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## Surgery for acute infective endocarditis: epidemiological data from a Spanish nationwide hospital-based registry<sup>†</sup>

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### Abstract

**OBJECTIVES:** Infective endocarditis (IE) is a serious and eventually lethal disease with rising incidence in the past couple of decades. The aim of this study was to evaluate the contemporary epidemiological trends of surgical endocarditis patients, to analyse the clinical outcomes and to study their profile, associated prognostic factors and costs.

**METHODS:** This is a retrospective study of all patients admitted for IE in Spanish hospitals and discharged between 1 January 1997 and 31 December 2014. Data were extracted from the minimum basic data set of the National Surveillance System for Hospital Data in Spain provided by the Spanish Ministry of Health. Hospitalizations, comorbidities, outcomes and costs were analysed.

**RESULTS:** In total, 34 399 patients with IE were included; 15.7% of patients received surgical treatment and 84.3% received medical treatment only. Surgical patients were mostly men (71.9%) and had a lower mean age ( $59.2 \pm 16.08$  years) than the medical treatment group ( $P < 0.0001$ ). Mortality among surgical patients showed a decreasing trend between 1997 (32.0%) and 2014 (22.7%) and increased with age (47.6% in  $\geq 85$  years of age). Length of hospital stay and the percentage of patients with organ dysfunction were also higher in this group. The cost of the surgical treatment group was higher and increased since 1997 (15 259.22 euros), remaining stable from 2010 (40 700 euros) ( $P < 0.0001$ ).

**CONCLUSIONS:** Surgical treatment in IE has trended upwards in Spain during the last 2 decades. Patients are getting older and more frequently experience organ dysfunction. Mortality ratio steadily declined without changes in the length of hospital stay.

**Keywords:** Infective endocarditis • Epidemiology • Cardiac surgery • Mortality • Costs

### INTRODUCTION

Infective endocarditis (IE) is an uncommon disease with a poor prognosis with rising incidence in the past couple of decades. The most recent epidemiological study reports an incidence of 3–10 cases per 100 000 persons/year [1–8]. The prognosis has not improved despite the improvements in the diagnosis and treatment, and nowadays, mortality rate remains high in spite of recent

medical and surgical advances. Mortality is 15–50% depending on the series [7, 9–11], and this is probably due to an increase in microbiological resistance, comorbidities and association with healthcare [1, 2, 12].

The latest guidelines of the European Society of Cardiology (ESC) endorsed by the European Association for Cardio-Thoracic Surgery (EACTS) on IE contemplate the management of IE by the endocarditis team. An appropriate team approach aims at reducing antimicrobials and surgery. In some cases, as peripheral aneurysms, percutaneous approaches are required [13–15].

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Surgical treatment (ST) is performed in diverse proportions according to different studies. One possible explanation includes sample sizes, lack of homogeneity and different study designs. Surgical indications are well defined in the guidelines, and the main indication for surgery is heart failure [3, 5, 6, 16, 17]. Surgery is a part of an effective treatment in IE and provides good results in the short term, medium term and long term. Different studies analyse the impact of early surgery on outcomes. Case-control studies and a single randomized study aimed to elucidate this. However, heterogeneity is an issue and makes the interpretation of results difficult [18–20].

Epidemiological studies have some limitations but are useful for the understanding of the history of the disease. There is scarce information on the epidemiology of the ST of IE in Spain. The aim of this study was to define the current profile of IE, the need for ST and analyse the cost of surgery.

## METHODS

### Study design

This is a retrospective study of all patients admitted for IE in hospitals in Spain and were discharged between 1 January 1997 and 31 December 2014.

### Data collection

Data were extracted from the basic minimum data set (BMDS) of the National Surveillance System for Hospital Data in Spain provided by the Spanish Ministry of Health [in Spanish 'Conjunto Minimo Basico de Datos' (CMBD)]. The BMDS (also called national registry of hospital discharges) is the largest database of clinical data on hospitalized patients in the country and the most important source of treated morbidity data [21]. BMDS provides valuable although limited information on multiple healthcare-related topics.

Informed consent was waived as this is a retrospective study based on public data. Data collected from the BMDS were encoded to avoid duplicity and were dissociated from any information that could uncover the identity of the patients. The minimum basic data set provides the encrypted patient identification number, gender, date of birth, dates of hospital admission and discharge, medical institutions providing the services, the diagnosis and procedure codes according to the International Classification of Diseases 9th edition, Clinical Modification (ICD-9-CM) and the outcome at discharge [22].

### Case identification

Cases were identified using the ICD-9CM code for IE (421, acute and subacute endocarditis) among the discharges between 1 January 1997 and 31 December 2014. All Spanish hospitals record the ICD-9CM codes for the main diagnosis and comorbidities of each patient on BMDS (see [Supplementary Material, Appendix A1–A4](#)). Demographic data (sex and age), presence of comorbidities, associated organ dysfunction, Charlson's index and mortality data were extracted from the minimum basic data set.

