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Effect of Pharmacist-Led Intervention in Elderly Patients through a Comprehensive Medication Reconciliation: A Randomized Clinical Trial

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Purpose: Polypharmacy can cause drug-related problems, such as potentially inappropriate medication (PIM) use and medication regimen complexity in the elderly. This study aimed to investigate the feasibility and effectiveness of a collaborative medication review and comprehensive medication reconciliation intervention by a pharmacist and hospitalist for older patients.

Materials and Methods: This comprehensive medication reconciliation study was designed as a prospective, open-label, randomized clinical trial with patients aged 65 years or older from July to December 2020. Comprehensive medication reconciliation comprised medication reviews based on the PIM criteria. The discharge of medication was simplified to reduce regimen complexity. The primary outcome was the difference in adverse drug events (ADEs) throughout hospitalization and 30 days after discharge. Changes in regimen complexity were evaluated using the Korean version of the medication regimen complexity index (MRCI-K).

Results: Of the 32 patients, 34.4% (n=11/32) reported ADEs before discharge, and 19.2% (n=5/26) ADEs were reported at the 30-day phone call. No ADEs were reported in the intervention group, whereas five events were reported in the control group (p=0.039) on the 30-day phone call. The mean acceptance rate of medication reconciliation was 83%. The mean decreases of MRCI-K between at the admission and the discharge were 6.2 vs. 2.4, although it was not significant (p=0.159).

Conclusion: As a result, we identified the effect of pharmacist-led interventions using comprehensive medication reconciliation, including the criteria of the PIMs and the MRCI-K, and the differences in ADEs between the intervention and control groups at the 30-day follow-up after discharge in elderly patients.

Trial Registration: (Clinical trial number: KCT0005994)

Key Words: Medication reconciliation, elderly, adverse drug event, potentially inappropriate medication, medication regimen complexity

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INTRODUCTION

Polypharmacy, usually defined as the use of five or more medications, is common in the elderly population.[1] Polypharmacy can cause potentially inappropriate medication (PIM) use in the elderly, which may lead to drug-related problems.[2] A study found that 75% of discharged patients were prescribed a PIM, and the number of PIMs was thought to be associated with an increased risk of adverse drug events (ADEs) and all cause adverse events.[3] PIMs have a significant effect on healthcare service use, especially hospitalization, among elderly patients.[4]

Polypharmacy can affect the complexity of the medication regimen, which may have a negative effect on clinical outcomes. A study indicated that complex regimens can lead to not only a higher likelihood of medication non-adherence but also hospitalization in older people.[5] Furthermore, hospitalization itself was associated with increased medication regimen complexity in older patients during the inpatient period. Complex medication regimens at hospital admission were predictive of rehospitalizations for ADEs.[6]

In addition, polypharmacy results in medication discrepancy and complexity.[7] Pharmacist-led activities to correct an inaccurate medication list at all transition points are called medication reconciliation, and they are conducted to promote patient safety in care transitions. There are divisions about the role of the pharmacist in the process, which varies depending on the hospital.[8] However, pharmacists could contribute to resolving medication discrepancies after hospital discharge as well as during hospitalization, but data on effectiveness in terms of the clinical relevance of resolving discrepancies and healthcare utilization is not clear.[9]

Pharmacist-led medication reviews have been proposed as an important part of the solution to medication-related problems in terms of PIM, regimen complexity, and medication discrepancies. Studies have shown that inappropriate prescribing in older patients has significantly decreased with collaboration between pharmacists and physicians in multidisciplinary teams onward across sectors.[10] Pharmaceutical care has improved the appropriate use of medicines not only during a hospital stay but also after discharge.[11] Clinical pharmacist medication reviews could reduce the effect of hospitalization on the complexity of medication regimens of older patients.[12] In particular, participation of clinical pharmacists in hospital discharge transitions of care, including medication reconciliation, review, counseling, and post-discharge follow-up, had a positive effect on reduction in post-discharge hospital visits.[13] Studies have found that medication-related interventions, such as medication reconciliation, patient education, professional education, and transitional care, are more effective in preventing hospital readmission in older people.[14,15]

To date, randomized control studies of pharmacist intervention in elderly patients with polypharmacy, including medication review and reconciliation, are lacking, although comprehensive approaches have been recommended to resolve drug-related problems among older adults with multimorbidity.[16]

Therefore, this study aimed to investigate the feasibility and effectiveness of a collaborative medication review and comprehensive medication reconciliation intervention by a pharmacist and hospitalist for older patients.

