https://doi.org/10.4082/kjfm.21.0086 • Korean J Fam Med 2022;43:125-131

KJFM
Korean Journal of Family Medicine

eISSN: 2092-6715

■ Original Article

Risk Factors Related to Serious Adverse Drug Reactions Reported through Electronic Submission during Hospitalization in Elderly Patients

Seon-Hye Won[1], Sang-Yeon Suh[1,2,*], Eunji Yim[3], Hong-Yup Ahn[4]

[1]Department of Family Medicine, Dongguk University Ilsan Hospital, Goyang, Korea
[2]Department of Medicine, Dongguk University, Seoul, Korea
[3]Department of Neurology, University of Michigan Hospital, Ann Arbor, MI, USA
[4]Department of Statistics, Dongguk University, Seoul, Korea

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Background: Many studies have assessed the risk factors for adverse drug reactions (ADRs) in elderly patients. However, most of these studies have focused on risk factors for ADRs, not serious ADRs (s-ADRs). s-ADRs are commonly found in hospitalized patients. s-ADRs warrant imminent but thorough investigations, given their critical impact on patient health. Therefore, this retrospective study aimed to assess the associated risk factors for s-ADRs in elderly hospitalized patients.

Methods: In-patients aged >65 years having ADRs during hospitalization at a university hospital in Korea between 2010 and 2012 were included. Medical professionals spontaneously reported ADRs using an electronic submission system at the study hospital. Further, all descriptions of ADRs were characterized and categorized through the screening of electronic medical records. We compared the characteristics of patients having s-ADRs with those of patients not having s-ADRs.

Results: There were 353 cases of ADRs, 67 of which were s-ADRs. Patients taking more than eight concomitant drugs showed the highest odds ratio (OR, 11.99; 95% confidence interval [CI], 3.42–42.03). The ratio of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) was also significantly related to s-ADRs (OR, 2.78; 95% CI, 1.33–5.81). The use of antibiotics (OR, 2.39; 95% CI, 1.13–5.02) and antineoplastics (OR, 4.17; 95% CI, 1.09–15.94) were significant risk factors.

Conclusion: Our findings highlight the importance of polypharmacy. Liver function tests (AST/ALT ratio) must be monitored carefully within high-risk groups for ADRs.

Keywords: Adverse Drug Reactions; Aged; Polypharmacy; Liver Function Tests; Geriatrics

Received: April 12, 2021, Revised: June 28, 2021, Accepted: July 20, 2021
*Corresponding Author: **Sang-Yeon Suh** https://orcid.org/0000-0002-6145-1150
Tel: +82-31-961-7490, Fax: +82-31-961-7969, E-mail: lisasuhmd@dumc.or.kr

INTRODUCTION

The elderly population is usually defined as individuals aged over 65 years,[1] which is rapidly growing in modernized society due to advances in medical treatment. Extended longevity is inevitably accompanied by a medical phenomenon called polypharmacy. Polypharmacy is a well-known risk factor for adverse drug reactions (ADRs).[2-6] Elderly patients are susceptible to ADRs, according to the definition established by the World Health Organization (WHO).[7] Elderly patients are at high risk for ADRs due to decreased renal function, altered drug metabolism in the body, and multiple comorbidities. However, recent studies have shown that an increasing number of drugs taken or comorbidities are the major factors for ADRs, rather than advanced age itself.[8,9] Thus, it is possible to prevent ADRs if clinicians have sufficient knowledge of such risk factors and pay close attention to them.

The impact of ADRs increases the cost of patient care.[10] ADRs require further investigation or treatment in many cases. In serious cases, they can induce a longer hospital stay, which may even be fatal. Serious ADRs (s-ADRs) are defined as follows[11]: an ADR which "results in death," "requires hospitalization," "prolongs existing hospitalization," "results in persistent or significant disability/incapacity," or "is life-threatening." However, only a few studies have assessed the related risk factors for s-ADRs. Studies on ADRs as the cause of hospitalizations or emergencies might be acknowledged as studies on s-ADRs. However, given its seriousness, s-ADRs should not be a single subset of ADRs. Most studies have focused on the predictors and risk factors for ADRs rather than s-ADRs. Moreover, the investigators of a few previous studies that compared patients with ADRs and patients without ADRs relied on Caucasian subjects. ADRs are likely to differ according to the health care system and patient ethnicity. Evidently, s-ADRs also have a more demanding impact than ADRs regarding health outcomes and the cost of patient hospital care. If the risk factors for s-ADRs can be thoroughly outlined, more effective strategies can be sought to prevent s-ADRs.

