pain relief after injection.

Key words: Epidural steroid injection, handgrip strength, psoas muscle index, pain management, sarcopenia, spinal stenosis

IRB compliance statement and ethical adherence: This study was written in compliance with our institutional ethical review board (IRB # 4-2019-1112). Patient consent was not required due to the retrospective nature of the study and deidentified nature of the data collected.

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arcopenia is a recently emerging geriatric syndrome characterized by the age-related decline of skeletal muscle, low muscle strength, and physical performance (1,2). Handgrip strength (HGS), a measure of voluntary muscle function, has commonly been used as an indicator of global muscle strength, and measuring HGS is the first step in diagnosing sarcopenia (2). Low HGS is a powerful predictor of poor patient outcomes such as longer hospitalization, increased physical limitations, poor health-related quality of life, and mortality (3,4). In addition, low psoas muscle index (PMI) has been shown to be a useful prognostic indicator to predict postoperative mortality and adverse events after various surgical procedures (5-7).

Epidural steroid injection (ESI) is a common intervention used to manage low back or radicular pain (8-10). In a recent systemic review, ESI was shown to improve walking distance, pain intensity, function, and quality of life for lumbar spinal stenosis (11). A high prevalence of sarcopenia was consistently observed in chronic pain patients with lumbar spinal stenosis (12-14). However, the influence of pre-procedural sarcopenic status on treatment outcomes after ESI in elderly patients has not been investigated in previous studies. We hypothesized that HGS representing global skeletal muscle strength and PMI indicating back muscle mass associated with mobility and stability of the lumbar spine may affect treatment outcomes differently after ESI.

Therefore, in this retrospective observational study, whether pre-procedural HGS or PMI predicts analgesic efficacy of ESI in elderly patients with degenerative lumbar spinal disease was investigated. In addition, whether HGS or PMI is a more useful predictor for better pain relief in the present study population was evaluated.

METHODS

Study Population

The study protocol of this retrospective observational study was approved by the Institutional Review Board (IRB) of Yonsei University Health System, Seoul, Republic of Korea (No. 4-2019-1112). The requirement for obtaining informed consent from the patients was waived due to the retrospective observational design of this study. This manuscript adheres to the applicable STROBE checklists for observational studies. Patients who underwent fluoroscopy-guided lumbar ESI, including interlaminar, transforaminal, and caudal approaches, in our pain clinic from November 2016 to June 2017 were enrolled in the study. The inclusion criterion was patients \geq 65 years of age diagnosed with degenerative lumbar spinal disease. Patients with psychiatric problems or cancer, or patients without a measured pain score were excluded. In addition, patients with incomplete medical records or who were lost to follow-up < 4 weeks after the ESI were excluded.

HGS and PMI Measures

HGS was measured 3 times each on the left and right sides using a Smedley-type handheld dynamometer (EH101; CAMRY, Guangdong, China) on the first visit. The patients were requested to sit in a comfortable position with their elbows open to the side and squeeze the dynamometer to the best of their ability. According to the Asian Working Group for Sarcopenia (AWGS) 2019, the highest among the 3 measurements was recorded and used for analysis (1).

PMI was calculated using pre-procedural T1weighted magnetic resonance imaging (MRI) following the standard protocol. The total cross-sectional area (CSA) of the bilateral psoas muscles at the L3 vertebral body was normalized to body height (cm²/m²). The total CSA was measured through manual outlining of the bilateral psoas muscles at the first axial cut in the craniocaudal direction, in which both transverse processes were visible at the L3 level (7). The measurements were performed 2 times by 2 investigators to improve interobserver reliability and the average value recorded. All measurements were obtained using the ImageJ software (Version 1.53n, NIH, Bethesda, MD).

Fluoroscopy-Guided Lumbar ESI

Two operators with similar clinical experience performed all procedures. The patients were placed in the prone position and the affected lower back was sterilely draped. Local anesthesia was applied to the marked needle entry area after confirming the needle entry points for each different approach at the intended level based on fluoroscopy. For the interlaminar approach, a 22-gauge, 7-cm Tuohy needle was inserted via the paramedian approach using the anteroposterior fluoroscopic view. The needle was advanced to the epidural space using the loss of resistance technique with saline. When loss of resistance was achieved, a lateral view was obtained to confirm the needle tip was at the margin of the posterior epidural space. For the transforaminal approach, after confirming the typical Scotty dog view, the final target point was confirmed at 6 o'clock directly below the pedicle. A 22-gauge, 8-cm Quincke tip needle was inserted and carefully advanced below the pedicle with intermittent fluoroscopic guidance in a tunnel vision fashion. An anteroposterior view was obtained to ensure the needle tip was located within the lateral half of the pedicle, and a lateral view was obtained to confirm the needle tip was placed in the anterior epidural space. For the caudal approach, the sacral hiatus was identified in the lateral view as an abrupt dropoff at the caudal end of the S4 lamina. A 22-gauge, 6-cm Quincke tip needle was inserted into the sacral canal through the sacral hiatus and advanced to the mid-S3 level. In all injections, 1-2 mL of contrast media was administered to ensure an appropriate epidural spread. After confirming correct epidural flow, a local anesthetic agent mixed with a typical dose of 5 mg of dexamethasone was injected.