MATERIALS AND METHODS

Study design

The study was an open-label, randomized controlled trial conducted in a tertiary-level hospital in South Korea (Clinical trial number: KCT0005994). The study was performed in accordance with the Declaration of Helsinki, and all participants provided written informed consent prior to inclusion in the study. The protocol was approved by the Institutional Review Board (IRB) of Inha Hospital (IRB# 2020-06-029).

Participants

Patients aged 65 years or older admitted to the Department of Hospital Medicine at Inha University Hospital from July to December 2020, who were taking at least five medications, were included. Written informed consent was obtained from patients or caregivers prior to inclusion. Patients who were discharged within 24 h and those with a life expectancy of less than 3 months were excluded. Patients were randomly assigned to the intervention or control group using randomly generated blocks prior to patient enrollment.

Data collection

Demographic information and laboratory data, including hemoglobin, sodium, potassium, albumin, alanine aminotransferase, alkaline phosphatase, and creatinine clearance, were calculated using the Cockcroft-Gault equation and recorded. Clinical data, including the International Classification of Diseases 10th edition-Clinical Modification, length of stay, and destination after discharge were obtained from the hospital's electronic medical record system. A face-to-face interview was conducted for all patients within 24 h of inclusion. The interview involved questions about the swallowing ability, patient-reported adverse events, use of over-the-counter drugs, and complementary and alternative medicines. In addition, medical history, including syncope, delirium, dementia, cognitive impairment, gastric ulcer, constipation, and falls or fractures, were collected to identify PIMs that were not recommended for use due to drug-disease interactions, according to the BEER 2019.[17] Antibiotic use and duration were recorded from medication history during hospitalization. The regimen complexity at admission was evaluated using the Korean version of the medication regimen complexity index (MRCI-K).[18]

The identified ADEs of the patients were recorded in the ADE reporting system at Inha University Hospital. Reports of ad-

verse events completed during discharge were recorded. ADEs and serious adverse events (SAEs) were detected by patients, pharmacists, or physicians. Once they were reported, the pharmacist as an investigator evaluated them first, and the physician as a principal investigator confirmed them. The pharmacist contacted all participants by telephone 30 days after discharge to follow-up patient-reported ADEs. The pharmacist contacted the next of kin or the caregiver of patients who were unable to communicate coherently. In addition, the degree of regimen complexity measured as MRCI-K was compared with the difference in scores between the intervention and control groups. After discharge, a follow-up telephone call to patients 30 days after discharge was conducted for reconfirmed medication use and patient-reported ADEs.

Comprehensive medication reconciliation activity

Comprehensive medication reconciliation is a series of clinical pharmacist activities, including medication reconciliation through a face-to-face interview at admission and daily medication review, reducing regimen complexity and daily review of adverse events. The intervention group received a clinical pharmacy service from Monday to Friday, with a full-time pharmacist as an investigator, and the contents of the intervention were all recorded in case report forms, whereas the control group received the usual care during the inpatient period. The clinical pharmacy service provided to patients in the intervention group was as follows: within 24 h of admission, a comprehensive list of current drugs was checked during a face-to-face interview with the pharmacist to identify medication discrepancies with self-medications and to evaluate the PIMs based on PIM criteria. Once assigned to the intervention group, omissions, duplication, and dosage errors were corrected through a complete understanding of all medications of patients. The analysis of PIMs was checked when initially performed at admission and then checked again at the end of hospitalization.

During the hospital stay, medication reviews were conducted based on the BEER 2019,[17] screening tool of older persons' prescriptions (STOPP), and screening tool to alert to right treatment (START) 2015;[19] and recommendations were given to physicians on drug selection, monitoring requirements, renal dose adjustment according to renal function (CrCl), and drug-drug interactions based on Lexicomp®, with the final decision made by the physician in charge. In addition, in order to reduce regimen complexity, the instructions were simplified during patient education about discharge medications, which resulted in reduced dosing frequency by matching the administration times of patients' medications. All ADEs confirmed by the investigators were also reported in the ADE reporting system.