Serious ADRs are probably reported more systematically than ADRs because ADRs are only reported voluntarily by clinicians.[12] As suggested by a previous study, spontaneous reporting can be limited in terms of its low reporting rate. In 2006, the Korea Food and Drug Administration established nationwide regional pharmacovigilance centers (RPVCs) to encourage ADR reporting.[13] Currently, there are 27 RPVCs in Korea, mostly located within university hospitals.[14] The establishment of RPVCs in Korea has dramatically increased the reporting of ADRs. Although there is still room for development in terms of quality and quantity, Korean RPVCs have made efforts to facilitate valuable reports. One such effort is to set up computerized access to an ADR reporting system to increase the reporting rate by making it faster and more convenient to report ADRs. We investigated the risk factors for s-ADRs through electronic submission (e-sub) in elderly inpatients.

METHODS

1. Design

A retrospective observational study was conducted to compare the characteristics of patients having s-ADRs with patients having non-serious ADRs (non s-ADRs) during hospitalization (IRB no., DUIH 2012-25). The requirement for informed consent was waived by Dongguk University Ilsan Hospital instutional review board due to the retrospective nature of the study and the minimal risk involved in the study.

2. Patient Population

This study was conducted at Dongguk University Ilsan Hospital in a metropolitan area of South Korea, in a satellite city from the capital. Elderly patients were defined as those aged >65 years. There were 353 cases, of which 56.1% were comprised of women. The mean age was 73.74±6.56 years. The most frequent diagnoses were respiratory diseases (86 cases, 24.4%), infection (83 cases, 23.5%), cardiovascular diseases (65 cases, 18.4%), and neoplasms (46 cases, 13.0%), in descending order.

3. Data Collection and Reporting Sources

A total of 353 ADRs were gathered from e-subs between April 2010 and January 2012. We collected comprehensive data of ADRs not only from spontaneous reporting through the ADR reporting system by doctors and nurses but also from the deduction of descriptions about ADRs in medical records with the help of a medical informatics team. As the medical record system is completely electronic in the study hospital, we believe that all s-ADRs during the study period have been accounted for. Medical professionals reported ADRs using an ADR-reporting electronic interface. The reporters were asked to provide information on suggested culprit drugs, organ-specific adverse reactions (e.g., systemic fever, skin itching), severity, and duration. The history of medication was investigated using medical records of one day before the incident of ADRs. Laboratory tests were performed within 1–7 days prior to ADRs in the morning when the patients were in a fasting state. The e-sub was then transformed into a database for analyzing causal relationships by a medical informatics team comprising a drug allergist, pharmacists, and specialized nurses.

4. Assessment of Electronically Submitted Adverse Drug Reactions

Reported and collected ADR data were reviewed by the ADR monitoring council in an RPVC within the hospital using the WHO-Uppsala Monitoring Center (WHO-UMC) criteria.[15] The WHO-UMC causality assessment was performed for all the cases. There are four grades of causality: "unlikely," "possible," "probable," and "certain." We distinguished ADRs from the "possible" grade or more. The severity of ADRs was classified as serious or non-serious. s-ADRs included death, life-threatening events, permanent disabilities, prolonged hospitalization, and other important medical events defined by medical professionals. Specialized nurses and pharmacists cross-checked the causality;

moreover, an allergist assessed questionable cases.

5. Statistical Analysis

The present study compared the characteristics of elderly patients having s-ADRs with patients having non s-ADRs during admission. Frequencies were compared using the chi-square test. T-tests were used to compare alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ratios. Logistic regression was performed to assess the significance and odds ratios (ORs) of the predictors related to s-ADR. Variables found to be statistically significant (P<0.05) in the univariate analysis were included in the multivariate analysis. All selected variables were assessed for correlation to avoid multicollinearity. Statistical analysis was performed using SPSS ver. 16.02 (SPSS Inc., Chicago, IL, USA).

