



Original Article

Procedural and clinical risk factors of infective endocarditis – A nationwide case-control study in South Korea



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ABSTRACT

Background: Infective endocarditis (IE) causes high mortality and morbidity, posing a significant burden on healthcare systems. Although the incidence of IE is rising globally, its risk factors, particularly procedure-related risks, remain unclear. This study aimed to investigate the clinical and procedural risk factors associated with IE using nationwide data from South Korea.

Methods: We analyzed data from the Korean National Health Insurance Service between 2003 and 2018. A total of 8487 patients with IE and 33,535 matched controls based on age, sex, and the Charlson Comorbidity Index were included. Procedural risk factors were categorized as dental, gastrointestinal, respiratory, and genitourinary, with analysis periods of 90 and 60 days for dental and other procedures, respectively. Logistic regression models were used to evaluate the associations, with statistical significance set at $P < 0.05$.

Results: Traditional risk factors including dialysis, immunosuppression, congenital heart disease, and valvular disease were significantly associated with IE. Additionally, invasive procedures, such as intravenous catheter insertion (odds ratio [OR], 18.94) and respiratory (OR, 4.05), gastrointestinal (OR, 3.09), and genitourinary procedures (OR, 3.97), were strongly associated with an increased risk of IE (all $P < 0.001$). Dental procedures without antibiotic prophylaxis were also associated with a higher risk of IE (OR, 1.19; $P = 0.001$), whereas those with prophylaxis were not (OR, 1.07; $P = 0.256$).

Conclusions: Both clinical factors and procedural interventions significantly contributed to the risk of IE. Our findings support the need for expanded preventive strategies, particularly considering nondental invasive procedures and high-risk patient groups.

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Introduction

Infective endocarditis (IE) is a life-threatening disease associated with mortality and morbidity that imposes a substantial healthcare burden. The incidence of IE ranges from 2 to 8 cases/100,000 person-years and continues to rise [1]. The high burden of IE is caused not only by its high prevalence but also by serious complications, a high mortality rate, and the need for emergent surgical correction. In-hospital mortality rates range from 15% to 20%, and the one-year crude mortality rate is as high as 40% [2]. Considering the high

mortality and complication rates despite surgical and medical improvements, the importance of identifying the risk factors for IE and its prevention cannot be overemphasized.

In developing countries, IE is mainly associated with rheumatic fever [2], but in developed countries, the profile of IE has shifted over the past decades. In developed regions, IE commonly occurs in older adults and is more closely related to the healthcare-associated [3]. It also occurs at a higher rate in patients with chronic intravenous (IV) access or IV drug use; history of endocarditis; presence of cardiovascular implantable electronic devices; valvular predisposition factors such as degeneration, prosthesis, or congenital valve anomaly; and diabetes or an immunocompromised host [4]. In addition, interest in various risk factors related to healthcare-associated IE is increasing; however, the association between these factors lacks evidence.

Currently, only antibiotic prophylaxis for dental procedures in high-risk profiles with a low level of evidence is recommended for the prevention of IE; other situations have not been precisely defined [5]. Nonetheless, because previous studies have shown procedure-related risks for IE, we attempted to identify procedural risk factors and the incidence of IE using large-scale nationwide data.

Methods

Data sources

We used data from the Korean National Health Insurance Service (NHIS) spanning January 2003 and December 2018. Personal and medical information including age, sex, underlying diseases, and surgical or medical treatment were obtained from the database. The diagnoses for all diseases were coded according to the International Classification of Diseases, 10th Revision, while all medical procedures were coded according to the Health Insurance Review and Assessment Service codes.

This study was approved by the Institutional Review Board of Severance Hospital (approval number: 4-2020-0400). The requirement for informed consent was waived by the Institutional Review Board of Severance Hospital because of the retrospective nature of the study. In addition, all methods were performed in accordance with the relevant guidelines and regulations.

