Development and Application of the Korean version of Medication Regimen Complexity Index (MRCI-K)

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Development and Application of the Korean version of Medication Regimen Complexity Index

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LIST OF ABBREVIATIONS

MRCI: medication regimen complexity index

MRCI-K: Korean version of Medication regimen complexity index

ADE: adverse drug event

LOS: length of stay

COPD: chronic obstruction pulmonary disease

ICC: intraclass correlation coefficient

MMAS-4: Morisky medication-taking adherence Scale-4

PIM: potentially inappropriate medication

CCI: charlson comorbidity

SAE: serious adverse event

STOPP: screening tool of older people's potentially inappropriate prescriptions,

START: screening tool to alert to right treatment

OTC: over-the counter

ABSTRACT

Development and Application of the Korean Version of the Medication Regimen Complexity Index (MRCI-K)

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Background:

Polypharmacy may increase medication regimen complexity. The regimens with increased complexity could lead to undesirable health outcomes, such as adverse reactions, hospitalization, and decreased medication adherence. However, verified assessment tools for medication regimen complexity have not been introduced in Korea. The objectives of this research were to develop the Korean version of the Medication Regimen Complexity Index (MRCI-K) and to identify its feasibility as an evaluation tool in a hospital pharmacy practice.

Methods:

Part 1. Development of the MRCI-K: The development process encompasses cross-cultural adaptation, a reliability analysis and a validity analysis. The cross-cultural

adaptation includes translation, back-translation, consolidation by the committee, and pilot testing, which were performed using virtual prescriptions. First, we evaluated the inter-rater and test–retest analysis to confirm the reliability of MRCI-K. In addition, three phases for validation evaluation were performed including convergent validity, discriminant validity, and criterion validity. In the evaluation of validity, the study population consisted of all patients discharged (100 outpatients) from the respiratory medicine ward from January 2016 to March 2016 . Modification of the instructions was introduced in order to evaluate the score in multi-dose dispensing. The convergent and discriminant correlation analyses were conducted to evaluate the validity of the modified MRCI-K as well. To estimate inter-rater reliability, the modified MRCI-K reliability was evaluated with 25 individuals randomly selected from the total sample population.

Part 2. Application of MRCI-K: The medication reconciliation study was designed as a prospective, open, randomized controlled study with patients aged 65 or older admitted to the ward of hospital medicine from July 2020 to December 2020. A comprehensive medication reconciliation encompassed medication review based on BEER 2019, a screening tool of older persons' prescriptions (STOPP) and a screening tool to alert to right treatment (START) 2015, recommendations for drug selection, monitoring requirements, renal dose adjustment according to renal function (CrCl) and drug-drug interaction based on Lexicomp®. In addition, the simplification of the instructions of the discharge medication such as food and administration time matching was conducted to reduce the regimen complexity prior to discharge. Adverse drug events (ADEs) were

monitored throughout the hospitalization process and follow-up telephone calls to were made to patients 30 days after discharge. The changes of MRCI-K and the modified MRCI-K were compared with the difference in scores between intervention and control groups in order to confirm the pharmacist intervention effect.

Results:

Part 1. Development of the MRCI-K: The reliability analysis demonstrated excellent internal consistency showing the intra-class correlation coefficient exceeded 0.90 for all cases in the MRCI-K and the modified MRCI-K. Validity was confirmed as a result of a strong correlation between the MRCI-K score and drug number with a Pearson's correlation coefficient of 0.955 and a weak correlation with length of stay (0.242, $p < 0.001$) and age (0.155, $p = 0.005$). Criterion validity was confirmed as a result of the good concordance between nine experts' panel rankings of patient-level medication regimen complexity with the MRCI-K. The validity of the modified MRCI-K was identified as a result of a positive correlation between the modified MRCI score and drug number with a Pearson's correlation coefficient of 0.444 and a weak correlation with diagnosis number (0.134, $p = 0.185$) and age (-0.262, $p = 0.003$).

Part 2. Application of the MRCI-K: A total of 32 patients were included and 26 patient finished the follow-up 30 days after discharge. Eleven events (34.4%) were reported as drug-related adverse events before the end of the discharge period. Five patients (19.2%) reported drug-related adverse events at the 30-day phone call. Three cases of severe

adverse events (SAE) were detected such as hypoglycemia and drug-induced hepatitis. The number of adverse events that were reported on the 30-day phone call was less in the non-intervention group. There were higher scores reduction in the intervention group as compared to the control group in the MRCI-K (-6.2 vs -2.4, p=0.159) and the modified MRCI-K (-2.5 vs 0, p=0.067). We confirmed that the score reduction in the intervention group was greater than that of the control group as a result of the simplification intervention by the pharmacist.

Conclusions: Compared with previous studies, this study showed satisfactory validity and reliability of the MRCI-K for the measurement of regimen complexity in Korea. Increased regimen complexity was observed compared to previous studies with polypharmacy, and dosage modification can be a major means of reducing administration time for regimen simplification in hospital pharmacy practice. In the comprehensive medication reconciliation process, we found that regimen complexity was reduced by the simplification intervention, and it could be evaluated as the MRCI-K and the modified MRCI-K. Further studies are needed to use the modified MRCI-K for all patients as an evaluation tool of pharmacist`s intervention.

Keywords: Medication Regimen Complexity Index; MRCI; Polypharmacy; Adverse events; Intervention; Medication reconciliation; Pharmacist; Multi dose dispensing

1. Introduction

1.1. Research Background

1.1.1 Polypharmacy and Regimen Complexity

Due to the complex morbidity, drug treatment for patients with chronic diseases has increased and polypharmacy is prevalent as well. Polypharmacy is usually defined as the number of drugs used at the same time in general adult populations in the range of two to 11 drugs, which in long-term care facilities is assumed to be the maximum number of drugs. When polypharmacy was defined as five, nine and 10 medications, the prevalence of polypharmacy was 91%, 74% and 65%, respectively (Jokanovic et al. 2015). In Korea, polypharmacy of older adults with multimorbidity has been escalating according to the Korean Health Insurance Claims Database, which reported that 9.5% of the elderly in the yearly-based analysis were exposed to polypharmacy and up to 44.1% in the monthly-based analysis between 2010 and 2011 (Park et al. 2016). Another study of the Korean elderly found that up to 86.3%, 44.9%, and 3.0% were at risk of polypharmacy when taking more than six, 11, and 21 medications, respectively (Kim et al. 2014).

Although polypharmacy is commonly defined as the increasing number of medications prescribed, it can affect the complexity of the medication regimen which may lead to a negative impact on clinical consequences. Complex regimens can be challenging for patients, which is considered a primary medication-related reason for medication non-

adherence. The complex regimen caused by dosage frequency and difficult instructions has a negative effect on medication compliance, although the same medications were prescribed (Pantuzza et al. 2017). A study indicated that complex regimens can lead to not only a higher likelihood of medication non-adherence but also hospitalization in older people (Wimmer et al. 2017). Furthermore, hospitalization itself was associated with increased medication regimen complexity for older patients during the inpatient period. Complex medication regimens at hospital admission were predictive of rehospitalizations for adverse drug event (ADE) (Willson et al. 2014). These regimens have been a target for intervention in pharmaceutical care, considering the significant effect on clinical outcomes (Wimmer et al. 2017).

There are studies that quantify and evaluate complex regimens using index tools based on prescription contents. Several measures have been introduced for quantifying regimen complexity, potentially useful for different clinical populations, although dose frequency has been a main factor affecting complexity (Mansur et al. 2012). Indices were composed of regimen related factors such as dosage form, frequency and special instructions that need to be followed. Scoring methods for quantification were usually applied to express the degree of complexity. The medication regimen complexity index (MRCI) developed in Australia is representative among indices, and was the most widely used scale to quantify regimen complexity and was applied in clinical studies (George et al. 2004).

1.1.2 Medication regimen complexity index (MRCI)

Several indexes that evaluate all components based on prescriptions in a weighted score have been suggested since 2004. Of all indexes used, the Medication regimen Complex Index (MRCI) developed in Australia has been recognized as the most validated and reliable in clinical studies (Mansur et al. 2012).

MRCI is composed of 3 section; section A (dosage form), section B (dose frequency) and section C (weighted score additional instructions) (George et al. 2004). The evaluator imposes a score of complexity weighted on each of the items on the prescription without arbitrary judgment and sums the number of each section (Figure1). Scoring numbers based on index instruction presents the degree of complexity as higher the number expressed the more complex it is.

Section A was scored by analyzing the prescription's dosage in the range of 1 and 5 points. Duplication scoring needs not be calculated in the case of the same dosage. Section B was weighted by charging the number of frequencies for each medication in the range of 1 and 12.5 points. For example, two drugs twice a day will be charged 4 points in the section B. Section C covered the aspects of additional instruction such as administration time and food related instruction as score weight in the range 1 and 2 for each assigned instruction.

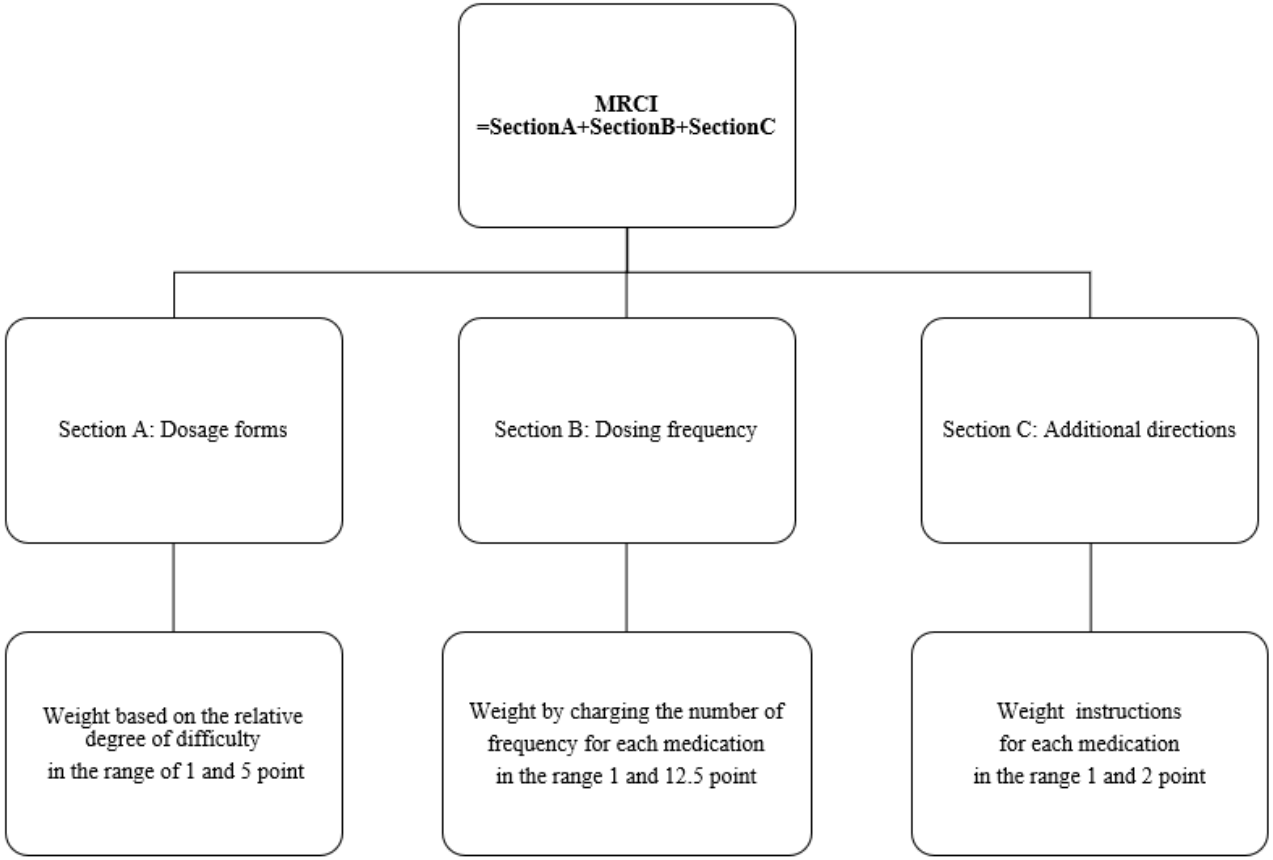

Figure 1. Medication Regimen Complexity Index (MRCI)

1.1.3 Previous validation studies on MRCI

Because MRCI was recognized as a primary scale as a complexity analysis tool, validation research based on MRCI has been continuously conducted abroad. A summary of validation studies is presented in Table 1, and the methods for the validation studies is described in Table 2. The validation studies were performed in accordance with global guidelines on cross-cultural adaptation. Cross-cultural adaptation methods commonly include translation, back-translation and pilot studies to achieve equivalence between the original and adapted questionnaires (Epstein et al. 2015).

