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Healthcare utilization of lung cancer patients associated with exposure to fine particulate matter: A Korean cohort study

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Abstract

Background: Higher concentrations of particulate matter (PM) have been shown to cause deterioration of the symptoms of respiratory and cardiovascular disease in several regional studies. Here, we aimed to investigate the healthcare utilization of lung cancer patients associated with short-term exposure to PM at the national level in Korea.

Methods: We extracted the data of 210 558 subjects over a period of 3 years (2015–2017), who were diagnosed with lung cancer before 2015 and benefited from the National Health Insurance Sharing Service. We performed the interpolation method using the geographic information system to calculate the estimated mean $PM_{2.5}$ and PM_{10} concentrations by regions and classified three groups as high (upper 10%), intermediate (10%–90%), and low (bottom 10%) based on the mean PM mass concentrations of the month.

Results: The monthly average number of outpatient visits was significantly increased in high $PM_{2.5}$ urban areas (46.296 vs. 50.646, p=0.015). In high $PM_{2.5}$ nationwide regions, the monthly average number of emergency admission was significantly increased (0.528 vs. 0.785, p=0.001). The outpatient visits tended to change with $PM_{2.5}$ concentration and correlated with $PM_{10}/PM_{2.5}$ concentrations in urban and nationwide areas. In high $PM_{2.5}$ urban regions, there was a significant increase in bronchodilator prescriptions (3.102 vs. 3.758, p=0.008). Concerning high $PM_{2.5}$ nationwide regions, there were significantly increased prescriptions of antibiotics, steroids, bronchodilators, antihistamines, and mucolytics.

Conclusions: This study suggests that exposure to PM_{2.5} is significantly associated with hospital utilization and drug prescription in lung cancer patients.

KEYWORDS

healthcare utilization, lung cancer, particulate matter

INTRODUCTION

Particulate matter (PM) is suspended dust that has a diameter of <10 μ m (PM₁₀) and can be inhaled by humans and deposited in the lungs, particularly the alveoli. In addition to PM₁₀, PM with diameter <2.5 μ m (PM_{2.5}) and <0.1 μ m (PM_{0.1}) is classified as fine and ultrafine PM, respectively. PM can cause various diseases including respiratory, allergic, cardiocerebrovascular,

neurological, and psychiatric diseases. Furthermore, higher concentrations of PM cause deterioration of the symptoms of respiratory and cardiovascular disease as well as increase the associated risk, incidence, and mortality. Short-term exposure to PM_{2.5} also increases the risk for hospital admission for cardiovascular and respiratory diseases. Therefore, reduction of the total amount of PM is considered to be important for vulnerable patients, and proper early management of exacerbated patients will be needed in the future.

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Medical deterioration due to PM affects healthcare utilization. In a previous study, 10 µm/m³ elevation in PM_{2.5} concentration increased the risk of hospital admissions by 1.39% for citizens aged 65 years and older in 204 US urban counties during 1999-2002.4 In another study, it was shown that 10 µm/m³ elevation in two-day averaged PM_{2.5} concentration increased the risk of hospital admissions due to respiratory disease by 2.07% in 26 US communities during 2000–2003. In addition, a study showed a 1.15% increase of respiratory admissions per 10 μm/m³ increase in PM_{2.5} mass in southern Europe.⁶ In Korea, for 10 μm/m³ increase in PM_{2.5} concentration, there was an 8.84% (95% confidence interval [CI]: 6.09-11.66%) increase in the risk of respiratory admissions for people aged 65 years and older in Seoul.7 Moreover, there was a 0.46% increase in respiratory outpatient visits and a 0.05% increase in respiratory admissions per 1% increase in PM_{2.5}.8 A multivariate analysis showed a significant increase in respiratory-related admissions with increasing PM levels and a decreasing relative humidity. Higher PM_{2.5} levels had a greater effect on respiratoryrelated hospital admission than did PM₁₀ levels. Children and the elderly were the most susceptible to hospital admission for respiratory disease. However, the previous studies have examined only specific provinces in Korea and the general population.

Thus, in this study, we aimed to investigate the health-care utilization of lung cancer patients associated with short-term exposure to PM at the national level in Korea. Specifically, we investigated the association between hospital utilization and PM by using 3 years of the National Health Insurance Service (NHIS) database of patients who were diagnosed with lung cancer.