Table 1. Demographic and medical characteristics of the study sample of 353 elderly inpatients

Characteristic	ADRs but not serious (n=286)	Serious ADRs (n=67)	P-value
Gender			0.072*
Female	167 (58.4)	31 (46.3)	
Male	119 (41.6)	36 (53.7)	
Age (y)	73.26±6.321	75.79±7.187	0.004†
No. of concomitant drugs			<0.001*
≥8	135 (47.2)	55 (82.1)	
≤7	151 (52.8)	12 (17.9)	
AST (IU/L)	21.0 (6–205)	22.2 (9–165)	0.232‡
ALT (IU/L)	15.5 (4–144)	14.0 (2–174)	0.793‡
Creatinine (mg/dL)	0.9 (0–20)	0.84 (0–6)	0.626‡
Clinical manifestations			
Skin lesion, itching	115 (40.2)	24 (35.8)	0.058*
Gastrointestinal symptoms§	105 (36.7)	13 (19.4)	<0.001*
Dizziness	31 (10.8)	3 (4.5)	0.041*
Impaired renal function	22 (7.7)	7 (10.4)	0.887*
Dyspnea	17 (5.9)	6 (9.0)	0.725*
Abnormal haematological finding‖	14 (4.9)	39 (58.2)	<0.001*
Anaphylaxis	9 (3.1)	10 (15.0)	0.004*
Increase in AST, ALT level	7 (2.4)	5 (7.5)	0.159*
Etc.¶	77 (26.9)	12 (17.9)	
Culprit drugs			
Antibiotics	95 (33.2)	52 (77.6)	<0.001*
Anti-tuberculosis drugs	60 (21.0)	1 (1.5)	<0.001*
Antihypertensive agents	42 (14.7)	8 (12.0)	0.522*
Antihistamine	26 (9.1)	0	0.010*
Antineoplastics	15 (5.2)	11 (16.4)	0.003*
Antacid	17 (6.0)	5 (7.5)	0.782#
Parenteral nutrition	20 (7.0)	1 (1.5)	0.095#
Anticonvulsants	17 (6.0)	2 (3.0)	0.553#
Nonsteroidal anti-inflammatory drugs	16 (5.6)	3 (4.5)	>0.999#
Others	136 (47.6)	24 (35.8)	
Major diagnoses			
Respiratory diseases	73 (25.5)	13 (19.4)	0.201*
Infection	63 (22.0)	20 (29.9)	0.321*
Cardiovascular diseases	52 (18.2)	13 (19.4)	0.978*
Neoplasms	31 (10.8)	15 (22.4)	0.026*
Cerebrovascular diseases	33 (11.5)	5 (7.5)	0.264*
Musculoskeletal diseases	34 (11.9)	2 (3.0)	0.023*
Gastrointestinal/hepatic diseases	22 (7.7)	1 (1.5)	0.061#
Endocrinologic diseases	16 (5.6)	6 (9.0)	0.414#
Chronic renal failure	18 (6.3)	2 (3.0)	0.392#
Neuropsychiatric diseases	5 (1.7)	2 (3.0)	0.632#
hematologic disease	3 (1.0)	4 (6.0)	0.033#
Etc.**	31 (10.8)	13 (19.4)	0.102*

Values are presented as numbers (%), mean±standard deviation, or median (min–max).
ADR, adverse drug reaction; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
*By chi-square test. †By independent t-test. ‡By Mann-Whitney test. §Nausea, vomiting, diarrhea, constipation. ‖Eosinophilia, neutropenia. ¶Edema, arrhythmia, fever, confusion, chest discomfort. #By Fisher's exact test. **Dermatitis, electrolyte imbalance, eye diseases, urologic diseases.

https://doi.org/10.4082/kjfm.21.0086

RESULTS

1. Basic Characteristics of the Study Population

There were 353 cases of ADRs, of which 67 were s-ADRs (18.9%). Out of 3,640 elderly patients admitted to the Department of Internal Medicine at the study hospital, 353 patients with ADRs were included in the study. A total of 26,810 adult patients were admitted to the study hospital during the study period. Furthermore, 1,650 ADR cases were reported (1,560/26,810, 5.8%). Thus, the proportion of ADRs in elderly patients (9.7% [353/3,640]) was higher than the ADR incidence in adult patients. A total of 56.1% of the cases were comprised of women, and the mean age was 73.74±6.56 years. The median number of concomitant drugs in all ADRs was eight, 12 in s-ADRs, and seven in non s-ADRs (Table 1). The major diagnoses were similar in both s-ADRs and non s-ADRs.

