ESC European Society of Cardiology

European Heart Journal - Quality of Care and Clinical Outcomes (2025) **00**, 1–14
https://doi.org/10.1093/ehjqcco/qcaf145

ORIGINAL ARTICLE

Clinical characteristics, management and outcomes of enterococcal infective endocarditis: an ancillary study from the ESC-EORP EURO-ENDO registry

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Received 6 August 2025; revised 1 November 2025; accepted 19 November 2025

Aims Enterococcal infective endocarditis (EIE) represents a growing proportion of infective endocarditis (IE) cases, particularly among elderly and comorbid patients. EIE poses diagnostic and therapeutic challenges, notably regarding optimal antimicrobial therapy and surgical decision-making. We aimed to compare the clinical characteristics, management, and outcomes of EIE vs. non-enterococcal IE (NEIE) in the ESC-EORP EURO-ENDO registry.

Methods and results This ancillary analysis of the prospective EURO-ENDO registry included adult patients with definite or possible IE enrolled between January 2016 and March 2018. Patients with monomicrobial EIE were compared with those with NEIE. Clinical, microbiological, imaging, and therapeutic data were analysed. Multivariable logistic regression including EuroSCORE II and valve status identified independent predictors of in-hospital mortality. Among 3083 patients, 365 (12%) had monomicrobial EIE. Compared with NEIE, EIE patients were older (mean 68 vs. 58 years), had more comorbidities, and more frequent prosthetic valve involvement (41% vs. 26%). Aortic valve localization and colonic uptake on PET/CT were also more common. In-hospital mortality was similar (16% vs. 17%). After adjustment for EuroSCORE II and valve status, EIE was not independently associated with higher in-hospital mortality (adjusted OR 0.67 [95% confidence interval 0.42–1.04]; $P = 0.083$). Among 195 EIE patients with 1-year follow-up, recurrence occurred in 6%. Healthcare-associated acquisition, prosthetic valve infection, and recurrence were associated with worse outcomes and lower surgical rates.

Conclusion EIE affects older, high-risk patients. After adjustment for operative risk, mortality was comparable to other aetiologies, highlighting the need for tailored diagnostic and therapeutic strategies.

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Lay summary

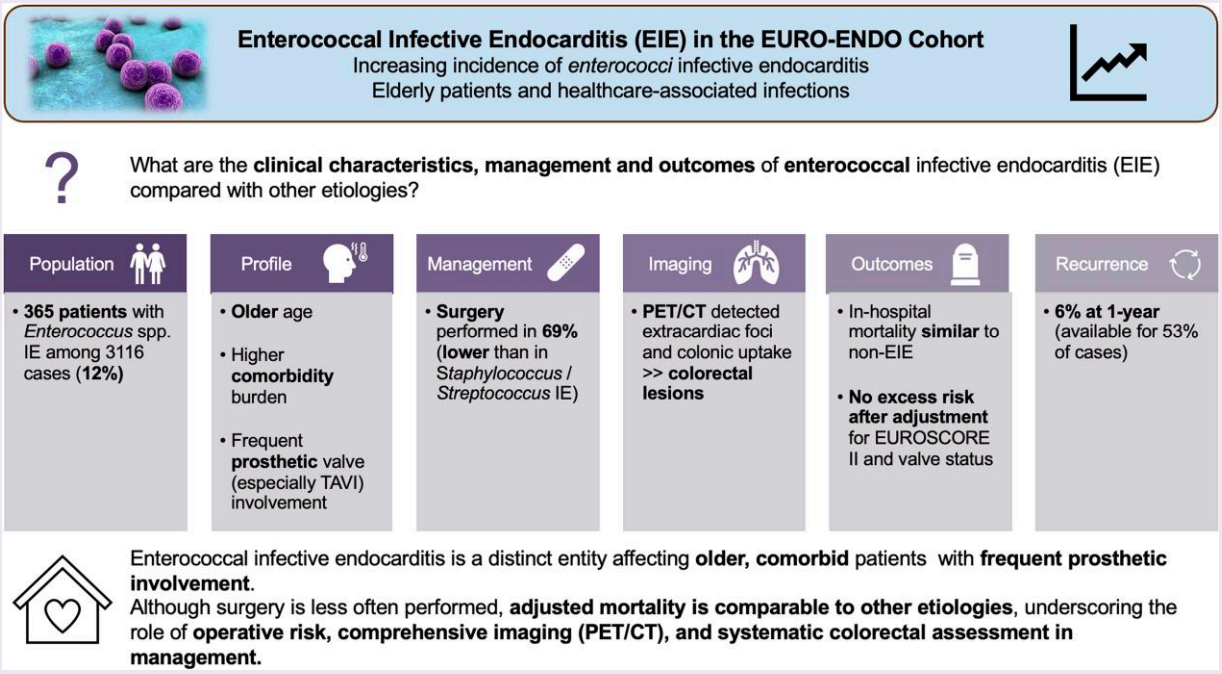
Infective endocarditis (IE) is a serious infection of the heart valves. One specific form, called enterococcal endocarditis, is becoming more common, especially in older patients with other health problems and in those who have had recent contact with hospitals or medical procedures.