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Table 1. Previous studies on validation of MRCI

Study description						Patient	Medication number				
#	**Year**	**Country**	**Author**	**Age Mean (SD)**	**N**		**Prescribed medications Mean (SD)**	**Section A Dosage Mean (SD)**	**Section B Frequency Mean (SD)**	**Section C Instruction Mean (SD)**	**Sum A+B+C Mean (SD)**
1	2004	Australia	George J	69 (9.8)	134	COPD	8.2 (4.0)	ND	ND	ND	ND
2	2007	Brazilian Portuguese	Ana Carolina Melchiors	58.5	95	Diabetes	4.5 (2.5)	ND	ND	ND	15.7 (8.36).

3	2010	German	Dorit Stange	58.9 (13.8)	20	8 patients (Endocrine disorders), 12 patients (Renal conditions)	9.95 (4.12)	4.65 (3.05)	13.75 (5.74)	3.50 (3.14)	21.90 (9.58)
4	2014	USA	Jan D. Hirsch	CU site; 81.3 (6.1), SD site; 74.3 (7.4)	CU site; 400 SD site; 400	CU site; Diabetes, SD site; Multiple-disease	CU site; 12.1 (4.9), SD site; 7.1 (3.7)	ND	ND	ND	CU site; 25.4 (11.7) SD site; 17.6 (10.0)
5	2016	Turkish	Betul Okuyan	74.9 (7.6)	100	Elderly	4.75 (2.34)	ND	ND	ND	13.84 (8.89)

6	2016	Spanish	Javier Saez de la Fuente,	82.1 (4.7)	60	Discharge treatment	9.8 (3.8)	6.7 (4.5)	14.1 (6.0)	6.4 (4.1)	27.2 (11.9)
7	2018	Brazilian	Laís LN Pantuzza	71.4 (7.5).	227	Older adults in primary care	5.2 (2.3)	1	7.5	3	12
8	2019	USA	Morgan E Gwynn	57.9 (14.6)	130	Intensive care unit	16.7 (5.2)	ND	ND	ND	ND
9	2020	Japan	Shoichi Masumoto	84.3 (8.0)	72	Chronic disease	7.4 (3.7)	3.5 (2.5)	12.0 (6.9)	7.8(4.1)	23.3 (11.6)

COPD, Chronic Obstruction Pulmonary Disease; CU, University of Colorado Anschutz Medical Campus; SD, San Diego
ND, not detectable

Table 2. Description of validation studies based on MRCI

Study description			Method				
#	**Year**	**Country**	**Cross cultural adaptation**	**Convergent validation**	**Discriminant validation**	**Criteria validation**	**Reliability analysis**
1	2004	Australia		■	■	■	■
2	2007	Brazilian Portuguese	■	■	■		■
3	2010	German	■				■
4	2014	USA		■	■	■	
5	2016	Turkish	■	■	■		■
6	2016	Spanish	■	■	■	■	■
7	2018	Brazilian	■	■	■		■
8	2019	USA		■	■	■	■
9	2020	Japan	■	■	■		■

Shaded cells: Indicates assessment within study

1.1.4 Previous intervention studies on the MRCI

Elliott R. investigated that hospitalization could lead to increased complex regimens in 2013 and found that an educational intervention and medication review of clinical pharmacists can affect hospitalization on the complexity of older patients' medication regimens, and that there was a change in the MRCI value as a result of clinical pharmacist intervention. A before-after study involving elderly patients was undertaken to find that the mean increase in MRCI score during hospitalization was significantly smaller in the 205 intervention patients than in the 186 usual care patients (2.5 vs. 4.0, $p = 0.02$; adjusted difference 1.6, 95 % CI 0.3, 2.9) (R. A. Elliott et al. 2013).

Dorit Stange et al. conducted an interventional study in 2013 to identify whether reducing medication complexity through counseling targeting hospital medical staff and producing additional information at discharge could impact on patient adherence. Reduced medication complexity was significantly observed in interventional group but alone did not have a positive effect on good medication compliance without sustainable simplification information about the modifications(Stange et al. 2013).

Since MRCI was validated as an intervention tool for Medication Therapy Management, it has been used as an indicator for the evaluation of clinical pharmacist services in the USA. Candis M conducted the interventional study in patients with type 2 diabetes focusing on regimen simplification and patient-specific diabetes education over 6 months. It was demonstrated that a collaborative pharmacist-endocrinologist model could

be effective for achieving glycemic control without increasing complexity, which was measured with mean MRCI scores (C. M. Morello et al. 2018).

A cluster-randomized controlled trial for long term care residents was conducted to evaluate the impact of regimen simplification on medication administration times, falls, hospitalization, and mortality over 12 months in Australia. The pharmacist simplification intervention affected the number of daily administration times over 12 months. The structured tool could be effective in applying an interdisciplinary approach to aged care. An incidence of falls was higher in intervention arm over 12-months compared to the comparison arm. There were no significant differences in hospitalizations and mortality (Sluggett et al. 2020)

Table 3. Description of intervention studies based on MRCI

Author Year	Country	Age Mean (SD)	N	Patient	Intervention	Outcome	Conclusions
Elliott R. A 2013	Australia	81.3	205	Discharged inpatients	Educational intervention, Simplification during medication regimen reviews	Proportion of pharmacist-led MRCI changes	Simplification of older inpatients' regimens is feasible when training in regimen simplification is provided.

Dorit Stange 2013	Germa n	63.8 (13.8)	240	Inpatients with hypertension, diabetes, and/or dyslipidemia	Simplifications of cardiovascular and antidiabetic medications, additional explanatory information	Adherence, MRCI-D, Patient quality of life (QoL), satisfaction with information	The complexity of cardiovascular and antidiabetic hospital medications can be reduced. For a sustainable simplification of outpatient medication, information about the modifications was needed.
Candis M 2018	USA	DIM M 62.2 (8.1) PCP 62.4 (10.0)	DI M M (99) PC P (56)	Type2 diabetes	Education during an average of three 60-minute visits over 6 months	Medication Regimen Complexity, Glycemic Control.	Treating patients with an innovative DIMM model can help complex T2D patients achieve glycemic control without increasing the MRC to more than a comparator group.

Sluggett JK 2020	Australia	85.0 (7.5)	Intervention (99) Comparison (143)	Residents of aged care facilities	Simplification medication regimens	Medication administration times, falls, hospitalization, and mortality	The pharmacist simplification intervention of complex regimen resulted in the reduced number of daily administration times and higher incidence of falls over 12 months.

MRCI, Medication Regimen Complexity Index; MRCI-D, German version of MRCI; DIMM, Diabetes Intense Medical Management; PCP, primary care provider; T2D, type2 diabetes; MRC, Medication Regimen

1.2. Need for the research

As polypharmacy occupies a higher proportion of pharmacotherapy and leads to complex regimens, it is necessary to evaluate the complex regimen and effects on medication adherence in pharmacotherapy. Until now, no studies have objectively quantified complex regimens in Korea. This study was conducted to develop the Korean version of medication regimen complexity (MRCI-K) for quantification and evaluation. In addition, this pilot study identifies the feasibility of an interventional study and to determine its effects using the MRCI-K.

1.3. Objectives of the study

The objectives of the study were to develop the Korean version of the medication regimen complexity index (MRCI) and apply it during the reconciliation process in Korea. Besides, this study aims to identify the feasibility of application to clinical studies as an evaluation tool.

The detailed objectives for this study are as follows:

Firstly, based on the original MRCI developed in Australia, the validation study of the Korean version of the medication regimen complexity index (MRCI-K) was conducted. This study was comprised of 335 discharged patients and 100 outpatients of a tertiary hospital in Korea and was conducted to determine internal and external validation. The modified MRCI-K was applied to evaluate complex regimens in a pharmacy practice. Reliability analysis of the index was performed as well.

Secondly, an application study using the MRCI-K and the modified MRCI-K was performed to identify feasibility in both practice and research. This study investigated the correlation with the index and variables such as adverse drug events (ADE) and length of stay (LOS). Furthermore, the interventional study was designed to demonstrate the effect size of a pharmacy service that reduces the complexity of regimens during the medication reconciliation process.

1.4. Framework of the study

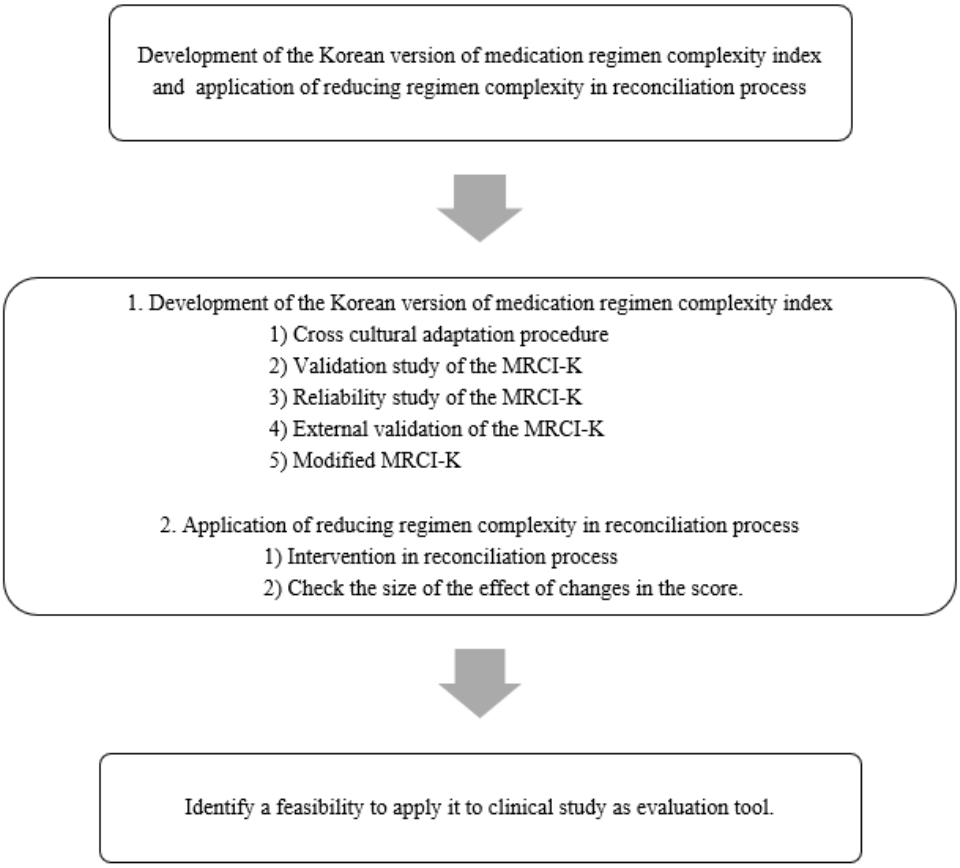


Figure 2. Conceptual framework of the study

Part 1. Development of the Korean version of medication regimen complexity index (MRCI-K)

2. Method

2.1. Cross culutral adaptation procedure

The cross-cultural adaptation methodology study, which encompasses translation and back translation and consolidation by the committee to achieve semantic, idiomatic, experiential, and conceptual equivalence across cultures, was carried out (Beaton et al. 2000). The MRCI-K consists of three sections, based on the original MRCI. The original MRCI was translated into Korean by two clinical Korean pharmacists who are fluent in English, work in a hospital as clinical pharmacists in the USA and Korea, and are naive to the index at the time of the study independently (MRCI-K-1). A consensual Korean version was generated through reconciliation after discussion of the discrepancies. Then, the Korean version was back translated into English by two translators whose native language was English and who were not informed about the concepts of the index (MRCI-K-2). This English version was compared again with the original MRCI, and a new version was translated into created by correcting casual discrepancies. Two other Korean clinical pharmacists reviewed the comprehensibility of each question. The final MRCI-K was generated after checking semantic, idiomatic, cultural, and conceptual equivalence. The replicability with index was tested by four pharmacists who had not yet participated in the study conducted a pilot test of the MRCI-K using virtual prescriptions. The authors

reviewed questions that the pharmacist could not fully understand and corrected them using more familiar expressions or additional examples.