The study period was arbitrarily divided into calendar years and 4 calendar periods (1997–1999, 2000–2004, 2005–2009 and 2010–2014). The primary end point was ST. Secondary end

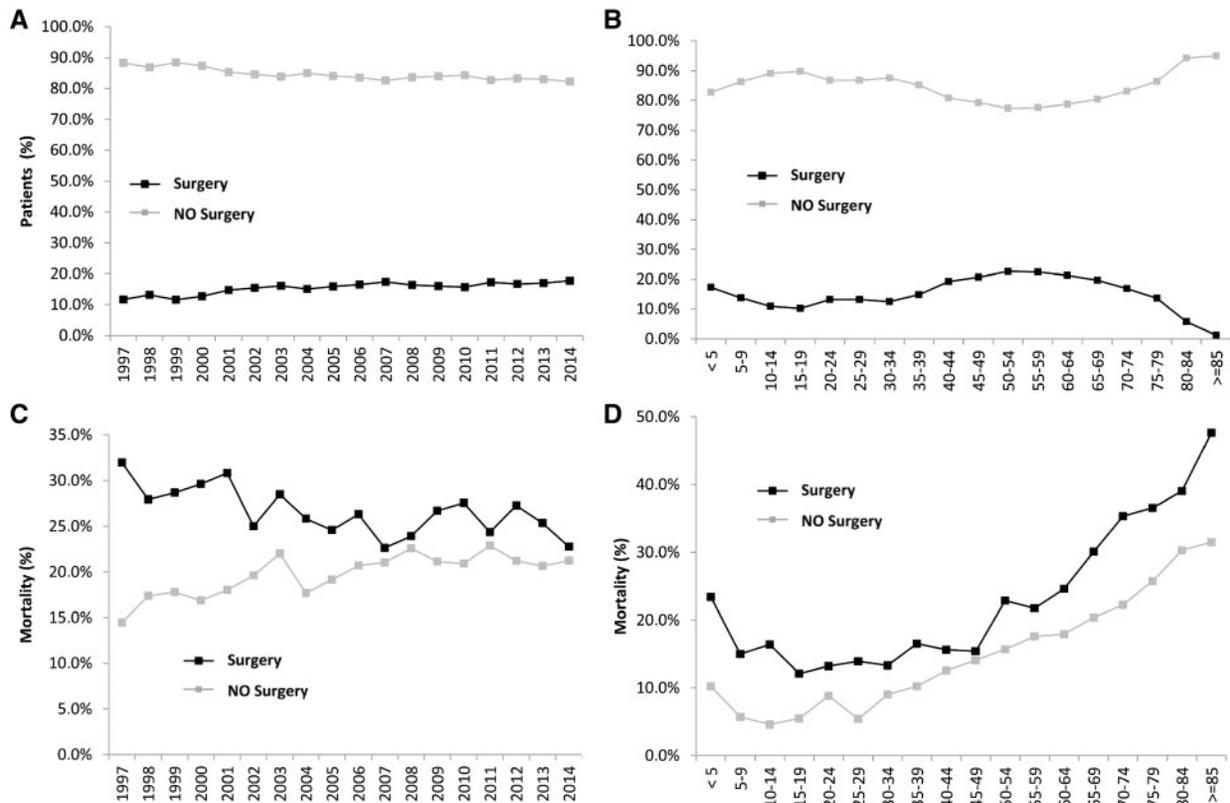
**Table 1:** Clinical, epidemiological and microbiological characteristics of patients with infective endocarditis who received surgical treatment versus medical treatment

	Medical treatment	Surgical treatment
<b>Number of patients</b>		
All period	28 985 (84.3)	5414 (15.7)
1997–1999	3724 (12.8)	515 (9.5)
2000–2004	6785 (23.4)	1190 (22.0)
2005–2009	8416 (29.0)	1658 (30.6)
2010–2014	10 060 (34.7)	2051 (37.9)
Age (years)	62.31 ± 18.80	59.25 ± 16.08
<b>Gender</b>		
Male	19 150 (66.07)	3895 (71.94)
Female	9835 (33.93)	1518 (28.04)
Unknown	0 (0.00)	1 (0.02)
<b>Underlying condition</b>		
Ischaemic heart disease	1368 (4.7)	257 (4.7)
Heart failure	6833 (23.6)	1738 (32.1)
Peripheral vascular disease	1362 (4.7)	332 (6.1)
Stroke	1243 (4.3)	169 (3.1)
Dementia	452 (1.6)	11 (0.2)
Chronic lung disease	4052 (14.0)	746 (13.8)
Rheumatic disease	484 (1.7)	70 (1.3)
Mild liver disease	1386 (4.8)	136 (2.5)
Mild-to-moderate DM	4110 (14.2)	605 (11.2)
DM with chronic complications	1105 (3.8)	122 (2.3)
Hemiplegia	514 (1.8)	94 (1.7)
Chronic renal disease	1641 (5.7)	260 (4.8)
Moderate-to-severe liver disease	772 (2.7)	72 (1.3)
<b>Charlson index</b>		
<i>Valor medio</i>	1.14 ± 1.41	1.00 ± 1.13
0	11 851 (40.9)	2162 (39.9)
1	8651 (29.8)	1889 (34.9)
2	4756 (16.4)	869 (16.1)
>2	3727 (12.9)	494 (9.1)
<b>Acute organ dysfunction</b>		
Cardiovascular	436 (1.5)	141 (2.6)
Haematological	1202 (4.1)	310 (5.7)
Hepatic	511 (1.8)	126 (2.3)
Neurological	391 (1.3)	62 (1.1)
Renal	4629 (16.0)	1494 (27.6)
Respiratory	227 (0.8)	357 (6.6)
Metabolic	371 (1.3)	116 (2.1)
<b>Micro-organisms</b>		
Gram-positive cocci	2338 (8.1)	313 (5.8)
Gram-negative bacilli	1426 (4.9)	340 (6.3)
Anaerobes	19 (0.1)	8 (0.1)
Fungi	151 (0.5)	44 (0.8)
Readmission	5793 (20.0)	562 (10.4)
Emergency admission	24 659 (85.07)	3647 (67.36)
Exitus	5737 (20.1)	1396 (26.0)

