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Original article

# Trends in epidemiology, surgical management, and prognosis of infective endocarditis during the XXI century in Spain: A population-based nationwide study

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ABSTRACT

*Background:* Few population-based studies have evaluated the epidemiology of infective endocarditis (IE). Changes in population demographics and guidelines on IE may have affected both the incidence and outcomes of IE. Therefore, the aim of our study is to provide contemporary population-based epidemiological data of IE in Spain.

*Methods:* Retrospective nationwide observational study using data from the Spanish National Health System Discharge Database. We included all patients hospitalized with IE from January 2000 to December 2019.

*Results:* A total of 64,550 IE episodes were included. The incidence of IE rose from 5.25 cases/100,000 person-year in 2000 to 7.21 in 2019, with a 2% annual percentage change (95% CI 1.3–2.6). IE incidence was higher among those aged 85 or older (43.5 cases/100.000 person-years). Trends across the study period varied with sex and age.

Patients with IE were progressively older (63.9 years in 2000–2004 to 70.0 in 2015–2019, $p < 0.001$) and had more frequent comorbidities and predispositions, including, previous valvular prosthesis (12.1% vs 20.9%, $p < 0.001$). After adjustment, a progressive reduction in mortality was noted including in 2015–2019 compared to 2010–2014 (adjusted odds ratio 0.93, 95% confident interval 0.88–0.99, $p = 0.023$)., which was associated with more frequent cardiac surgery in recent years (15.1% in 2010–2014 vs 19.9% in 2015–2019).

*Conclusions:* In Spain, the incidence of IE has increased during the XXI century, with a more pronounced increase in elderly individuals. Adjusted-mortality decreased over the years, which could be related to a higher percentage of surgery. Our results highlight the changing epidemiology of IE.



## Introduction

Despite advances in diagnosis, management, and prevention, IE remains a significant cause of morbidity and mortality worldwide. It has an estimated annual incidence of 3–10 cases per 100,000 person-years [1,2] with reported mortality rates ranging from 15% to 30% [2,3] and a high rate of complications [4,5].

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In recent decades, variations in population demographics, the increasing use of implantable cardiac devices, and changes in international guidelines regarding prevention and management of IE, could have affected both the incidence and outcomes of IE [6,7]. Studies performed in tertiary care referral centers have described these trends, including a rising prevalence of older adult patients with degenerative valve disease, prosthetic valves, and intracardiac device infections, a decline in patients with rheumatic heart disease, and an increasing incidence of staphylococcal and enterococcal infections [8–13]. However, these studies may be influenced by selection and referral bias (i.e., a possible underrepresentation of institutions with a lower likelihood of reporting their cases). Moreover, population-based studies can be more reliable in providing more representative information of IE epidemiology [1]. Unfortunately, well-designed epidemiological studies are scarce. The above mentioned may justify the conflicting results regarding IE epidemiology and incidence trends found in published studies [1,2,10,14,15]. Therefore, the current state-of-the-art of IE epidemiology is incomplete, and there is a need for comprehensive, population-based studies to fill this knowledge gap.

In the light of the aforementioned, the main aim of our study is to provide population-based epidemiological data of IE in Spain during the XXI century and to evaluate temporal trends in IE incidence by using a nationwide database. We have also investigated the change in IE patient's profile, including demographics, comorbidities, and analyse the trends in surgical management and prognosis of IE during the study period.

## Patients and methods

We performed a retrospective observational cohort study using data from The Spanish National Health System Discharge Database (SNHSDD), a registry belonging to the Spanish Ministry of Health. This database has anonymized and standardized data corresponding to the Spanish Minimum Basic Dataset of all hospital discharges. The database includes information about age, sex, admission and discharge dates, type of hospital discharge, diagnosis (up to 20 diagnosis), procedures performed during hospitalization. Both public and private hospital are obligated to send their data on hospital discharges to the Ministry of Health, which controls its quality and integrity, and freely provides the requested databases to investigators [16]. The database was coded using the International Classification of Diseases- 9th Revision (ICD-9) until 2015 and the International Classification of Diseases- 10th revision (ICD-10) from 2016 onwards. The use of this database has been proven useful and reliable in several infectious diseases [17–24]. In recent studies, the ICD-9 and ICD-10 codes have proven adequate accuracy in identifying patients with infective endocarditis [25,26].

### *Patient population*

We included all episodes with a diagnosis of IE according either to ICD-9 (421.0, 421.1, 421.9, 424.90, 424.91) or ICD-10 (I33.0, I33.9, I38, I39) from January 2000 to December 2019. We included episodes of IE and not individual patients with IE.

We excluded patients in which the diagnosis of IE was not present in the first 10 positions (indicating a previous diagnosis rather than an incident episode). In order to avoid overcounting, those patients initially admitted to 1 hospital and then transferred to another hospital were accounted as a single episode, with admission date corresponding to the admission of the first hospital and discharge date corresponding to the discharge of the second hospital.