METHODS

Patients and study design

NHIS provides mandatory national health insurance services to all citizens through government subsidies in Korea. Based on this service, they provide National Health Insurance Sharing Service (NHISS) and support research related to national health data.

We extracted the data of 210 558 subjects over a period of 3 years (2015–2017), who were diagnosed with lung cancer before January 1, 2015 and benefited from NHISS (Figure 1). We excluded 127 978 subjects who were aged <20 in 2014 or died before 2014 or missing values; 22 484 subjects with secondary lung malignancy; 29 996 subjects who were randomly half sampled; and 5564 subjects who died in 2014. Finally, 24 536 remaining subjects were eligible for our analysis. In each year, the number of subjects varied due to a lack of follow-up during the period.

The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The data in the present study were extracted from the research database provided by NHISS and approved by the NHIS review board (NHIS-2018-1-215).

Variables

The PM mass concentration data were obtained from the National Institute of Environmental Research (NIER), which provides air pollution measurement data. We used

Extracted Subjects (N= 210,558)					
				Γ	
				Excluded Subjects	(N=186,022)
				Aged < 20 in 2014, Died before 2014, Missing values	(n=127,978)
			Secondary lung cancer	(n=22,484)	
				Selected randomly by the half sampling rate	(n=29,996)
				Died in 2014	(n=5,564)
Final Analysis Subjects (N=24,536)					
2015 (n=24,532)	201 (n=20,		2017 (n=18,237)		

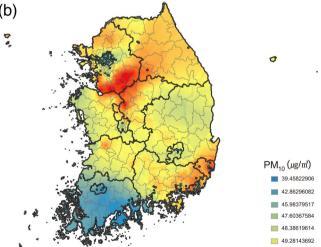
FIGURE 1 Study population.

annual mean PM_{2.5} and PM₁₀ as measurements of exposure to fine PM. Frequencies of respiratory care admission, outpatient visit, emergency admission, and prescription were chosen as the outcome variables. The respiratory diseases were chosen according to seventh edition of Korean standard classification of disease (KCD-7) including acute upper respiratory infections; pneumonia; other acute lower respiratory infections; other diseases of upper respiratory tract; chronic lower respiratory diseases; pulmonary diseases due to external agents; other respiratory diseases principally affecting the interstitium; suppurative and necrotic conditions of the lower respiratory tract; other diseases of pleura; and other diseases of the respiratory system. Demographic information included sex (male or female), age (20s, 30s, 40s, 50s, 60s, 70s and 80s), and regions (17 regions defined as metropolis or province, Table S1).

Statistical analysis

We performed the interpolation method using the geographic information system (GIS) to calculate the estimated mean $PM_{2.5}$ and PM_{10} concentrations by regions. $PM_{2.5}$ and PM_{10} concentrations were the highest in February during 2015, the first year of the study period. Therefore, we classified three groups as high (upper 10%), intermediate (10%–90%), and low (bottom 10%) based on the mean PM mass concentrations of the month. We used the Scheffe test for the two extremes (high and low levels) to examine the effects of exposure to PM on hospital utilization. The statistical analyses were performed using SAS (version 9.4; SAS Institute), and a p-value <0.05 was considered statistically significant.

(a) (b) PM_{2.5} (μg/m) 39.45822906



50.50027771

56.92549896

FIGURE 2 National contour graph of average mass concentrations of (a) PM_{2.5} and (b) PM₁₀ in 3 years. Spatial and temporal distribution of the concentrations were calculated by spatial interpolation methods using geographic information system.

47.60357594

50.50027771

60.13370514

RESULTS

Average mass concentrations of PM in 3 years

We introduced the GIS analysis method for PM mass concentrations data. Figure 2 is the contour graph of average PM mass concentrations for the years 2015–2017. Gyeonggi-do, Chungcheongnam-do, Jeollabuk-do, Ulsan, and Busan had relatively higher $\rm PM_{2.5}$ concentrations, and Gyeonggi-do, Chungcheongbuk-do, Ulsan, and Busan had higher $\rm PM_{10}$ concentrations. The lowest concentration of $\rm PM_{2.5}$ and $\rm PM_{10}$ was observed in Jeollanam-do.