Patient Demographics and Clinical Data Measurements

Patient characteristics, pain-related factors, and clinical factors were collected by electronic medical record chart review. Patient characteristics included age, gender, body mass index (BMI), diagnosed comorbid medical conditions with current medication (cardiovascular disease, diabetes mellitus, osteopenia/osteoporosis), and previous spinal surgery history. Duration of pain, baseline numeric rating scale (NRS), and opioid usage \geq 1 month before injection were identified as pain-related factors. Based on the MRI findings from an independent radiologist's final report, the presence of herniated disc, foraminal or central stenosis with grading (15,16), compression fracture, and spondylolisthesis were analyzed. The approach used for ESI (interlaminar, transforaminal, or caudal) was identified in the study population. In addition, patients who underwent surgery, indicating transition from conservative care to surgical treatment, within one year after epidural injection were investigated. For the purpose of this study, good analgesia after ESI was defined as \geq 50% reduction in pain score without any increase in analgesic medication at 4 weeks after ESI.

Statistical Analysis

Descriptive data were presented as mean ± standard deviation (SD) for continuous variables and as numbers (percentage) for categorical variables. Ordinal data and continuous variables not normally distributed were presented as the median and interquartile range (IQR). The normality of distribution was assessed using the Shapiro-Wilk test. Demographics and clinical parameters were analyzed using an independent t-test, chi-squared test, or Fisher's exact test, when appropriate. The Mann-Whitney U test was utilized for continuous variables with non-normal distribution. Significant univariate variables with a P value threshold of 0.1 were included in multivariate logistic regression analyses to identify the predictors of good analgesia after lumbar ESI, and the adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated. The receiver operating characteristic curve (ROC) analysis was performed, and area under the curve (AUC) values with 95% CI were calculated for HGS. Gender-specific handgrip cutoff values for predicting good analgesic outcomes after ESI was determined using ROC analysis and the Youden index. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 25.0 (IBM Corp, Armonk, NY). A P value < 0.05 was considered statistically significant.

RESULTS

Within the study period, 462 patients underwent fluoroscopy-guided ESI in our clinic, and 203 patients were excluded based on the exclusion criteria. A total of 259 patients, 155 patients in the good analgesia group and 104 patients in the poor analgesia group, were finally included for analysis in this study (Fig. 1).

The patient baseline characteristics are listed in Table 1. The study included 89 men and 170 women with a mean age of 73.54 years (range 65-98 years). The median duration of pain was 6 months, and the mean baseline pain score before injection was 7.17 on NRS.

Patient demographics and clinical data were compared between the 2 groups (Table 2). The patient age was significantly lower in the good analgesia group than in the poor analgesia group (72.58 ± 5.45 vs. 74.98 \pm 6.33 years, P = 0.001). Other patient characteristics, including gender, BMI, medical comorbidities, osteopenia/osteoporosis, and spine surgery history, were similar for both groups. The pain-related factors, baseline pain score, duration of pain, and opioid usage before injection were comparable between the 2 groups. The presence of herniated disc, central stenosis, compression fracture, and spondylolisthesis on MRI did not differ between the 2 groups. However, the proportion of foraminal stenosis present with moderate to severe grade was higher in the poor analgesia group (85.6% vs 72.3%, P = 0.015). In addition, the approach method of ESI and transition rate to spine surgery within one



year after ESI were similar between the 2 groups. HGS was significantly higher in the good analgesia group than in the poor analgesia group (23.12 \pm 7.54 vs 16.55 \pm 6.66 kg, *P* < 0.001). However, the PMI did not differ between the 2 groups (5.25 \pm 1.55 vs 5.08 \pm 1.69 cm²/ m², *P* = 0.406).