Study population and procedure definition

This study included 8487 patients with IE between 2003 and 2018 from the Korean NHIS database and assessed their baseline information, including age, sex, medications, and comorbid conditions. The Charlson Comorbidity Index (CCI) [6] was used to

categorize patient comorbidities. Additionally, 33,535 age-, sex-, and CCI-matched controls were extracted from the database. Predisposing medical invasive or non-invasive procedures were classified by site into four categories: 1) dental procedures involving periodontal procedures; 2) gastrointestinal procedures, including percutaneous endoscopic gastrostomy, biopsy, mucosal resection, and submucosal dissection; 3) respiratory procedures, including endobronchial ultrasound-guided transbronchial needle aspiration, tracheostomy, and maxillary sinus surgery; and 4) genitourinary procedures, including prostate biopsy, ureteral stent insertion, and percutaneous nephrostomy catheter insertion. The criteria and codes for the classification of invasive or non-invasive procedures are presented in Supplement 1. Previous procedural events were included when performed within 90 days before IE hospitalization for dental procedures and within 60 days for all other procedures.

Statistical analysis

Categorical variables are presented as percentages, and continuous variables are described as means with standard deviations. We used the analysis of variance test for continuous variables and the chi-square test or Fisher's exact test for categorical variables to examine the differences among the study groups. Age- and sex-matched participants were also extracted, and propensity score matching (PSM) with age, sex, and CCI scores was used for the analysis.

Baseline clinical and procedural histories were compared between the groups. Univariate and multivariate logistic regression analyses were performed to assess factors associated with IE diagnosis. Other values with significantly different *P* values (< 0.05) were re-examined using multivariate logistic regression. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using the R software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

The patient selection and exclusion are shown in Fig. 1. Of the 8,487 patients, 6617 (78 %) had native valve IE, followed by prosthetic valve ($n = 1678$, 20 %) and cardiac device-related ($n = 192$, 2 %) IE. Table 1 presents the general characteristics of patients with IE and the control group after PSM; age (59.8 ± 17.2 vs. 60.0 ± 16.9 , $P = 0.258$) and sex (proportion of females in IE group (3705, 43.6 %) vs. in control group (14,715, 43.9 %, $P = 0.710$) were similar between the two groups. In addition, the two groups consisted of a similar proportion of patients with each CCI score, with no significant difference between the groups (P for difference = 0.602). The IE group

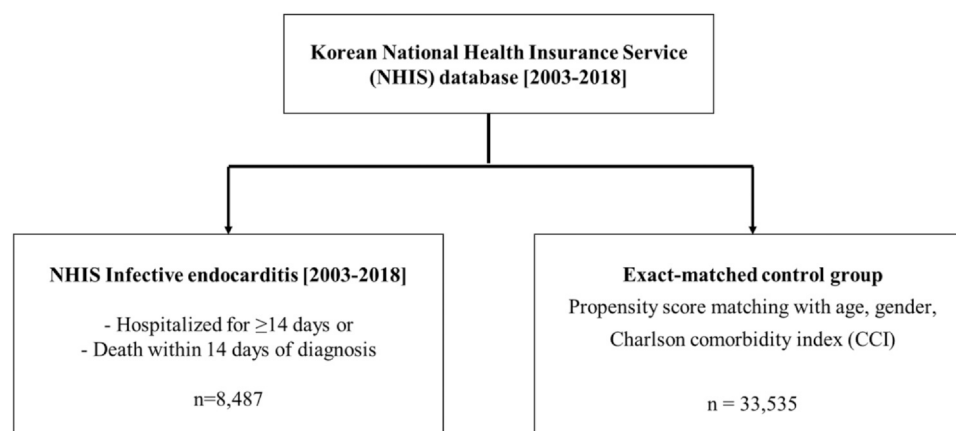


Fig. 1. Flowsheet of the study.

Table 1
Baseline characteristics after propensity score matching.