Associations between mass concentrations of PM and frequency of hospital utilization

We categorized the regions as urban (74 regions) and nation-wide (253 regions), and the average mass concentrations of $PM_{2.5}$ and PM_{10} in February 2015 as high (upper 10%), intermediate (10%–90%), and low (bottom 10%) group. The values in admission and outpatient visit were defined as monthly average counts per hundred patients. We conducted Scheffe test including high and low PM concentrations (Table 1).

Regarding PM_{10} and urban regions, the monthly average number of inpatient admissions was significantly different between two groups (low: 1.554 vs. high: 1.150, p=0.009). In connection with the nationwide regions and PM_{10} , monthly average numbers of inpatient admissions (2.787 vs. 1.19, p<0.001) and outpatient visits (58.85 vs. 43.114, p<0.001) were significantly different. In total, we found that as the level of PM_{10} concentration increased nationwide, the monthly average number of hospital utilization decreased (62.333 vs. 45.091, p<0.001).

Concerning urban regions and PM_{2.5}, the monthly average number of outpatient visits was significantly increased in high group (46.296 vs. 50.646, p=0.015). Concerning PM_{2.5} and nationwide regions, monthly average numbers of emergency admissions (0.528 vs. 0.785, p=0.001) and outpatient visits (51.178 vs. 45.923, p<0.001) were significantly different between the two groups.

Associations between mass concentrations of PM and frequency of drug prescription

In the urban regions, we found that the average monthly numbers of prescriptions differed significantly between high and low PM₁₀ concentrations for three categories of drugs: steroids (0.353 vs. 0.638, p < 0.001), antihistamines (1.147 vs. 1.373, p = 0.014), and mucolytic agents (3.331 vs. 4.023, p < 0.001) (Table 2). Concerning nationwide regions, we noticed a statistically significant difference between low and high PM₁₀ levels in antibiotics (1.283 vs. 1.148, p = 0.019), bronchodilators (5.277 vs. 4.222, p < 0.001), antihistamines (1.387 vs. 1.591, p = 0.002), and mucolytic agents (4.661 vs. 4.239, p = 0.004).

Regarding PM_{2.5} and urban regions, there was a significant increase in bronchodilator prescriptions (3.102 vs. 3.758, p = 0.008). The mean count of mucolytic agents showed increasing tendency between high and low groups (3.359 vs. 3.777, p = 0.059). Concerning the nationwide

TABLE 1 Average frequency of hospital utilization by mass concentrations of PM_{2.5} and PM₁₀ in 3 years.

Urban				Nationwide				
PM ₁₀	Low	High	p-value ^c	PM ₁₀	Low	High	p-value	
Emergency admission	0.458	0.585	0.324	Emergency admission	0.695	0.788	0.407	
Inpatient admission	1.554	1.150	< 0.009	Inpatient admission	2.787	1.190	< 0.001	
Outpatient visit	47.179	47.883	0.895	Outpatient visit	58.85	43.114	< 0.001	
Total	49.19	49.618	0.962	Total	62.333	45.091	< 0.001	
Urban				Nationwide				
PM _{2.5}	Low	High	<i>p</i> -value	PM _{2.5}	Low	High	p-value	
Emergency admission	0.466	0.475	0.995	Emergency admission	0.528	0.785	0.001	
Inpatient admission	1.136	1.113	0.986	Inpatient admission	1.342	1.529	0.234	
Outpatient visit	46.296	50.646	0.015	Outpatient visit	51.178	45.923	< 0.001	
Total	47.897	52.234	0.019	Total	53.048	48.236	< 0.001	

^aMonthly average number of admissions or visits per hundred patients.

TABLE 2 Average frequency of drug prescription in 3 years by mass concentrations of PM_{2.5} and PM₁₀.

Urban				Nationwide				
PM ₁₀	Low	High	<i>p</i> -value ^c	PM ₁₀	Low	High	<i>p</i> -value	
Antibiotics	0.989	1.130	0.080	Antibiotics	1.283	1.148	0.019	
Steroids	0.353	0.638	< 0.001	Steroids	0.611	0.700	0.113	
Bronchodilators	3.300	3.168	0.824	Bronchodilators	5.277	4.222	< 0.001	
Antihistamines	1.147	1.373	0.014	Antihistamines	1.387	1.591	0.002	
Mucolytic agents	3.331	4.023	< 0.001	Mucolytic agents	4.661	4.239	0.004	
Urban				Nationwide				
PM _{2.5}	Low	High	p-value	PM _{2.5}	Low	High	<i>p</i> -value	
Antibiotics	1.067	1.007	0.636	Antibiotics	1.075	1.348	< 0.001	
Steroids	0.510	0.418	0.108	Steroids	0.472	0.896	< 0.001	
Bronchodilators	3.102	3.758	0.008	Bronchodilators	3.597	5.043	< 0.001	
Antihistamines	1.362	1.465	0.416	Antihistamines	1.394	1.634	< 0.001	
Mucolytic agents	3.359	3.777	0.059	Mucolytic agents	3.926	4.387	0.001	

