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Risk factors of anaphylaxis in Korea

Identifying drug-induced anaphylaxis culprits using big data

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Abstract

Drug-induced anaphylaxis is a fatal medical condition whose incidence has been increasing continuously. Due to differences between genetic backgrounds and health care systems, different populations may be prone to various causative drugs. Using the Health Insurance Service and Assessment Service database, we investigated culprit drugs for drug-induced anaphylaxis and common medication risk factors in the Korean general population. We collected medical prescription histories within 3 days prior to anaphylaxis between January 2011 and December 2019 from the HIRA database. Designed as a case-crossover study, the attributable visits (case visits) were matched to medical visits (control visits) with the drug sets for each visit. We collected a list of medication risk factors for anaphylaxis and calculated the risk ratio of each agent using the chi-square test and conditional logistic regression analysis. A total of 159,473 individuals were listed in the database with a diagnosis of anaphylaxis in the HIRA from 2011 to 2019. After evaluating the suitability of control visits for matching with a case visit, 8168 subjects and 767 drugs were analyzed. The chi-square analysis identified 31 drugs as potential risk factors for drug-induced anaphylaxis in Korea. After applying a conditional logistic regression analysis for each agent, 5 drugs were found to be the common medication risk factors for drug-induced anaphylaxis: cefaclor, iopromide, iohexol, iomeprol, and tolperisone. We found 5 medication risk factors that showed the highest risk of drug-induced anaphylaxis and their degree of risk using an objective methodology in the Korean general population.

Abbreviations: CI = confidence interval,CT = computed tomography, HIRA = Health Insurance Review and Assessment Service, ICM = iodinated contrast media, NSAID = non-steroidal anti-inflammatory drug.

Keywords: anaphylaxis, drug allergy, hypersensitivity, risk factor

1. Introduction

Anaphylaxis is a form of rapid-onset severe hypersensitivity, which is a potentially life-threatening systemic reaction.[1] This fatal reaction in response to exogenous stimuli may cause systemic involvement and may eventually result in a multi-organ failure. The lifetime prevalence of this hypersensitivity is very rare, approximately 0.05% to 2% in the USA[2] and 3% in Europe.[3] There have been a number of previous studies on the epidemiology of anaphylaxis in Korean adults, with various prevalence rates ranging from 0.010% to 0.026%.[4–6] Although these prevalence rates were relatively lower than those of other nations, the incidence of anaphylaxis in Korea has accelerated over time. In a recent study of anaphylaxis using a nationwide administrative database, the Korean National Health Insurance, its incidence almost doubled in 6 years and has continued to increase slowly,[4] which is in line with previous reports in other countries.[7,8]

Among the various triggers of anaphylaxis, drugs are one of the most common causes in adults.[9–11] In previous reports, the prevalence of drug-induced cases ranged from 6% to 51.2% of the total number of anaphylaxis cases, depending on various settings of datasets and study subjects.[4,12,13] This nonprecise estimation of drug-induced anaphylaxis is probably due to the fact that most reports on anaphylaxis rely on voluntary reports from patients or a single medical center. Numerous attempts have been made to investigate the epidemiological features of drug-induced anaphylaxis in many countries. However, most studies rely on a single health center[1,14–16] or multiple university hospitals,[9,17,18] which makes it difficult to make a more precise approximation in the general population. To solve this discrepancy between the analyzed data in voluntary reports and real-world data, big data such as the Health Insurance Review and Assessment Service (HIRA) may play an important role in the evaluation of drug-related anaphylaxis. In particular, voluntary reports are

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often described based on the presumption of causative agents that can be imprecise.

Due to differences between various genetic backgrounds and healthcare systems, each ethnic group may be prone to different causative drugs. Finding the culprit drugs for specific ethnic groups not only helps clinicians refine the differential diagnostic process but also improves health policies to become more practical and convenient. The aim of this study was to investigate the causative agents of drug-induced anaphylaxis in Korean patients using a national database.

2. Methods

2.1. Data sources

Study subjects and their medical information were collected using data from the Korean HIRA database.[19] Medical information was collected between January 2011 and December 2019. The database included age, sex, outpatient or inpatient status, prescriptions, dosages, prescription duration, method of administration, and diagnosis information. The prescription data included the brand name and generic name of the drugs, the prescription dates, the medication amounts, and medication durations. Diagnoses were coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision. This study was approved by the Institutional Review Board of Seoul National University Boramae Medical Center, and informed consent was waived as all data were previously collected and deidentified (IRB approval waive ID: no. 07-2020-10).