2. General Characteristics of Adverse Drug Reactions Collected by Electronic Submission

ADRs were reported by doctors (281 cases, 79.6%) and nurses (71 cases, 20.1%). A total of 80.6% of s-ADRs were reported by doctors. The causality assessment showed certain causality in 20 cases (5.7%), possible causality in 246 cases (69.7%), and probable causality in 87 cases (24.6%), of all ADR cases. There was an even distribution of causality assessment among s-ADRs and non s-ADRs.

3. Clinical Features of Adverse Drug Reactions and the Drugs Involved in Adverse Drug Reactions

The most frequent ADR clinical manifestation was skin lesions, including itching (115 matters, 40.2%) (Table 1). Gastrointestinal problems, abnormal hematologic findings, and dizziness followed in descending order of frequency. Abnormal hematologic findings (leukopenia, eosinophilia: 58.2% of s-ADR cases) and anaphylaxis (15.0% of s-ADR cases) were more significantly prevalent in s-ADRs, as expected (P<0.001 and 0.004, respectively). In non s-ADRs, gastrointestinal problems (nausea, vomiting, diarrhea, constipation: 105 matters, 36.7% of non s-ADR cases) and dizziness (10.8% of non s-ADR cases) were more significantly common in s-ADRs (P<0.001 and 0.041, respectively).

The drugs causing ADRs included antibiotics (147 cases, 41.6%), antituberculosis agents (61 cases, 17.3%), antihypertensive agents (50 cases, 17.3%), antihistamines (26 cases, 7.4%), anticonvulsants (19 cases, 5.4%), and non-steroidal anti-inflammatory drugs (19 cases, 5.4%). The three most common drugs involved in s-ADRs were antibiotics (77.6%), antineoplastic agents (16.4%), and antihypertensive agents (12.0%). In comparison, the drugs involved in non s-ADRs were antibiotics (33.2%), antituberculosis agents (21.0%), and antihypertensive agents (14.7%). Antibiotics and antineoplastic agents were more often involved in s-ADRs (P<0.001 and 0.003, respectively). Other culprit drugs were listed in Supplement 1.

4. Assessed Risk Factors for Serious Adverse Drug Reactions

In the univariate analysis, there were no differences in gender between ADR and s-ADR cases. The mean age was higher in s-ADRs than in non s-ADRs (P<0.001) (Table 1). The median values of liver function and renal function tests were not different between s-ADRs and non s-ADRs. In the multivariate analysis, the number of concomitant drugs showed the highest OR. The number of pharmaceuticals (more than eight) was selected based on statistical significance in the multivariate analysis. Taking more than eight drugs increased the risk of s-ADR as high as 11.99-fold (95% confidence interval [CI], 3.42–42.03) (Table 2). The ratio of liver function, AST/ALT, was also significantly related to s-ADR (OR, 2.78; 95% CI, 1.33–5.81). Namely, AST exceeding ALT by more than 1.3 folds is related to a 2.78-fold greater hazard for an s-ADR. This ratio of AST/ALT was chosen based on the median value of our data. Taking antibiotics and antineoplastics were significant risk factors for s-ADR, which had ORs of 2.39 (95% CI, 1.13–5.02) and 4.17 (95% CI, 1.09–15.94), respectively.

DISCUSSION

Identifying the risk factors for s-ADRs is the first step in their prevention. Our study revealed two important risk factors for s-ADRs in the elderly. One is a well-known risk factor for ADRs, polypharmacy. The other is liver function, which is a less-known factor. To the best of our knowledge, this is a new marker for s-ADRs.