Values are expressed as absolute n (%) and mean ± standard deviation. DM: diabetes mellitus.

points were length of hospital stay (LOHS), years of potential life lost and cost related to endocarditis. We divided the study sample into 2 groups: patients undergoing ST and non-surgical (NS). Mortality by years and periods was calculated to understand the trends. We analysed the correlation between age and type of treatment as well as the mortality between groups.

LOHS was calculated as the number of days from admission (Day 0) to discharge or death at any time during the treatment. When patients were admitted and discharged the same day, 1 day of stay was assigned. Mean stay was estimated for the total group and separately by survival, year, type of treatment and



**Figure 1:** Percentage of patients with infective endocarditis, who were operated and not operated and mortality in Spain from 1997 to 2014. (A) Evolution over time, (B) evolution by age, (C) evolution of mortality and (D) mortality by age.

age. Costs were calculated by diagnosis-related group, which classifies inpatients into groups based on their diagnosis and attributes a specific hospital cost to each group. Diagnosis-related group data were extracted from the minimum basic data set. All costs shown were adjusted for the increment of the inflation in the same period in Spain.

### Statistical analysis

Categorical variables are expressed as absolute and relative (%) frequencies, and continuous variables were expressed as the mean and standard deviation. Differences between groups were compared using the *t*-test with continuous variables and using the  $\chi^2$  test or Fisher's exact test with categorical variables. Statistical significance was established as  $P \leq 0.05$ . Incidence and mortality rates were calculated for patients with a diagnosis of IE by year (1997–2014), which allowed assessing tendencies during the study period. The incidence and mortality associated with IE were calculated by year and by age group, for the total group, the ST and NS groups and by gender. Therefore, age- and gender-adjusted analysis of incidence and mortality were performed. The number of events within each calendar year was used as a numerator, and the number of persons at risk within each calendar year as the denominator [the number of persons registered in the census of Spain (National Statistics Institute; <http://www.ine.es/>)]. All statistical procedures were performed using the SPSS 21.0 software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, USA: IBM Corp.).

## RESULTS

### Patient characteristics

From 1997 to 2014, 34 399 IE patients were diagnosed in Spain. The incidence per 100 000 inhabitants was 3.17% in 1997 and 5.56% in 2014. It was more prevalent in men. ST was performed in 5414 (15.7%) patients and medical treatment in 28 985 (84.3%). Patients who underwent ST were younger ( $59.2 \pm 16.08$  years ST and  $62.3 \pm 18.8$  years NS,  $P < 0.0001$ ), had less comorbidities and a lower Charlson index ( $1.00 \pm 1.13$  ST and  $1.14 \pm 1.41$  NS,  $P < 0.0001$ ), with more organ dysfunction, mainly renal failure (27.6%). Mortality in the ST group was higher (26.0% ST vs 20.1% NS). ST patients had a 30-day readmission rate lower than the NS patients (10.4% ST vs 20.0% NS) (Table 1).

The percentage of patients who underwent ST increased from 11.7% in 1997 to 17.8% in 2014;  $P < 0.05$  (Fig. 1A). In all age groups, ST was less frequent. In 2 age groups, slightly above mean percentages were observed: in children younger than 5 years (17.3%) and in patients aged between 45 (20.7%) and 64 (21.3%) years (Fig. 1B). The NS patients were significantly older and had more comorbidities than ST patients. There was also a trend towards a higher incidence of New York Heart Association (NYHA) Class IV and congestive heart failure among ST patients (Table 2). The most common micro-organisms involved were Gram-negative bacilli (340; 6.3%), followed by Gram-positive cocci (313; 5.8%), fungi (44; 0.8%) and anaerobes (8; 0.1%).