2.2. Definition of cases

This study targeted patients who visited medical clinics anywhere in South Korea for anaphylaxis from July 1, 2009, to December 31, 2019. Patients who were categorized using primary, secondary, or tertiary anaphylaxis diagnostic ranking codes were included (International Statistical Classification of Diseases and Related Health Problems, 10th revision: T78.0, T78.2, T80.5, and T88.6). Patients with diagnostic codes for anaphylaxis prior to 2011 were excluded to increase the probability of the index date being the first event of anaphylaxis. The day on which the diagnostic code of anaphylaxis first appeared was defined as an 'index date, and individuals who were prescribed medication under other diagnostic codes within 3 days prior to the index date were enrolled. The visits with a set of medications prescribed 3 days prior to the index date were referred to as "case visits," in which the prescriptions provided on these dates were considered as having a high possibility of containing a culprit agent. Medical prescriptions on the index dates under the diagnosis of anaphylaxis were considered as treatment medications for anaphylaxis and were excluded. Visits with a set of medications under the same diagnostic codes as the case visit were referred to as "control visits" (Fig. 1).

2.3. Study design and control of study period

This study was based on a case-crossover design, in which each case visit of the patient was paired with a medical visit with a set of medications for attributable medical conditions under identical diagnostic codes for case visits after the index date. We collected the prescription data of each patient who was diagnosed with anaphylaxis and confirmed whether there was any exposure during the case and control visits. Beginning 28 days after the index date following the refractory period of anaphylaxis after the systemic reactions,[20,21] the first 3 control visits matched the case visits, creating setting pairs at ratios of 1:1–3.[22,23] The overall schematization of the current study is demonstrated in Figure 1.

Patients who did not have prescribed medication for medical conditions other than anaphylaxis within 3 days prior to the index date were excluded. Individuals who did not have a visit suitable for the predefined proper control visit and individuals with prescription drugs that were included in both case and control visits were excluded. Patients who were prescribed predefined excluded drugs were also excluded. Predefined excluded drugs were either elements that were less likely to be causative agents such as vitamins, trace chemical elements, and intravenous fluids such as normal saline and dextrose, or medications with unknown components such as oriental herbal medications. In addition, the following drugs used for anaphylaxis treatment were also excluded: antihistamine, corticosteroid, epinephrine, inhaled salbutamol, and inotropes including dopamine, vasopressin, and norepinephrine.

2.4. Statistical analysis

By excluding and adjusting for the drugs that were less likely to be the causative agents, we collected a list of drugs to analyze the risk ratio of anaphylaxis after exposure to each drug. A set of drugs that were candidates for the causative agents of anaphylaxis were collected using a chi-square analysis. To compare the risk of anaphylaxis, we performed a univariate conditional logistic regression analysis with a list of candidate agents in each individual. To gain further insight into the culprit drugs, we performed a multivariable conditional logistic regression analysis among multiple candidates to evaluate the risk ratio of anaphylaxis. All analyses were performed using SAS Enterprise Guided 7.1, and R version 3.5.1. (SAS Institute Inc., Cary, NC) Two-sided *P*-values <.05 were considered statistically significant. A