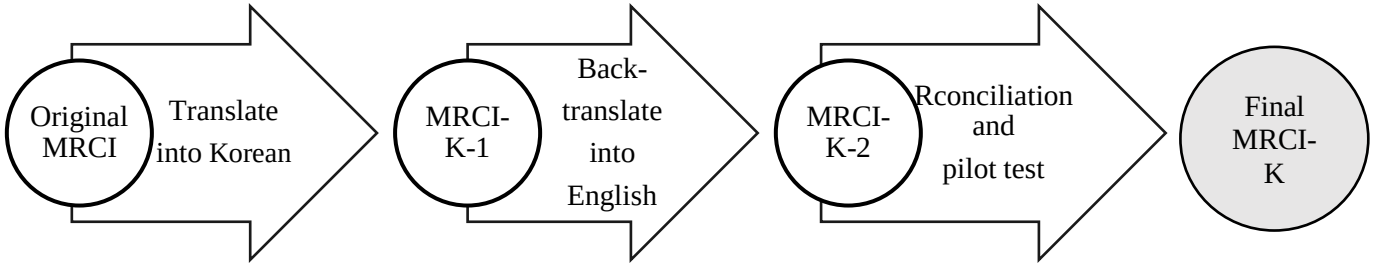


Figure 3. Cross-cultural adaptation of MRCI-K

2.2. Reliability study of the MRCI-K

Reliability analysis is used to confirm agreement using a scale which includes inter-raters and test-retest methods. To estimate inter-rater reliability, MRCI-K reliability was evaluated with 25 sample randomly selected from the total sample population. Six pharmacists who had not been involved in the study independently calculated the MRCI-K score with the same prescriptions and repeated the first calculation on a second occasion 2 months later without contact with the MRCI-K between the 2 time periods. The reliability analysis was confirmed by calculating the intraclass correlation coefficient (ICC). To interpret the ICC, we considered low reliability as ICC < 0.5, moderate reliability as 0.50 < ICC < 0.75, good reliability as 0.75 < ICC < 0.90, and excellent reliability as ICC > 0.90 (Terry K Koo and Mae Y Li 2016). All statistical analyses were conducted with IBM SPSS Statistics for Windows version 24.0 (IBM Corp. Armonk, NY).

2.3. Study design and setting

This retrospective, cross-sectional study was undertaken on all individuals hospitalized in and discharged from the respiratory medicine ward, a university-affiliated tertiary hospital in Incheon, South Korea, between January 2016 to March 2016. In addition, excluding duplicate visits, 100 out of 21578 outpatients were selected for external validity analysis during January 2016. All examined medications from prescriptions were obtained retrospectively from electronic medical records (EMRs) and included all the medications

taken due to underlying diseases, including non-prescription drugs (over-the counter [OTC] drugs). The study was approved by the institutional review board (IRB) at Inha Hospital (IRB# 2017-04-015) and was conducted in accordance with the principles of the Declaration of Helsinki and good clinical practice guidelines.

2.4. Study population

Patients were included if they were admitted to a respiratory medicine ward, and received at least one medication from the Inha University Hospital pharmacies. Patients were excluded if they were prescribed no regularly scheduled medications at discharge, or if they were re-hospitalized patients during the observation.

2.5. Validation study of the MRCI-K

Construct validity is described by convergent validation and discriminant validation. Convergent validity is determined by confirming that the number of drugs has a strong correlation with MRCI, and discriminant validity is identified by confirming that the variables that are not relevant to medication number, such as gender, age showing a weak correlation with MRCI. Criterion validity was evaluated by confirming the agreement between the degree of regimen complexity and the MRCI score.

The validity consisted of three phases: convergent validity, discriminant validity, and criterion validity. Data including baseline characteristics were collected retrospectively from EMRs for a population descriptive analysis. Baseline characteristics include age, sex, length of stay, types of health insurance, diagnosis upon admission, and hospital-based ADE reports. Regimen complexity was measured using the MRCI-K which was scored by analyzing the patient's prescription. The convergent validity was evaluated by testing the correlation between the MRCI-K and the number of medications using Pearson's correlation coefficient. The discriminant validity was confirmed by testing the correlation between the MRCI-K with age, sex, length of stay and ADE report using Pearson's correlation coefficient and the Mann-Whitney test. The MRCI-K scoring tool was applied to randomly selected 100 regimens from outpatients during January 2016. All of 100 regimens were rescored using the MRCI-K scoring tool to determine the external validity of the tool. Convergent validity was examined by determining a

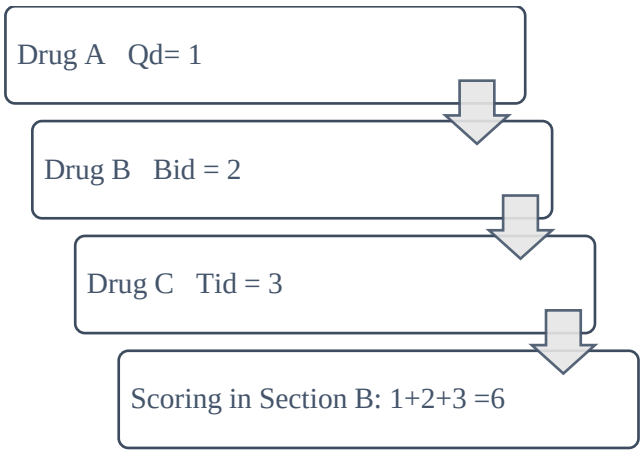
correlation between MRCI-K and the number of medications. Discriminant validity was examined by comparing MRCI-K scores with sex, age and ADE.

To determine criterion validity, a nine-member expert group consisted of three local pharmacists, three local internal medicine physicians, and three hospital nurses with no previous experience using the MRCI tool and independently ranked six regimens with 10-point intervals. Six regimens with 10-point intervals were chosen after the exclusion of points below the 5th percentile and above the 95th percentile. The criterion of validity was examined with concordance of MRCI-K-based rankings with expert rankings conducted on the basis of their clinical opinions. The agreement level was interpreted as a weak agreement as $0.40 <$ weighted $\kappa < 0.59$, a moderate agreement as $0.60 <$ weighted $\kappa < 0.79$, a strong agreement as $0.80 <$ weighted $\kappa < 0.90$, and an almost perfect agreement as weighted $\kappa > 0.90$ (McHugh 2012).

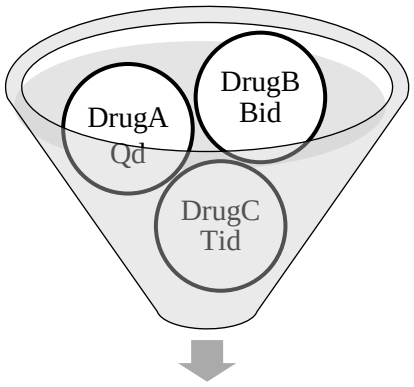
2.6. The modified MRCI-K

Multi-dose dispensing methods, based on automatic dispensing machines, have been widely used in hospitals as dose administration aids. Medication packing with automatic dispensing machines could reduce dosing frequency by preparing individual drugs together into packaging. Because the MRCI assumed that individual drugs are taken separately, the administration of hospital medications may not be reflected with the original MRCI. Considering hospital pharmacy practices, the modified MRCI-K was introduced and examined its application through reliability analysis. Dispensed frequency in the B section item is calculated by reflecting this packaging state. Also, in case of split tablets and multi doses, no score is charged in the C section. All other instructions are scored to reflect packaging conditions, because other instructions increase the dosing frequency. To determine inter-rater and test–retest reliability with the modified MRCI-K, a pharmacist who had no involvement with the development or validation of the tool scored 25 regimens twice with a gap of 4 weeks between scores. Intra-class correlation coefficient (ICC) was used to evaluate inter-rater and test–retest agreement. In addition, the validity of the index was identified by evaluting the correlation between the modified MRCI-K scores and the number of medications, and non-medication related variables such as age, sex, and diagnosis number.

(A) Non-multi-dose



(B) multi-dose administration



Scoring in Section B: 3

Figure 4. Scoring of modified MRCI-K in section B.
(A) Non-multi-dose, (B) multi-dose administration

3. Results

3.1. The MRCI-K and the modified MRCI-K

The final version of the MRCI-K and the modifiec MRCI-K were as follows:

한국형 처방 복잡도 평가 지수 (MRCI-K)

이름	생년월일	검사일	검사자

의약품 개수 (필요 시 처방 포함)	Section A	Section B	Section C	MRCI-K

지시사항

1. MRCI-K는 처방된 의약품을 대상으로만 평가합니다. 기재 시에는 조제나 불출 시의 조제라벨 혹은 약력 정보를 근거로 기입하고 임상적인 개수(필요 추정하여서는 안됩니다.
2. 본 척도는 세가지 영역으로 구성되어 습니다. 각 영역을 완료한 후 다음 영역으로 진행하시기 바랍니다. 모든 영역을 완료한 후 세가지 영역의 점수를 합하여 MRCI-K를 구합니다.
3. 만약 한 처방전에 동일 약물(동일 상표, 동일 제형)이 다른 용량으로 1회 이상 처방되면,

   한가지 약물로 간주합니다. (예 와파린 5mg, 2mg 의사지시대로)

4. 만약 용량용법이 유동적인 경우 가장 적은 용량과 복용 횟수를 선택합니다.

   (예 벤토린 MDI, 1~2 번 흡입, 하루 2~3 번 사용일 경우, 점수는 MDI, 가변 용량('1 회 투약 시 복수 단위'가 아님.), 하루 2 번으로 계산합니다.

5. 경우에 따라서는 복용 횟수를 계산해야 합니다
   (예 큐란 아침 1 번, 자기 전 1 번은 하루 2 번으로 계산)
6. 만약 `의사 지시대로`라는 지시 사항이 있을 경우 복용 횟수 영역에서는 점수를 부과하지

   않습니다. (예, 소론도 5mg 의사지시대로)

7. 복용횟수에 대한 지시가 한 가지 이상 있는 경우 모든 지시사항에 대한 점수를 계산합니다. (예

벤토린 MDI, 1회 2 puff씩 하루 2 회 흡입 용법 이외에도 필요 시마다 흡입 용법이 처방되는 경우 'MDI', '한번에 복수 단위', '하루 2번', '필요 시마다'의 모든 점수를 합산)

8. **2개 이상의 의약품이 상호 배타적인 경우, 지시된 용법을 필요시 용법으로 바꾸어 모든 점수를 계산한다. (예 벤토린MDI 혹은 벤토린 네뷸라이저 하루 2회일 경우 제형에서 MDI 와 네뷸라이저, 복용 횟수에서 하루 2회 필요시를 두 번 계산해야 한다.)**

9. **만약 해당되는 선택지가 없는 경우 의미가 가장 가까운 항목을 선택합니다. (예 매일 6번은 매 4시간마다로 선택)**

A. 처방전에 있는 각 제형에 해당하는 점수에 O표를 합니다.
(단 제형 중복 시 한번만 체크)

제형		점수
경구제	캡슐제/정제	1
	가글제/구강청결제	2
	껌제/트로키제	2
	액제	2
	산제/과립제	2
	설하 스프레이제/설하정	2
외용제	크림제/겔제/연고제	2
	드레싱	3
	도포제/외용액제	2
	페이스트제	3
	경피흡수제	2
	스프레이제	1
점이, 점비, 점안제	점이제/이크림제/이연고제	3
	점안제	3
	점안겔제/안연고	3
	점비액제/비크림/비연고	3
	비강 스프레이제	2
흡입제	흡입 분말제, DPI (dry-powder inhaler)	3
	정량분무흡입제 MDI (metered-dosed inhaler)	4
	네뷸라이져	5
	산소발생기	3
	터부할러	3
	에어로졸제	3
기타	투석제	5
	관장제	2
	주사제: 충전 앰플/ 충전 바이엘	3 4
	질삽입 기구	3

	환자조절 진통제 PCA	2
	좌제 (질정 포함)	2
	질크림제	2
A총합		

B. 처방전의 각 약물의 복용 횟수에 해당하는 만큼 체크(√) 표시를 합니다. 각 항목의 체크한 수를 더하고 부과된 가중치를 곱합니다. 일치하는 항목이 없는 경우 가장 적절한 항목을 선택합니다.

투여횟수	약품														가중치	가중치와 약품수의 곱
하루1번															1	
필요시 하루1번															0.5	
하루2번															2	
필요시 하루2번															1	
하루3번															3	
필요시 하루3번															1.5	
하루4번															4	
필요시하루4번															2	
12시간마다															2.5	
필요시 12시간마다															1.5	
8시간마다															3.5	
필요시 8시간마다															2	
6시간마다															4.5	
필요시 6시간마다															2.5	
4시간마다															6.5	
필요시 4시간마다															3.5	
2시간마다															12.5	
필요 시 2시간마다															6.5	
필요 시/응급 시															0.5	
격일로/그외 보다 낮은빈도로															2	
필요시 산소흡입															1	

산소흡입< 15시간															2	
산소흡입> 15시간															3	
B총합																

C. 처방에 추가된 지시사항이 있으면 해당하는 곳에 체크한다. 각 항목의 체크한 수를 더하고 부과된 가중치를 곱한다.

지시사항	약품								합	가중치	가중치와 약품수의 곱
1.정제를 자르거나 빻으시오										1	
2.정제나 산제를 녹이시오										1	
3. 1회 투약시 복수 단위 (예 2정씩, 2회 흡입)										1	
4.가변 용량 (예 1-2정, 2-3회 흡입)										1	
5.특정시간에 복용 (예 아침에, 자기전, 아침 8시)										1	
6.음식과 관련된 복용 (예 식후, 식전, 음식과 함께)										1	
7.특정 음료와 함께 복용										1	
8.지시대로 복용/사용										2	
9.점진적인 용량감소/ 점진적인 용량증가										2	
10. 1회 복용이 교대로 바뀌는 투약 (예 아침에 1회와 자기전에2회, 격일로 1회나 2회)										2	
C총합											

Figure 5. Korean version of medication regimen complexity index (MRCI-K)

변형된 한국형 처방 복잡도 평가 지수 (modified MRCI-K)

B.1 처방전의 약품이 포장된 경우(Multi-dose drug dispensing), 조제된 상태를 고려하여 투약 횟수(frequency)를 계산합니다.