**Table 2:** Epidemiological, clinical and microbiological characteristics of patients with infective endocarditis who received surgical treatment versus medical treatment in Spain during 1997–2014

	1997–1999		2000–2004		2005–2009		2010–2014	
	Non-surgery	Surgery	Non-surgery	Surgery	Non-surgery	Surgery	Non-surgery	Surgery
Number of patients	3724 (87.85) <sup>a</sup>	515 (12.15) <sup>a</sup>	6785 (85.08) <sup>a</sup>	1190 (14.92) <sup>a</sup>	8416 (83.54) <sup>a</sup>	1658 (16.46) <sup>a</sup>	10 060 (83.06) <sup>a</sup>	2051 (16.93) <sup>a</sup>
Gender								
Male	2573 (69.1)	370 (71.8)	4484 (66.1)	861 (72.4)	5464 (64.9)	1192 (71.9)	6629 (65.9)	1472 (71.8)
Female	1151 (30.90)	145 (28.15)	2301 (33.91)	328 (27.56)	2952 (35.07)	466 (28.10)	3431 (34.10)	579 (28.23)
Unknown	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Age (years)	53.04 ± 20.37	53.53 ± 16.71	59.46 ± 18.81	58.03 (16.03)	62.96 ± 18.26	59.36 ± 15.66	67.12 ± 16.94	61.31 ± 15.87
Comorbid condition								
Ischaemic heart disease	102 (2.7)	15 (2.9)	323 (4.8)	67 (5.6)	466 (5.5)	83 (5.0)	477 (4.7)	92 (4.5)
Heart failure	588 (15.8)	105 (20.4)	1364 (20.1)	373 (31.3)	1988 (23.6)	532 (32.1)	2893 (28.8)	728 (35.5)
Peripheral vascular disease	76 (2.0)	15 (2.9)	288 (4.2)	55 (4.6)	417 (5.0)	96 (5.8)	581 (5.8)	166 (8.1)
Stroke	126 (3.4)	19 (3.7)	324 (4.8)	24 (2.0)	317 (3.8)	49 (3.0)	476 (4.7)	77 (3.8)
Dementia	32 (0.9)	1 (0.2)	107 (1.6)	3 (0.3)	120 (1.4)	4 (0.2)	193 (1.9)	3 (0.1)
Chronic lung disease	278 (7.5)	40 (7.8)	749 (11.0)	157 (13.2)	1255 (14.9)	241 (14.5)	1770 (17.6)	308 (15.0)
Rheumatic disease	31 (0.8)	4 (0.8)	93 (1.4)	12 (1.0)	172 (2.0)	23 (1.4)	188 (1.9)	31 (1.5)
Mild liver disease	118 (3.2)	13 (2.5)	283 (4.2)	18 (1.5)	441 (5.2)	47 (2.8)	544 (5.4)	58 (2.8)
Mild-to-moderate DM	271 (7.3)	31 (6.0)	811 (12.0)	113 (9.5)	1290 (15.3)	203 (12.2)	1738 (17.3)	258 (12.6)
DM with chronic complications	50 (1.3)	9 (1.7)	200 (2.9)	12 (1.0)	338 (4.0)	40 (2.4)	517 (5.1)	61 (3.0)
Hemiplegia	48 (1.3)	7 (1.4)	105 (1.5)	19 (1.6)	123 (1.5)	15 (0.9)	238 (2.4)	53 (2.6)
Chronic renal disease	255 (6.8)	31 (6.0)	547 (8.1)	95 (8.0)	609 (7.2)	93 (5.6)	230 (2.3)	41 (2.0)
Moderate-to-severe liver disease	67 (1.8)	4 (0.8)	152 (2.2)	14 (1.2)	238 (2.8)	18 (1.1)	315 (3.1)	36 (1.8)
Charlson index								
<i>Valor medio</i>	0.72 ± 1.10	0.69 ± 1.02	1.05 ± 1.37	0.97 ± 1.12	1.21 ± 1.44	1.00 ± 1.09	1.30 ± 1.46	1.10 ± 1.16
0	2171 (58.3)	286 (55.5)	3089 (45.5)	499 (41.9)	3245 (38.6)	665 (40.1)	3346 (33.3)	712 (34.7)
1	883 (23.7)	155 (30.1)	1886 (27.8)	397 (33.4)	2562 (30.4)	558 (33.7)	3320 (33.0)	779 (38.0)
2	396 (10.6)	43 (8.3)	961 (14.2)	188 (15.8)	1406 (16.7)	288 (17.4)	1993 (19.8)	350 (17.1)
>2	274 (7.4)	31 (6.0)	849 (12.5)	106 (8.9)	1203 (14.3)	147 (8.9)	1401 (13.9)	210 (10.2)
Acute organ dysfunction								
Cardiovascular	41 (1.1)	13 (2.5)	82 (1.2)	32 (2.7)	132 (1.6)	37 (2.2)	181 (1.8)	59 (2.9)
Haematological	106 (2.8)	19 (3.7)	246 (3.6)	60 (5.0)	351 (4.2)	101 (6.1)	499 (5.0)	130 (6.3)
Hepatic	33 (0.9)	7 (1.4)	89 (1.3)	16 (1.3)	163 (1.9)	25 (1.5)	226 (2.2)	78 (3.8)
Neurological	33 (0.9)	10 (1.9)	96 (1.4)	17 (1.4)	112 (1.3)	11 (0.7)	150 (1.5)	24 (1.2)
Renal	300 (8.1)	78 (15.1)	820 (12.1)	261 (21.9)	1402 (16.7)	449 (27.1)	2107 (20.9)	706 (34.4)
Respiratory	25 (0.7)	22 (4.3)	52 (0.8)	70 (5.9)	82 (1.0)	131 (7.9)	68 (0.7)	134 (6.5)
Metabolic	13 (0.3)	5 (1.0)	44 (0.6)	19 (1.6)	107 (1.3)	27 (1.6)	207 (2.1)	65 (3.2)
Micro-organisms								
Gram-positive cocci	192 (5.2)	14 (2.7)	569 (8.4)	58 (4.9)	768 (9.1)	113 (6.8)	809 (8.0)	128 (6.2)
Gram-negative bacilli	110 (3.0)	13 (2.5)	253 (3.7)	44 (3.7)	427 (5.1)	101 (6.1)	636 (6.3)	182 (8.9)
Fungi	17 (0.5)	2 (0.4)	31 (0.5)	16 (1.3)	43 (0.5)	11 (0.7)	60 (0.6)	15 (0.7)
Emergency admission	3205 (86.1)	344 (66.8)	5777 (85.1)	794 (66.7)	7181 (85.3)	1093 (65.9)	8496 (84.5)	1416 (69.0)
Readmission	614 (16.5)	57 (11.1)	1234 (18.2)	108 (9.1)	1684 (20.0)	170 (10.3)	2261 (22.5)	227 (11.1)
Exitus	610 (16.7)	151 (29.3)	1273 (18.9)	341 (28.8)	1749 (21.0)	392 (23.7)	2105 (21.4)	512 (25.3)