The gender-specific comparison showed that HGS was higher in patients with good analgesia after ESI for both men (30.55 ± 5.56 vs 23.15 ± 6.85 kg, P < 0.001)

and women (18.68 \pm 4.41 vs 13.75 \pm 4.15 kg, *P* < 0.001). However, a significant difference was not observed in the PMI between the 2 groups for both men and women (Table 3).

Multivariate logistic regression analysis revealed that presence of low-grade foraminal stenosis (OR = 0.403, 95% CI = 0.199–0.814, P = 0.011) and higher HGS (OR = 1.142, 95% CI = 1.094-1.193, P < 0.001) were independent predictors associated with good analgesia

after ESI (Table 4). However, older age (OR = 0.975, 95% CI = 0.928-1.024, P = 0.305) and opioid usage before ESI (OR = 0.661, 95% CI = 0.368-1.188, P = 0.166) were not significantly associated with good analgesic efficacy of ESI after adjusting for other variables.

The AUC for HGS was 0.819 (95% CI = 0.718-0.920) in men and 0.800 (95% CI = 0.732-0.869) in women (Fig. 2). In addition, gender-specific optimal HGS cutoff values for predicting good analgesic outcome after ESI were 26.5 kg in men (sensitivity = 0.845, specificity = 0.774, Youden index = 0.619) and 16.5 kg in women (sensitivity = 0.794, specificity = 0.795, Youden index = 0.589).

DISCUSSION

This study was designed to evaluate whether pre-procedural HGS or PMI are predictive of analgesic effects of ESI in elderly people with degenerative lumbar spinal disease. In this study, pre-procedural HGS provided meaningful prognostic information regarding the analgesic effects of ESI; however, the PMI was not associated with pain relief after ESI in this study population.

Several prognostic factors were previously proposed to predict patient outcomes after ESI. Lowgrade nerve root compression observed on MRI and elevated interferon gamma from epidural lavage fluid were associated with good analgesia after ESI (17). In addition, intraepineural and paraneural dispersal patterns of contrast during the procedure showed a clinically significant reduction in pain up to 2 months after transforaminal ESI (18). However, how pre-procedural HGS or PMI reflects pain relief after ESI has not been investigated in previous studies.

HGS is a well-validated technique to measure global muscle strength and the most important tool for screening and diagnosing sarcopenia. HGS is simple, cost-effective, and an easy-to-use technique, unlike the muscle mass estimation that is difficult to measure accurately or cannot be applied in some clinical settings (1). In several studies, a linear relationship was shown between HGS and disability for activities of daily living and surgical outcomes (19-21). Recently, the European Working Group on Sarcopenia in Older People (EWG-SOP) emphasized low muscle strength rather than low muscle mass as a principal determinant in diagnosing sarcopenia and predicting adverse outcomes (20). Furthermore, HGS appears valuable for evaluating sarcopenia in spinal stenosis patients because spinal stenosis is associated with declined nerve functions of

Variables	n = 259			
Patient characteristics				
Age, years	73.54 ± 5.91 (65-98)			
Gender, M/F	89 (34.4)/170 (65.6)			
BMI, kg/m ²	24.71 ± 3.35 (16.36-36.72)			
Comorbid medical disease, n				
Cardiovascular disease	61 (23.6)			
Diabetes mellitus	75 (29.0)			
Osteopenia/osteoporosis	18 (6.9)			
Spine surgery history	71 (27.4)			
Pain-related data				
Pain duration, months	6.00 (2.00-24.00)			
Baseline pain score, NRS 0-10	7.17 ± 1.69 (3-10)			
Opioid usage	89 (34.4)			
Pre-procedural MRI findings, n				
Herniated disc	253 (97.7)			
Foraminal stenosis	201 (77.6)			
Central stenosis	136 (52.5)			
Compression fracture	44 (17.0)			
Spondylolisthesis	53 (20.5)			
Epidural approaches, n				
Interlaminar	7 (2.7)			
Transforaminal	nsforaminal 224 (86.5)			
Caudal	28 (10.8)			
HGS, kg				
Right	19.67 ± 7.88 (3.20-38.10)			
Left	18.37 ± 7.76 (1.30-38.80)			
Maximum	20.49 ± 7.86 (5.20-38.80)			
PMI, cm ² /m ²				
Right	2.53 ± 0.83 (0.86-5.10)			
Left	2.65 ± 0.84 (0.84-5.08)			
Bilateral	5.18 ± 1.60 (2.11-9.68)			

Table 1. Baseline characteristics of the study patients.