### *Variables and definitions*

Using all the ICD-9 and ICD-10 codes from IE hospitalization, information about previous comorbidities and cardiac predisposing conditions were extracted from each patients. Simple and age-adjusted Comorbidity Charlson Index (CCI) was computed from these codes, as explained elsewhere [24,27]. We additionally elicited information about cardiac interventions performed during hospital admission and time from hospital admission to surgery. Specific codes used to identify each conditions are showed in supplementary table S1. Specifically, we used codes for previous underlying heart valves conditions, including previous valvular prosthesis, rhematic valvular diseases without prothesis, congenital cyanotic cardiopathies, and other significant natural valvular disease of unspecified cause (with, at least, moderate valvular insufficiency or stenosis) in patients without prothesis.

In order to compare patients' differences across the study period, episodes were classified into 4 groups; group 1 corresponding to years 2000 to 2004; group 2 2005 to 2009; group 3 2010 to 2014 and group 4 2014 to 2019.

### *Statistical analysis*

The incidence rates of IE are expressed as number of cases per 100,000 person-years, assuming that the entire population was at risk. Continuous variables are expressed as mean and standard deviation (SD) (or median and interquartile range (IQR) if appropriate). Categorical variables are expressed as percentage and total number.

To assess temporal trends in incidence rates during the study period, we used a Poisson regression models including joinpoint analysis [28–32]. We included jump model adjustment to account for possible difference because of the coding system change in 2016 [33]. We performed subgroup analysis according to age and sex subgroups. Annual percentage changes (APC), Incidence risk ratios (IRR) and their 95% CI are provided [32].

To assess epidemiological, cardiac interventions and prognosis differences across time, a univariate analysis was performed, comparing categorical variables using Chi-square test and continuous variables using T-student test (or Mann-Whitney's U when necessary). Each 5-year period was compared to the previous.

To assess changes of in-hospital mortality, we performed a single-step multivariate logistic model including age, baseline comorbidities, and cardiac interventions as independent variables and in-hospital mortality as the dependent variable. We added to this model the 5-year period groups, using the previous group as reference (for example, for the 2010–2014 period, the 2005–2009 period was used as reference). Odds ratios (OR) and its 95% confidence interval were provided.

Bilateral exact p-values lower than 0.05 were considered statistically significant. Poisson regression models were performed using Joinpoint regression software, version 4.9.1.0, April 2022 (Statistical Research and Applications Branch, National Cancer Institute). The rest of the statistical analysis was performed using SPSS software, version 25 (IBM, Armonk, NY).

### *Ethical aspects*

The access to the SNHSDD is universal under request via an online formulary remitted to the Spanish Ministry of Health. All data provided by the SNHSDD are anonymized. According to The Spanish legislation, the use of this registry for investigational purposes is exempt from additional approbation by an ethics committee and from individual written consent.

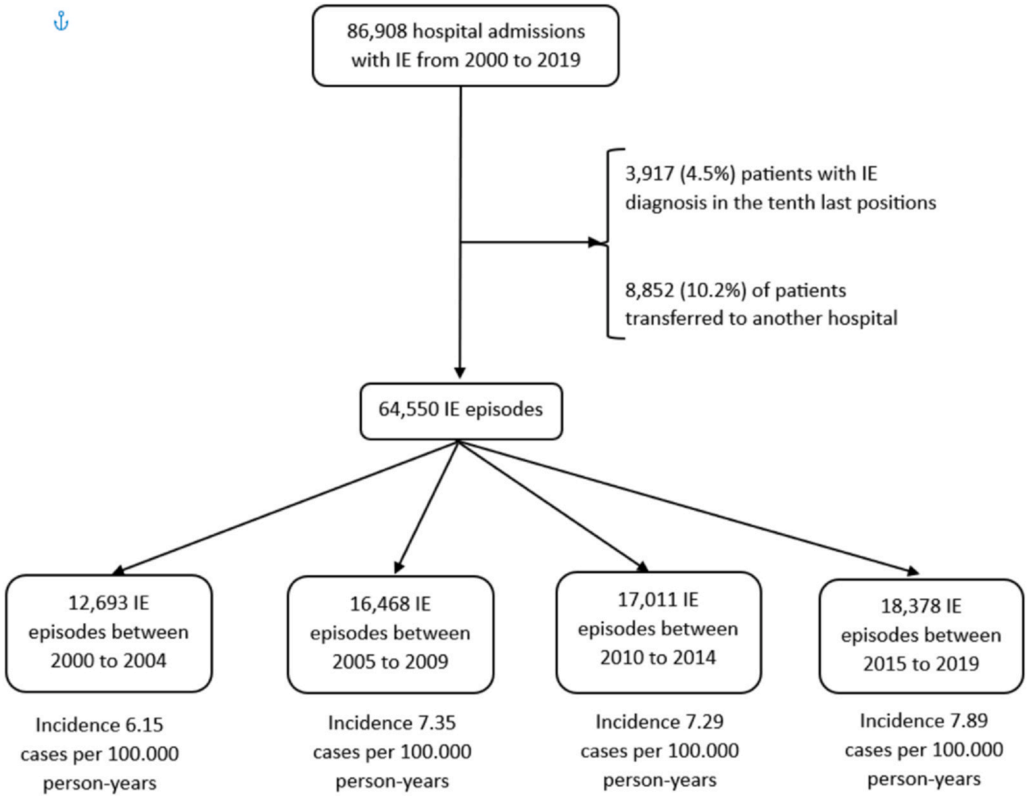


**Fig. 1.** Patient's flowchart. Incidence rates between 5-year period group were compared using chi-square tests. IE: Infective endocarditis.