	Infective endocarditis (n = 8487)	Exact matched Control group (n = 33,535)	P-value
Age (years ± SD)	59.8 ± 17.2	60.0 ± 16.9	0.258
Females, n (%)	3705 (43.6)	14,715 (43.9)	0.710
Comorbidity, n (%)			
Hypertension	4563 (53.8)	14,892 (44.4)	< 0.001
Diabetes mellitus	3839 (45.2)	14,563 (43.4)	0.003
Congestive heart failure	2014 (23.7)	2072 (6.2)	< 0.001
Ischemic heart disease	1583 (18.7)	3243 (9.7)	< 0.001
History of CVA	1993 (23.5)	4965 (14.8)	< 0.001
Atrial fibrillation	1580 (18.6)	1212 (3.6)	< 0.001
Chronic kidney disease	745 (8.8)	861 (2.6)	< 0.001
Dialysis	454 (5.3)	179 (0.5)	< 0.001
Chronic pulmonary disease	4780 (56.3)	13,095 (39.0)	< 0.001
Chronic liver disease	470 (5.5)	1304 (3.9)	< 0.001
History of cancer	1282 (15.1)	6341 (18.9)	< 0.001
Connective tissue disease	292 (3.4)	649 (1.9)	< 0.001
Charlson comorbidity index (CCI)			0.602
CCI score 1	2564 (30.2)	10,264 (30.6)	
CCI score 2	1043 (12.3)	4191 (12.5)	
CCI score 3	4880 (57.5)	19,080 (56.9)	
Clinical Risk factors, n (%)			
Congenital heart disease	323 (3.8)	23 (0.1)	< 0.001
Cyanotic	67 (0.8)	3 (< 0.1)	< 0.001
Acyanotic	298 (3.5)	20 (0.1)	< 0.001
Valvular regurgitation	1628 (19.2)	44 (0.1)	< 0.001
Mitral	1059 (12.5)	27 (0.1)	< 0.001
Aortic	722 (8.5)	19 (0.1)	< 0.001
Tricuspid	116 (1.4)	0 (0.0)	< 0.001
MR with mitral valve prolapse	176 (2.1)	0 (0.0)	< 0.001
Valvular stenosis	2293 (27.0)	2794 (8.3)	< 0.001
Aortic	606 (7.1)	11 (< 0.1)	< 0.001
Mitral	614 (7.2)	52 (0.2)	< 0.001
Pulmonary	20 (0.2)	0 (0.0)	< 0.001
Immunosuppressive treatment	321 (3.8)	562 (1.7)	< 0.001
Long corticosteroid therapy	597 (7.0)	1056 (3.1)	< 0.001
Antibiotics within 30 days	3818 (45.0)	5981 (17.8)	< 0.001
Heart transplantation	2 (< 0.0)	0 (0.0)	0.005
Hypertrophic cardiomyopathy	65 (0.8)	30 (0.1)	< 0.001
Procedural Risk Factors, n (%)			
Intravenous catheter	1437 (16.9)	948 (2.8)	< 0.001
Respiratory (previous 60 days)	711 (8.4)	923 (2.8)	< 0.001
Invasive	170 (2.0)	375 (1.1)	< 0.001
Noninvasive	604 (7.1)	609 (1.8)	< 0.001
Gastrointestinal (60 days)	1711 (20.2)	3662 (10.9)	< 0.001
Invasive	261 (3.1)	703 (2.1)	< 0.001
Noninvasive	1685 (19.9)	3630 (10.8)	< 0.001
Genitourinary (60 days)	328 (3.9)	390 (1.2)	< 0.001
Invasive	25 (0.3)	83 (0.2)	0.444
Noninvasive	322 (3.8)	356 (1.1)	< 0.001
Previous dental procedure (within 90 days)	1066 (12.6)	3662 (10.9)	< 0.001
with antibiotics prophylaxis	430 (5.1)	1620 (4.8)	0.368
without antibiotics prophylaxis	636 (7.5)	2042 (6.1)	< 0.001

CVA, cerebrovascular accident; MR, mitral regurgitation.

exhibited significantly higher rates of all comorbidities than the control group (all $P < 0.001$). Similarly, the IE group showed significantly higher rates of all clinical and procedural risk factors, except previous dental procedure involving antibiotic prophylaxis ($P = 0.368$).

Logistic regression (Table 2, Fig. 2) showed significantly higher odds ratios (OR) for dialysis, immunosuppression, congenital heart disease, valvular regurgitation, and valvular stenosis for IE

occurrence. After adjustment with these parameters, there was significant association of all previous procedures with IE occurrence including IV catheter insertion (OR, 18.94 [15.75–22.77]; $P < 0.001$) and respiratory (OR, 4.05 [3.55–4.61]; $P < 0.001$), gastrointestinal (OR, 3.09 [2.86–3.34]; $P < 0.001$), and genitourinary procedures (OR, 3.97 [3.27–4.91]; $P < 0.001$). Dental procedures without antibiotic treatment showed significantly increased risk (OR, 1.19 [1.07–1.32]; $P = 0.001$), but those with antibiotic treatment were not associated with an elevated risk of IE (OR, 1.07 [0.95–1.21]; $P = 0.256$).