Values are expressed as absolute *n* (%) and mean ± standard deviation.

<sup>a</sup>Percentage calculated based on the total cases of endocarditis in each period of time.

DM: diabetes mellitus.

Overall mortality was higher in the surgical group (surgical 26.0% vs NS 20.1%). During the study, there was a decrease in mortality in the surgical group (32.7% in 1997 to 22.0% in 2014) (Fig. 1C). Although mortality in the NS group increased slightly (14.9% in 1997 to 21.1% in 2014). Another relevant issue was that the mortality of patients undergoing surgery increased with age, reaching 47.6% in those older than 85 years (Fig. 1D).

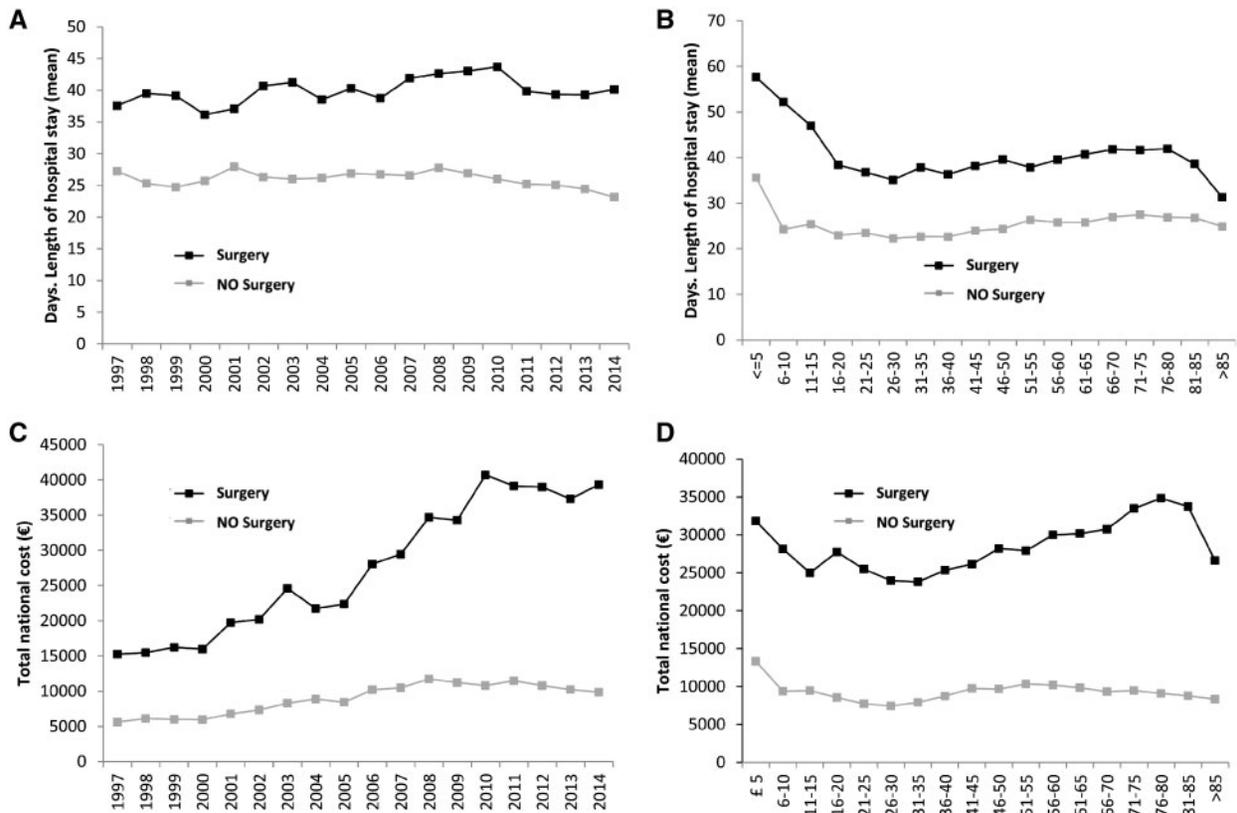
### Evolution of length of hospital stay and cost of patients with infective endocarditis