Polypharmacy is a well-established risk factor for ADRs.[16] Polypharmacy is defined as the use of six or more medications per day.[17] Most studies have reported five drugs as the mean number of drugs in an ADR group.[18] Another recent study concluded that the absolute number of concurrently used drugs was the strongest predictor of ADRs[4]; for five to seven concomitant drugs, the OR increased 1.9-fold. For more than eight drugs, the OR increased as high as 4.07 in this study. Eight concomitant drugs corresponded to a significant risk factor for s-

Table 2. Factors associated with serious adverse drug reactions in multivariate logistic regression model

Variable	Odds ratio (95% confidence interval)	P-value
Gender		0.458
Male	1.32 (0.63–2.76)	
Female	-	
Age	1.01 (0.95–1.06)	0.839
No. of pharmaceutical		<0.001
≥8	11.99 (3.42–42.03)	
≤7	-	
AST/ALT ratio		0.007
≥1.3*	2.78 (1.33–5.81)	
<1.3	-	
Taking antibiotics	2.39 (1.13–5.03)	0.022
Taking antineoplastics	4.17 (1.09–15.94)	0.037

Reference group is non-serious adverse drug reactions.
AST, aspartate aminotransferase; ALT, alanine aminotransferase.
*1.3 was the median value of AST/ALT ratio in this data.

ADRs in our study. Our study findings highlight the importance of polypharmacy in terms of s-ADRs. This is practically useful because the use of multiple medications is modifiable. Evidently, polypharmacy is a major risk factor for ADRs, as well as s-ADRs. As s-ADR is a type of ADR, it is reasonable to prove that an increasing number of drugs is an important risk factor for s-ADRs. Polypharmacy is a notable phenomenon in elderly patients who are also vulnerable to s-ADRs. Therefore, the importance of minimizing the number of concurrent drugs for these patients cannot be overemphasized. We found that the number of drugs was a matter of paramount importance to s-ADRs in elderly patients.

Our study identified liver function as a new risk factor for s-ADR. The liver plays a major role in the metabolism of many drugs; thus, liver function reflects the degree of damage caused by drugs. AST is known to be a marker for hepatic dysfunction due to drugs or alcohol.[19] Aging has been known to diminish the hepatic clearance of drugs due to a decline in hepatic blood flow and volume, although there is interindividual variability in the geriatric population.[20] Our findings demonstrated that AST could be a useful surrogate marker and prognostic factor for the prediction of s-ADRs. We confirmed that the AST/ALT ratio was maintained within the normal range of liver function in our study participants (data not shown). Some questions may arise regarding the necessity of blood tests. However, in-patients usually undergo routine laboratory tests to screen for organ function and potential complications of treatments. The significant laboratory findings we checked were performed within the range of clinical practice through chart review. Thus, careful attention to liver function (AST) is worthwhile for predicting s-ADRs. Further studies are required to confirm this phenomenon.

Clinical manifestations were different in s-ADRs compared with non s-ADRs. Anaphylaxis and abnormal hematological findings were significantly more frequent in s-ADRs than in non s-ADRs. On the contrary, dizziness and gastrointestinal disturbances were significantly more frequent in non s-ADRs, as assessed in previous studies.[21,22] Drugs involved in s-ADRs were antibiotics and antineoplastic agents, while those involved in non s-ADRs were antituberculosis drugs and antihistamines. Antineoplastics and antibiotics are known to be high-risk drugs for s-ADRs, according to previous studies.[2,7,8] These medications are potent but also have high innate toxicities.[21] A recent study in Spain also reported that antineoplastic drugs were most commonly associated with ADR-related hospitalization.[23] This is consistent with Australian data, which used a hospital morbidity data system for the elderly. Antibiotics are the most common drug related to ADR in Korea,[13] whereas cardiovascular drugs are the most common in Western countries. We demonstrated that antibiotics are also the causative drugs of s-ADRs. As there are insufficient studies on s-ADRs, it is unclear at this point whether drugs involved in s-ADRs result from differences in disease prevalence or the severity of ADR from country to country.