^aMonthly average number of drug prescriptions per patient.

^bWe categorized mass concentrations of PM_{2.5} and PM₁₀ in February 2015 into three groups: high (upper 10%), intermediate (10%–90%), and low (bottom 10%). In this table, the post hoc analysis between the high and low concentration groups is presented.

^cp-value was calculated by Scheffe test.

^bWe categorized mass concentrations of PM_{2.5} and PM₁₀ in February 2015 into three groups: high (upper 10%), intermediate (10%–90%), and low (bottom 10%). In this table, the post hoc analysis between the high and low concentration groups is presented.

^cp-value was calculated by Scheffe test.

regions and PM_{2.5}, the mean counts of all drugs showed statistically significant increase in high PM_{2.5} group; antibiotics (1.075 vs. 1.348, p < 0.001), steroids (0.472 vs. 0.896, p < 0.001), bronchodilators (3.597 vs. 5.043, p < 0.001), antihistamines (1.394 vs. 1.634, p < 0.001), and mucolytic agents (3.926 vs. 4.387, p = 0.001).

Trend of outpatient visits in high PM concentration group by the levels of $PM_{2.5}$ / PM_{10}

As we found that the number of outpatient visits was significantly associated with $PM_{2.5}$ in the previous analysis, we plotted the monthly average number of outpatient visits based on the regions (urban/nationwide) and $PM_{2.5}$ and PM_{10} concentrations in the high PM concentration groups (based on the levels of $PM_{2.5}$ in February 2015) in 3 years (Figure 3). The plots suggest that the monthly average numbers of outpatient visits move up and down along with $PM_{2.5}$ concentration regardless of its level.

Correlation between mass concentrations of PM and the number of outpatient visits

Figure 4 shows the correlation between monthly average numbers of outpatient visits related to respiratory disease and $PM_{2.5}$ and PM_{10} level in the high PM concentration groups by the levels of $PM_{2.5}$ in February 2015. In urban areas, the number of outpatient visits showed positive correlations with the level of PM_{10} (r=0.7425, p<0.001) and $PM_{2.5}$ concentration (r=0.6618, p<0.001). With regard to nationwide regions, the positive correlations were also observed between the number of appointments and the levels of PM_{10} and $PM_{2.5}$ concentration (p<0.001 in both).

DISCUSSION

In this cohort study in Korea, we stratified by PM concentration and region to examine associations between levels of PM concentrations and hospital utilization during a period of 3 years. Overall, we found that higher levels of PM_{2.5} and PM₁₀ are associated with higher rates of all types of hospital utilization and prescriptions due to an increase of respiratory disease. Although the health care utilization according to PM₁₀ concentration was difficult to interpret because of the various factors that we could not include in this analysis, PM_{2.5}'s harmful effects on lung cancer patients' health seem more obvious. In urban regions, we found that as the level of PM_{2.5} concentration increased, the number of outpatient visits also increased (p = 0.015). Although the number of admissions (emergency or inpatient) did not differ according to high versus low PM_{2.5} concentration, the overall hospital utilization showed statistical significance (p = 0.019) because of the outpatient visits. However, regarding the

nationwide regions, the results were reversed. As the level of $PM_{2.5}$ concentration increased, the number of outpatient visits decreased (p < 0.001). One reason for this reversal relates to the number of outpatient visits in the other regions except urban regions.