The mean length of hospital stay during the study increased slightly in the surgical group (37.5 days in 1997 to 40.1 days in 2014) when compared with a decrease in the medical treatment group (27.2 days in 1997 to 23.1 days in 2014) (Fig. 2A). The mean length of stay was higher in the surgical group, with the highest being observed in the group of children younger than 5 years (57.6 days ST) (Fig. 2B).

Regarding the cost per patient and year, it was higher in those who received ST during the whole period analysed and experienced a considerable increase from 15 259.22 euros/patient in 1997 to 39 317.70 euros/patient in 2014. The maximum cost was observed in 2010 (40 000 euros/patient), remaining stable until 2014. In the NS group, costs also increased but in a lower proportion, from 5630.61 euros/patient in 1997 to 9851.46 euros/patient in 2014 (Fig. 2C). The greatest differences in costs were observed in patients aged between 70 and 85 years (ST 35 000 euros vs NS 12 000 euros) and in children younger than 5 years (ST 33 000 euros vs NS 12 000 euros) (Fig. 2D). The mean cost for surgical patients during the study was 30 073.10 ± 18 383.78 euros and 9257.73 ± 8541.72 euros in the medical group.

### DISCUSSION

In our study—which included all cases of IE registered between 1997 and 2014—the incidence of IE in Spain increased (from 3.17% in 1997 to 5.56% in 2014), as well as the mean age of these patients,



**Figure 2:** Evolution of length of hospital stay and cost of patients with infective endocarditis, who were operated on and not operated in Spain between 1997 and 2014. (A) Mean length of hospital stay per patient for surgical treatment and non-surgical treatment by study period, (B) mean length of hospital stay per patient for surgical treatment and non-surgical treatment by age group, (C) mean cost per patient for surgical treatment and non-surgical treatment by year and (D) mean cost per patient for surgical treatment and non-surgical treatment by age group.

and similar results in Europe have been reported by other authors in smaller series [2, 6]. Data from the Danish registry, in the same period time, reported an incidence of 3.93 and 7.55 cases per 100 000/persons/year [1]. This increase in incidences and age may be related to an improvement in diagnostic techniques and a change in the profile of patients. They are older, present with more comorbidities and present with healthcare-related IE [1, 6, 23, 24]. These ranges, however, vary widely, reaching 12.7% [3]. When analysing the incidence of IE, it is important to take into consideration the characteristics of the healthcare centre where the study was conducted and the design of the study. The International Collaboration on Endocarditis-Pro prospective Cohort Study (ICE-PCS) included data from 25 countries from different continents [25]. This means the epidemiological characteristics of the sample or differences in clinical practice may influence the incidence.

One of the most relevant data of our study was the low percentage of patients who underwent ST. This percentage increased during the study period from 11.7% to 17.8% but is lower than reported by other series in which it reaches 48.2% in the ICE-PCS and 52% or 58.7% in the Euro Heart Survey [26]. Nevertheless, other authors reported lower rates 22.8% or 9.6% [6]. These differences may be due to the fact that some of the studies were carried out in reference centres where very ill patients were referred, and therefore, the percentage of patients who underwent ST was higher [2, 3, 25].

The results observed in terms of in-hospital mortality vary according to the type of centre and the experience of the teams in the treatment of endocarditis. In the Spanish dataset, we observed that mortality decreased throughout the study (32.7% in

1997 vs 22.0% in 2014); however, it was higher than those reported by other groups. This might be explained by variability in the characteristics of patients, such as age, comorbidities and Charlson index at diagnosis [2, 7, 10]. Data published by the Euro Heart Survey show lower mortality for both groups; mortality among the patients treated medically was 10.4% and 15.6% in the surgical group. Recently, Olmos *et al.* [26] reported a mortality rate of 28.6% in a study carried out in 3 reference centres for endocarditis patients in Spain.