The geriatric population has and will continue to grow rapidly, doubling to 1.4 billion or 14% of the world's population by 2040. Elderly individuals are at high risk for ADRs.[24,25] According to a meta-analysis, elderly individuals have four times the risk of hospitalization due to ADR-related problems compared with younger individuals.[26] The primary reasons are multiple drug regimens for various comorbidities and age-associated physiological changes, affecting the pharmacokinetics and pharmacodynamics of many drugs.[27,28] However, the reported prevalence of ADR has not increased over the past decade despite a tremendous increase in the use of medications. In Korea, the number of concomitant drugs is particularly high in elderly patients.[6] For instance, the average number of drugs taken by elderly in-patients in Korea is 18.0±13.7, and 5.8±5.6 in elderly out-patients.[29] Studies from the United States and England report an average of nine drugs for in-patients and three for out-patients in the elderly. However, because of the comparatively lower incidence of ADRs in Korea than in Western countries, awareness and reporting rates might also be low. One can also assume that voluntary reporting leads to considerable underreporting. Several factors limit spontaneous reporting.[12] Correct identification of ADRs is not feasible for all clinicians, nurses, pharmacists, or patients.[30] Moreover, individual factors such as carelessness for reporting or indifference to ADRs influence the reporting rate. Therefore, an easily accessible reporting system is necessary to enhance the reporting of ADRs. Fortunately, an e-sub system has become possible through advances in the Internet. This system was programmed as an integrated part of the electronic medical records in the hospital, aimed at enabling a convenient and imminent response to ADRs. Collected reports and data can be easily converted into a database for ADRs, with speed and accuracy for routine assessment and validation by experts. This system is also used to alert physicians and nurses of each patient's previous ADR in the study hospital. A need for accurate prediction tools for ADRs remains, even with the recent emergence of risk prediction models and programs for ADRs.[30] We believe that noticeable progress could be made by upgrading this e-sub system into a program that calculates each patient's risk score for ADRs or into an alarm system that prevents inappropriate prescriptions for the elderly. It would be ideal if each hospital's e-sub system for ADRs could be standardized and integrated into a national pharmacovigilance center.

Our study has the following strengths: the study population was comprised of in-patients; thus, they could not self-medicate or take health supplements without medical supervision. Possible ADRs were investigated using an electronic medical record system. It enhanced the reporting rate of all ADRs, particularly that of s-ADRs. As s-ADRs require medical assessments and emergent interventions, they should be avoided as quickly as possible. Among ADRs, s-ADRs take priority for investigation for the sake of patient health. Therefore, especially in elderly patients, focusing on s-ADRs and identifying their risk factors and prognostic factors is an urgent need. Our results showed that AST and the absolute number of drugs were significantly higher in s-ADRs than in non s-ADRs. Physicians should pay attention to patients' liver function and the concurrent use of drugs to lower s-ADRs in elderly patients.

This study has certain limitations. First, multi-comorbidity is known

to be an important risk factor for ADR in elderly patients.[8,31] However, the influence of comorbidities was not considered in this study. Future studies should include information on comorbidities. Second, this study was based on data from in-patients in a single hospital; thus, it may be limited in terms of generalization. Third, this was a retrospective study; therefore, it could be exposed to bias due to its design. Furthermore, data on the previous occurrence of ADRs or inappropriate prescriptions were unavailable. Fourth, various laboratory data on renal function were not considered in the current study. Although we checked that elevated serum creatinine did not affect our results, it would be needed for future studies on ADRs in the elderly to include more tests such as blood urea nitrogen, serum electrolyte level, and glomerular filtration rate tests. Lastly, multiple logistic regression was used to prove the significant number of pharmaceuticals taken in this study. However, the area under the receiver operating characteristic (ROC) curve is also an established method to investigate cutoff values. Thus, it would be helpful to generate ROCs to evaluate the cutoff values of the number of pharmaceuticals in further studies.

A prospective study on the risk factors for s-ADRs based on community-dwelling elderly patients is necessary. We suggest more evolved reporting systems, such as a software with electronic prescribing databases that enable efficient detection of ADRs in the elderly both on in-hospital and community bases.

CONFLICT OF INTEREST

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

ACKNOWLEDGMENTS

We appreciate the research nurse Sun Young Jung in the regional pharmacovigilance center of the study hospital for her assistance.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4082/kjfm.21.0086. Supplement 1. List of "other" culprit drugs of non-serious adverse drug reaction vs. serious adverse drug reaction group.

ORCID

Seon-Hye Won: https://orcid.org/0000-0001-8834-2395
Sang-Yeon Suh: https://orcid.org/0000-0002-6145-1150
Eunji Yim: https://orcid.org/0000-0002-1726-9706
Hong-Yup Ahn: https://orcid.org/0000-0001-8149-6981

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https://doi.org/10.4082/kjfm.21.0086