## Results

From 2000 to 2019, a total of 86,908 hospital admission with IE diagnosis were retrieved. After excluding duplicate episodes and those with secondary diagnosis of IE (indicating a previous diagnosis rather than an incident episode), a total of 64,550 unique IE episodes were included. Mean age was 68.1 years (SD 18.0), 44.8% (n = 28,931) were female. Fig. 1 shows episodes' flowchart.

### *Temporal trends in Infective Endocarditis incidence*

The global incidence of IE rose from 5.25 cases/100,000 person-years (95% CI 5.25–5.75) in 2000 to 7.21 cases/100,000 person-years in 2019 (95% CI 7.16–7.27), at 2% per year (95% CI 1.3–2.6, $p < 0.001$) (Fig. 2). The increase in the rate of IE incidence was not uniform, and two periods could be determined using joinpoint analysis (supplemental Fig. S1). The first period corresponded to years 2000 to 2007, with an APC of 4.7% (95% CI 3.4–6.0, $p < 0.001$). The second period corresponded to years 2010 to 2019, with a lower APC (1.3%, 95% CI 0.5–2.6, $p = 0.003$).

### *Trends in incidence according to sex*

Incidence of IE was higher in male than female: 8.07 cases/100,000 person-years vs 6.35 (IRR 1.27, 95% CI 1.25–1.29, $p < 0.001$) (Fig. 3).

However, the trend in IE over time was not parallel for both sexes, with a rate of increase in incidence of 2.4% per year in males (95% CI 1.0–3.8) and 1.3% in females (APC difference 1.1%, 95% CI 0.6–2.0, $p < 0.001$ for parallelism comparison between sexes, supplemental Fig. S2). Notably, while incidence in men increased during all the study, the incidence in females decreased from 2007 to 2019 (APC −0.8%, 95% CI (−0.1) -(−2.5)). Accordingly, the IRR gradually rose from 1.19 (95% CI 1.09–1.29) in 2000 to 1.57 (95% CI 1.47, 1.68) in 2019 ($p < 0.001$).

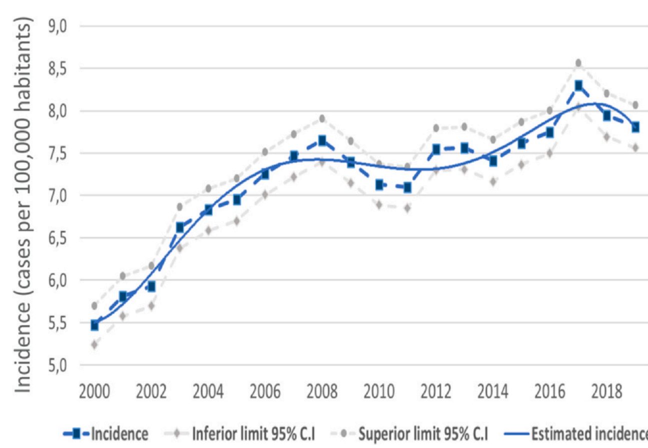


**Fig. 2.** Temporal trends in incidence of infective endocarditis across study period. Incidence is expressed in cases per 100.000 person-years. Blue squares and dashed line represents each year's crude incidence rate. Grey dots and dashed lines represents 95% C.I. bounds for the crude rate. Continuous blue line represents estimated incidence using Poisson regression. C.I.: Confidence interval.

### *Trends in incidence according to age*

Incidence of IE demonstrated a gradual increased with age, from 0.76 cases/100.000 person-years in individuals younger than 20 years to 43.50 cases/100.000 person-years for those aged 85 years or older (Fig. 4).

Temporal trends in incidence varied across age groups, as outlined in supplemental table S2**.** It should be noted that the incidence gradually increased in population between 75 and 84 years (2.4% per year, 95% CI 1.6–3.2, supplementary Fig. S3) and in those aged 85 years or older (5.0% per year, 95% CI 3.7–6.3, supplementary Fig. S4).