Study outcomes

The primary outcome of this study was the difference in the number of ADEs reported during hospitalization and at the 30-day follow-up after discharge between the intervention and control groups. All discharged patients were subject to drug side effect monitoring. Basically, an interview was conducted with the patient, while information on the complaints about ADEs were collected from the main caregiver in case contact with the patient was not possible. The secondary outcomes were the differences in the change of medication regimen complexity index, the number of PIMs, and the number of drugs between the intervention and control groups. The PIMs were evaluated based on the BEER criteria,[17] STOPP, and START 2015.[19] The number of PIMS was checked according to the criteria, excluding overlapping drugs. The complexity of the medication regimen between admission and discharge was evaluated using the validated Korean MRCI-K.[18]

Statistical analyses

For power calculation, we estimated the ADE incidence to be 3.4% in the intervention group and 40% in the control group, based on previous randomized control studies that had a study design similar to the current study.[20,21] Based on an 80% power of detection, there was a significant difference between the intervention and control groups at the 95% confidence limit. A targeted sample size of 20 patients was calculated with the expected 10% rate of loss to follow-up (α=0.05, 1–β=0.80).

Patient characteristics were presented as median, interquartile range, and percentile (%). The chi-square test and Mann-Whitney U test were used to assess the differences between the intervention and control groups. Changes in the number of medications, MRCI-K, and PIMs between groups were analyzed using the Mann–Whitney U test. The Fischer exact and chi-squared tests were used to measure differences in the prevalence of ADE reports between the two groups at discharge and 30-day follow-up phone calls. Analyses were performed using IBM SPSS Statistics for Windows (version 24.0; IBM Corp. Armonk, NY, USA).

RESULTS

Patient characteristics

Forty patients were screened for participation in this study. Among them, eight patients were excluded due to readmission to the intensive care unit (n=4), decline to enroll (n=3), and death before the intervention was finalized (n=1).

A total of 32 patients completed the study process during admission, and 26 patients completed the follow-up 30 days after discharge. Fig. 1 shows the flow of patients throughout the study. Patient characteristics (n=32) are shown in Table 1. The number of medications and the number of PIMs were similar between the groups. In the process of reconciliation, self-medication discrepancies in primary non-prescription drugs, such as health supplements and vitamins, were observed in both groups. There was no statistically significant difference between the groups in all values of MRCI-K, Charlson Comor-

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bidity Index, and length of stay.

Effects of pharmacist intervention in the medication reconciliation process

In total, 41 suggested actions were identified in the 14 intervention groups during the study period. The most frequent suggestions were changes in drug therapy (n=13), reduction in dosage (n=8), and initiation of drug therapy (n=6). Suggested actions were implemented in 83% of the cases corresponding to 2.4 per person. A summary of the recommendations and acceptance is described in Table 2.

The changes from admission to discharge in the number of medications, MRCI-K, and PIMs are shown in Table 3. A total of 31 patient prescriptions were analyzed, excluding one patient with incomplete prescription information. The intervention group had higher score changes at discharge than at ad-

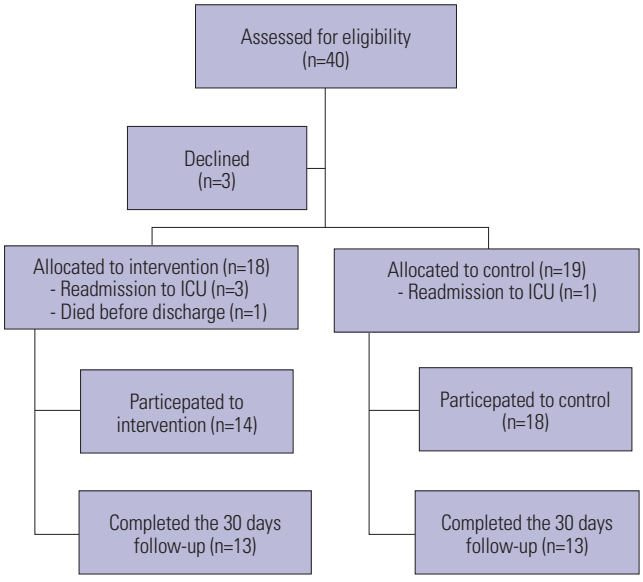

Fig. 1. Patient flow diagram. ICU, intensive care unit.