Values are presented as mean \pm standard deviation (SD, range), median (interquartile range), or number of patients (%). NRS, numeric rating scale; BMI, body mass index; MRI, magnetic resonance imaging; HGS, handgrip strength; PSI, psoas muscle index

the lower extremities, which influence physical performance and/or muscle mass (12). Therefore, whether pre-procedural HGS could be a useful marker to predict the therapeutic effects after ESI was investigated in the present study.

A significant difference was not observed in the PMI between the good and poor analgesia groups in the present study. Gellhorn et al (22) showed that CSA of lumbar back muscles did not provide meaningful predictive information regarding medium- and

Variables	Good analgesia (n = 155)	Poor analgesia (n = 104)	P value
Patient characteristics			
Age, years	72.58 ± 5.45 (65-85)	74.98 ± 6.33 (65-98)	0.001
< 80	136 (87.7)	75 (72.1)	0.002
≥ 80	19 (12.3)	29 (27.9)	
Gender, M/F	58 (37.4)/97 (62.6)	31(29.8)/73 (70.2)	0.231
BMI, kg/m ²	24.54 (22.72;26.30)	24.23 (22.55;27.12)	0.959
< 25	92 (59.4)	58 (55.8)	0.608
≥ 25	63 (40.6)	46 (44.2)	
Medical comorbidities, n	67 (43.2)	48 (46.2)	0.702
Osteopenia/osteoporosis, n	8 (5.2)	10 (9.6)	0.213
Spine surgery history, n	40 (25.8)	31 (29.8)	0.482
Pain-related data			
Pain duration, months	6.00 (1.00-21.00)	8.50 (2.00-24.00)	0.219
< 12 months	95 (61.3)	55 (52.9)	0.200
\geq 12 months	60 (38.7)	49 (47.1)	
Baseline pain score, NRS 0-10	7.17 ± 1.60	7.16 ± 1.83	0.960
NRS < 7	59 (38.1)	35 (33.7)	0.511
NRS ≥ 7	96 (61.9)	69 (66.3)	
Opioid usage, n	46 (29.7)	43 (41.3)	0.062
Pre-procedural MRI findings, n			
Herniated disc	152 (98.1)	101 (97.1)	0.687
Foraminal stenosis			0.015
No to mild	43 (27.7)	15 (14.4)	
Moderate to severe	112 (72.3)	89 (85.6)	
Central stenosis			0.324
No to mild	116 (74.8)	72 (69.2)	
Moderate to severe	39 (25.2)	32 (30.8)	
Compression fracture	26 (16.8)	18 (17.3)	0.911
Spondylolisthesis	28 (18.1)	25 (24.0)	0.273
Epidural approaches, n			
Interlaminar	4 (2.6)	3 (2.9)	0.525
Transforaminal	137 (88.4)	87 (83.7)	
Caudal	14 (9.0)	14 (13.5)	
Transition to spine surgery within 1 year after	18 (11.6)	19 (18.3)	0.149
ESI, n			
HGS, kg	1	1	1
Maximum	23.12 ± 7.54	16.55 ± 6.66	< 0.001
PMI, cm ² /m ²	1		1
Bilateral	5.25 ± 1.55	5.08 ± 1.69	0.406

Table 2. Comparison of patient characteristics and clinical data between patients with good and poor analgesia after ESI.

Values are presented as mean ± standard deviation (SD, range), median (interquartile range), or a number of patients (%). Medical comorbidities: hypertension, diabetes mellitus, and coronary artery occlusive disease. ESI, epidural steroid injection; NRS, numeric rating scale; BMI, body mass index; MRI, magnetic resonance imaging; HGS, handgrip strength; PMI, psoas muscle index

	Men		Women			
	Good analgesia (n = 58)	Poor analgesia (n = 31)	P value	Good analgesia (n = 97)	Poor analgesia (n = 73)	P value
HGS, kg	30.55 ± 5.56	23.15 ± 6.85	< 0.001	18.68 ± 4.41	13.75 ± 4.15	< 0.001
PMI, cm ² /m ²	6.29 ± 1.60	6.64 ± 1.70	0.338	4.63 ± 1.14	4.42 ± 1.18	0.240

Table 3. Gender-specific comparison of HGS and PMI between patients with good and poor analgesia after ESI.

Values are presented as mean \pm standard deviation (SD).