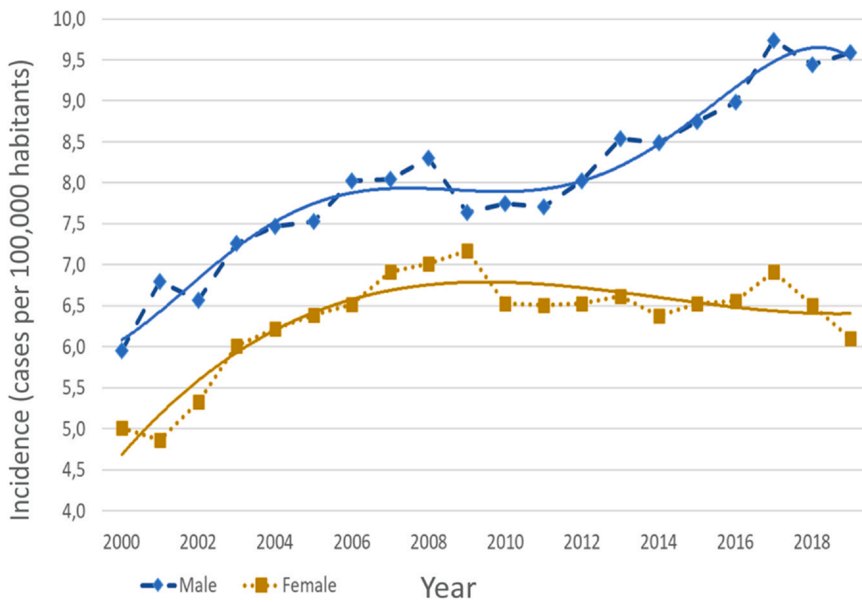


**Fig. 3.** Temporal trends in incidence of infective endocarditis according to gender across study period. Incidence is expressed in cases per 100.000 person-years. Blue squares and dashed line represents crude incidence rate in males. Yellow squares and dashed line represents crude incidence rate in females. Blue and yellow continuous lines represent estimated incidence using Poisson regression in male and female, respectively.

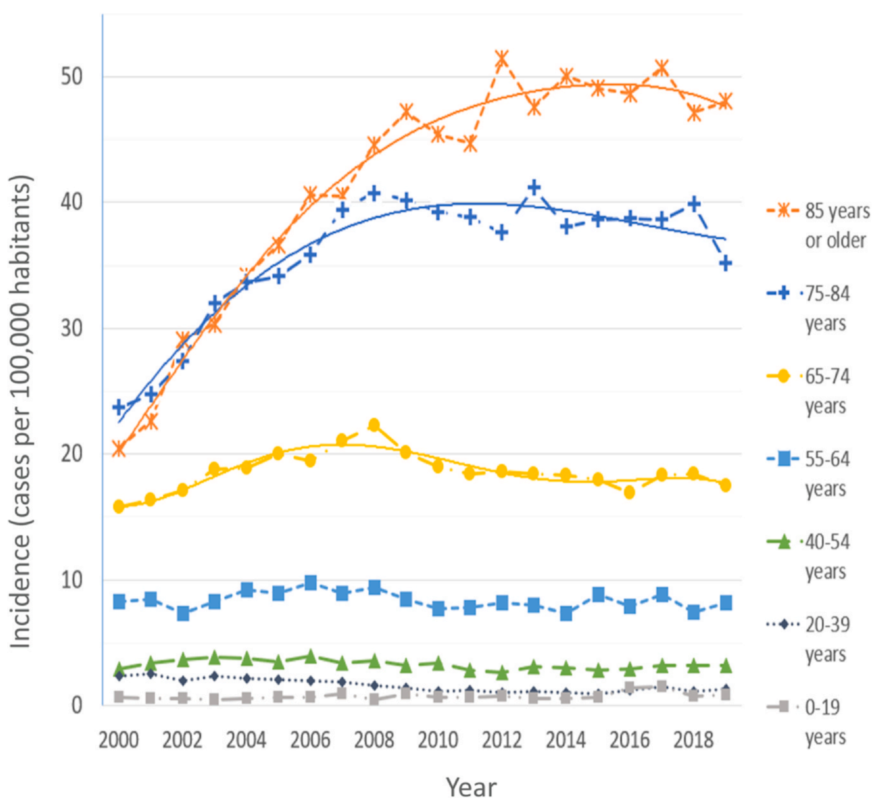


**Fig. 4.** Temporal trends in incidence of infective endocarditis according to age across study period. Incidence is expressed in cases per 100.000 person-years. Total incidence during the study period (2000–2019) in persons younger than 20 years (grey dots and dot-dashed line) was 0.76 cases/100,000 person/years; in persons between 20 and 39 years old (dark blue dots and dot line) 1.63 cases/100,000 person/years; in persons between 40 and 54 years old (green triangles and dashed line) 3.26 cases/100,000 person-years; in persons between 55 and 64 years old (light blue squares and dashed line) 8.36 cases/100,000 person-year; in persons between 65 and 74 years old (yellow circles and dashed line) 18.55 cases/100.000 person-years; in persons between 75 and 84 years old (blue crosses and dashed line) 36.39 cases/100,000 person-years, and in persons 85 years or older (orange stars and dashed line) 43.50 cases/100,000 person-years. Continuous lines represents estimated incidence using Poisson regression modeling (yellow 65–74 years old, blue 75–84 years old, orange 85 years or older).