As reported in the results, the percentage of patients with full microbiology documentation was low. The most common micro-organisms were Gram-negative bacilli (6.3%). From the current database, it is unlikely that the impact of specific pathogens on surgical patients can be appropriately assessed. It is agreed that this is a major limitation with administrative databases. On the other hand, substantial information on other specific variables in IE has been collected.

The mean hospital stay for both treatment groups varied a little during the study period, and the percentage of patients with dysfunction of any organ increased. The costs for both groups, and mainly in the surgical group, increased considerably. This was related to the profile of patients who were operated on in which the age increased discreetly (53.5–61.3%), and, as we have indicated, the percentage of dysfunction organs increased. The treatment of patients who present with organ dysfunction increases the cost associated with healthcare [9, 27]. These patients require intensive care more frequently and need combination therapies more often.

On cost issues, the maximum expenditure recorded was in 2010 (40 000 euros/patient). From 2010 to 2014, the cost seems to stay stable, and it is possible that the economic crisis has some influence [21, 28]. With each passing decade, healthcare has consumed a larger share of gross domestic product (GDP). In the USA, the healthcare expenditure share of GDP more than tripled between 1960 and 2004, as it rose from 5.2% to 16.0% of GDP. In Spain, during the period of study, health spending consumption of GDP did not increase, and during the economic crisis, between 2009 and 2014, it dropped from 6.7% to 6.0% of GDP [21].

When we compare the results of our study with other published studies, it is important to take into account that data on clinical presentation, complications and outcomes are mainly obtained from series collected over prolonged periods, in single centres or over shorter periods in multicentre, multinational studies from selected centres. Consequently, they do not necessarily represent the current situation of a whole country.

Most epidemiological studies on IE involve case series of referral centres encountering selection bias [29]. Population-based investigations are more accurate, but well-conducted prospective studies are few [25], study designs are often inaccurate, under-sized or lack important clinical data, criteria for definite diagnosis are not always clear and follow-up data sometimes incomplete, as highlighted in recent meta-analysis [30].

## Limitations

This study has important limitations related with the type of the design. It is clear that administrative databases have a number of limitations due to the type of coding and amount of information stored and should only be used for pure descriptive analysis. No clinical extrapolations must be inferred from those administrative databases. Other important limitations of this study in terms of incidence calculation are potential errors in the transcription of the diagnosis of IE into the corresponding ICD code. Regarding the aetiology of the disease, the microbiological profile of patients could not be determined, as microbiological test results were not appropriately documented on the CMBD. Microbiology findings have been documented in only 15% of the patients enrolled in the database, and therefore, it is not possible to know the eventual influence of microbiology in surgical patients. It should also be taken into account that we estimated mortality related to admissions for IE. As to the cost per patient, the limitation is that it was calculated only for the duration of hospital stay.

## CONCLUSION

ST in IE has trended upwards in Spain during the last 2 decades. Patients are getting older and more frequently experience organ dysfunction. Mortality ratio steadily declined without changes in the LOHS.

## SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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## REFERENCES