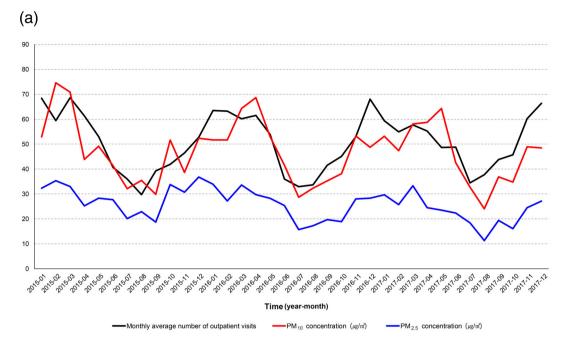
We reasonably assumed that healthcare utilization is related to the number of prescriptions; hence, we also investigated the associations between PM mass and the number of prescriptions. Regarding urban regions, the level of PM_{10} was significantly associated with a higher rate of steroids, antihistamines, and mucolytic agents. However, the high $PM_{2.5}$ concentration was significantly associated with an increased prescription of antibiotics, steroids, bronchodilators, antihistamines, and mucolytics nationwide. In particular, the prescription of bronchodilators significantly increased only in the high $PM_{2.5}$ concentration group, unlike the PM_{10} concentration group in urban regions and nationwide. This phenomenon might be because only $PM_{2.5}$ can reach alveoli and bronchioles.

In exploratory data analysis, we performed correlation analysis and visualized trends between PM mass and the number of outpatient visits. Across all levels of PM, we found a strong positive correlation (p < 0.001). Furthermore, the trends in outpatient visits also moved along with the value of PM. Linear regression also showed that hospital utilization increased significantly according to increase of the concentration of PM_{2.5} and PM₁₀ in urban regions and nationwide.

Exposure to PM leads to increased pulmonary inflammation and respiratory symptoms aggravated by oxidative stress and direct toxic injury. This is particularly dangerous for patients with pre-existing respiratory diseases, as exposure to PM can lead to acute exacerbation of their ailment. It has also been reported that long-term exposure to high concentrations of PM increases the prevalence of chronic obstructive pulmonary disease and lung cancer in adults, leading to a decline in pulmonary function.^{1,12} The high concentration of PM in the atmosphere has a profound effect on the prevalence of chronic respiratory diseases and the risk of acute exacerbation. ¹³ Additionally, PM_{2.5} exposure is associated with a long recovery time, more leading to an increase in both the mortality rate and the overall medical burden. Therefore, it is considerably important that effective policies and medical practices are put into place to minimize the public health risks associated with PM exposure.

In 2005, as outlined by the World Health Organization (WHO), the maximum acceptable annual average concentration of PM_{10} was $\leq 20~\mu g/m^3$, with a limit of $\leq 50~\mu g/m^3$ per 24-h period. In Korea, the annual and daily average concentrations of PM_{10} are <50 and $<100~\mu g/m^3$, respectively. The annual and daily average concentrations of $PM_{2.5}$ are <15 and $35~\mu g/m^3$, respectively. Overall concentrations of PM_{10} and $PM_{2.5}$ are above $81~\mu g/m^3$ and $36~\mu g/m^3$, respectively, and therefore the PM concentration forecast grade is designated as "bad" in Korea. 14

In 2013, the International Agency for Research on Cancer (IARC), an intergovernmental agency forming part



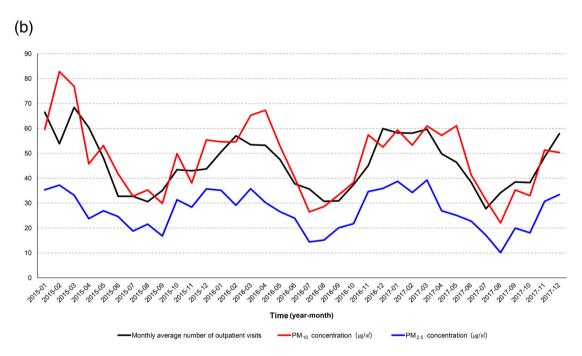


FIGURE 3 Trends in outpatient visits with levels of $PM_{2.5}$ and PM_{10} in (a) urban areas and (b) nationwide.