**Table 1**
Univariate analysis of demographic, comorbidities and predisposing cardiac conditions according to 5-year study period.

| Variable | 2000-2004 (n = 12,693) | 2005-2009 (n = 16,468) | p1 | 2010-2014 (n = 17,011) | p2 | 2015-2019 (n = 18,378) | p3 |
|---|---|---|---|---|---|---|---|
| **Age (years) (mean, SD)** | 63.9 (18.6) | 67.1 (18.1) | < 0.001 | 70.1 (17.0) | < 0.001 | 70.0 (18.1) | 0.523 |
| *Equal or greater than 65 years (%)* | 60.6% (7694) | 66.8% (10,995) | < 0.001 | 72.4% (12,314) | < 0.001 | 71.3% (13,098) | 0.219 |
| *Equal or greater than 75 years (%)* | 33.8% (4296) | 43.1% (7092) | < 0.001 | 50.9% (8661) | < 0.001 | 49.7% (9140) | 0.267 |
| **Sex (female)** | 43.5% (5781) | 46.8% (7715) | 0.028 | 45.2% (7695) | 0.003 | 42.1% (7739) | < 0.001 |
| **Simple Charlson Index (median, IQR)** | 1 (0-2) | 1 (0-2) | < 0.001 | 1 (0-2) | < 0.001 | 1 (0-2) | 0.003 |
| *Equal or greater than 1* | 55.3% (7017) | 61.4% (10,113) | < 0.001 | 69.6% (11,841) | < 0.001 | 72.9% (13,402) | < 0.001 |
| *Equal or greater than 3* | 13.9% (1770) | 17.5% (2882) | < 0.001 | 22.9% (3895) | < 0.001 | 24.2% (4447) | 0.007 |
| **Age-adjusted Charlson Index (median, IQR)** | 3[2–5] | 4[2–5] | < 0.001 | 4[3–6] | < 0.001 | 4[3–6] | 0.069 |
| *Equal or greater than 4* | 47.2% (5992) | 56.2% (9.248) | < 0.001 | 64.9% (11,036) | < 0.001 | 66.3% (12,191) | 0.004 |
| **Diabetes mellitus** | 16.1% (2040) | 20.6% (3399) | < 0.001 | 23.1% (3931) | < 0.001 | 25.6% (4701) | < 0.001 |
| **Chronic heart failure** | 12.4% (1578) | 15.7% (2580) | < 0.001 | 22.4% (3804) | < 0.001 | 27.3% (5022) | < 0.001 |
| **Chronic lung disease** | 6.5% (830) | 8.8% (1447) | < 0.001 | 9.4% (1603) | 0.044 | 15.9% (2913) | < 0.001 |
| **Chronic kidney injury** | 4.8% (610) | 9.3% (1532) | < 0.001 | 18.2% (3098) | < 0.001 | 18.6% (3418) | 0.355 |
| **Liver cirrhosis** | 1.6% (200) | 1.9% (312) | 0.043 | 2.3% (383) | 0.024 | 2.6% (483) | 0.023 |
| **Active cancer** | 6.1% (779) | 7.6% (1259) | < 0.001 | 8.5% (1446) | 0.004 | 8.3% (1526) | 0.514 |
| **Hematological malignancy** | 1.5% (191) | 1.7% (275) | 0.362 | 2.2% (378) | 0.001 | 2.2% (397) | 0.644 |
| **Previous stroke** | 8.4% (1070) | 9.8% (1610) | < 0.001 | 11.3% (1925) | < 0.001 | 13.2% (2431) | < 0.001 |
| **Human immunodeficiency virus infection** | 3.8% (476) | 2.0% (326) | < 0.001 | 1.0% (163) | < 0.001 | 0.9% (162) | 0.469 |
| **Intravenous drug user** | 0.3%[36] | 0.4% [65] | 0.131 | 0.4% [68] | 1.000 | 1.8% (325) | < 0.001 |
| **Underlying heart valve diseases*** | 32.6% (4143) | 36.2% (5969) | < 0.001 | 47.5% (8086) | < 0.001 | 51.4% (9451) | < 0.001 |
| *Previous valvular prosthesis* | 12.1% (1532) | 13.9% (2296) | < 0.001 | 19.0% (3225) | < 0.001 | 20.9% (3843) | < 0.001 |
| *Rheumatic valvular disease* | 6.8% (869) | 6.7% (1098) | 0.556 | 6.9% (1174) | 0.397 | 6.5% (1193) | 0.125 |
| *Congenital cardiopathy* | 1.5% (193) | 1.7% (277) | 0.281 | 1.9% (322) | 0.149 | 2.2% (402) | 0.027 |
| *Other unspecified natural valvular disease* | 12.3% (1549) | 14.0% (2298) | < 0.001 | 19.8% (3365) | < 0.001 | 27.1% (4013) | < 0.001 |
| **Cardiac implantable electronic device** | 3.6% (454) | 4.9% (802) | < 0.001 | 6.0% (1023) | < 0.001 | 7.7% (1411) | < 0.001 |