Table 1. Baseline Characteristics (n=32)

	Intervention group (n=14)	Control group (n=18)	*p* value
Sex, female	8 (57.1)	13 (72.2)	0.555
Age, yr	83 (71–87)	84.5 (72–94)	0.235
Medication management			0.777
Assisted	8 (57.1)	11 (61.1)	
Tube-feeding	5 (35.7)	7 (38.9)	
Self-administered	1 (7.2)	0 (0.0)	
Number of medications	8.5 (4–14)	8.5 (3–15)	0.866
Self-medication discrepancy			0.457
Nonprescription drugs	2 (14.2)	5 (27.8)	
Prescription drugs	1 (7.1)	0	
Main diagnosis at admission			0.589
Pneumonia	3 (21.4)	7 (38.8)	
Sepsis	2 (14.2)	2 (11.1)	
Diabetes mellitus with hypoglycemia	0	2 (11.1)	
Acute cholecystitis	1 (7.2)	1 (5.5)	
Acute kidney injury	1 (7.2)	1 (5.5)	
Others	7 (50)	4 (28)	
PIMs criteria medication	1.5 (0–6)	3 (0–5)	0.253
Medical condition related to PIM criteria			0.723
Dementia	7 (50)	9 (50)	
Delirium	5 (35.7)	7 (38.9)	
Falls history	6 (42.9)	10 (55.5)	
Diabetes mellitus	9 (64.2)	11 (61.1)	
CCI	5 (3–6)	4.5 (3–7)	0.301
Antibiotic use	12 (85.7)	17 (94.4)	0.199
Antibiotic duration	8 (3–41)	8 (3–39)	
Length of stay	7 (3–51)	8 (2–39)	0.837
Destination after discharge			0.446
Home	9 (64.2)	8 (44.4)	
Nursing home	3 (21.4)	5 (27.8)	
Transferred to another hospital	2 (14.4)	5 (27.8)	

PIM, potentially inappropriate medication; CCI, Charlson Comorbidity Index. Data are presented as n (%) or median (Q1–Q3). Data were analyzed using the Fisher exact test, chi-square test, and Mann-Whitney U test.

Table 2. Number of Recommendations and Accepted Recommendations (n=14)

Recommendation	Number identified	Number accepted	Reference	Acceptance rate (%)
Dosage adjustment				
Dosage low	1	1	Lexicomp®	100
Dosage too high	8	8		100
Need for additional therapy	6	2	PIMs criteria (‡START)	33.3
Change drug therapy	13	11	PIMs criteria (*BEER and †STOPP)	84.6
Drug-drug interactions	2	1	Lexicomp®	50
Drug duplication	1	1	Lexicomp®	100
Self-medication discrepancy	1	1	NA	100
Medication regimen simplification				
Dose time	5	5	NA	100
Instruction modification	4	4		100
Total	41	34	NA	83
Number per person (/person)	2.9	2.4	NA	

PIM, potentially inappropriate medication.
*BEER Criteria 2019; †STOPP 2015: Screening Tool of Older People's Potentially Inappropriate Prescriptions; ‡START 2015 (Screening Tool to Alert to Right Treatment).

Table 3. Scores at Admission and Discharge and Change from Admission

	Intervention group (n=14)			Control group (n=18)			*p* value
	Admission	Discharge	Change	Admission	Discharge	Change	
Number of medications	9 (4–14)	8 (3–11)	-1 (-5–3)	9 (3–15)	9 (4–12)	0 (-9–5)	0.566
MRCI-K	29.5 (16–60)	29.2 (7–45)	-8 (-21–17)	30 (14–58)	31 (14–56)	2 (-30–19)	0.159
PIM	1.5 (0–6)	0 (0–3)	-0.5 (-6–0)	3 (0–5)	1 (0–4)	-1 (-4–1)	0.968

MRCI-K, Korean version of medication regimen complexity index; PIM, potentially inappropriate medication.
Data are presented as median (Q1–Q3). Data were analyzed using the Mann-Whitney U test.

Table 4. Comparisons of ADEs Reporting between the Medication Reconciliation Group and Control Group

	Intervention group	Control group	*p* value
ADE reported during hospitalization*	3 (21.4)	8 (44.4)	0.266
SAE reported during the study period*	0	3 (16.7)	0.529
ADE reported at 30-day phone call†	0	5 (38.5)	0.039

ADE, adverse drug event; SAE, serious adverse event.
Data were analyzed using the Fisher's exact test.
*Intervention group (n=14), control group (n=18); †Intervention group (n=13), control group (n=13).

mission, whereas the control group had lower score changes at discharge than at admission in all indices. There is a trend of decreasing in MRCI-K after intervention between two groups (6.2 vs. 2.4), although it was not statistically significant (p=0.159).