(예) 1tab qd, 1tab bid, 1tab tid 인 처방이 같이 포장되어 조제된 경우

B 항목(투약횟수)에서는 포장된 투약 횟수 3점을 부과합니다.

C.1 처방전의 약품이 포장된 경우(Multi-dose drug dispensing), 조제된 상태를 고려하여 1번, 2번, 3번에 대한 점수를 부과하지 않습니다.

(예) 0.5정, 2정 등에 점수를 부과하지 않음

C.2 처방전의 약품이 포장된 경우(Multi-dose drug dispensing), 조제된 상태를 고려하여 용법(Instruction) 상 5번, 6번에 각각 다른 경우를 모두 점수로 부과합니다.

(예) 용법에 아침, 저녁, 자기전에 용법이 있는 경우: 3점 부과

(예) 용법에 식전30분, 식후 직후, 식후 2시간이 있는 경우: 3점 부과

Figure 6. Instruction of the modified Korean version of medication regimen complexity index (modified MRCI-K)

3.2. Patient characteristics

Among the 335 discharged patients admitted during the study period, 331 patients were included except for 4 patients due to prescription instruction errors. Table 4 displays the baseline characteristics of the 331 patients. For the MRCI-K validation test, a total of 331adults were included in the study, with a mean age of 68.7 years (SD 15.3 years). A total of 57.4% of the patients were male. On discharge, the average number of prescribed drugs was 6.1 ± 3.3, with a mean MRCI-K score of 28.2 ± 14.2. The mean score on the MRCI-K in section A, section B, and section C was 2.4 (SD 1.7, range 1–11points), 11.8 (SD 6, range 0.5–33 points), 14 (SD 8.1, range 2–44 points), respectively. The most prevalent admission diagnoses included pneumonia (n=128). Those who were prescribed more than 5 drugs, namely called polypharmacys, accounted for 206 people (62%). There were 64 people (13.4%) who have reported adverse drug events (ADEs) on the EMR.

Table 4. Baseline characteristics of the patients included in the analysis (n = 331).

Characteristics		Number (%)
Age, years (mean ± SD) (range)		68.7 ± 15.3 (19 – 95)
Male gender		190 (57.4%)
Hospital length of stay (days)		14.2 ± 14.9
Types of health insurance		
	National health insurance	303 (91.5%)
	Medical aid	27 (8.2%)
	Others	1 (0.3%)
Diagnosis		
	Pneumonia	128 (39%)
	NSCLC	24 (7%)
	Tuberculosis	19 (6%)
	COPD	19 (6%)
	Hemoptysis	10 (3%)
	SCLC	10 (3%)
	Influenza	9 (2.7%),
	Bronchitis	6 (1.8%)
	Others	106 (31.5%)
Polypharmacy (≥5 medications)		206 (62%)
ADE reports		64 (19.3%)
Number of medications (mean ± SD) (range)		6.1 ± 3.3 (1 – 18)
MRCI-K score (mean ± SD) (range)		28.2 ± 14.2 (4 – 72)
	Section A score	2.4 ± 1.7 (1 – 11)
	Section B score	11.8 ± 6.0 (0.5 – 33)
	Section C score	14.0 ± 8.1 (2 – 44)

COPD, chronic obstructive pulmonary disease; MRCI-K, medication regimen complexity index Korean version; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

3.3. Reliability analysis

The randomly selected 25 individuals from total study populations included in the reliability analysis, the majority (52%) were diagnosed with pneumonia. A similar MRCI-K score was observed with an MRCI-K score of 28.9 ± 13.6 compared to all patients (MRCI-K; 28.2 ± 14.2 (mean ± SD). The results of the inter-rater/test-retest reliability analysis are described in Table 5. A high correlation was observed between the scores obtained by six observers and the same evaluator after 2 months, indicating excellent agreement between scoring and confirming the inter-rater and test–retest reliability.

Table 5. Inter-rater and test–retest reliability of MRCI-K

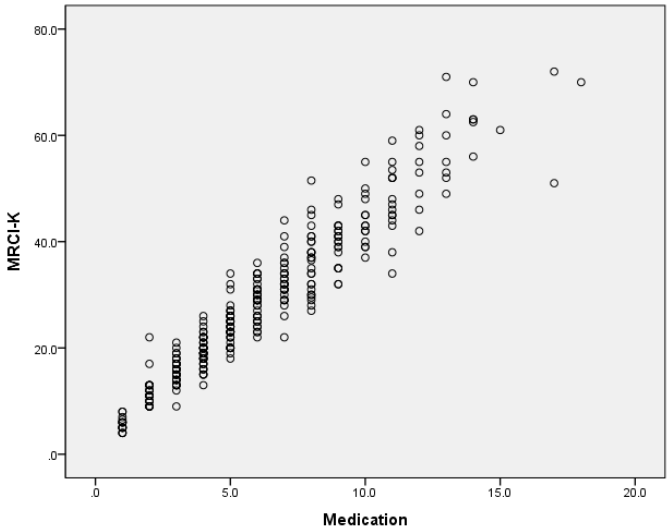
MRCI-K	ICC (95% CI)	
	Inter-rater	Test-retest
Section A	0.915 (0.851–0.958)	0.98 (0.955–0.991)
Section B	0.987 (0.978–0.994)	0.985 (0.966–0.993)
Section C	0.823 (0.689–0.912)	0.957 (0.903–0.981)
Total	0.977 (0.96–0.989)	0.991 (0.979–0.996)

ICC, intraclass correlation coefficient; MRCI-K, medication regimen complexity index Korean version

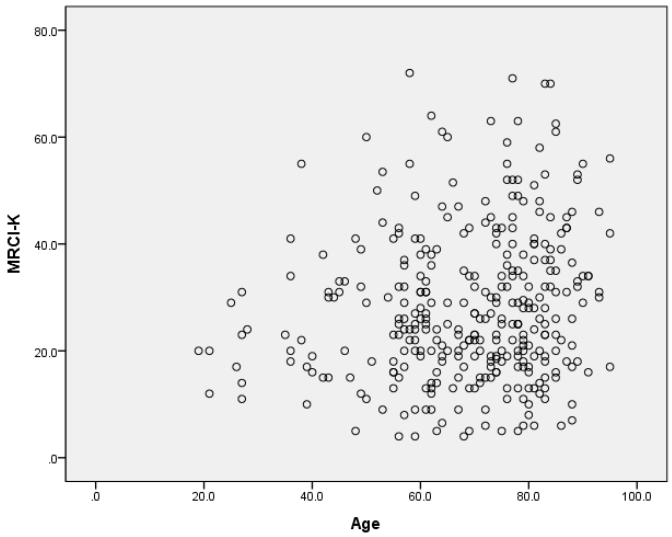
3.4. Validity analysis

The convergent validity was confirmed as a result of a strong correlation between the MRCI score and drug number with Pearson's correlation coefficient of 0.955 (Table 6). The discriminant validity was evaluated as a result that MRCI-K also showed a weak correlation with length of stay (0.242, $p < 0.001$) and age (0.155, $p = 0.005$). The scores of the two groups were compared by the presence of ADE reporting in the ADE reporting system. If the group with the ADE report had a higher MRCI-K score than the group without the report. The two groups were statistically different from each other depending on ADE reporting ($p = 0.007$). The mean value of the group with ADE reporting (mean = 31.8) was higher than that of the other group without ADE reporting (mean = 27.3). There was a significant difference between the three categorical medication number groups and MRCI-K ($p = 0.001$).

(a) Convergent validity: Correlation between medication number and MRCI-K (Inpatient) r=0.935 (*p*=0.000)



(b) Discriminant validity: Correlation between age and MRCI-K (Inpatient) r=0.155 (*p*=0.005)



(c) Discriminant validity: Correlation between hospital length of stay and MRCI-K (Inpatient) r=0.242 (p=0.000)

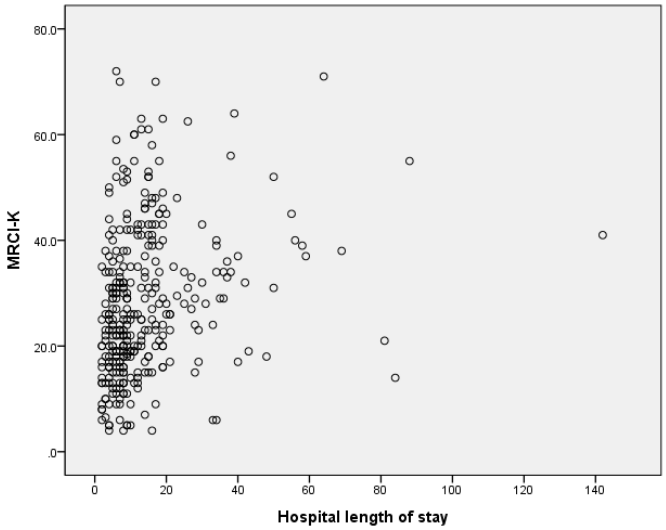


Figure 7. Correlation between variable and MRCI-K

Table 6. Correlation between the Korean Medication Regimen Complexity Index (MRCI-K) scores and characteristics of the 331 participants.

		Section A	Section B	Section C	Total	*p* value	Correlation with MRCI–K scores
Age, years (mean ± SD)	≤20 – 49	2.0 ± 0.2	10.8 ± 0.7	11.4 ± 0.9	24.2 ± 1.7	0.079	0.155*
	50 – 69	2.4 ± 0.1	11.4 ± 0.5	13.2 ± 0.7	27.0 ± 1.3		
	≥70	2.4 ± 0.1	12.1 ± 0.4	15.0 ± 0.6	29.6 ± 1.0		
Medication number (mean ± SD)	1 – 4	1.8 ± 0.0	6.4 ± 0.2	14.2 ± 0.7	22.7 ± 0.8	0.001*	0.955*
	5 – 9	2.3 ± 0.1	13.1 ± 0.3	13.3 ± 0.6	28.7 ± 0.6		
	≥10	3.5 ± 0.3	20.3 ± 0.6	15.7 ± 1.0	39.6 ± 1.2		
Hospital length of stay, week (mean ± SD)	1	2.1 ± 0.1	10.3 ± 0.5	11.3 ± 0.6	23.8 ± 1.1	0.001*	0.242*
	2	2.4 ± 0.1	11.2 ± 0.6	13.0 ± 0.7	26.6 ± 1.4		
	≥3	2.5 ± 0.1	13.5 ± 0.5	17.5 ± 0.7	33.6 ± 1.2		
ADEs, reported (mean ± SD)		2.5 ± 0.2	13.6 ± 0.7	15.6 ± 0.9	31.8 ± 1.6	0.007*	NA
No ADEs, reported (mean ± SD)		2.3 ± 0.1	11.3 ± 0.3	13.6 ± 0.5	27.3 ± 0.8	0.007*	NA

ADE, adverse drug event; MRCI-K, Korean version of Medication regimen complexity index *p <0.05

A strong correlation between MRCI-K scores and medication numbers, with a Pearson's correlation coefficient of 0.914 was observed (Table 7). There was no correlation between MRCI-K and diagnosis number or age. MRCI-K scores did not statistically differ from each other according to ADE reporting and gender.

