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Trends in Epidemiology, Clinical Characteristics, and Outcomes of Infective Endocarditis: A 16-Year Nationwide Cohort Study in Korea

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ABSTRACT

Background: Infective endocarditis (IE) is a life-threatening disease, the profile of which varies across countries. This nationwide cohort study aimed to assess the epidemiology, clinical characteristics, and outcomes of IE.
Methods: Patients diagnosed with IE between 2003 and 2018 were included in this study based on data from the National Health Insurance System of South Korea. The patients' baseline characteristics, treatment modalities, and survival outcomes were analyzed. The incidence and in-hospital mortality rates were calculated and adjusted for age.
Results: A total of 8,487 IE cases were included: 6,617 (78.0%), 1,678 (19.8%), and 192 (2.3%) cases of native valve IE, prosthetic valve IE, and cardiac device-related IE (CDRIE), respectively. The incidence rate (per 1,000,000) of IE increased from 7.24 in 2003 to 17.47 in 2018. Furthermore, the in-hospital mortality rate for IE (per 1,000,000 person-years) increased from 0.59 in 2003 to 2.76 in 2018. The proportions of prosthetic valve IE and CDRIE cases increased over time, whereas that of native valve IE cases decreased. The number of surgeries for IE showed a consistent upward trend, with a notable increase occurring from 2014 onward.
Conclusion: IE is a health burden with an increasing incidence and high mortality rates. Understanding the epidemiology and characteristics of IE is crucial to establish future treatment strategies.

Keywords: Infective Endocarditis; Epidemiology; Cohort Study; Korea

INTRODUCTION

Infective endocarditis (IE) is a challenging disease with high morbidity and mortality despite advances in its management.[1] Although IE is known to be rare, with an incidence of 3–10

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Ha KE, Kim WD, Cho I, Hwang JW. Data curation: Gwak SY, Kim K, Lee HJ, Shim CY, Hong GR, Ha JW, Cho I. Formal analysis: Ko KY, Kim H. Funding acquisition: Cho I. Investigation: Kim H, Gwak SY, Kim K, Lee HJ, Shim CY, Hong GR, Ha JW. Methodology: Kim H. Validation: Gwak SY, Kim K, Lee HJ, Shim CY, Hong GR, Ha JW. Writing - original draft: Ha KE, Cho I. Writing - review & editing: Ha KE, Hwang JW, Cho I.

per 100,000 people, recent studies in Europe and the USA have reported an increasing trend in IE incidence since the beginning of the 21st century.[2-4] Multiple factors have been identified as potential contributors to this increase, including epidemiological changes among IE patients, such as aging and the rise in comorbidities, as well as advancements in diagnosis.[2-9] The growing use of invasive procedures in contemporary healthcare also plays a role, although the impact of restricted antibiotic prophylaxis in these procedures warrants further investigation.[10,11] In addition to these healthcare-associated factors, the emergence of antibiotic-resistant organisms has become an increasing clinical concern, complicating the treatment of IE, worsening clinical outcomes, and potentially increasing both incidence and mortality.[12,13]

However, there is a paucity of data regarding the incidence and outcomes of IE in Asian populations. South Korea's rapid transition to an aging society, accompanied by a concomitant increase in chronic diseases, may be pertinent to the risk of IE. Given the advancements in treatment guidelines for IE over the last two decades, it is crucial to examine how these changes have influenced the epidemiology and mortality rates. Furthermore, while the current guidelines recommend restricted surgical indications, growing evidence in favor of expanding the surgical indications for IE may have implications for treatment strategies and outcomes.[14-16] Therefore, in this study, we aimed to investigate trends in the incidence, demographics, treatment, and outcomes of IE by using nationwide registry data collected for patients over the age of 16 years in South Korea.