HGS, handgrip strength; PMI, psoas muscle index; ESI, epidural steroid injection

long-term clinical outcomes in spinal stenosis patients. Similarly, a relationship was not found between the CSA of paraspinal muscles and pain intensity or disability in patients with chronic low back pain (23). Furthermore, sarcopenia defined based on CSA of paraspinal muscles did not affect the clinical success of lumbar fusion for degenerative spondylolisthesis (24). This result may be because the muscles are partially substituted with fat in the process of aging and degeneration (known as myosteatosis), although the CSA may be constant (25). Thus, the PMI appears to have limitations in measuring muscle quality. Furthermore, the PMI does not reflect functional muscle strength. Consequently, a multi-component risk index was recently proposed for the evaluation of back muscle degeneration with morphologic muscle mass, fat infiltration rate, and muscle strength (26).

The results of the present study also showed the presence of foraminal stenosis correlated with poor analgesic effects of ESI. The foraminal stenosis occurs as a result of degeneration of both the facet joints and the intervertebral discs. Chang et al (15) reported transforaminal ESI can reduce chronic radicular pain regardless of the severity of foraminal stenosis. However, severe foraminal stenosis showed poorer response compared with mild to moderate foraminal stenosis in their study. Mechanical stimulation and inflammation of the nociceptive nerves continued, and actual epidural spreading of injectate might be decreased in patients with severe foraminal stenosis. In the present study, younger age was associated with a more favorable response after ESI; however, age was not an independent predictor in multivariate analysis. In a previous study, the effectiveness of ESI was poorer as patient age increased based on changes in a 6-minute walk test (27). Therefore, the results of our study indicated that HGS, representing global muscle strength, might be a more important factor than the patient's chronological age to predict the analgesic efficacy of ESI. In a previous study, pre-injection opioid use did not affect long-term outcomes after lumbar and cervical ESI (28). Although the opioid usage before injection was more frequently

Table 4. Factors associated	with good	analgesia	after lumbar
ESI based on multivariate	logistic re	gression a	nalysis.

Variables	OR	95% CI	P value
Age, years	0.975	0.928-1.024	0.305
Moderate to severe foraminal stenosis (yes)	0.403	0.199-0.814	0.011
Opioid usage before injection (yes)	0.661	0.368-1.188	0.166
HGS, kg	1.142	1.094-1.193	< 0.001

ESI, epidural steroid injection; OR, odds ratio; CI, confidence interval; HGS, handgrip strength

observed in patients with poor analgesia after ESI in the present study, the difference did not reach statistical significance.

Limitations

This study has several limitations and directions for future studies. This study was managed in a single clinical setting that includes a relatively small sample size with a homogeneous racial background. Due to the retrospective design, selection and information bias may have occurred. The gait speed test could not be conducted because most of the study subjects showed neurogenic claudication symptoms. Thus, low HGS or PMI alone does not fully satisfy the current diagnosis criteria for sarcopenia in this study. However, in a recent study, HGS was shown to correlate with walking speed and distance in patients with lumbar spinal stenosis (29). In addition, post-procedural clinical data associated with the disability or quality of life other than pain reduction could not be collected. In this study, a real-world clinical practice model was used in which attending physicians decided on the timing of the decision for ESI or analgesic use. The study results reflect only a cross-sectional relationship between HGS and analgesic efficacy of ESI; thus, a prospective longitudinal cohort study is necessary for which the causal relationship among the variables is evaluated, especially using both muscle morphology and function in this population. The evidence for the benefits of resistance



Fig. 2. Receiver operator characteristic curves for the handgrip strength (HGS) in the prediction of good analgesia at 4 weeks after epidural steroid injection. The area under the curve values with 95% confidence interval for the HGS were 0.819 (0.718–0.920) in males (A) and 0.800 (0.732–0.869) in females (B).

exercise in improving muscle strength is compelling, and there is a growing body of evidence for its benefit in diagnosed sarcopenia (30,31). Therefore, further studies are needed to test whether a pre-procedural intervention such as resistance exercise can improve the analgesic efficacy of ESI, especially for patients with impaired HGS.

CONCLUSION

In conclusion, pre-procedural HGS value was significantly associated with analgesic efficacy of ESI in elderly patients with degenerative lumbar spinal disease. However, the PMI could not predict pain relief after ESI. Therefore, the analgesic efficacy of ESI appears associated with global muscle weakness rather than loss of localized back muscle mass in the present study population.

Authors' Contributions

Shin Hyung Kim: Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision; Writing - original draft, review & editing; Sang Jun Park: Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision; Writing - original draft, review & editing; Kyung Bong Yoon: Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision; Writing - review & editing; Eun-Kyung Jun: Data curation, Formal analysis, Investigation, Supervision; Writing - review & editing; Jaehee Cho: Data curation, Formal analysis, Supervision; Writing - review & editing; Hee Jung Kim: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision; Writing - original draft, review & editing.

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