Table 7. Correlation between the MRCI scores and variables in 100 outpatients

	Correlation with MRCI-K score			
	Section A	**Section B**	**Section C**	**Total**
Medication number	0.343 * (p = 0.000)	0.705 * (p = 0.000)	0.925 * (p = 0.000)	0.914 * (p = 0.000)
Diagnosis number	0.063 (p = 0.523)	0.133 (p = 0.188)	0.148 (p = 0.140)	0.159 (p = 0.114)
Age	-0.279 * (p = 0.005)	-0.031 (p = 0.762)	0.113 (p = 0.263)	-0.009 (p = 0.929)
Sex				
Male	1.9 (1.4)	6.2 (4.8)	7.2 (4.5)	15.4 (8.8)
Female	1.6 (1.4)	5.8 (3.6)	6.6 (3.5)	14.1 (6.9)
	p = 0.421	p = 0.833	p = 0.423	p = 0.440
ADE report				
ADEs, reported	2.2 (1.9)	6.9 (5.3)	7.3 (4.0)	16.5 (7.2)
No ADEs, reported	1.7 (1.3)	5.8 (4.1)	6.9 (4.1)	14.5 (8.2)
	p = 0.291	p = 0.347	p = 0.670	p = 0.347

ADE, adverse drug event; MRCI-K, Korean version of Medication regimen complexity index
* p <0.05

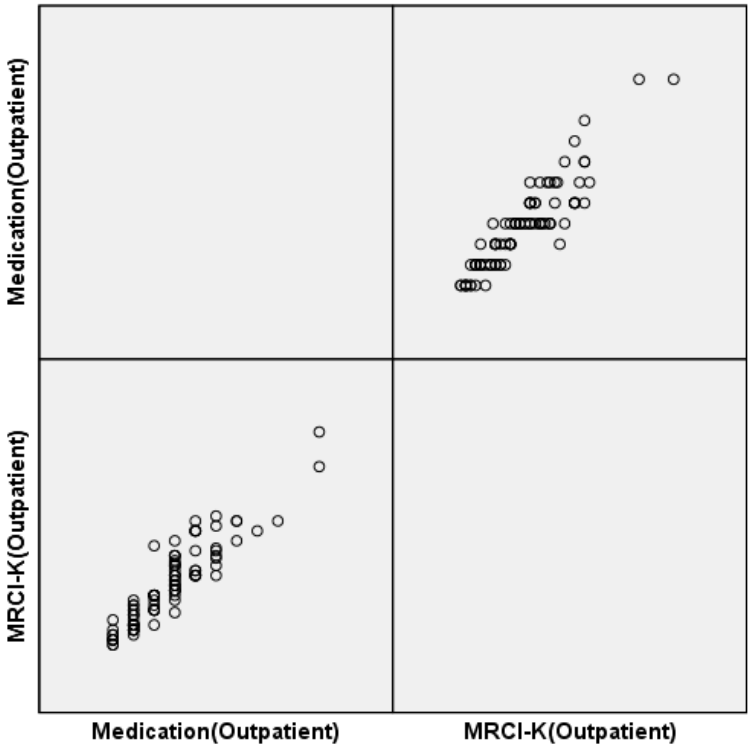


Figure 8. Correlation between medication number and MRCI-K (outpatient) r=0.914 (*p* =.000)

The Rankings performed by the nine experts are more consistent with the MRCI-K than the medication numbers, which is confirmed by the result of the κ values of concordance in Table 8. The result of the concordance between nine experts' panel rankings of patient-level medication regimen complexity with MRCI-K showed good reliability, exceeding 0.8 except for two experts (T. K. Koo and M. Y. Li 2016). Concordance with medication numbers was lower than the concordance of MRCI-K. The concordance between the two nurses was weak.

Table 8. Concordance of expert panel ranking with MRCI-K score and medication count rankings quadratic weighted κ (95% CI).

	Quadratic Weighted κ (95% CI)	
	MRCI-K ranking	**Medication number ranking**
Pharmacist 1	1 (1 – 1)	0.83 (0.65 – 1)
Pharmacist 2	0.83 (0.65 – 1)	0.66 (0.34 – 0.97)
Pharmacist 3	0.82 (0.60 – 1)	1 (1 – 1)
Internal medicine physician 1	1 (1 – 1)	0.83 (0.60 – 1)
Internal medicine physician 2	1 (1–1)	0.83 (0.60 – 1)
Internal medicine physician 3	0.83 (0.65 – 1)	0.66 (0.34 – 0.97)
Nurse 1	0.31 (0.03 – 0.60)	0.31 (-0.03 – 0.66)
Nurse 2	0.31 (-0.21 – 0.84)	0.49 (-0.02 – 0.99)
Nurse 3	1 (1 – 1)	0.83 (0.60 – 1)

MRCI-K, Korean version of Medication regimen complexity index

3.5. Development of modified MRCI-K

The modified MRCI-K was applied focusing on the fact that multi dose dispensing is provided to patients at discharge. Multi-dose dispensing results in reduced dose frequency by putting each oral medication into a package together. In addition, the dispensing process encompasses splitting tablets and multidose for patients, making it unnecessary to follow instructions. The modified MRCI-K based on the original MRCI represents the status of dispensed medications at discharge with scoring as follows: the dispensed frequency is used as dose frequency in section B; splitting tablet and multidose is not scored as instruction in section C; all different instructions including administration time and food-related time is scored considering that different instructions lead to increase the dosing frequency during dispensing. The same samples used in the MRCI-K reliability analysis were assessed with the modified MRCI-K. The results of inter-rater/test-retest reliability analysis are described in Table 9. There was a high correlation between the scores obtained by two observers and the same evaluators after one month, indicating excellent agreement between scorings and confirming the inter-rater and test–retest reliability with the modified MRCI-K.

A significant positive correlation was found between the modified MRCI-K score and the number of medications in Table 10. There was no correlation with non-medication related variables such as diagnosis number, age and sex. In addition, there was a significant positive correlation found between the modified MRCI-K score and MRCI-K.

Table 9. Inter-rater and test–retest reliability of the Modified MRCI-K

Modified MRCI-K	ICC (95% CI)	
	Inter-rater	Test–retest
Section A	0.981 (0.956 – 0.991)	0.984 (0.963 – 0.993)
Section B	0.908 (0.791 – 0.959)	0.970 (0.933 – 0.987)
Section C	0.878 (0.724 – 0.946)	0.909 (0.749 – 0.960)
Total	0.958 (0.905 – 0.981)	0.978 (0.950 – 0.990)

ICC, intraclass correlation coefficient; MRCI-K, medication regimen complexity index Korean version

Table 10. Correlation between the modified MRCI scores and variables in 100 outpatients

	Correlation with the modified MRCI-K score			
	Section A	**Section B**	**Section C**	**Total**
MRCI-K	0.412 * (p < 0.001)	0.562* (p < 0.001)	0.603* (p < 0.001)	0.639* (p < 0.001)
Medication number	0.343 * (p = 0.000)	0.320* (p = 0.008)	0.487* (p = 0.000)	0.444* (p = 0.000)
Diagnosis number	0.065 (p = 0.523)	0.201* (p = 0.045)	0.017 (p = 0.863)	0.134 (p = 0.185)
Age	-0.279 * (p = 0.005)	-0.199 * (p = 0.047)	-0.220 * (p = 0.028)	-0.262 * (p = 0.003)
Sex				
Male	1.9 (1.4)	3.3 (3.8)	3.9 (2.4)	9.1 (8.8)
Female	1.6 (1.4)	2.8 (1.9)	3.6 (1.6)	8.1 (6.9)
	p = 0.421	p = 0.513	p = 0.429	p = 0.402
ADE report				
ADEs, reported	2.2 (1.9)	3.8 (5.2)	4.5 (2.7)	10.5 (6.8)
No ADEs, reported	1.7 (1.3)	2.9 (2.5)	3.6 (1.9)	8.3 (5.4)
	p = 0.176	p = 0.405	p = 0.121	p = 0.166

ADE, adverse drug event; MRCI-K, Korean version of Medication regimen complexity index
* p <0.05

4. Discussion

Higher medication regimen complexity is associated with negative clinical outcomes such as higher rates of hospital admission, hospital discharge destination, hospital readmission, emergency sector visits, and even higher mortality (Alves-Conceicao et al. 2018). Although many different methods were used to quantify the complexity of medication regimens, the medication regimen complexity index (MRCI) has been regarded the gold standard as a tool that quantifies regimen complexity beyond the number of medications, which considers dosages and frequency as well as additional directions (Paquin et al. 2013).

The MRCI, developed by George et al., is written in English and applied in Australia. To date, the MRCI was translated and validated into several countries in a population of patients with different morbidities, showing good performance for the validity and reliability of the tool. Idiomatic and experiential differences in the translation process, due to different medical environments, required us to make several changes to the scale according to Korean practice, whereas the index maintains the scale's international comparability. Although translations and back-translations followed the original instruction of the MRCI, unused products such as pessaries and oxygen/concentrators were translated into similar formulations semantically. Scoring for new devices was assigned based on the original questionnaire; that is, three points for dry-powder inhaler and four points for metered-dosed inhaler. The pilot test with MRCI-K allowed us to identify factors on possible discrepancies when the MRCI-K was applied to various prescriptions in Korea.

The present results confirmed the validity and reliability of MRCI showing satisfactory psychometric properties for the measurement of regimen complexity. All drugs taken by patients such as non-prescription medications were included in the analysis to ensure that the MRCI-K would be valid in the wide field of pharmacotherapy. In the validation analysis, there was a very high correlation between MRCI-K scores and medication numbers, and a lack of correlation between MRCI-K scores and variables not related to medications. These results were similar to the original MRCI development evaluation (George et al. 2004) and other validation studies (Masumoto et al. 2020; Melchiors et al. 2007; Pantuzza et al. 2018; Saez de la Fuente et al. 2016; Stange et al. 2012). Comparable results were observed in 100 randomly selected outpatients as well. In the criterion validation analysis, we found there was a difference in the agreement between the nurses and the agreement between the doctors and pharmacists. Because nurses in hospitals are responsible for providing timely administration of medications to patients, regimen complexity due to dispensing may explain the inconsistency observed among healthcare professionals. In addition, we confirmed that the MRCI-K and the modified MRCI-K showed high test–retest and inter-rater reliabilities as similar studies.

The findings of this study demonstrated the MRCI-K mean scores were higher than those of other studies with more medication numbers, but similar to a previous validation study in the elderly (Advinha et al. 2014; Bryant et al. 2016; Saez de la Fuente et al. 2016). The present study included self-medication at admission to reflect the whole medication regimen of each patient. The mean MRCI-K score was 28.2, and the mean total medication count was 6.1. In comparison, a similar MRCI score distribution (mean = 23.3) was observed in a Japanese study

with 7.4 medications, showing relatively lower scores considering the difference in medication numbers (Masumoto et al. 2020). The results in this study reflected that inpatients at discharge in Korea have difficulty following a medication regimen which could lead to issues such as medication compliance. In another MRCI analysis of entire prescriptions, including OTC drugs, the mean score was 29.1 with 13.1 medications (Bryant et al. 2016). The most decisive factors contributing to complexity are usually considered the number of drugs and dosage frequency (Paquin et al. 2013). However, higher scores in Korea are presumably due to high section C scores. The validation results demonstrate that the scores of section C were higher than those of section B (Melchiors et al. 2007). Typically, prescribed medications contained instructions for administration time and food-related directions, even if food was irrelevant to the regimen leading to medication regimen complexity as a result of increased dosing frequency. Misunderstanding medication instructions, including food-related instructions and drug-drug interactions, leads to overcomplexity especially for the elderly. The medication regimens could be simplified by consolidating administration times (Lindquist et al. 2014).

We found that patients with adverse drug events reported had higher score distribution in the MRCI-K than those without. As the length of hospitalization increased, the score of complexity of prescriptions also increased showing differences between hospitalization periods. These findings imply that further studies are needed on the associations between adverse events and length of stay according to the MRCI-K score.

Dispensing multiple drugs in one pack according to their usage is common in hospital pharmacy practice. The dispensing process leads to decreased medication complexity, including the reducing frequency of dosing and splitting, crushing, and opening of tablets or capsules. However, the original MRCI has a limitation in that it cannot explain dispensing status in a way that assumes that each drug is taken separately. The modified MRCI-K was designed to reflect the status of the dispensing by adding instructions. Scoring the dispensed frequency enables the MRCI-K to account for the effect of decreased dosing frequency after dispensing. In section C, each of the different instructions was calculated as a factor to increase regimen complexity as different instructions results in increased dose frequency.