METHODS

Data sources and extraction

The online electronic database of the National Health Insurance System of South Korea was used to extract data for this study. The International Classification of Diseases, 10th Revision (ICD-10), was used to categorize all baseline comorbidities and treatment-related problems, and Health Insurance Review and Assessment service codes were used to code any inpatient procedures or surgeries. Acute and subacute endocarditis (I33), endocarditis, unidentified valve (I38), and endocarditis, and heart valve abnormalities in diseases classified elsewhere (I39) were used as ICD-10 codes for IE. Demographic and clinical characteristics of the patients, including age, sex, socioeconomic status (SES), stroke, hypertension, diabetes, chronic renal failure, chronic obstructive pulmonary disease (COPD) or asthma, cancer, and immunosuppressive therapy, were extracted and analyzed. The Charlson Comorbidity Index (CCI) was used to compare baseline homogeneity among groups. To classify the SES of patients, their income was estimated using health insurance premiums. Patients' income status was classified as high (income quantile ≥ 14), moderate (income quantile 7–14), or low (income quantile < 7 or need for medical aid) based on National Health Insurance System premium quantiles and the population.

Study population

Between January 2003 and December 2018, patients with a diagnosis of IE who were hospitalized for ≥ 14 days were identified. Based on previous studies indicating that the positive predictive value of an IE diagnosis increases from 65% for hospitalizations of less than 14 days to 90% for those lasting 14 days or more,[17,18] patients hospitalized for less than 14 days who survived or those who died within 14 days were excluded to minimize the risk of misdiagnosis. The patients were divided into 3 groups based on the valve type. Patients with

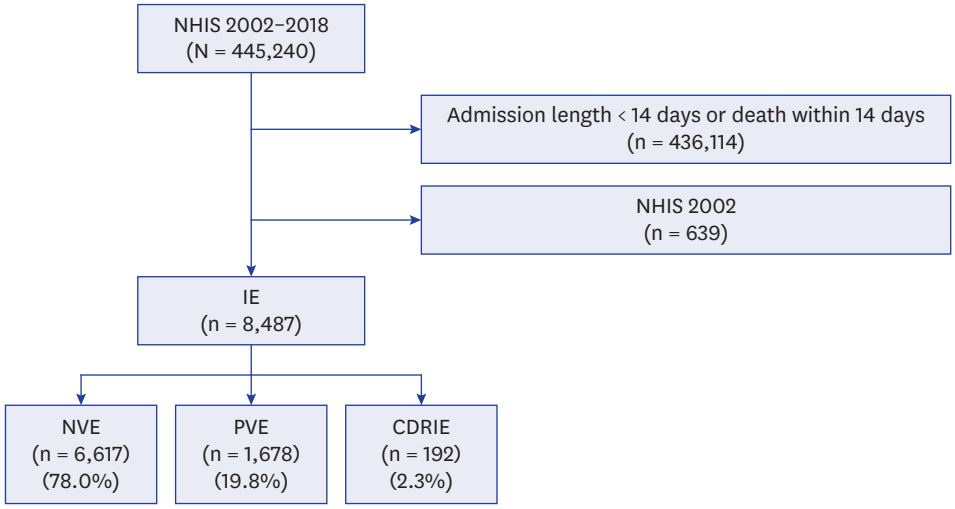

Fig. 1. Flowchart of this study.
NHIS = National Health Insurance Service, IE = infective endocarditis, NVE = native valve endocarditis, PVE = prosthetic valve endocarditis, CDRIE = cardiac device-related infective endocarditis.

a history of prosthetic valve replacement or repair were classified into the prosthetic valve endocarditis (PVE) group, whereas those with intracardiac devices, such as pacemakers, implantable cardioverter defibrillators, and ventricular assist devices were categorized into the cardiac device-related IE (CDRIE) group. The native valve endocarditis (NVE) group included patients without a history of intracardiac device implantation or valve replacement (**Fig. 1**).

Statistical analysis

Data were analyzed using the SAS software (version 9.4; SAS Institute, Cary, NC, USA). Continuous data are presented as mean ± standard deviation values, and categorial data are presented as frequencies and percentages. A two-sided *t*-test or χ^2 test was used to analyze intergroup differences. The incidence rates of IE and the number of IE cases divided by the denominator, as estimated from the census figures of South Korea, were calculated. The rates were age adjusted for the study population. Poisson regression analysis was used to estimate temporal trends in the incidence of IE. Statistical significance was set at $P < 0.05$.

Ethics statement

This study was approved by the Institutional Review Board of Severance Hospital (approval number: 4-2020-0400). The requirement of obtaining informed consent was waived because of the retrospective nature of this study.