Discussion

In the present study, we investigated the risk factors and incidence of IE. In the NHIS database of South Korea, traditional risk factors, including dialysis, immunocompromised hosts, congenital heart disease, and valvular predisposition were also significantly associated with the diagnosis of IE. When adjusted for these factors, previous medical procedures, including respiratory, gastrointestinal, genitourinary, and dental procedures, and IV catheter insertion, appeared to significantly increase the risk of IE, with the exception of dental procedures involving antibiotic prophylaxis.

As reported in previous studies, the characteristics of patients affected by IE are gradually changing. The average age of patients with IE has increased from the mid-40s in the early 1980s to > 70 in recent years [7]. This shift likely reflects changes in healthcare access, advancements in medical procedures, and an aging population with higher prevalence of comorbidities. Healthcare-associated IE, characterized by older age and the presence of conditions such as cancer, diabetes, and the use of cardiac devices, has become more prevalent, underscoring the need for targeted preventive strategies for this patient population [8,9].

A previous study reported healthcare-associated IE as the sum of nosocomial or hospital-acquired and non-nosocomial or outpatient-acquired IE, accounting for 25–30% of contemporary cohorts [8]. Approximately 10% of cases of nosocomial bacteremia results in IE [10], and *Staphylococcus aureus* is the causative organism in approximately one-third of healthcare-associated IE. In keeping with the affected patient population and underlying microbiology, in-hospital mortality for patients with healthcare-associated IE was reported to be significantly higher than that for community-acquired infections (31.1% vs. 20.3%; $P < 0.01$) [11].

Patients with frequent healthcare contact due to other comorbidities are frequently exposed to invasive procedures and implanted prosthetic vascular catheters, including hemodialysis catheters and chemoports. This increases the likelihood of transient bacteremia, which is the first step in developing IE [9]. In addition, two previous case-crossover studies also mentioned the correlation between non-dental invasive procedures and IE. Janszky et al. found that patients with IE were more likely to have undergone an inpatient or outpatient invasive procedure (like transfusion, bronchoscopy, dialysis etc.) in the 12 weeks preceding their diagnosis compared to the control period a year prior [12]. Similarly, Thornhill et al. observed a significantly increased risk of IE after several medical procedures, including cardiac implantable electronic device procedures, gastrointestinal endoscopy, bone marrow biopsy, blood transfusion, and bronchoscopy, with the risk being particularly pronounced in high-risk individuals. Another retrospective cohort study also reported a more frequent development of IE after non-dental medical procedures in patients with cancer [13]. Results from the International Collaboration on Endocarditis - Prospective Cohort Study also revealed that, depending on the region, 25–32% of the 2781 patients with definite endocarditis had undergone an invasive procedure within 60 days prior to diagnosis [4].

Our study showed similar results. Unlike previous case-crossover studies, this study was conducted as a case-control study, which implements PS matching to select an appropriate control group and

Table 2

Baseline characteristics and logistic regression analysis for risk factors and procedural associations with infective endocarditis.

Baseline Characteristics of Propensity Score Matching					
Characteristic	Infective Endocarditis (N = 8487)		Control (N = 33,535)		P-value
	N	%	N	%	
Age, years ± SD	59.8 ± 17.2	-	60.0 ± 16.9	-	0.258
Females	3705	43.7	14,715	43.9	0.710
Dialysis	454	5.3	179	0.5	<.001
Immunosuppressive treatment	776	9.1	1421	4.2	<.001
Congenital heart disease	323	3.8	23	0.1	<.001
Valvular regurgitation	1628	19.2	44	0.1	<.001
Valvular stenosis	1078	12.7	63	0.2	<.001
Congestive heart failure	2014	23.7	2072	6.2	<.001
Univariate Logistic Regression for Infective Endocarditis Occurrence					
Risk Factor	Odd Ratio	95 % Confidence limits		P-value	
Dialysis	10.5	8.8	12.5	<.001	
Immunosuppressive treatment	2.3	2.1	2.5	<.001	
Congenital heart disease	57.6	37.7	88.1	<.001	
Valvular regurgitation	180.6	133.7	244.0	<.001	
Valvular stenosis	77.3	59.9	99.8	<.001	
Previous Procedures and Infective Endocarditis Occurrence					
Procedure	Odd Ratio*	95 % Confidence limits		P-value	
Intravenous catheter	19.7	16.4	23.7	<.001	
Respiratory procedure	4.0	3.5	4.6	<.001	
Gastrointestinal procedure	3.1	2.9	3.4	<.001	
Genitourinary procedure	4.0	3.3	4.9	<.001	
Dental procedure	1.0	0.9	1.2	0.256	
(with antibiotics)					
Dental procedure	1.2	1.1	1.3	0.001	
(without antibiotics)					

P-value for two-sided test.