- [1] Erichsen P, Gislason GH, Bruun NE. The increasing incidence of infective endocarditis in Denmark, 1994-2011. *Eur J Intern Med* 2016;35: 95-9.
- [2] Muñoz P, Kestler M, De Alarcon A, Miro JM, Bermejo J, Rodríguez-Abella H *et al.* Current epidemiology and outcome of infective endocarditis: a multicenter, prospective, cohort study. *Medicine (Baltimore)* 2015;94:e1816.
- [3] Bor DH, Woolhandler S, Nardin R, Bruschi J, Himmelstein DU. Infective endocarditis in the U.S., 1998-2009: a nationwide study. *PLoS One* 2013; 8:e60033.
- [4] Slipczuk L, Codolosa JN, Davila CD, Romero-Corral A, Yun J, Pressman GS *et al.* Infective endocarditis epidemiology over five decades: a systematic review. *PLoS One* 2013;8:e82665.
- [5] Pant S, Patel NJ, Deshmukh A, Golwala H, Patel N, Badheka A *et al.* Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. *J Am Coll Cardiol* 2015;65:2070-6.
- [6] Cresti A, Chiavarelli M, Scalese M, Nencioni C, Valentini S, Guerrini F *et al.* Epidemiological and mortality trends in infective endocarditis, a 17-year population-based prospective study. *Cardiovasc Diagn Ther* 2017;7:27-35.
- [7] Fedeli U, Schievano E, Buonfrate D, Pellizzer G, Spolaore P. Increasing incidence and mortality of infective endocarditis: a population-based study through a record-linkage system. *BMC Infect Dis* 2011;11:48.
- [8] Federspiel JJ, Stearns SC, Peppercorn AF, Chu VH, Fowler VG. Increasing US rates of endocarditis with *Staphylococcus aureus*: 1999-2008. *Arch Intern Med* 2012;172:363-5.
- [9] Leroy O, Georges H, Devos P, Bitton S, De Sa N, Dedrie C *et al.* Infective endocarditis requiring ICU admission: epidemiology and prognosis. *Ann Intensive Care* 2015;5:45.
- [10] Sunder S, Grammatico-Guillon L, Baron S, Gaborit C, Bernard-Brunet A, Garot D *et al.* Clinical and economic outcomes of infective endocarditis. *Infect Dis (Lond)* 2015;47:80-7.
- [11] Bustamante J, Tamayo E, Flórez S, Telleria JJ, Bustamante E, López J *et al.* Toll-like receptor 2 R753Q polymorphisms are associated with an increased risk of infective endocarditis. *Rev Esp Cardiol* 2011;64: 1056-9.
- [12] Khan O, Shafi AM, Timmis A. International guideline changes and the incidence of infective endocarditis: a systematic review. *Open Heart* 2016; 3:e000498.
- [13] Figuerola-Tejerina A, Rodríguez-Caravaca G, Bustamante-Munguira J, SanRomán-Montero JM, Durán-Poveda M. Epidemiological surveillance and surgical site infection risk factors after cardiac surgery: prospective cohort study. *Rev Esp Cardiol* 2016;69:842-8.
- [14] O'Gara PT. Infective endocarditis 2006: indications for surgery. *Trans Am Clin Climatol Assoc* 2007;118:187-98.
- [15] Baddour LM, Wilson WR, Bayer AS, Fowler VG, Tleyjeh IM, Rybak MJ *et al.* Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation* 2015; 132:1435-86.
- [16] Head SJ, Mokhles MM, Osnabrugge RL, Bogers AJ, Kappetein AP. Surgery in current therapy for infective endocarditis. *Vasc Health Risk Manag* 2011;7:255-63.

- [17] Bin Abdulhak AA, Tleyjeh IM. Indications of surgery in infective endocarditis. *Curr Infect Dis Rep* 2017;19:10.
- [18] Kim DH, Kang DH, Lee MZ, Yun SC, Kim YJ, Song JM *et al.* Impact of early surgery on embolic events in patients with infective endocarditis. *Circulation* 2010;122:S17-22.
- [19] Liang F, Song B, Liu R, Yang L, Tang H, Li Y. Optimal timing for early surgery in infective endocarditis: a meta-analysis. *Interact CardioVasc Thorac Surg* 2016;22:336-45.
- [20] Kang DH, Kim YJ, Kim SH, Sun BJ, Kim DH, Yun SC *et al.* Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med* 2012;366:2466-73.
- [21] Informe de hospitalización-CMBD-Registro de altas. Informe Resumen 2014. Estadística de Gasto Sanitario Público (EGSP). Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad, 2016.
- [22] Alkaline Software Inc. The Web's Free 2014 Medical Coding Reference. 2010 ICD-9-CM Diagnosis Codes. <http://www.icd9data.com/>.
- [23] Hoen B, Alla F, Selton-Suty C, Béguinot I, Bouvet A, Briançon S *et al.* Changing profile of infective endocarditis: results of a 1-year survey in France. *JAMA* 2002;288:75-81.
- [24] Tornos P, lung B, Permanyer-Miralda G, Baron G, Delahaye F, Gohlke-Bärwolf C *et al.* Infective endocarditis in Europe: lessons from the Euro heart survey. *Heart* 2005;91:571-5.
- [25] Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG Jr, Bayer AS *et al.* Clinical presentation, etiology and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Pro prospective Cohort Study. *Arch Intern Med* 2009;169:463-73.
- [26] Olmos C, Vilacosta I, Habib G, Maroto L, Fernández C, López J *et al.* Risk score for cardiac surgery in active left-sided infective endocarditis. *Heart* 2017;103:1435-42.
- [27] Kemp CD, Arnaoutakis GJ, George TJ, Smith MA, Patel ND, Cameron DE *et al.* Valve surgery for infective endocarditis is associated with high hospital charges. *J Heart Valve Dis* 2013;22:110-17.
- [28] Blázquez C, González N, Moreno P. Pharmaceutical expenditure as a determinant of health outcomes in EU countries. *Estudios de Economía Aplicada* 2013;379-96.
- [29] Kanafani ZA, Kanj SS, Cabell CH, Cecchi E, Oliveira Ramos A, Lejko-Zupanc T *et al.* Revisiting the effect of referral bias on the clinical spectrum of infective endocarditis in adults. *Eur J Clin Microbiol Infect Dis* 2010;29:1203-10.
- [30] Bin Abdulhak AA, Baddour LM, Erwin PJ, Hoen B, Chu VH, Mensah GA *et al.* Global and regional burden of infective endocarditis, 1990-2010: a systematic review of the literature. *Glob Heart* 2014;9:131-43.