RESULTS

Trends in the incidence of IE

A total of 8,487 IE cases from 2003 to 2018 were included in the final analysis. The trends in IE incidence during the observation period are presented in **Fig. 2**. The crude incidence rate (per 1,000,000 person-years) of IE exhibited a significant increasing trend, rising from 7.24 in 2003 to 17.47 in 2018 ($P < 0.001$). Similarly, the age-adjusted incidence rate for IE also showed a significant increase from 7.94 in 2003 to 14.48 in 2018 ($P < 0.001$). However,

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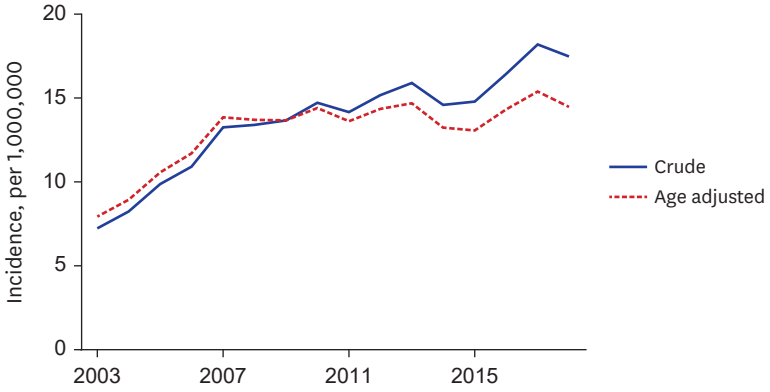

Fig. 2. Temporal trends in the incidence of infective endocarditis in South Korea from 2003 to 2018.

the rate of increase slowed after 2007, with no significant increase in incidence rates observed from 2007 to 2018 ($P = 0.143$).

Annual trends in demographics and clinical characteristics

Table 1 summarizes the demographics and clinical characteristics of the study population aggregated at 4-year intervals throughout the entire observation period. The median patient age was 60 years and 56% of the patients were male. The low SES group had the highest proportion of patients among the SES subgroups, and this trend persisted throughout the observation period. NVE had the highest incidence among the valve types followed by PVE and CDRIE. Interestingly, the proportions of cases of PVE and CDRIE increased while that of NVE decreased (**Fig. 3**). There was a notable increase in the incidence of cardiovascular risk factors, including previous stroke, hypertension, and diabetes. The number of patients with a CCI of 3 or higher increased, whereas that of patients with a CCI of 2 or lower decreased. A substantial number of patients (40%) were diagnosed with COPD or asthma, and this proportion increased from 20% to 51% over time. The proportion of patients receiving long-term corticotherapy increased from 5% to 9%.

Trends in in-hospital mortality due to IE

Trends in in-hospital mortality due to IE are presented in **Fig. 4A**. The crude in-hospital mortality rate (per 1,000,000 person-years) associated with IE increased from 0.59 in 2003 to 2.76 in 2018. Similarly, age-adjusted in-hospital mortality showed an upward trend, rising from 0.68 in 2003 to 2.07 in 2018. Notably, blunting was observed in both the crude and age-adjusted mortality rates from 2013 onward. In the valve-type subgroup analysis, NVE was associated with an increase in the in-hospital mortality rate, along with blunting similar to that observed in the overall group. Meanwhile, PVE and CDRIE were associated with stable in-hospital mortality rates over time.

Trends in the surgical treatment of IE

The number of patients who underwent surgical treatment for IE increased from 73 in 2003 to 424 in 2018. Since 2014, there has been a notable increase in the number of surgeries performed, which corresponds to the timing of in-hospital mortality blunting. The NVE group was also associated with a trend similar to that in the overall study population, whereas there was minimal change in the PVE and CDRIE groups (**Fig. 4B**).