We analysed data from over 3000 patients in the large European EURO-ENDO registry to better understand how enterococcal endocarditis differs from other forms of IE. We found that patients with enterococcal IE were older, sicker, and more likely to have artificial heart valves, such as those implanted during open-heart surgery or through transcatheter techniques (TAVI).

Although their symptoms were sometimes less severe at the beginning, these patients had fewer surgeries and more frequent recurrences of the infection. We also found that early surgery and better imaging techniques, such as PET scans, were linked to better outcomes.

This study highlights the need for personalized treatment strategies in this vulnerable population, including better diagnostic tools, more consistent use of surgery when needed, and thorough investigation for hidden sources of infection, such as colon cancer. Improving the care of patients with enterococcal endocarditis could help prevent relapses and save lives.

Graphical abstract



Keywords

Enterococcal endocarditis • Prosthetic valve infection • Surgical management • Recurrence • Healthcare-associated infection • Dual beta-lactam therapy

Key Learning Points

- Enterococcal infective endocarditis (EIE) primarily affects older, comorbid patients and is frequently associated with prosthetic valves and healthcare-associated acquisition.
- Despite high rates of surgical indication, surgery is often underused in EIE, particularly in prosthetic valve infections, and this is associated with worse outcomes.
- Advanced imaging techniques (notably PET/CT) and systematic colorectal evaluation are underutilized but may improve diagnosis and guide treatment in EIE.
- Recurrence within 1 year, although relatively infrequent, highlights the complexity of antimicrobial management and the importance of optimized source control.
- Tailored management strategies, including multidisciplinary heart team evaluation and individualized antibiotic regimens, are essential to improve outcomes in this high-risk population.

Introduction

Infective endocarditis (IE) remains a life-threatening disease with shifting epidemiology in high-income countries.[1] Among its causative agents, enterococci have emerged as the third most frequent pathogens, after *Staphylococcus aureus* and streptococci, accounting for ~10–15% of all IE cases.[1,2] *Enterococcus faecalis* is the predominant species, responsible for more than 90% of cases, but other species—such as *E. faecium*, *E. gallinarum*, and *E. hirae*—may occasionally be involved and pose additional diagnostic and therapeutic challenges.

Enterococcal infective endocarditis (EIE) predominantly affects elderly patients[3] with substantial comorbidities and frequent prior exposure to healthcare environments.[4,5] Given the increasing use of TAVI procedures and the vulnerability of this population to nosocomial infections, enterococcal IE is emerging as a particularly relevant threat in this subgroup.[6] These features were already highlighted in the large Spanish prospective cohort by Pericàs *et al.*[7] in 2020, which established a robust clinical and microbiological profile of EIE in real-world settings. EIE is increasingly recognized as a healthcare-associated infection[4,5,8] and is often underdiagnosed due to its subacute presentation[3] and lack of systematic echocardiographic screening in persistent bacteraemia. Tools such as the NOVA score may help stratify risk and optimize diagnostic yield in this context.[9-12] Compared to other aetiologies, EIE exhibits a distinct clinical and microbiological profile, marked by fewer embolic complications but a higher incidence of persistent or relapsing infection.[3,5,7,13-16]