The modified MRCI-K was developed by adding instructions based on the MRCI-K. We performed the same validity evaluation as the MRCI-K. Our results are consistent with the validity analysis showing a convergent validity and discriminant validity. The reliability analysis demonstrated an excellent internal consistency. However, we identified results different from MRCI-K showing a low correlation with the medication number and a negative correlation with age. This result suggests that additional validation studies are needed because the modified MRCI-K is expected to have a different distribution from the MRCI-K.

The modified MRCI-K could be a useful tool in identifying complexity distinguishing the potential reasons of complexity. Further research is required to investigate the modified MRCI-K as a risk assessment tool for validity in various clinical practices.

Part 2. Application of the Korean version of medication regimen complexity index (MRCI-K)

2. Methods

2.1. Study design and setting

The study was designed as a prospective, open, randomized controlled study and conducted in accordance with the Declaration of Helsinki, and all participants gave written informed consent prior to inclusion in the study. The protocol was approved by the institutional review board (IRB) at Inha Hospital (IRB# 2020-06-029).

2.2. Study population

Patients aged 65 or older admitted to the ward of hospital medicine from July 2020 to December 2020, who were taking at least 5 medications were included. All written informed consent of patient or caregivers was obtained prior to inclusion. Patients who could not be contacted after 30 days after discharge, discharged within 24 hours and those whose life expectancy was less than 3 months were excluded. Patients were randomly assigned to the intervention or control groups among 20 randomly generated blocks prior to patient enrollment. (each block contained 10 intervention and 10 control allocations).

2.3. Baseline data collection within 24 h after admission

Demographic information and lab data including hemoglobin, sodium, potassium, albumin, alanine aminotransferase, alkaline phosphatase, and creatinine clearance calculated using equations from Cockcroft-Gault Equation based on creatinine were recorded. A face-to face interview was conducted with all patients within 24 hours at inclusion. The contents of the interview at the time of admission are presented in Table 11. The interview involved questions about adherence using the Morisky Medication-Taking Adherence Scale-4 (MMAS-4), swallowing ability, patient reported adverse events, use of OTC, complementary and alternative medicines. In addition, medical history including syncope, delirium, dementia, cognitive impairment, gastric ulcer, constipation and fall or fracture were collected to identify potentially inappropriate medications (PIMs) which were not recommended for use due to drug-disease interactions according to BEER 2019 (Panel et al. 2019).

2.4. Intervention

A clinical pharmacist provided the pharmaceutical care service to patients in the intervention group as follows: Within 24 hours on admission, a comprehensive list of current drugs was checked during a face-to-face interview with the pharmacist to ensure whether prescriptions and self-care drugs were correct or not. Medication reviews were conducted based on BEER 2019 (Panel et al. 2019), screening tool of older persons' prescriptions (STOPP) and screening tool to alert to right treatment (START) 2015 (O'Mahony et al. 2015), and recommendations were given to physicians on drug selection, monitoring requirements, renal dose adjustment according to renal function (CrCl) and drug-drug interaction based on Lexicomp®, with the final decision made by the physician in charge. The intervention group received a clinical pharmacy service from Monday to Friday, with a full-time pharmacist, and the contents of the intervention were all recorded in case report form, whereas the control group received the usual care are during inpatient period. In addition, the simplification of the instructions for the discharge medication such as food and administration time matching was conducted to reduce the regimen complexity prior to discharge. The pharmacist educated the patients about the instructions and the discharge medication, as it was difficult to make the instruction changes from the doctor. The ADE were monitored throughout the hospitalization process and recorded in the ADE reporting system if the doctor and pharmacist agreed to a medication-related ADE.

A follow-up telephone call to patients 30 days after discharge was conducted for reconfirmed medication use and patient reported ADE events after discharge.

Table 11. Interview at the time of admission

Person who gives you the medications?	Self/Guardian	
Able to swallow	Yes/ No	
Need to grind	Yes/ No	
Taking OTC	Yes/ No	
Complementary and alternative medicines	Yes/ No	
Oriental medicine	Yes/ No	
MMAS-4	Do you ever forget to take your medications?	Yes/ No
	Are you careless at times about taking your medications?	Yes/ No
	When you feel better, do you sometimes stop taking your medication?	Yes/ No
	Sometimes if you feel worse when take your medication do you stop taking it?	Yes/ No
Side-effects	Yes/ No	
Medications that cause side effects		
Symptoms of side effects		
Current number of medications		

MAI(score)	
MRCI-K(score)	
Syncope	Yes/ No
Dementia	Yes/ No
Cognitive impairment	Yes/ No
Delirium	Yes/ No
Gastrointestinal ulcers	Yes/ No
Constipation,	Yes/ No
Falls	Yes/ No
Fractures	Yes/ No
BEER number of medications	
STOPP number of medications	
START number of medications	

OTC, over-the counter; MMAS-4, Morisky medication adherence scale 4 item; MAI, Medication Appropriateness Index for polypharmacy; MRCI-K, Korean version of Medication regimen complexity index; BEER, BEER Criteria 2019; STOPP 2015, Screening Tool of Older People's potentially inappropriate Prescriptions 2015, START 2015, Screening Tool to Alert to Right Treatment 2015

2.5. ADE differences

Relevant ADEs for the patient were monitored and discussed with the physician throughout the hospital stay. The identified ADEs of patients were recorded in the ADE reporting system in the Inha University Hospital. Reports of adverse events that were completed at discharge were recorded as primary outcomes. Serious adverse events (SAEs) that met one of the criteria including death, life-threatening, hospitalization, or prolongation of hospitalization were evaluated and recorded as incidents by a pharmacist. Pharmacists contacted all the patients by telephone 30 days after discharge to ensure patient reported ADE and use of PIMs medication. The pharmacist contacted the next of kin or caregiver of patients who were unable to communicate coherently. In addition, the degree of regimen complexity measured as MRCI-K and modified MRCI-K was compared with the difference in scores between intervention and control groups in order to confirm the pharmacist intervention effect.

2.6 Statistical Analysis

The patient characteristics were presented as the median and interquartile range (IQR) and percentile (%). Changes in numbers of medications, MRCI-K, modified MRCI-K and PIMs between groups were analyzed with the Mann –Whitney U test. For analysis of ADE reports differences between both groups, Data was analyzed utilizing the Fischer exact and chi-squared test. Analyses were performed using IBM SPSS Statistics for Windows version 24.0 (IBM Corp. Armonk, NY).

3. Results

3.1. Patient characteristics

A total of 40 older patients were screened, eight patients were excluded due to readmission of ICU (n=4), decline to enroll (n=3) and expired before the intervention was finalized (n=1). A total of 32 patients completed both the intervention and control sessions and 26 patient finished the follow-up 30 days after discharge. Figure 7 shows the flow of patients through the study. Patient characteristics (n = 32) are shown in Table 12. Baseline characteristics between the two groups were well balanced in every respect. The number of medications and the number of PIMs were similar between both 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 both groups in all values of MRCI-K, CCI and length of stay as well.

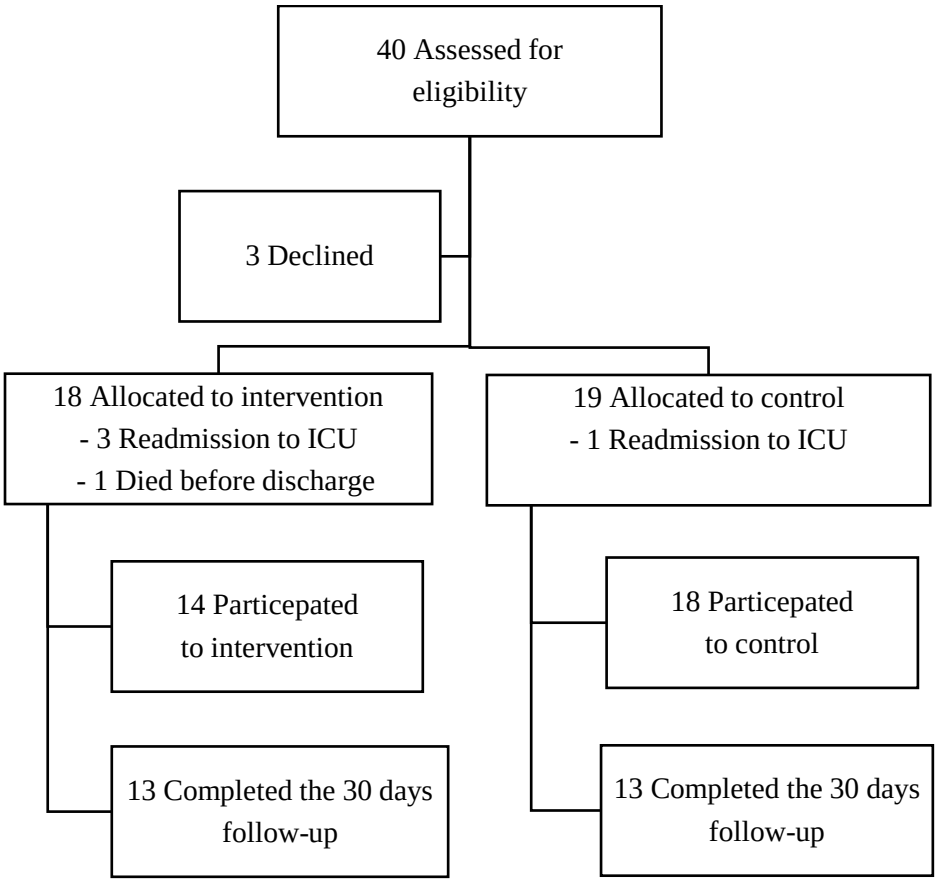


Figure 9. Patient flow diagram

Table 12. Baseline characteristics (n=32)

	Intervention group (n=14)	Control group (n=18)	
Gender, female, n (%)	8 (57.1)	13 (72.2)	$p = 0.555$
Age, years, median(range)	83 (71 – 87)	84.5 (72 – 94)	$p = 0.235$
Medication management			
Assisted, n (%)	8 (57.1)	11 (61.1)	$p = 0.821$
Tube-feeding, n (%)	5 (35.7)	7 (38.9)	$p = 0.854$
Number of medications, median (range)	8.5 (4 – 14)	8.5 (3 – 15)	$p = 0.866$
Self-medication Discrepancy,			
Nonprescription drugs n (%)	2 (14.2)	5 (27.8)	$p = 0.457$
Prescription drugs n (%)	1 (7.1)		
MMAS-4 median (range)	4 (0 – 4)	4 (0 – 4)	$p = 0.536$
PIMs criteria medication, mean (SD)	1.5 (0 – 6)	3 (0 – 5)	$p = 0.253$
Medical condition related to PIMs criteria			
Dementia, n (%)	7 (50)	9 (50)	$p = 1$
Delirium, n (%)	5 (35.7)	7 (38.9)	$p = 0.854$
Falls history, n (%)	6 (42.9)	10 (55.5)	$p = 0.476$
CCI, median (range)	5 (3 – 6)	4.5 (3 – 7)	$p = 0.301$
Length of stay Median (range)	7 (3 – 51)	8 (2 – 39)	$p = 0.837$

MRCI-K, Korean version of medication regimen complexity index; ADE, adverse drug events; PIM, potentially inappropriate medication; CCI, Charlson Comorbidity; MMAS-4, Morisky Medication Adherence Scale
Data were analyzed using Fischer exact, chi-squared distribution, Mann-Whitney U test

3.2. Effects of pharmacist intervention in the medication reconciliation process

In total, 41 suggested actions were identified for the 14 intervention group 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. The summary of recommendations and acceptances are described in Table 13.

The changes from admission to discharge in the number of medications, MRCI-K, modified MRCI-K and PIMs are shown in Table 14. A total of 31 patient prescriptions were analyzed, excluding one patient with incomplete prescription information. The intervention group had higher scores change at discharge than admission, whereas the control group had lower scores change at discharge compared to admission in all indices. However, there was no significant difference between both groups in the score change. In addition, the score reduction after regimen simplification intervention was dominant in section C which was statistically significant (p = 0.005).