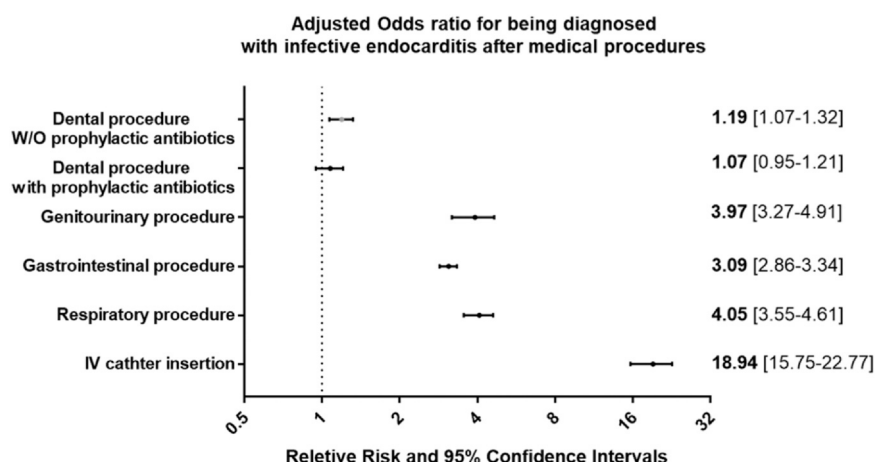
*Adjusted with dialysis, immunosuppressive treatment, congenital heart disease, valvular regurgitation, valvular stenosis.

accounting for inter-individual confounders. Despite being a 1:4 case cohort study after PSM, several comorbidities showed substantial differences between the groups, making correction challenging. This was especially true for variables such as hemodialysis, indicating inferentially that these variables have a strong correlation with infective endocarditis. However, even after matching confounding factors and performing multivariate analysis with traditional risk factors, medical procedures, including IV catheter insertion and respiratory, gastrointestinal, and genitourinary procedures within 2 months prior to IE diagnosis, showed a significant OR. For dental procedures performed within 90 days, the occurrence of IE differed according to prophylactic antibiotic use. This result may show the practical effect of preventing IE related to dental procedures in a large population and suggests a possible relationship between other nondental procedures and IE. As the population at risk is growing

[8], and the needs and accessibility of medical care are increasing, procedures may contribute to an increase in either hospital-acquired or outpatient-acquired IE.

Before 2007, the guidelines recommended the use of prophylactic antibiotics to reduce the likelihood of bacteremia following extensive invasive procedures. However, because of the lack of conclusive evidence on whether these invasive procedures are associated with IE and the effectiveness of prophylactic antibiotics in preventing it, the guidelines have reduced the scope of designating high-risk groups and limited the use of antibiotics for preventive purposes [2,14]. Therefore, several procedures associated with a risk of endocarditis in the present study were excluded from the high-risk procedures described in the revised guidelines.

After the application of the revised guidelines, the trend in IE incidence became controversial, showing differences in various

**Fig. 2.** Relative risk for being diagnosed infective endocarditis after medical procedures.

studies. Some studies were conducted with a relatively small sample size or a short follow-up period, showing a non-significant change in IE incidence compared to that before 2007. However, a retrospective trend study based on UK national data revealed that since the new NICE guidelines were applied, following the decreased prescription of prophylactic antibiotics, the incidence of IE showed statistically significant increase by 0.11 cases per 10 million people per month [15]. In addition, a significant increase in the incidence of *Streptococcal* IE since 2007 was observed in a US retrospective observational cohort study published in 2015 [16]. Although these data cannot prove a cause-and-effect relationship between a decline in antibiotic prophylaxis and an increase in the incidence of IE due to the study design, it appears that other procedures, in addition to those recommended by the guidelines for prescribing preventive antibiotics, may also influence the emergence of IE [9]. The current antibiotic prophylactic strategy may not cover all of these causes.