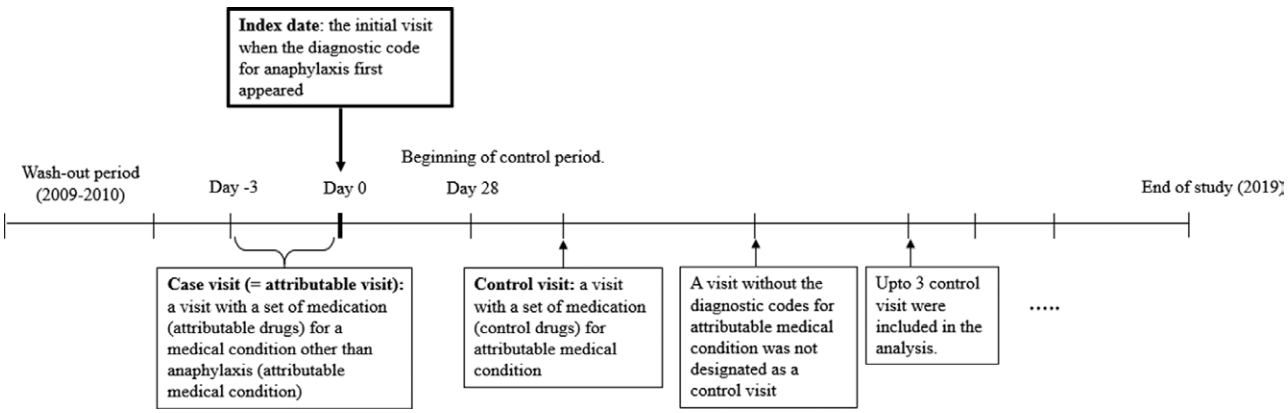

Figure 1. Illustration of study design.

Bonferroni correction was additionally applied in the logistic regression analysis. Variables were presented using the number of valid cases (N), means ± standard deviations, or medians (interquartile ranges).

3. Results

3.1. General description of population

A total of 159,473 individuals were listed in the database with a diagnosis of anaphylaxis in the HIRA from 2011 to 2019. Among them, 130,245 individuals were excluded due to a lack of medical prescriptions within 3 days prior to the index date. After evaluating the suitability of control visits for matching with a case visit and adjusting the predefined excluded drugs, 8168 study subjects satisfied the enrollment criteria (Fig. 2). The number of female patients was 4509 (55.2%), and the median age was 52 years (0.9–95). The average number of control visits per 1 case visit was 2.34 ± 0.86, and the average number of drugs prescribed in case and control visits of each individual was 2.8 ± 1.49 and 4.8 ± 3.9, respectively (Table 1).

3.2. Drugs with increased risk of anaphylaxis after univariate conditional logistic regression and multivariable conditional logistic regression analyses

From the 8168 study subjects, we included 767 drugs in the analysis to identify possible causative agents of anaphylaxis. Due to the extensive amount of drug candidates, the list of medications suggested were analyzed using a Chi-square analysis, with 31 drugs finally collected as candidate medication risk factors for anaphylaxis ($P < .05$). Considering the case-crossover design, we assessed the association between medication and anaphylactic events using univariate conditional logistic regression analyses for each drug. The medication list was narrowed down to 7 agents: iopromide, cefaclor, fluorescein, iomeprol, tolperisone, ioversol, and iohexol (Table 2). Among them, iopromide (crude odds ratio = 4.27, $P = 4.25 \times 10^{-7}$) and cefaclor (crude odds ratio = 1.41, $P = 8.82 \times 10^{-8}$) were statistically significant following the Bonferroni correction. To eliminate bias from the combined usage of causative agents in prescriptions with multiple medications, we performed a multivariate conditional logistic regression analysis of 31 drugs. Five drugs that were related to the increased risk of anaphylaxis after the multivariate conditional logistic regression analysis included iopromide (adjusted odds ratio [aOR] = 4.82, $P = 3.17 \times 10^{-12}$), cefaclor (aOR = 1.59, $P = 1.96 \times 10$), tolperisone (aOR = 5.59, $P = .01$), iohexol (aOR = 2.31, $P = .02$), and iomeprol (aOR = 11.17, $P = .02$) (Table 3).

4. Discussion

To our knowledge, this study is the first to estimate the causative agents and their respective risks using the HIRA data in Korea for drug-induced anaphylaxis. In a total of 8168 study subjects, female patients (55.2%) tended to experience drug-induced anaphylaxis more frequently than male patients, which was in line with previous studies.[24–26] Of 767 candidate drugs in 8168 anaphylaxis patients, 5 drugs were identified as medication risk factors. Three of 5 agents were computed tomography (CT) iodinated contrast media (ICM) (iopromide, iohexol, and iomeprol), 1 was an antibiotic (cefaclor), and 1 was a skeletal muscle relaxant (tolperisone).

Table 1

Baseline characteristics of the participants.