Table 13. 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, 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 14. Scores on admission and at discharge and change from admission

	Intervention (n=14)			Control (n=17)			
	Admission	Discharge	Change	Admission	Discharge	Change	
Number of medications*	8.5 (4 – 14)	7.5 (3 – 11)	-1.4 (-5 – 3)	8.5 (3 – 15)	8.5 (4 – 12)	0 (-9 – 5)	p = 0.566
MRCI-K**	31.8 (11.5)	25.6 (13.8)	-6.2 (10.4)	32.0 (16.9)	29.6 (12.7)	-2.4 (14.0)	p = 0.159
Section A*	1 (1 – 7)	1 (1 – 5)	0 (-6 – 2)	1 (1 – 7)	3 (1 – 7)	0 (-2 – 4)	p = 0.399
Section B**	12.4 (7.3)	11.6 (6.2)	-0.8 (4.7)	13.6 (6.6)	12.1 (6.1)	-1.4 (6)	p = 0.783
Section C**	16.9 (4.1)	12.2 (7.7)	-4.6 (5.8)	17.5 (7.7)	15.7 (4.4)	-1.8 (6.9)	p = 0.203
Modified MRCI-K*	9 (4 – 16)	6.5 (4 – 17)	-2.5 (-10 – 9)	12 (4 – 17)	11 (4 – 19)	0 (-5 – 11)	p = 0.067
Section A*	1 (1 – 7)	1 (1 – 5)	0 (-6 – 2)	1 (1 – 7)	3 (1 – 7)	0(-2 – 4)	p = 0.399

Section B*	3 (1 – 8)	3 (1 – 6)	0(-5 – 1)	3 (1 – 5)	3 (1 – 4)	0(-6 – 6)	p = 0.855
Section C**	4.4 (1.7)	2.7 (2.4)	-1.6 (2.9)	4.7 (1.2)	5.2 (1.7)	0.4 (1.3)	p = 0.005
PIM Mean *	3 (0 – 5)	1 (0 – 4)	-1 (-4 – 1)	1.5 (0 – 6)	0 (0 – 3)	-0.5 (-6 – 0)	p = 0.985

MRCI-K, Korean version of medication regimen complexity index; PIM, potentially inappropriate medication, *Median (range), ** mean (standard deviation)
Data were analyzed utilizing Mann-Whitney U test.

3.3. Adverse drug events in the medication reconciliation process

The comparison of ADE and SAE during the study are shown in Table 15. More adverse events were reported in the control group (44.4%, n=8) than in the intervention group (21.4%, n=3). Of 32 patients, 34.4% (n=11) reported drug related adverse events before the end of discharge period. Of 26 follow-up patients, 19.2% (n=5) were identified as patient reported drug related adverse events at the 30-day phone call. In the control group, three cases of SAE occurred due to hypoglycemia and drug-induced hepatitis. The number of side effects did not differ significantly between groups. However, a significant difference was observed in the number of adverse events on the 30-day phone call.

Eleven events confirmed by the physician and the pharmacist were identified during the study period. Of 11 drug-related ADEs, three were in the intervention group, and eight were in the control group. Three patients in the control group had SAEs. Five patients reported adverse events at the 30-day call, and three out of five were the same patients who had adverse events during hospitalization. Patient 4 reported adverse events from the same drug, glimepiride.

Table 15. Comparisons of adverse drug events reporting between medication reconciliation group and control group

	Intervention group	Control group	
[a]ADE reported during the study period, n (%)	3 (21.4)	8 (44.4)	$p = 0.266$
[a]SAE reported during the study period, n (%)	0	3(16.7)	$p = 0.529$
[b]ADE reported at 30-day phone call	0	5 (38.5)	$p = 0.039$

ADE, adverse drug events, SAE, serious adverse event

[a] Intervention group (n=14), Control group (n=18)
[b] Intervention group (n=13), Control group (n=13)
Data were analyzed utilizing Fisher's exact test.

4. Discussion

Because the MRCI was developed to objectively assess the complexity of prescriptions, it has also been applied as a risk assessment tool in pharmaceutical care (Alves-Conceicao et al. 2018). The MRCI-K is able to be studied not only as an evaluation tool for regimen complexity, but also as an index with correlations to clinical health outcomes as well. This study was performed to evaluate the results of pharmacist intervention using the MRCI-K and identify the effectiveness of a structured multidisciplinary approach in medication reconciliation.

Studies demonstrate that interventions by clinical pharmacists can affect positive clinical outcomes in both inpatient and outpatient care facilities, although the results are controversial with regards to hospital readmissions and length of in-hospital stay (Gillespie et al. 2009; Gustafsson et al. 2017). Intensive pharmacist intervention is essential for reducing the occurrence of medication discrepancies that may lead to ADEs. Especially, it is required to target the intervention to a high-risk patient population such as the elderly (Mueller et al. 2012). Pharmacy-led medication reconciliation interventions have a greater impact when conducted at either admission or discharge (Alemayehu B Mekonnen et al. 2016). To our knowledge, this is the only randomized controlled study of the effectiveness of pharmacist interventions for old age with tools including MRCI-K, and PIMs at the time of admission and discharge.

All ADEs were clearly recorded after evaluation by the pharmacist and doctor during hospitalization, and the results after discontinuation were also identified on the

electronic medical record (EMR). This study differs from other studies in that primary outcome was determined not as a preventable adverse drug event measured by medication discrepancy, but as a result of adverse events confirmed in multidisciplinary team and patient-reported adverse event in reconciliation process (Redmond et al. 2018). The control group had more ADEs and SAEs than the intervention group, although the differences between groups were not significant. Furthermore, there was a statistically significant difference in side effects reported by patients between the intervention group and the control group at 30 day follow-up phone calls. Among the patients who had adverse events in the control group, three patients repeatedly reported medication related adverse events after 30 days. Patient 4 in the control group complained of adverse drug reactions due to the same drug, glimepiride in particular. There was a more substantial reduction of adverse drug event-related hospital revisits, emergency department (ED) and hospital readmissions as a result of pharmacist led intervention, whereas there was no significant differences among mortality, composite readmission and/or ED visit (A. B. Mekonnen et al. 2016). Our result could also explain the reduction of ADEs considering the difference in the number of adverse drug reactions between the groups and the results of subsequent adverse events reported at the 30-day call, although further research is needed.

Not only medication review but also risk assessment criteria targeting the elderly was introduced in the intervention group. To evaluate whether a pharmacist-led medication review is effective during medication reconciliation, the PIMs number including BEER 2019, STOPP 2015, and START 2015 were identified. The index is utilized as drug related

risk assessment tool for old age (Gillespie et al. 2013). Our recommendations based on PIMs criteria were highly implemented by physicians (84.6%). Both medication numbers and PIMs in intervention were reduced as compared to control, although no significant difference was seen when comparing the change in drug-related problems between the groups. In particular, there were reports of adverse events from glimepiride which PIMs recommend to avoid (n=4, 36.3%), and that side effects from this drug were repeated in the control group. As a result, it was possible to identify the feasibility of preventing the adverse event of the criteria, and the need for pharmacist intervention in medication reconciliation.

We identified the regimen complexity due to section C with MRCI-K evaluation in the development of the MRCI-K study. Therefore, instruction modifications such as administration time and food-related instructions have become a major intervention target for simplification of prescription complexity. The overall change in score of regimen complexity expressed by MRCI-K and modified MRCI-K was reduced after simplification of regimen complexity. In particular, the score reduction in section C was significant after intervention. The 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 (Rohan A Elliott et al. 2013; Candis M Morello et al. 2018; Sluggett et al. 2020). A study found that modification of multiple doses is the most advantageous in simplifying the dosage regimen (Witticke et al. 2013). Dose modifications such as fixed-dose combination, and once-daily dosing have been used in the

simplification strategies for medication regimen (Elnaem et al. 2020). However, modifying usage such as administering drugs at the same time is a priority to consolidate prescription regimens in the most efficient manner, as this is how multiple doses are already dispensed in the Korean pharmacy practice. A study found reductions in medication administration times as the regimen simplification was sustained as a result of pharmacist intervention at 12 month follow-up (Sluggett et al. 2020). Our study found that simplification of the dosage is a major means of reducing administration time in hospital pharmacy practice. The score changes of section C occupied a large portion of the overall the MRCI-K score. When conducting routine in-hospital medication reviews, the simplification strategy for regimen complexity can help to minimize the impact of hospitalization on the complexity of discharge medication regimens. The modified MRCI-K is effective in evaluating multidose dispensing and different instructions in terms of counting frequency change after dispensing. There has been a need for the development of a regimen complexity assessment tool suitable for various clinical environments (Masumoto et al. 2020; Paquin et al. 2013). Our study is the first approach to evaluate the results of multi dose dispensing, and further research would be required to obtain validity through an international comparative study.

There are several limitations in the present study. First, we introduced the modified MRCI-K to apply to the Korean hospital practice showing high reliability as a modified form of the MRCI-K, it also showed a different distribution and validity results from the MRCI-K. Therefore, it is necessary to confirm validity in both clinical practice and research.

Second, this study was limited by its small sample size (intervention = 14, control = 18). However, this is consistent with the Whitehead et al. recommended pilot trial sample sizes per treatment arm of 14 for standardized effect sizes medium (0.5) for a main trial designed with 80% power and two-sided 5% significance (Whitehead et al. 2016). Another study recommended 12 subjects per group as pilot studies considering feasibility, precision about the mean and variance and regulatory considerations (Julious 2005). This study is of significance as a preliminary study as a descriptive study with limitations in deriving decisive results. We identified the feasibility of using the MRCI-K and the Modified MRCI-K in the randomized study. We expect that differences in the distribution of scores and adverse events between the two groups can be utilized as a basis for future research. Third, this study was conducted at a single-center and lacked information on disease severity. We expect these findings to have an implication on providing an effect size for a further study based on pharmacy led intervention in multi-center research. Fourth, the patient reported adverse event at the 30-day phone call could be subjective, whereas the adverse event during hospitalization was confirmed by the pharmacist and the physician. However, all ADE including patient reporting has been monitored and recorded in ADE reporting system in Inha hospital.

5. Conclusions

We concluded that compared with previous studies, this study showed satisfactory validity and reliability of the MRCI-K for the measurement of regimen complexity in Korea. Increased regimen complexity was observed compared to previous studies with polypharmacy, and dosage modification can be a major means of reducing administration time for simplification of regimen in hospital pharmacy practice. In the comprehensive medication reconciliation process, we found regimen complexity was reduced by the simplification intervention, and it could be evaluated as the MRCI-K and the modified MRCI-K. Further studies would be needed to use the modified MRCI-K for all patients as an evaluation tool of pharmacist`s intervention. Although there were some limitations, these results have implication on the first approach toward developing the MRCI-K and modified MRCI-K and providing the effect size of pharmacy-led intervention.

References

Advinha AM, S de Oliveira-Martins, V Mateus, SG Pajote and MJ Lopes. 2014. *Medication regimen complexity in institutionalized elderly people in an aging society*. Int J Clin Pharm, 36(4):750-6.

Alves-Conceicao V, KSS Rocha, FVN Silva, ROS Silva, DTD Silva and DP Lyra-Jr. 2018. *Medication Regimen Complexity Measured by MRCI: A Systematic Review to Identify Health Outcomes*. Ann Pharmacother:1060028018773691.

Beaton DE, C Bombardier, F Guillemin and MB Ferraz. 2000. *Guidelines for the process of cross-cultural adaptation of self-report measures*. Spine, 25(24):3186-91.

Bryant BM, AM Libby, KR Metz, RL Page, 2nd, AV Ambardekar, J Lindenfeld and CL Aquilante. 2016. *Evaluating Patient-Level Medication Regimen Complexity Over Time in Heart Transplant Recipients*. Ann Pharmacother, 50(11):926-34.

Elliott RA, C O'Callaghan, E Paul and J George. 2013. *Impact of an intervention to reduce medication regimen complexity for older hospital inpatients*. Int J Clin Pharm, 35(2):217-24.

Elliott RA, C O'Callaghan, E Paul and J George. 2013. *Impact of an intervention to reduce medication regimen complexity for older hospital inpatients*. International journal of clinical pharmacy, 35(2):217-24.

Elnaem MH, NA Irwan, U Abubakar, SA Syed Sulaiman, ME Elrggal and E Cheema. 2020. *Impact of Medication Regimen Simplification on Medication Adherence and Clinical Outcomes in Patients with Long-Term Medical Conditions*. Patient Prefer Adherence, 14:2135-45.

Epstein J, RM Santo and F Guillemin. 2015. *A review of guidelines for cross-cultural adaptation of questionnaires could not bring out a consensus*. Journal of clinical epidemiology, 68(4):435-41.

George J, YT Phun, MJ Bailey, DC Kong and K Stewart. 2004. *Development and validation of the medication regimen complexity index*. Ann Pharmacother, 38(9):1369-76.