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Table 1. Baseline demographics and clinical characteristics overall and trends by years

Characteristics	Overall (N = 8,487)	2003–2006 (n = 1,306)	2007–2010 (n = 2,072)	2011–2014 (n = 2,354)	2015–2018 (n = 2,755)	*P* value
Demography						
Age, yr	59.8 ± 17.2	-	-	-	-	
Males	4,782 (56.3)	-	-	-	-	
Socioeconomic status						
Low	3,233 (38.1)	472 (36.1)	826 (39.9)	906 (38.5)	1,029 (37.4)	
Medium	2,542 (30.0)	429 (32.9)	610 (29.4)	699 (29.7)	804 (29.2)	0.228
High	2,712 (32.0)	405 (31.0)	636 (30.7)	749 (31.8)	922 (33.5)	
Valve type						
NVE	6,617 (78)	1,082 (83)	1,619 (78)	1,854 (79)	2,062 (75)	
PVE	1,678 (20)	207 (16)	408 (20)	445 (19)	618 (22)	< 0.001
CDRIE	192 (0.02)	17 (0.01)	45 (0.02)	55 (0.02)	75 (0.03)	
Comorbid conditions						
Previous stroke or TIA	1,993 (23.5)	170 (13.0)	437 (21.1)	593 (25.2)	793 (28.8)	< 0.0001
Hypertension	4,563 (53.8)	492 (37.7)	1,049 (50.6)	1,319 (56.0)	1,703 (61.8)	< 0.0001
Diabetes	3,839 (45.2)	336 (25.7)	849 (41.0)	1,145 (48.6)	1,509 (54.8)	< 0.0001
Charlson Comorbidity Index						
≤ 1	2,564 (30.2)	490 (37.5)	651 (31.4)	707 (30.0)	716 (26.0)	
2	1,043 (12.3)	166 (12.7)	261 (12.6)	295 (12.5)	321 (11.7)	< 0.0001
≥ 3	4,880 (57.5)	650 (49.8)	1,160 (56.0)	1,352 (57.4)	1,718 (62.4)	
COPD or asthma	3,424 (40.3)	267 (20.4)	718 (34.7)	1,037 (44.1)	1,402 (50.9)	< 0.0001
Chronic renal failure	745 (8.8)	35 (2.7)	149 (7.2)	216 (9.2)	345 (12.5)	< 0.0001
Dialysis	454 (5.3)	20 (1.5)	81 (3.1)	138 (5.9)	215 (7.8)	< 0.0001
Cancer	1,282 (15.1)	136 (10.4)	255 (12.3)	346 (14.7)	545 (19.8)	< 0.0001
Immunosuppressive treatment	321 (3.8)	17 (1.3)	54 (2.6)	74 (3.1)	176 (6.4)	< 0.0001
Long corticotherapy	597 (7.0)	68 (5.2)	109 (5.3)	168 (7.1)	252 (9.1)	< 0.0001
Congenital heart disease	323 (3.8)	55 (4.2)	72 (3.5)	87 (3.7)	109 (4.0)	0.982
Congestive heart failure	2,014 (23.7)	211 (16.2)	423 (20.4)	588 (25.0)	792 (28.8)	< 0.0001
Ischemic heart disease	1,583 (18.7)	168 (12.9)	363 (17.5)	451 (19.2)	601 (21.8)	< 0.0001
Liver disease	696 (8.2)	73 (5.6)	151 (7.3)	219 (9.3)	253 (9.2)	< 0.0001
Connective tissue disease	292 (3.4)	30 (2.3)	65 (3.1)	83 (3.5)	114 (4.1)	0.002

Values are presented as mean ± standard deviation or number (%).
NVE = native valve endocarditis, PVE = prosthetic valve endocarditis, CDRIE = cardiac device-related infective endocarditis, TIA = transient ischemic attack, COPD = chronic obstructive pulmonary disease.

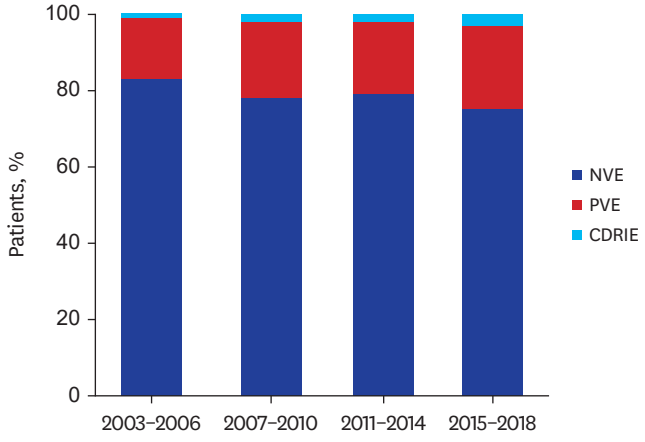

Fig. 3. Temporal trends in the incidence of infective endocarditis by valve type subgroups from 2003 to 2018.
NVE = native valve endocarditis, PVE = prosthetic valve endocarditis, CDRIE = cardiac device-related infective endocarditis.