ADEs in the medication reconciliation process

A comparison of the ADEs and SAEs is shown in Table 4. ADEs confirmed by physicians and pharmacists were identified during the study period. Of the 32 patients, 34.4% (n=11) reported drug-related adverse events before the end of the discharge period. More ADEs were reported in the control group (44.4%, n=8) than in the intervention group (21.4%, n=3) during the overall study period, but the difference was not statistically significant (p=0.266). Among them, three patients in the control group had SAEs. No SAEs were reported in the intervention group compared with the control group with SAEs due to hypoglycemia and drug-induced hepatitis.

Of the 26 follow-up patients, 19.2% (n=5) of ADEs were reported at the 30-day phone call. Among them, no ADEs were reported in the intervention group, whereas five events were reported in the control group (p=0.039), with a significant statistical difference in the number of adverse events on the 30-day phone call. Of the five patients who reported adverse events at the 30-day call, three patients in the control group were the same patients who had adverse events during hospitalization. Patient 4 reported adverse events from the same drug, glimepiride (Table 5).

DISCUSSION

Studies have demonstrated that interventions by clinical pharmacists can improve drug-related problems and affect positive clinical outcomes in both inpatient and outpatient care facilities.[22,23] Pharmacy-led interventions via medication reconciliation are essential for reducing the occurrence of medication discrepancies that may lead to ADEs in the care transition processes.[24] In particular, it is necessary to target interventions for high-risk patient populations, such as the elderly.[25] Pharmacy-led medication reconciliation interventions have a greater impact when conducted at either admission or discharge.[26] However, studies have found that not only medication discrepancies, but also comprehensive approaches, such as structured medication review and multidisciplinary cooperation, are required to resolve drug-related problems.[27,28] To more clearly investigate the outcomes of pharmacist interventions, a comprehensive reconciliation process is required to evaluate the outcomes based on drug-related measurements, such as regimen complexity, inappropriate prescribing, and adherence. We conducted a randomized clinical study to investigate the effectiveness of pharmacist interventions for old age using tools, such as MRCI-K and PIMs, during hospital stays and at discharge.

The intervention group had fewer ADEs and no SAEs compared to the control group, although the differences between the groups were not significant. Furthermore, there was a significant difference in ADEs reported by patients between the intervention and control groups at the 30-day follow-up phone calls. This result was consistent with previous findings, which showed that intervention comprising medication reconciliation by a pharmacist reduced the rate of preventable ADEs 30 days post-discharge.[29] Among the patients who had ADEs in the control group, three, as reported before discharge, repeatedly reported ADEs after 30 days. In addition, two patients in the control group newly reported ADEs after discharge. Patient 4, whose main diagnosis was pneumonia at admission in the control group, complained of adverse drug reactions due to the same drug, glimepiride. Our results could explain why clinical pharmacy services could lead to the reduction of ADEs after discharge, although there was no further clinical pharmacy service. This means that clinical pharmacy services during hospitalization could affect the safety of the drug even after discharge.

In addition to medication review, risk assessment criteria targeting the elderly were introduced in the intervention group. To evaluate whether a pharmacist-led medication review is effective during medication reconciliation, the number of PIMs using the BEER 2019, STOPP 2015, and START 2015 were identified. Both medication numbers and PIMs in the intervention

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Table 5. Detailed Description of Adverse Events Reported

Patient number	Group	Related medication	ADEs	SAE	ADEs at 30-day phone call
6	Intervention	Indapamide	Hypotension	No	No
5	Intervention	Glimepiride	Hypoglycemia	No	No
27	Intervention	Tamsulosin	Hypotension	No	No
37	Control	Glimepiride	Hypoglycemia	Yes	No
4	Control	Glimepiride	Hypoglycemia	Yes	Yes
7	Control	Glimepiride	Hypoglycemia	No	No
9	Control	Ampicillin+sulbactam	Thrombocytopenia	No	No
12	Control	Piperacillin tazobactam	Drug fever	No	No
15	Control	Ciprofloxacin	Diarrhea	No	Yes
36	Control	Dexibuprofen	Drug induced hepatitis	Yes	No
18	Control	Cefotaxime	Thrombocytopenia	No	Yes