	N = 8168
Sex	
Male	3659 (44.8%)
Female	4509 (55.2%)
Age, yr (median)	52 (33, 64)
Numbers of medications included in the analysis	
Case visit	2.8 ± 1.5
Control visit	4.8 ± 3.9
Comorbid allergic diseases	
Asthma	496 (6.1%)
Allergic rhinitis	1625 (19.9%)
Atopic dermatitis	99 (1.2%)
Urticaria	1389 (17.0%)

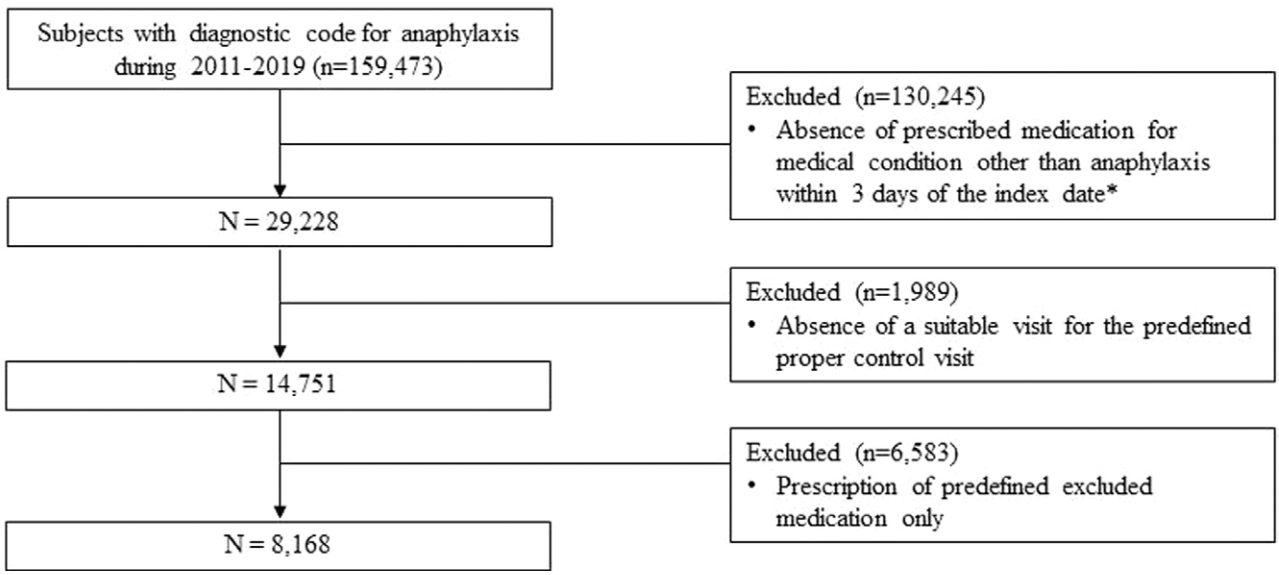

Figure 2. Flow diagram of criteria for inclusion and exclusion. *The date when the diagnostic code for anaphylaxis first appears is defined as the index date.

Table 2

Drugs related to an increased risk of anaphylaxis after the univariate conditional logistic regression analysis.

	Case		Control			95% confidence interval		
	N	%	N	%	Crude odds ratio	Lower	Upper	*P* value
Iopromide	64	0.78	15	0.18	4.27	2.43	7.49	4.25×10^{-7}
Cefaclor	590	7.22	420	5.14	1.41	1.24	1.60	8.82×10^{-8}
Fluorescein	12	0.15	0	0.00	12.00	1.56	92.29	.02
Iomeprol	27	0.33	12	0.15	2.25	1.14	4.44	.02
Tolperisone	12	0.15	3	0.04	4.00	1.13	14.17	.03
Ioversol	29	0.36	16	0.20	1.81	0.98	3.34	.06
Iohexol	79	0.97	57	0.70	1.39	0.99	1.96	.06

Table 3

Drugs related to the increased risk of anaphylaxis after the multivariate conditional logistic regression analysis.