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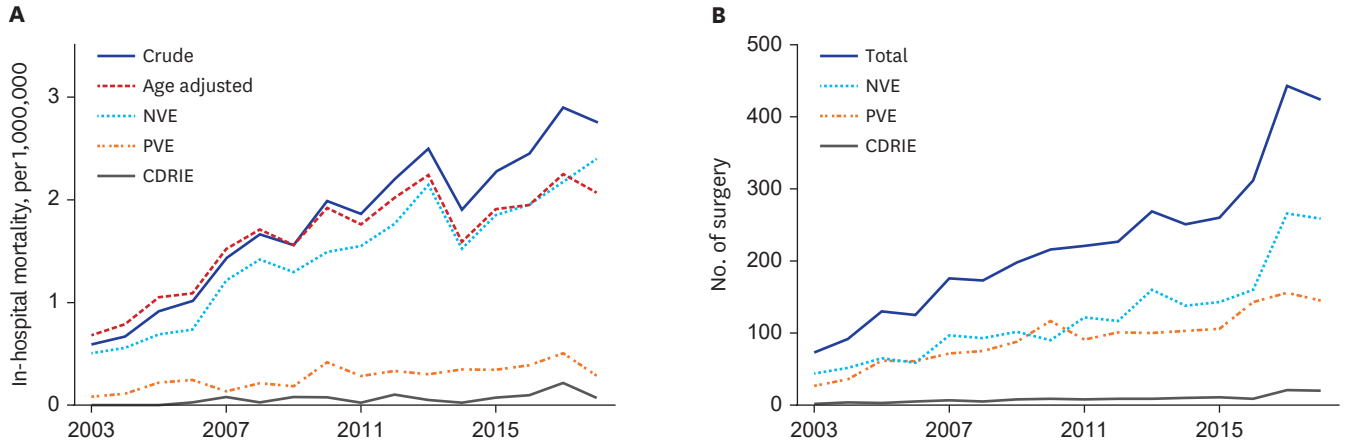

Fig. 4. Temporal trends in infective endocarditis from 2003 to 2018, illustrating (**A**) annual changes in in-hospital mortality rates and (**B**) annual trends in surgical treatment frequencies.
NVE = native valve endocarditis, PVE = prosthetic valve endocarditis, CDRIE = cardiac device-related infective endocarditis.

DISCUSSION

The principal findings of this nationwide population-based cohort study were as follows. First, the incidence of IE increased from 7.94 in 2003 to 14.48 in 2018 (per 1,000,000 person-years) over the study period; however, this increase has plateaued since 2007. Second, the proportions of cases of both PVE and CDRIE increased, whereas that of NVE cases decreased, although NVE had the highest incidence among the valve-type subgroups over the entire study period. Third, the in-hospital mortality rate of IE showed an increasing trend, although there was a temporary blunting between 2013 and 2014.

Given the heterogeneous nature of IE, which is influenced by a variety of continuously evolving factors, monitoring its epidemiological trends is essential for formulating effective treatment strategies.[19] Consistent with the results of previous studies in western countries.[2-4,18,20,21] our study showed an overall increasing trend in the incidence of IE throughout the observation period. Meanwhile, data on the temporal incidence trends of IE in Asian countries remain scarce, particularly following the guideline revisions on prophylactic antibiotic use. Notably, a study from a large Chinese population reported a stable incidence of IE over two decades.[22] The higher proportion of rheumatic valve disease compared with western populations is considered one of the major factors contributing to this stable incidence. However, the incidence is predicted to increase due to factors such as the anticipated rise in transcatheter valvular interventions.[22] Several factors may have contributed to the increase in our study, although it was challenging to establish a direct relationship. Aging populations and increasing concurrent comorbidities are considered the primary factors.[1,2,23] Hemodialysis and cancer, although accounting for a relatively small proportion of our cohort, may partially explain the observed increase.[24-26] The increasing proportions of PVE and CDRIE cases may also have contributed to this increase.[27,28] Interestingly, COPD or asthma, accounting for a substantial proportion of cases in our cohort (approximately 40%) may have contributed to this observed increase. COPD is indicative of a potential link to invasive bacterial infections beyond respiratory tract infections, likely attributable to compromised defense mechanisms and corticosteroid use.[29]