From a therapeutic standpoint, EIE represents a significant challenge. Enterococci display intrinsic resistance to many antibiotics, limiting the efficacy of monotherapy and requiring synergistic regimens. While aminoglycoside–β-lactam combinations have long been considered standard,[2] their use is now questioned due to nephrotoxicity and increasing resistance.[17] Dual β-lactam therapy (e.g. ampicillin–ceftriaxone) has emerged as a promising alternative,[17-19] though long-term outcomes and relapse rates remain insufficiently studied.[20,21] Moreover, the role of surgery in this frail population is often debated, and recurrence rates are among the highest of all IE pathogens.[14]

Despite its growing importance, EIE remains poorly characterized in large prospective cohorts.[7] Most existing data derive from single-centred series or retrospective studies, often lacking in microbiological granularity or long-term follow-up. In this context, the ESC-EORP EURO-ENDO registry[22] offers a unique opportunity to study EIE within a contemporary, multicentre, and adjudicated prospective cohort.

This ancillary study of the EURO-ENDO registry specifically aims to characterize the clinical profile, management, and outcomes of EIE in comparison with non-enterococcal IE (NEIE), with particular emphasis on subgroups defined by valve status, healthcare-association, and recurrence. Given the growing body of literature linking *E. faecalis* IE to underlying colorectal pathology,[23-25] such associations deserve further exploration. This analysis addresses an important gap in the literature and may help guide more tailored, evidence-based strategies for the diagnosis and management of this increasingly prevalent form of IE.

Methods

Study design and population

This is an ancillary analysis of the prospective European Society of Cardiology (ESC) EURObservational Research Programme (EORP) EURO-ENDO registry.[22] The design and main results of the registry have been previously published. In brief, EURO-ENDO is a multicentre, observational registry that prospectively included adult patients (aged ≥18 years) with a diagnosis of IE according to the 2015 ESC diagnostic criteria.[26] Patients were enrolled between January 2016 and March 2018 in 156 centres across 40 countries, corresponding to the official ESC-EORP data collection period. These represent the most recent validated and quality-checked data available from the EURO-ENDO registry at the time of analysis.

For the present analysis, we selected all patients with *Enterococcus* spp. IE, defined as either definite or possible IE, and with at least one positive blood culture for *Enterococcus* species or molecular identification from valvular tissue. Patients with polymicrobial endocarditis, including *Enterococcus* spp. and any other pathogen, were excluded. The comparator group comprised all patients with non-enterococcal monomicrobial IE.

We performed a comprehensive comparison of baseline characteristics, clinical presentation, echocardiographic findings, management, and outcomes between EIE and non-EIE cases. In addition, we conducted predefined subgroup analyses among patients with EIE: native valve vs. prosthetic valve EIE; healthcare-associated vs. community-acquired EIE; recurrent vs. non-recurrent EIE; and comparison of EIE with the two other most frequent bacterial species associated with monomicrobial IE: *S. aureus* and streptococcal species.

Data collection

Data were collected prospectively using a standardized electronic case report form (eCRF). Collected variables included demographics, comorbidities, clinical presentation, microbiological data, echocardiographic and advanced imaging findings, treatment strategies (including antibiotic regimens, surgical indications, and procedures), and outcomes at hospital discharge and 1-year follow-up.

Definitions

IE was classified as definite or possible according to the modified Duke criteria, in accordance with the 2015 ESC guidelines,[26] which incorporate findings from transthoracic (TTE) and transoesophageal echocardiography (TEE), as well as additional imaging modalities (PET-CT, cardiac CT).

EIE was defined as a microbiologically confirmed *Enterococcus* spp. infection in the context of definite or possible IE.

Healthcare-associated IE was defined as an IE occurring in patients with recent exposure to a healthcare environment (such as hospitalization or invasive procedures within the previous 90 days), chronic haemodialysis, or residence in a nursing home.

Early surgery was defined as valve surgery performed during the initial hospital admission.

Relapse was defined as a new episode of IE due to the same *Enterococcus* species occurring within 6 months of initial diagnosis.