of WHO, classified outdoor air pollution as a Group 1 agent—carcinogenic to humans. In Europe, a multinational prospective cohort study showed a hazard ratio (HR) of 1.22 per $10~\mu\text{m/m}^3$ increase in PM_{10} , and an HR of 1.18 per $5~\mu\text{m/m}^3$ increase in $PM_{2.5}$ for lung cancer. In a comprehensive meta-analysis conducted in Korea in 2015, the risk of lung cancer increased by 1.09-fold (95% CI: 1.01–1.14) when the concentration of $PM_{2.5}$ increased by $10~\mu\text{g/m}^3$. A correlation between PM_{10} concentration and lung cancer incidence was also observed; however, the correlation was comparatively weak compared to that between lung cancer

risk and $PM_{2.5}$ concentration (1.08-fold increased risk; 95% CI: 1.00–1.17). ¹⁴ In addition, lung cancer incidence was higher in smokers who were exposed to high amounts of $PM_{2.5}$; it was confirmed that fine PM affects smokers' lung cancer development to a significantly greater degree relative to healthy people. ^{10,16} It is estimated that about 500 000 lung cancer deaths can be attributed to air pollution. ¹⁷ Both PM_{10} and $PM_{2.5}$ were reported to significantly increase the mortality rate of lung cancer patients in 2017 and 2018 meta-analyses. ¹⁸ Thus, to reduce lung cancer prevalence and mortality, control of PM generation and avoidance of PM

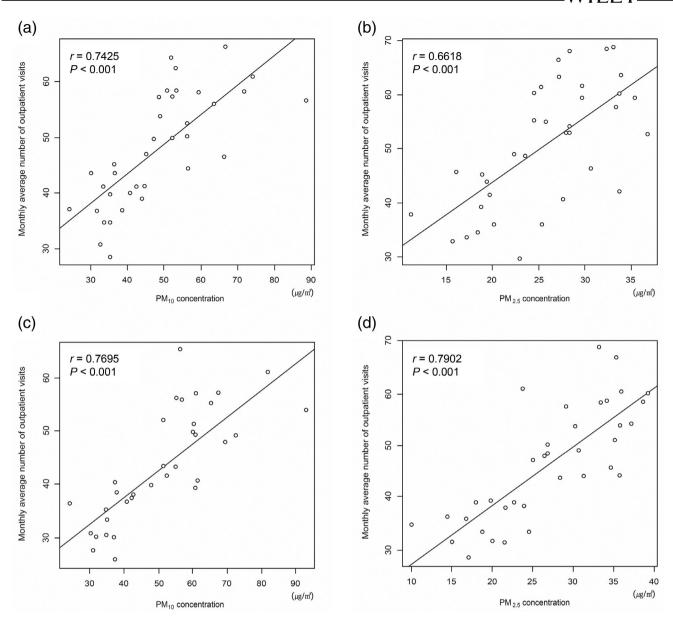


FIGURE 4 Correlation graph between particulate matter (PM) concentrations and the number of outpatient visits in (a) urban high PM_{10} , (b) urban high $PM_{2.5}$, (c) nationwide high PM_{10} , and (d) nationwide high $PM_{2.5}$ areas.

exposure, together with smoking cessation, are of the utmost importance. ^{1,19}

This study had several limitations. First, although this was a nationwide large-scale study, regional and environmental factors should be considered when applied outside of Korea. Second, unlike with PM_{2.5}, consistent results were not shown for PM₁₀ concentration and healthcare utilization rate, which requires consideration for a wider range of environmental factors. Third, the association between PM concentration and the frequency of drug prescription for respiratory symptom control was possible, but we could not present any relevance to ongoing lung cancer treatment (e.g., chemotherapy or radiation therapy). Fourth, we did not perform the subanalysis of a specific group such as gender in which PM may have more impact. Female patients

tend to have smaller absolute lung volumes, and the proportions of smokers and pathological subtypes are different when compared to their male counterparts.

In conclusion, this study suggests that exposure to $PM_{2.5}$ is significantly associated with hospital utilization and drug prescription in lung cancer patients although we did not obtain long-term PM data. Moreover, we used large data based on NHISS, so that our study can be used as a reference for the national healthcare policy.

AUTHOR CONTRIBUTIONS

Conceptualization: Oh IJ, Yang SH. Data curation: Oh IJ, Yang SH. Formal analysis: Oh IJ, Yang SH Funding acquisition: Oh IJ. Investigation: Oh IJ, Park CK, Chung C, Yoon SH, Yang SH. Methodology: Oh IJ, Kim CS, Yang

SH. Software: Oh IJ. Validation: Kim CS. Visualization: Min KB, Min JY. Writing—original draft: Oh IJ. Writing—review and editing: Oh IJ, Park CK, Chung C, Yoon SH, Yang SH.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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