Two distinctive characteristics of the incidence trends were noted in our analysis. First, blunting was observed since 2007. Decreasing trends in the proportion of NVE cases were

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considered as potential factors contributing to the blunting. The higher prevalence of NVE observed in Asian studies compared with those in the studies from the US and Europe has been reported to be associated with a higher prevalence of chronic rheumatic heart disease.[20,30] Compared to other Asian studies, in our study, the proportion of NVE was approximately 10% lower and 10% higher, respectively, than that in the US.[22] This suggests that South Korea is undergoing a transitional phase from an era when rheumatic heart disease was predominant to a pattern more consistent with that in advanced countries, where PVE is the prevailing form. In contrast, considering South Korea's rapid progression into a super-aged society, the increasing trends in aging and its associated comorbidities alone do not appear sufficient to fully explain this blunting. When the effect of aging was removed through age adjustment, the observed blunting of the incidence trend became even more pronounced, suggesting the presence of other underlying factors beyond aging. While the prevalence of aging and comorbidities has risen, improvements in cardiovascular care, infection control, and preventive measures targeting high-risk populations may collectively account for this blunting.[31]

Second, a significantly lower incidence of IE was observed compared with that in other countries. In contrast to most studies conducted in other countries, our study excluded patients hospitalized for less than 14 days without death to avoid potential inaccuracies in IE diagnosis. The strict exclusion criteria aimed to maintain diagnostic precision but might have contributed to the lower incidence observed. However, even a national cohort study in Denmark, which also required a minimum of 2 weeks of hospitalization, reported a much higher incidence rate (5–10.5 per 100,000) than that in our study.[18] Therefore, our strict inclusion criteria did not fully account for the low incidence rates. Another possible reason is the likelihood of underestimating IE cases in the real world, owing to the challenges in accurately diagnosing the disease, which has diverse and unspecified clinical manifestations. Further research is needed to clarify the reasons for the lower incidence and the possibility of underestimation. Considering the proven diagnostic accuracy of multimodal imaging, it is essential to assess its current utility in South Korea from an academic perspective.[32,33]

Despite advances in management, the in-hospital mortality rate of IE remains high, ranging from 15 to 30%.[34] Our findings demonstrated an overall increasing trend in in-hospital mortality from 8 to 14% over the study period, with blunting from 2013. After age adjustment, in-hospital mortality, though slightly attenuated compared to crude mortality, still showed an overall increasing trend. This suggests that aging was one of the major factors contributing to mortality in Korea consistent with prior studies.[21,35,36] Furthermore, it raises the possibility that factors other than aging may also play a role. The increasing trend of comorbidities observed in our study likely contributed the observed increase in mortality.[35,36] Although the current analysis did not adjust for comorbidities, future studies are warranted to perform mortality-adjusted analyses, enabling a more comprehensive evaluation of contributing factors. Sex differences in IE mortality represent an emerging clinical concern; however, limited data have been reported on this topic. Prior studies have demonstrated a male predominance in IE incidence, whereas mortality has been reported to be higher among female patients.[37] The underlying reasons for these sex differences remain unclear. Although sex-adjusted analyses were not conducted in the current study, future research should address this gap to better understand the impact of sex on IE outcomes.

Notably, blunting in in-hospital mortality since 2013 and a sharp increase in the number of surgeries since 2014 occurred sequentially. The role of surgical intervention in IE has been

progressively expanding, with current guidelines endorsing its importance.[34] The increase of surgical cases in our study may contribute to the blunting of in-hospital mortality. The increase was primarily driven by cases of NVE, with PVE contributing partially. In contrast, cases of CDRIE, often associated with right-sided IE, appear to have been deferred from surgical intervention due to a lower risk of embolism. In clinical practice, surgical treatment during the acute phase of IE remains underutilized, even in cases with clear surgical indications, despite evidence demonstrating its survival benefits.[38] Although the range of surgical indications for IE and the optimal timing of surgery have been controversial over the last few decades, there is growing evidence supporting the survival benefits of early surgical interventions.[14,39] A future study should analyze the extent to which recent research on the optimal timing of surgery and surgical indications for IE is reflected in clinical practice in South Korea. Additionally, it should explore the discrepancies between clinical practice and the established surgical guidelines for IE.