		95% confidence interval		
	Adjusted odds ratio	Lower	Upper	*P* value
Cefaclor	1.59	1.39	1.80	1.96×10^{-7}
Iopromide	4.82	2.67	8.71	3.17×10^{-12}
Tolperisone	5.59	1.49	20.94	.01
Iohexol	2.31	1.16	4.60	.02
Iomeprol	11.17	1.44	86.83	.02
Cimetidine	1.42	1.0	2.01	.05
Eperisone	1.77	0.9	3.29	.07
Iopamidol	1.95	0.9	4.12	.08

In this study, we assessed the medication risk factors for anaphylaxis in Korea. When exposure to a certain drug increases the occurrence of subsequent anaphylaxis, it can be referred to as a medication risk factor. Therefore, the medication risk factors for anaphylaxis have similar definitions, although not completely identical, to the causative drugs of drug-induced anaphylaxis at the population level. This is in line with a previous study of Steven-Johnson syndrome and toxic epidermal necrolysis patients by the EuroSCAR group, where researchers tried to categorize the medication risk factors for severe cutaneous adverse reactions.[27] In this study, the data were analyzed based on the assumption that specific medications would contribute to higher chances of anaphylaxis events. To ensure a temporal relationship between prescription and the onset of anaphylaxis, we included patients who were prescribed drugs within 3 days of the index date. Considering cases in which administration of medication could be delayed, an additional 3 days were accounted for prior to the index date, despite the fact that medication is generally taken immediately after being prescribed. The control visit was a later hospital visit under different diagnostic codes within the same patient. Before sensitization, no anaphylaxis occurred, even if the patient was exposed to a causative agent. Thus, the control visits were set after, and not before, the index date. This matching design was based on the assumption that a set of prescriptions would be most similar under an identical diagnosis, which may eliminate drugs included in the analysis. Twenty-eight extra days were also excluded after the index date because of the possible refractory period in which hypersensitivity is less likely to occur, even when the patient is exposed to the culprit drug. The list of medication risk factors were evaluated and narrowed to 31 drugs using a chi-square analysis. Five drugs were considered to have the highest risk for developing anaphylaxis in the Korean general population by the conditional logistic regression model after adjusting for the concomitant use of other risk medications. This method of evaluating medication risk factors from big data, such as national databases, not only helps clinicians to estimate the causative agents of drug-related anaphylaxis, but also is a useful reference for future health care policies.

This study had several strengths. First, this methodological approach can reduce the inaccuracy of predicting causative agents of drug-induced anaphylaxis, considering the fact that anaphylaxis cases are usually reported by voluntary reports. Second, the statistical approach of big national data used in the current study may determine the medication risk for a particular drug in anaphylaxis. Third, this method can also be applied when there is a claim database to identify possible causes of drug adverse reactions, including anaphylaxis, in a population with different ethnicities and dissimilar medical systems. Moreover, if the clinical presentation of a specific drug adverse reaction, other than anaphylaxis, is known, this method can be applied to identify possible culprit drugs for adverse drug reactions.

In recent medical diagnostic processes, ICM is one of the most essential tools for proper medical processes in diagnosis and treatment, with great convenience and accuracy. For this reason, the use of ICMs in CT and angiography has been rapidly growing in recent decades,[28] and approximately 4 million CT scans are performed each year in Korea.[29] Although ICMs can be generally tolerated, ICM hypersensitivity may occur,[30,31] which can result in fatal cases.[32] As the use of ICMs has increased, they have become one of the most common sources of drug hypersensitivity.[1] In the current study, the majority of attributable agents among candidate culprit drugs were ICMs. Because CT scans are generally performed in secondary or tertiary referral hospitals, there is still controversy over the representativeness of previous data in the general population. However, the majority of medication risk factors in our data also included iodinated contrast media, such as iopromide, iohexol, and iomeprol. In addition, another ICM, iopamidol, showed a possible association with anaphylaxis in the conditional logistic regression analysis (OR, 1.95; confidence interval [CI], 0.9–4.12, $P = .08$), although the difference was not statistically significant. There are several explanations for this phenomenon. First, ICMs are usually administered as an intravenous bolus with a relatively fast velocity. The difference between the injection speeds is likely responsible for the increased risk of anaphylaxis. A recent retrospective study showed a correlation between reduced ICM injection speeds and lower rates of acute hypersensitivity reactions.[33] Second, there is continuous growth in the use of CT scans in the general population[34] due to coverage by the Korean National Medical Insurance system and healthcare policy issues in Korea.[35,36] This easy access to CT contrast media exposure may have led to the higher chances of ICM hypersensitivity. Third, cross-reactions among ICMs may contribute to the

increased occurrence of ICM hypersensitivity. According to a number of recent studies, cross-reactivity among ICMs is not unusual, with a wide range from 20% to 75%.[37,38] Although the traditional concepts of ICM hypersensitivity are based on non-immunologic reactions, there has been a growing notion that some proportion of ICM hypersensitivity is related to immunologic mechanisms. In various studies, investigators have suggested the existence of immunologic cross-reactions between different agents.[39] In addition, other contrast agents used in diagnostic imaging procedures, such as barium sulfate, gadobuterol, and gadoteridol, did not show a statistically significant association.