ADE, adverse drug event; SAE, serious adverse event.

group were reduced compared to the control group, although no significant difference was found when comparing the change in drug-related problems between the groups. Although there was no difference in diabetic patients between the two groups in our study, there were reports of adverse events from glimepiride, which PIMs to avoid (n=4, 36.3%), and the side effects of this drug were repeated in the control group. Our finding that the same patient in the control group reported side effects of glimepiride explained the need for pharmacist intervention in medication review. PIM criteria as decision support tools were effective in reducing polypharmacy in older adults. However, the effect of the intervention on clinical outcomes is unclear.[30] Our results have demonstrated the effectiveness of pharmacist intervention by evaluating the patient-reported adverse effects related to PIMs, and further studies are needed for evidence-based practice.

We conducted drug instruction modifications, such as administration time and food-related instructions, to simplify prescription complexity. The overall change in the score of regimen complexity expressed using MRCI-K was reduced after simplification of regimen complexity, although there was no significant difference between both groups in the score change. MRCI has been used as a tool for evaluating pharmacist service activities at the time of hospitalization, and discharge and intervention studies are being conducted to establish guidelines and confirm effectiveness.[12,31,32] Modifying usage, such as administering drugs at the same time, was a priority to consolidate prescription regimens most efficiently, as this was how multiple doses were dispensed in the Korean pharmacy practice. Our study found that dosage simplification is a major means of reducing the administration time in hospital pharmacy practice. When conducting routine in-hospital medication reviews, the simplification strategy for regimen complexity can help minimize the impact of hospitalization on the complexity of discharge medication regimens.

Our study was conducted to evaluate comprehensive medication reconciliation and clinical outcomes in real clinical practice in the context of standardized clinical pharmacy service, including the MRCI-K, BEER 2019, STOPP, and START. Polypharmacy is associated with negative drug-related problems, such as increased medication regimen complexity and inappropriate drug use, which increase the care transition process and require intervention.[6,25] Further research is needed to evaluate drug-related problems using objective criteria at various stages and to standardize the collaborative clinical pharmacy to confirm clinical outcomes.[33,34] Thus, there is a need for a comprehensive pharmacist intervention approach to solve these problems, and an evaluation process must be developed.

There were some limitations to the present study. First, this was a preliminary descriptive study with limitations in deriving decisive results. We identified the feasibility of using the MRCI-K and PIM criteria as medication reconciliation tools in a randomized study. We expect that differences in the distribution of scores and adverse events between the two groups could be used as a basis for future research. However, with a small sample size, further work needs to be done to establish the effectiveness of intervention. In addition, this study was conducted at a single center and lacked information on disease severity at the 30-day follow-up. We expect these findings to be implicated in a pilot randomized control study for further investigation based on pharmacy-led intervention in multicenter research. Furthermore, the patients reported that adverse events at the 30-day phone call could be subjective which could be affected by confounders, whereas adverse events during hospitalization were confirmed by the pharmacist and the physician. However, all ADEs, including patient reporting, have been monitored and recorded in the ADE reporting system of Inha Hospital.

In the comprehensive medication reconciliation process conducted as a randomized study, we identified the feasibility of pharmacist-led interventions using medication review, including the PIM criteria and MRCI-K. As a result of pharmacist interventions, we found that the number of ADEs before discharge was lower in the intervention group than in the control group, and that there were differences in ADEs at the 30-day follow-up after discharge.

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AUTHOR CONTRIBUTIONS

Conceptualization: Sunmin Lee, Jung-Hwan Lee, and Min Jung Chang. Data curation: Sunmin Lee and Jung-Hwan Lee. Formal analysis: Sunmin Lee. Funding acquisition: Jung-Hwan Lee and Min Jung Chang. Investigation: Sunmin Lee, Jung-Hwan Lee, and Min Jung Chang. Methodology: all authors. Project administration: Jung-Hwan Lee and Min Jung Chang. Resources: Sunmin Lee and Jung-Hwan Lee. Software: Sunmin Lee. Supervision: Jung-Hwan Lee and Min Jung Chang. Validation: all authors. Visualization: Sunmin Lee. Writing—original draft: Sunmin Lee. Writing—review & editing: Jung-Hwan Lee and Min Jung Chang. Approval of final manuscript: all authors.

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