For mitral valve IE, repair has traditionally been preferred over replacement due to better reported outcomes, while aortic valve IE is more commonly treated with aortic valve replacement.[40] However, there is no absolute evidence favoring one type of surgical intervention over another.[41] Successful surgical and long-term outcomes depend on multiple factors, including the type of surgery performed, technical surgical considerations, and the experience of the medical center.[40] Although this study did not include a subgroup analysis based on surgical intervention types, documenting the current status and outcomes of surgical treatment is meaningful and may guide future therapeutic strategies. Further research, including detailed subgroup analyses, is warranted.

In this study, we demonstrated an overall increase in mortality rates during the study period for IE patients. However, we were unable to specifically analyze mortality rates among patients who underwent surgical treatment for IE. Prior studies suggest that surgery during IE hospitalization is associated with improved survival compared to medical therapy alone, particularly with a reduced risk of dying from heart failure and stroke.[42] Given the potential impact of surgery on long-term outcomes, future research should focus on evaluating the specific mortality trends and prognostic factors among surgically treated IE patients to guide clinical decision-making.

This retrospective study had some limitations. We utilized ICD-10 codes to identify diagnoses of IE and comorbidities. This method is highly time-efficient and has been frequently employed in previous observational studies. However, it carries the potential for misclassification due to coding inaccuracies and variability across healthcare institutions. Additionally, during the study period, the transition from ICD-9 to ICD-10 codes may have resulted in incomplete mapping between the two versions, potentially leading to missed diagnoses. Consequently, the prevalence of IE and its associated comorbidities might have been underestimated. Furthermore, similar to most prior studies, we did not validate the use of ICD-10 codes specifically for diagnosing IE. Nevertheless, for large population-based studies like ours, the use of administrative codes remains one of the most widely adopted methods due to its efficiency in gathering information over a short period.[43]

Despite the 2007 guideline revision, which emphasizes a more restrictive use of prophylaxis,[44] our database did not include information on antibiotic use, thus failing to reflect the impact of guideline changes on the epidemiology of IE. Previous studies have reported conflicting findings regarding the influence of prophylactic changes on IE

incidence. Some studies indicated no significant change in the incidence rate, whereas others demonstrated an increase in streptococcal IE cases after the guideline update.[4,45] Further investigations of antibiotic use would enhance our understanding of IE epidemiology. Additionally, the guidelines recommend tailoring antibiotic selection and duration based on the causative pathogen, microbial susceptibility, patient-specific factors, and IE-related complications.[34] Understanding whether these recommendations are adhered to in clinical practice is critical for optimizing future treatment strategies. Further investigations into antibiotic use and compliance with guideline-based recommendations are essential to improve our understanding of IE epidemiology and to inform future therapeutic approaches.

Identifying the specific causative bacteria in IE is crucial, because it not only provides vital information for tracing the infection source but also guides appropriate antibiotic treatments. While *Staphylococcus*, *Streptococcus*, and *Enterococcus* species remain the most common pathogens in IE,[46,47] the increasing prevalence of healthcare-associated IE, coupled with the rise of antibiotic-resistant organisms, has posed significant challenges to its management. Additionally, geographic variations in the microbiological profile of IE have been observed, highlighting the importance of identifying microbiological data.[48] Unfortunately, our database for this study did not include microbiological data on patients with IE. Addressing this limitation should be a priority in future research.

In this study, we classified IE cases into NVE, PVE, and CDRIE to analyze IE incidence, mortality, and the number of surgeries. However, we were unable to distinguish between right-sided and left-sided endocarditis. Such distinctions are critical, as they influence the pathophysiology of infection, treatment strategies, and the timing of surgical intervention. Further studies are needed to address these aspects.

This nationwide population-based study revealed a rising trend in the incidence and mortality of IE in South Korea. Future research should integrate microbiological data to better understand causative pathogens and resistance profiles, as well as detailed surgical timing and intervention types to assess their impact on outcomes. These insights will be pivotal in developing effective strategies to address the evolving IE landscape and improve patient care.

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