The other medication risk factors of drug-related anaphylaxis other than iodinated contrast media were cefaclor (OR, 1.59; CI, 1.39–1.80, $P = 1.96 \times 10$) and tolperisone (OR, 5.59; CI, 1.49–20.94, $P = .01$). Cefaclor is a second-generation cephalosporin, which was reported as one of the most frequently involved antibiotic drugs in anaphylaxis in Korea and in other countries.[40,41] However, other antibiotics, including penicillins such as amoxicillin, did not show a significant association with the occurrence of anaphylaxis. This may be because an excessive list of drugs were included in the analysis, which could make it difficult to consider drug-drug interactions and perform a suitable regression. Tolperisone, on the other hand, is a centrally acting muscle relaxant derived from piperidine derivative.[42] The increased risk observed from tolperisone, but not from eperisone, was unexpected because eperisone is one of the most widely used muscle relaxants, and anaphylaxis induced by eperisone was reported several times in Korea.[43–45] However, eperisone did not show increased medication risk in drug anaphylaxis. This result is likely due to the difference in the frequency of prescriptions between eperisone and tolperisone. According to previous case reports of tolperisone-induced anaphylaxis,[46,47] we suggest additional caution in the use of tolperisone.

Interestingly, non-steroidal anti-inflammatory drugs (NSAIDs) including diclofenac, aceclofenac, dexibuprofen, and loxoprofen, did not show increased medication risk. Hypersensitivity to NSAIDs has a wide spectrum of manifestations and NSAID-induced anaphylaxis has been continuously reported.[48,49] However, our data did not show increased OR values of NSAIDs with the occurrence of anaphylaxis, despite their usage and known high incidence of anaphylaxis.[50] This could be because the heterogeneity of the phenotypes of NSAID hypersensitivity may contribute to rates of underdiagnosis. Because hypersensitivity to NSAIDs have many diverse manifestations involving diverse patho-mechanisms, including NSAID-induced asthma and rhinosinusitis and NSAID-induced urticaria/angioedema, nonallergy specialists might have had difficulties differentiating between anaphylactic cases and non-anaphylaxis. In addition, the various cross-reactivity patterns of NSAIDs according to the phenotype of NSAID hypersensitivity may influence the results of the analysis.

This study has some limitations. First, the nature of the HIRA database prevents us from completely eliminating any discrepancies between the actual diseases in the real world and the diagnoses claimed by the healthcare providers, which may lead to over- or under-diagnosis of anaphylaxis. Second, the HIRA database does not include uncovered healthcare services and medications such as over-the-counter drugs recorded by the National Health Insurance Service in Korea, which may limit the investigation of causative drugs of anaphylaxis. Third, the possibility of underestimation in CT contrast media-related anaphylaxis exists due to the medical payment system in Korea. CT contrast media are usually included as CT scan material and CT scan fees are systematically paid on the day of examination. Despite the possibility of underestimation, our findings suggested CT contrast media as suspected drugs. Lastly, an arbitrary period of 3 days prior to the index date in defining culprit agent would lead to imprecision. In addition, further studies with the comparisons of the statistical results of the HIRA data and analytical tests such as skin test and laboratory exams are needed to investigate the underlying mechanisms of drug-induced anaphylaxis.

5. Conclusion

In summary, 5 medication risk factors, namely iopromide, iohexol, iomeprol, cefaclor, and tolperisone, need to be cautiously prescribed. Furthermore, the findings of this study indicate a potent usability analysis of domestic healthcare data for the precise analysis of different populations.

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Author contributions

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Supervision: Min-Suk Yang.
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Writing – review & editing: Kyung-Min Ahn, Byung-Keun Kim.

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