*The four categories in underlying heart valve disease were mutually exclusive. For example, if a patient had a previous valvula prothesis due to rheumatic heart disease a congenital valve disease or other valvopathy, this patient would only count as "previous valvular prothesis".
Continuous variables are expressed as mean (SD) and compared using T-student test, or as median (IQR) and compared using Mann-Whitney's U when necessary. Categorical variables are expressed as percentage (absolute number) and compared by means of Chi-square test. p1 represents univariate analysis between periods 2000-2004 and 2005-2009. p2 represents univariate analysis between periods 2005-2009 and 2010-2014. p3 represents univariate analysis between periods 2010-2014 and 2015-2019. SD: Standard deviation. IQR: interquartile range.

*Trends in demographic, comorbidities, and cardiac predisposing conditions*

Table 1 summarizes the demographic characteristics and comorbidities of patients according to 5-year periods. An increase in the mean age of patients was observed over time (supplemental Fig. S5), from 63.9 years (SD 18.6) in 2000–2004 to 70.0 years (SD 18.1) in 2015–2019 ($p < 0.001$ across time periods). Furthermore, a general increase in the prevalence of nearly all comorbidities was also noted. Predisposing cardiac conditions also increase over time, specifically, the presence of previous valvular prosthesis increased from 12.1% in 2000–2004 to 20.9% in 2015–2019 and the presence of a cardiac implantable electronic device increased from 3.6% in 2000–2004 to 7.7% in 2015–2019.

*Trends in surgical management and outcomes*

Table 2 shows hospital length of stay, cardiac interventions, and in-hospital mortality.

The percentage of patients operated gradually increased (supplemental Fig. S6) from 12.4% in 2000–2004 to 19.9% in 2015–2019. Time from hospital admission to cardiac surgery decreased from period 2005–2009 (mean 14.0 days (SD 4.7) to 2010–2014 (mean 12.0 days, SD 3.4), with a mean decrease of 2.0 days, 95% CI 1.0–3.0 days, $p < 0.001$), and from 2010–2014 to 2015–2019 (mean 11.2 days (SD 3.5), with a mean decrease of 0.7 days, 95% CI 0.1–1.5, $p = 0.017$) (supplemental Fig. S7).

In-hospital mortality slightly increased from 2005–2009 to 2010–2014 (17.9% vs 19.2%, $p < 0.001$), but remained stable between other periods. Notably, mortality among those who received surgery decreased over the years from 28.9% in 2000–2004 to 22.0% in 2015–2019. In the multivariable regression model, after adjustment for age, sex, baseline differences, and cardiac interventions, each 5-year period was associated with a reduction in mortality (Table 3).

*Factors associated with in-hospital mortality*

Table 3 shows the multivariable logistic regression model for in-hospital mortality.

Older age and male sex and comorbidities were associated with higher mortality. Intravenous drug use and congenital cardiopathy were associated with lower mortality (OR 0.76, 95% CI 0.56–1.00; and OR 0.74, 95% CI 0.61–0.91, respectively).

Noteworthily, delay in cardiac surgery among those who were operated was associated with higher in-hospital mortality (OR 1.11 per day, 95% CI 1.06–1.16, $p < 0.001$). Accordingly, those receiving cardiac surgery during the first 10 days of admission presented lower in-hospital mortality (21.9% vs 26.4%, $p < 0.001$).

## Discussion

In our population-based study, we provide a comprehensive analysis of changes in the incidence, epidemiology, and prognosis of infectious endocarditis over a 20-year period (2000–2019). Our main finding was a gradual rise of the incidence with an 2% annual increase, although the rise was less marked since 2007. Changes in the incidence of IE differed for different age and sex groups, highlighting particularly the increase in incidence in men and those aged 75 years or older. This rise in incidence was accompanied by a generalized increase in the age and in the prevalence of comorbidities in patients diagnosed with IE, especially the presence of cardiac valve prostheses and CIED. After adjusting for baseline differences, the risk of mortality decreased over the years, which was associated with a higher percentage of cardiac surgery and earlier surgical timing during the study period.