Gillespie U, A Alassaad, M Hammarlund-Udenaes, C Mörlin, D Henrohn, M Bertilsson and H Melhus. 2013. *Effects of pharmacists' interventions on appropriateness of prescribing and evaluation of the instruments'(MAI, STOPP and STARTs') ability to predict hospitalization–analyses from a randomized controlled trial*. PloS one, 8(5):e62401.

Gillespie U, A Alassaad, D Henrohn, H Garmo, M Hammarlund-Udenaes, H Toss, Å Kettis-Lindblad, H Melhus and C Mörlin. 2009. *A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial*. Archives of internal medicine, 169(9):894-900.

Gustafsson M, M Sjölander, B Pfister, J Jonsson, J Schneede and H Lövheim. 2017. *Pharmacist participation in hospital ward teams and hospital readmission rates among people with dementia: a randomized controlled trial*. European journal of clinical pharmacology, 73(7):827-35.

Jokanovic N, EC Tan, MJ Dooley, CM Kirkpatrick and JS Bell. 2015. *Prevalence and factors associated with polypharmacy in long-term care facilities: a systematic review*. J Am Med Dir Assoc, 16(6):535.e1-12.

Julious SA. 2005. *Sample size of 12 per group rule of thumb for a pilot study*. Pharmaceutical Statistics: The Journal of Applied Statistics in the Pharmaceutical Industry, 4(4):287-91.

Kim H-A, J-Y Shin, M-H Kim and B-J Park. 2014. *Prevalence and predictors of polypharmacy among Korean elderly*. PloS one, 9(6):e98043.

Koo TK and MY Li. 2016. *A guideline of selecting and reporting intraclass correlation coefficients for reliability research*. Journal of chiropractic medicine, 15(2):155-63.

Koo TK and MY Li. 2016. *A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research*. J Chiropr Med, 15(2):155-63.

Lindquist LA, LM Lindquist, L Zickuhr, E Friesema and MS Wolf. 2014. *Unnecessary complexity of home medication regimens among seniors*. Patient Educ Couns, 96(1):93-7.

Lisby M, A Thomsen, LP Nielsen, NM Lyhne, C Breum-Leer, U Fredberg, H Jørgensen and B Brock. 2010. *The effect of systematic medication review in elderly patients admitted to an acute ward of internal medicine*. Basic & clinical pharmacology & toxicology, 106(5):422-7.

Mansur N, A Weiss and Y Beloosesky. 2012. *Looking beyond polypharmacy: quantification of medication regimen complexity in the elderly*. Am J Geriatr Pharmacother, 10(4):223-9.

Masumoto S, M Sato, K Momo, A Matsushita, K Suzuki, H Shimamura, T Sasaki and J Hamano. 2020. *Development of medication regimen complexity index: Japanese version and application in elderly patients*. Int J Clin Pharm.

McHugh ML. 2012. *Interrater reliability: the kappa statistic*. Biochemia medica: Biochemia medica, 22(3):276-82.

Mekonnen AB, AJ McLachlan and JA Brien. 2016. *Effectiveness of pharmacist-led medication reconciliation programmes on clinical outcomes at hospital transitions: a systematic review and meta-analysis*. BMJ Open, 6(2):e010003.

Mekonnen AB, AJ McLachlan and JaE Brien. 2016. *Pharmacy-led medication reconciliation programmes at hospital transitions: a systematic review and meta-analysis*. Journal of clinical pharmacy and therapeutics, 41(2):128-44.

Melchiors AC, CJ Correr and F Fernandez-Llimos. 2007. *Translation and validation into Portuguese language of the medication regimen complexity index*. Arq Bras Cardiol, 89(4):210-8.

Morello CM, T Rotunno, J Khoan and JD Hirsch. 2018. *Improved Glycemic Control With Minimal Change in Medication Regimen Complexity in a Pharmacist-Endocrinologist Diabetes Intense Medical Management (DIMM) "Tune Up" Clinic*. Ann Pharmacother, 52(11):1091-7.

Morello CM, T Rotunno, J Khoan and JD Hirsch. 2018. *Improved glycemic control with minimal change in medication regimen complexity in a pharmacist-endocrinologist diabetes intense medical management (dimm)“tune up” clinic*. Annals of Pharmacotherapy, 52(11):1091-7.

Mueller SK, KC Sponsler, S Kripalani and JL Schnipper. 2012. *Hospital-based medication reconciliation practices: a systematic review*. Archives of internal medicine, 172(14):1057-69.

O'Mahony D, D O'Sullivan, S Byrne, MN O'Connor, C Ryan and P Gallagher. 2015. *STOPP/START criteria for potentially inappropriate prescribing in older people: version 2*. Age and ageing, 44(2):213-8.

Panel AGSBCUE, DM Fick, TP Semla, M Steinman, J Beizer, N Brandt, R Dombrowski, CE DuBeau, L Pezzullo and JJ Epplin. 2019. *American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults*. Journal of the American Geriatrics Society, 67(4):674-94.

Pantuzza LL, M Ceccato, MR Silveira, LMR Junqueira and AMM Reis. 2017. *Association between medication regimen complexity and pharmacotherapy adherence: a systematic review*. Eur J Clin Pharmacol, 73(11):1475-89.

Pantuzza LL, M Ceccato, MR Silveira, IV Pinto and AMM Reis. 2018. *Validation and standardization of the Brazilian version of the Medication Regimen*

Complexity Index for older adults in primary care. Geriatr Gerontol Int, 18(6):853-9.

Paquin AM, KM Zimmerman, TR Kostas, L Pelletier, A Hwang, M Simone, LM Skarf and JL Rudolph. 2013. *Complexity perplexity: a systematic review to describe the measurement of medication regimen complexity*. Expert opinion on drug safety, 12(6):829-40.

Park HY, HN Ryu, MK Shim, HS Sohn and JW Kwon. 2016. *Prescribed drugs and polypharmacy in healthcare service users in South Korea: an analysis based on National Health Insurance Claims data*. Int J Clin Pharmacol Ther, 54(5):369-77.

Redmond P, TC Grimes, R McDonnell, F Boland, C Hughes and T Fahey. 2018. *Impact of medication reconciliation for improving transitions of care*. Cochrane Database Syst Rev, 8(8):Cd010791.

Saez de la Fuente J, A Such Diaz, I Canamares-Orbis, E Ramila, E Izquierdo-Garcia, C Esteban and I Escobar-Rodriguez. 2016. *Cross-cultural Adaptation and*

Validation of the Medication Regimen Complexity Index Adapted to Spanish. Ann Pharmacother, 50(11):918-25.

Sluggett JK, RE Hopkins, EY Chen, J Ilomäki, M Corlis, J Van Emden, M Hogan, T Caporale, CE Ooi and SN Hilmer. 2020. *Impact of medication regimen simplification on medication administration times and health outcomes in residential aged care: 12 month follow up of the SIMPLER randomized controlled trial*. Journal of clinical medicine, 9(4):1053.

Stange D, L Kriston, C Langebrake, LK Cameron, JD Wollacott, M Baehr and DC Dartsch. 2012. *Development and psychometric evaluation of the German version of the Medication Regimen Complexity Index (MRCI-D)*. J Eval Clin Pract, 18(3):515-22.

Stange D, L Kriston, A von-Wolff, M Baehr and DC Dartsch. 2013. *Reducing cardiovascular medication complexity in a German university hospital: effects of a structured pharmaceutical management intervention on adherence*. J Manag Care Pharm, 19(5):396-407.

Whitehead AL, SA Julious, CL Cooper and MJ Campbell. 2016. *Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable*. Statistical methods in medical research, 25(3):1057-73.

Willson MN, CL Greer and DL Weeks. 2014. *Medication regimen complexity and hospital readmission for an adverse drug event*. Annals of Pharmacotherapy, 48(1):26-32.

Wimmer BC, AJ Cross, N Jokanovic, MD Wiese, J George, K Johnell, B Diug and JS Bell. 2017. *Clinical outcomes associated with medication regimen complexity in older people: a systematic review*. Journal of the American Geriatrics Society, 65(4):747-53.

Witticke D, HM Seidling, K Lohmann, AF Send and WE Haefeli. 2013. *Opportunities to reduce medication regimen complexity: a retrospective analysis of patients discharged from a university hospital in Germany*. Drug Saf, 36(1):31-41.

ABSTRACT (Korean)

한국형 처방 복잡도 지수의 개발과 적용

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I. 연구 배경 및 목표

최근 노인 인구와 병존 질환의 증가로 다약제 사용이 증가하고 있다. 사용 약물 개수의 증가는 처방이 복잡해지는 결과를 가져올 수 있다. 처방이 복잡해질수록 약물 부작용이 증가하고, 복약순응도는 저하되며, 재입원률이 높아지는 등 처방의 복잡도는 부정적인 임상 결과와 관련이 있다고 알려져 있다. 해외에서는 임상 약료 서비스의 하나로 복잡한 처방을 간소화하는 중재 연구가 진행되어 왔으나 한국에서는 다약제 사용이 증가함에도 불구하고 그에 따른 처방의 복잡도에 대한 평가와 중재 활동이 이루어지지 않는다. 본 연구에서는 한국형 처방 복잡도 지수(Korean version of Medication regimen complexity index, MRCI-K)를 개발하여 한국의 처방 복잡도 상황을 정량적으로 평가하고자

하였다. 또한 약사의 처방 간소화 중재 결과를 한국형 처방 복잡도 지수로 확인하여 추후 다약제 약물 중재 연구를 위한 기초 자료로 제공하고자 하였다.

II. 연구 내용 및 방법

본 연구는 한국 처방 복잡도 지수의 '개발'과 '적용', 두 단계로 진행되었다. 한국 처방 복잡도 지수의 개발은 후향적 관찰연구로 디자인되었다. 먼저 처방 복잡도 지수(Mediation regimen complexity index, MRCI)를 근거로 하여 번역과 문화적 적용(Translation and crosscultural adaptation) 과정을 거쳐 MRCI-K 를 준비하였다. 2016 년 1 월부터 3 월까지 인하대병원에서 퇴원한 331 명의 입원환자와 100 명의 외래환자를 대상으로 신뢰도와 타당도 검증을 시행하였다. 또한 병원에서 멀티도즈 단위 (Multi-dose dispensing)로 투약되는 상황을 고려하여 MRCI-K 에 지시사항을 추가하여 변형된 한국형 처방 복잡도 지수(Modified MRCI-K)를 준비하였다. 100 명의 외래환자를 대상으로 신뢰도와 타당도 검증을 시행하였다.

MRCI-K 의 적용은 전향적 무작위 배정 연구로 디자인되었다. 2020 년 7 월부터 12 월까지 인하대병원 입원의학과에서 5 가지 이상 약제를 투약 중인 65 세 이상의 입원 환자를 대상으로 중재 연구를 진행하였다. 입원 중의 약물

중재와 퇴원 시 처방 간소화 활동 후 환자군과 대조군 간의 처방 복잡도 지수의 점수 변화와 보고된 약물 부작용 건수의 차이를 확인하였다.

III. 연구 결과

MRCI-K 는 높은 신뢰도와 타당도를 나타냈다. 한국의 처방 복잡도는 해외보다 높은 수준으로 전체 점수에서 지시사항에 해당하는 점수가 높은 비중을 차지했다. 변형된 처방 복잡도 지수(Modified MRCI-K)는 높은 신뢰도를 나타냈으나 타당도 결과는 MRCI-K 의 타당도 검증 결과와 차이가 있었다. 입퇴원 시기 약사의 약물 중재 활동 결과로 중재군은 대조군에 비하여 전체 처방 복잡도 지수의 감소가 더 컸으며 용법의 간소화로 지시사항에 해당하는 부분의 점수 감소가 가장 컸다. 또한 중재군은 입원 중과 퇴원 후 30 일에 확인된 약물 부작용 보고 건수가 대조군보다 적었다.

IV. 결론

한국형 처방 복잡도 지수(MRCI-K)는 한국의 처방 복잡도 정도를 정량적으로 평가할 수 있는 지표로 높은 신뢰도와 타당도를 나타냈다. 해외 결과와 비교해 한국의 처방에서 높은 처방 복잡성이 관찰되었으며, 많은 지시사항은 처방 복잡성의 주요한 원인이었다. 처방 간소화 중재 활동의 결과로 처방 복잡도의

감소를 확인하였으며, 이는 MRCI-K 와 변형된 MRCI-K 점수 감소로 평가할 수 있었다.

핵심단어: 다약제, 약물 조정, 처방 복잡도, 약사 중재, Multi dose dispensing, 한국형 처방 복잡도 평가 지수