Recently, a different perspective has emerged on the use of antibiotics to prevent endocarditis. 2023 ESC guideline determined that it was not appropriate to maintain the existing Class III recommendation about antibiotic prophylaxis for high-risk patients undergoing non-dental medical procedures. They recommended that "Systemic antibiotic prophylaxis may be considered for high-risk patients undergoing an invasive diagnostic or therapeutic procedure of the respiratory, gastrointestinal, genitourinary tract, skin or musculoskeletal system." as Class IIB. This change reflects the results of several previous observational studies and the increase in the number of elderly and comorbidity-prone populations for whom surgical treatment of IE is not easy [17].

The 2023 AHA Science Advisory also suggests that the role of non-dental invasive procedures as risk factors associated with the subsequent development of IE, in particular, in those at high risk, should be re-evaluated [18]. It is necessary to be cautious that IE may occur in the high-risk group of IE that has implemented the non-dental invasive procedures within three months, and it has been revealed that discussions are underway on antibiotic prophylaxis for the high-risk group against typical colonizing bacteria.

Of course, the current guideline states that the use of prophylactic antibiotics in a restricted high-risk group [2], while our study also showed that many patients with IE included those without cyanotic heart disease or heart transplant recipients. This classification can overlook the group with non-cardiac risk factors such as poor oral hygiene, IV drug use, immunocompromised host, neoplasm, concomitant hemodialysis, and indwelling intravascular catheter [19]. These patients are susceptible to IE and have a poor prognosis depending on specific risk factors [13,20]. Further discussions on the scope of procedures to consider pre-antibiotic prescriptions and high-risk groups that easily develop IE are necessary.

Study limitations

This study has a few limitations. First, due to the non-randomized retrospective nature of our study, some clinical characteristics may have been overlooked. Although we employed PSM analysis to account for host-related variables and disease severity, unmeasured confounders may have affected our results. Also, due to the limitations of data, it is possible that the investigation was insufficient for other non-dental invasive procedures such as coronary angiography, blood transfusion, and bone marrow aspiration. These factors appeared to be associated with IE in a previous case-crossover study [21]. In addition, certain comorbidities demonstrated substantial differences between the two groups even after 1:4 PSM, necessitating additional adjustments using multivariate logistic regression analysis. Second, we did not consider the differences between various dental procedures. Third, this study was based on data from the National Health Care Database, which does not contain microbiological or echocardiographic data. Further prospective studies

with culture results and location where IE occurs may identify the causative microorganisms of IE and their relationship with medical procedures. Fourth, our research did not include information on the relationship between IE and cardiovascular implantable electronic devices. Finally, the study is based on Korean NHIS data, so the subjects are limited to Koreans, and it does not contain accurate geographic information even within Korea, resulting in difficulties in discerning regional patterns of IE. Even with this in mind, the results of the present investigation, which provide information on the clinical characteristics and risk factors of IE in the rapidly developing Asian continent, may be significant. In the future, national population-based research and international cohort studies may help resolve these difficulties.

Conclusions

Patients with IE tend to have higher rates of underlying diseases than the general population. PSM and multivariate logistic regression analysis revealed a significant association between clinical and procedural histories and IE occurrence. Dialysis, immunosuppression, congenital heart disease, valvular disease, and invasive procedures, particularly those involving IV catheters significantly increase the risk of developing IE. These findings suggest that prophylactic strategies should be expanded beyond dental procedures to include high-risk patients. Future research should aim to refine the preventive guidelines to address the growing burden of IE more effectively, especially in aging and medically complex populations.

CRediT authorship contribution statement

Hee Jeong Lee: Writing – original draft, Conceptualization, and review. **William D. Kim:** Writing – original draft. **Kyung Eun Ha:** Data curation, Resources. **Hyun-Jung Lee:** Data curation, Resources. **Dae-Young Kim:** Data curation, Resources. **Kyu-Yong Ko:** Data curation, Resources. **Jiwon Seo:** Data curation, Resources. **Hasung Kim:** Software, Methodology, Formal analysis, Data curation, Resources. **Chi Young Shim:** Conceptualization, Resources. **Geu-Ru Hong:** Conceptualization, Resources. **Jong-Won Ha:** Conceptualization, Resources. **Iksung Cho:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Ji-won Hwang:** Writing – review & editing.

Ethics Statement

This study was approved by the Institutional Review Board of Severance Hospital (approval number 4-2020-0400).

Disclosures

None.

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to personal privacy concerns but are available from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors declare no conflict of interest.

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None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.jiph.2025.102876](https://doi.org/10.1016/j.jiph.2025.102876).

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