**Table 2**
Hospital length of stay, cardiac intervention and mortality across the 5-years study periods.

| Variable | 2000-2004 (n = 12,693) | 2005-2009 (n = 16,468) | p1 | 2010-2014 (n = 17,011) | p2 | 2015-2019 (n = 18,378) | p3 |
|---|---|---|---|---|---|---|---|
| **Hospital length of stay (days) (mean, SD)** | 40.3 (23.7) | 41.7 (23.5) | 0.067 | 40.5 (21.9) | 0.356 | 41.1 (22.1) | 0.308 |
| **Cardiac surgery** | 12.4% (1575) | 13.2% (2170) | 0.052 | 15.1% (2575) | < 0.001 | 19.9% (3657) | < 0.001 |
| *Valvular surgery* | 9.5% (1209) | 9.9% (1636) | 0.248 | 11.3% (1930) | < 0.001 | 17.3% (3181) | < 0.001 |
| *Device extraction* | 3.2% (402) | 4.2% (684) | < 0.001 | 4.7% (805) | 0.011 | 5.8% (1063) | < 0.001 |
| *Other open cardiac surgery** | 1.8% (228) | 2.1% (354) | 0.035 | 2.7% (465) | 0.001 | 3.7% (686) | < 0.001 |
| **Days from admission to surgery (days) (mean, SD)** | 13.3 (SD 5.8) | 14.0 (SD 4.7) | 0.205 | 12.0 (SD 3.4) | < 0.001 | 11.2 (SD 3.5) | 0.017 |
| *Surgery during first 10 days* | 54.4% (612) | 49.6% (778) | 0.015 | 56.9% (1000) | < 0.001 | 59.0% (1712) | 0.085 |
| **In-hospital mortality** | 17.2% (2186) | 17.9% (2951) | 0.125 | 19.2% (3270) | 0.002 | 19.8% (3645) | 0.151 |
| *Mortality among those with surgery* | 28.9% (455) | 23.6% (512) | < 0.001 | 25.3% (651) | 0.178 | 22.0% (805) | 0.002 |
| *Mortality among those without surgery* | 15.6% (1731) | 17.1% (2439) | 0.001 | 18.1% (2619) | 0.016 | 19.3% (2840) | 0.012 |

Continuous variables are expressed as mean (SD) and compared using T-student test. Categorical variables are expressed as percentage (absolute number) and compared by means of Chi-square test. p1 represents univariate analysis between periods 2000-2004 and 2005-2009. p2 represents univariate analysis between periods 2005-2009 and 2010-2014. p3 represents univariate analysis between periods 2010-2014 and 2015-2019. SD: Standard deviation.

* Open cardiac procedures not primary different from valvular surgery

**Table 3**
Multivariable logistic regression model of factors associated with in-hospital mortality.

| Variable | *Odds ratio* | 95% Confident interval | p-value |
|---|---|---|---|
| **Year period*** | | | |
| **Years 2005-2009** (vs *2000-2004)* | 0.90 | 0.84-0.96 | 0.002 |
| **Years 2010-2014** (vs *2005-2009)* | 0.86 | 0.81-0.91 | < 0.001 |
| **Years 2015-2019** (vs *2010-2014)* | 0.93 | 0.88-0.99 | 0.023 |
| **Demographic** | | | |
| **Age (per year)** | 1.02 | 1.02-1.3 | < 0.001 |
| **Sex (female)** | 0.95 | 0.91-1.00 | 0.054 |
| **Comorbidities** | | | |
| **Diabetes mellitus** | 0.99 | 0.94-1.04 | 0.601 |
| **Chronic heart failure** | 1.57 | 1.49-1.65 | < 0.001 |
| **Chronic lung disease** | 1.24 | 1.16-1.32 | < 0.001 |
| **Chronic kidney injury** | 1.35 | 1.26-1.44 | < 0.001 |
| **Liver cirrhosis** | 3.10 | 2.75-3.49 | < 0.001 |
| **Active cancer** | 1.74 | 1.61-1.88 | < 0.001 |
| **Hematological malignancy** | 0.95 | 0.61-1.92 | 0.481 |
| **Previous stroke** | 2.25 | 2.12-2.39 | < 0.001 |
| **HIV/AIDS** | 1.33 | 1.11-1.59 | 0.001 |
| **Intravenous drug user** | 0.76 | 0.56-1.00 | 0.054 |
| **Underlying heart valve disease** | 1.20 | 1.10-1.28 | < 0.001 |
| **Congenital cardiopathy** | 0.74 | 0.61-0.91 | 0.003 |
| **Cardiac implantable electronic device** | 1.00 | 0.92-1.09 | 0.925 |
| **Management** | | | |
| **Cardiac surgery** | 1.09 | 1.02-1.18 | 0.019 |
| **Days from admission to surgery (per day)**** | 1.11 | 1.06-1.16 | < 0.001 |
| **Cardiac surgery during the first 10 days**** | 0.76 | 0.67-0.85 | < 0.001 |

* Each 5-year period was compared using the previous period as reference.
** These variables are considered in a separate logistic regression model including only patients receiving cardiac surgery during admission.

Our data confirms the findings of most population-based studies showing a widespread increase in the incidence of IE during the XXI century [2,3,15,34–39]. Notably, *Olmos* et al. [38], using a Spanish population-based database, observed an increase in incidence from 2.72 cases/100,000 person-years in 2003 to 3.49 cases/100,000 person-years in 2014. The lower incidence found by these authors is justified by the inclusion of only those patients with a first diagnosis of IE, which likely led to an underestimation of the real incidence in our country [23]. It should be noted that the annual increase in these studies was 2%, very similar to our findings [24,38]. The incidence found in our study is closer to that found in other population-based studies in other European countries. [1,15,35,37,39,40].

Remarkably, the increase in incidence in our population was not linear, and we found a less pronounced increase in the second half of the study. Other authors have reported similar trends [35]. It is noteworthy that we did not detect a higher increase in incidence after the changes in IE prophylaxis in high-risk interventions in the 2009 [6] or 2015 [5] European guidelines. Our results are consistent with those previously described by other authors [41] and support that applying the prophylaxis criteria of the current guidelines do not result in an increment in the population incidence of IE. However, further studies are still needed to better define high-risk patients and procedures [42].

Interestingly, we observed differences in the incidence trends of IE according to sex and age. Regarding differences in sexes, we found that the incidence of IE was higher in males than in females. Moreover, we found a greater increase in incidence in males in the most recent period. Other authors have previously reported similar findings [24,37]. Differences between both sexes in baseline comorbidities and diagnostic practices could be driving these differences. For example, increasing prevalence of prosthetic cardiac valves among males [43]. On the other hand, the incidence of the disease varied significantly across different age groups, with the highest incidence observed in individuals aged 75 years and older. This finding is consistent with previous studies [3,35,36,38,44]. However, the temporal trends in incidence varied across age groups. According to our findings, the incidence increased in those aged 75 years or older, with more pronounced increase in those aged 85 or older. This finding suggests that the age-specific changes in the incidence of IE may reflect changes in risk factors for IE. Other authors have previously described the increasingly frequent comorbidities, health care contact and cardiac interventions in older patients with IE [44,45]. This rise in comorbidities and predisposing conditions explains the aforementioned epidemiology trends in older patients. It is important for clinicians to be aware of these trends and to promote healthy lifestyle habits and early detection methods to mitigate the morbimortality risk associated with IE in elderly patients. For example, increase awareness of patients who have valve prosthesis could lead to a better compliance of preventive measures recommendations in these patients (skin care, oral hygiene, etc). Furthermore, a healthier lifestyle and early detection methods lead to a better control of the comorbidities and predisposing conditions, which results in a better prognosis of the IE [9,46–48] and, even, could hypothetically reduce the cases of IE.

Importantly, we found a progressive increase in crude in-hospital mortality during the study period. However, this increase in crude mortality seems to be due to higher patient age and comorbidity, including to more frequent previous heart valve disease. In fact, when adjusting for age and comorbidity, mortality in each 5-year period was lower than in the previous period. Although several studies have found conflicting results, most show a decrease or, at least, stability in IE mortality over time after adjusting for baseline differences [3,9–11,35–39,44]. This improvement in prognosis is probably linked to the increasing dissemination of clinical practice guidelines [4–6], as well as to the creation of the known "IE teams". It has been shown that both measures lead to better management of this pathology [49]. One of our results that supports this hypothesis is the increasingly frequent and earlier cardiac surgery. It is worth mentioning that, among the operated patients, we have found an association between early surgery and lower mortality, which has also been suggested by other authors [50,51]. The design of our study prevents us from adjusting for the presence of surgical indication and other clinical characteristics, so we cannot draw robust conclusions.

Our study has several strengths, including a large sample size and the use of data from a well-established population-based registry. However, there are some limitations that should be considered when interpreting the results. Despite these limitations, we consider that the size of the study population, the nationwide scope and the statistical strength of the analysis make our results clinically valuable. The main limitation is that the study is retrospective and based on an administrative database, so the accuracy of the data, including data on comorbidities and previous cardiac diseases, depends on adequate hospital coding. Although adequacy of hospital coding is described to be greater than 90% for IE and comorbidities [25–27], there may be incomplete data on some important variables, most importantly, microbiological data. Other important missing information, common to the rest of population-based studies, are clinical presentation of IE, presence of surgical indication, antibiotic treatments received, etc. Then again, because it used a population-based design, this study provides important new evidence that is not altered by referral or selection bias, giving strength to our conclusions. Secondly, we could not verify that all episodes included were incident episodes, and no previous diagnosis. We tried to minimize this bias by including only the firsts 10 codes positions, we cannot ascertain that our data led to a slight overestimation of incidence. Nevertheless, including only patients with IE code in the first position (or first two or three positions) would lead to a substantial underestimation, so we strongly believe that our approach allows us to estimate the most realistic incidence and temporal changes of IE in our country. Lastly, our study was performed in Europe, and nation-wide demographic studies on endocarditis are mainly performed in Europe and North America. Accordingly, the external validity of our conclusions to other settings (Africa or Asia) is limited.

In conclusion, we observed that the overall incidence of IE in Spain during the XXI century has increased, with a rate of 2% per year, with more pronounced increase in male and elderly individuals. The observed increase in incidence may be attributed to the aging of the population and the growing prevalence of predisposing conditions. Adjusted-mortality decreased over the years, which could be related to a higher percentage of cardiac surgery and, possible, to an earlier surgery timing during the study period.

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## CRediT authorship contribution statement

JCP: study design, statistical analysis, manuscript writing. ARM supervision. All other authors manuscript revision.

## Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

## Declaration of Competing Interest

The authors declare no conflicts of interest.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2024.03.011.

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