Recurrence was defined as a new episode of IE occurring more than 6 months after the initial diagnosis, regardless of the causative organism.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range), and categorical variables as absolute numbers and percentages. Comparisons between groups (e.g. enterococcal vs. streptococcal vs. staphylococcal IE; native vs. prosthetic valve IE; healthcare-associated vs. community-acquired IE; recurrent vs. non-recurrent IE) were performed using the Student's *t*-test or Mann–Whitney U-test for continuous variables, and the χ^2 or Fisher's exact test for categorical variables, as appropriate. Survival analysis was performed using Kaplan–Meier curves with log-rank testing to compare mortality between subgroups. To identify factors independently associated with in-hospital mortality, a multivariable logistic regression model was built with enterococcal aetiology as the exposure of interest. Covariates included EuroSCORE II (entered as a continuous variable), valve status (native vs. prosthetic), chronic kidney disease, cancer, heart failure, septic shock, healthcare-associated acquisition, and surgery performed. Variables already contained within EuroSCORE II (e.g. age, sex, renal dysfunction, diabetes) were not re-entered separately to avoid collinearity. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were reported. Missing data were handled by complete-case analysis. A two-tailed $P < 0.05$ was considered statistically significant. All analyses were conducted using R software (version 4.4.1).

Results (Structured Graphical Abstract)

Comparison of baseline characteristics, treatment strategies, and clinical outcomes between enterococcal and non-enterococcal infective endocarditis

Of the 3083 patients included in the EURO-ENDO registry, 365 (12%) had EIE. EIE patients were older than those with NEIE, with a mean age of 68 vs. 58 years ($P < 0.001$), and more frequently had diabetes (30% vs. 22%, $P < 0.001$), chronic kidney disease (23% vs. 17%, $P = 0.007$), and cancer (19% vs. 11%, $P < 0.001$). A history of prior surgical aortic valve replacement (38% vs. 23%, $P < 0.001$) or TAVI (24% vs. 12%, $P = 0.002$) and chronic heart failure (29% vs. 22%, P 0.007) was also more common in EIE.

Clinically, EIE was more often associated with prosthetic valve endocarditis (41% vs. 26%, $P < 0.001$) and more frequently presented with aortic valve involvement (63% vs. 49%, $P < 0.001$) and heart failure at admission (30% vs. 27%, $P = 0.007$), while device-related IE (6% vs. 10%, $P = 0.018$) and septic shock (4% vs. 7%, $P = 0.027$) were less frequent compared to NEIE. Splenic emboli (8% vs. 5%, $P < 0.001$), spondylodiscitis (8% vs. 4%, $P = 0.004$), and a suspected gastrointestinal or urinary source of infection (33% vs. 8%, $P < 0.001$) were also more common in EIE, with a higher rate of colonic PET-CT uptake (31% vs. 18%, $P = 0.040$). Rates of surgery indicated and performed did not differ between groups (surgery indicated in 69% and performed in 72% of EIE cases, vs. 70% and 74% in NEIE, respectively), with a mean EUROSCORE II[27] of 13.1 ± 15.4 in the EIE group and 11.3 ± 13.6 in the NEIE group ($P = 0.007$). In-hospital mortality was similar between groups (16% vs. 17%, $P = 0.579$), and the 1-year recurrence rate did not significantly differ (6% vs. 4%, $P = 0.161$), although Enterococcus spp. and gastrointestinal streptococci accounted for a higher proportion of recurrences in EIE (50% vs. 15%, $P = 0.013$) (*Table 1*).

Multivariable analysis of in-hospital mortality

To account for potential confounding related to age, comorbidity, and operative risk, a multivariable logistic regression model including EuroSCORE II and valve status was performed (*Table 2*). In this age- and comorbidity-adjusted model, EIE was not independently associated with higher in-hospital mortality (aOR 0.67, 95% CI 0.42–1.04; $P = 0.083$).

EuroSCORE II was a strong independent predictor of death (aOR 1.05 per point; $P < 0.001$).

Chronic kidney disease and heart failure showed borderline associations with mortality ($P \approx 0.05$–0.07), while surgery performed was consistently associated with lower mortality (aOR 0.23 [0.17–0.31]; $P < 0.001$).

Neither valve prosthesis status nor cancer reached statistical significance after full adjustment.

These findings indicate that crude differences in mortality between enterococcal and non-enterococcal IE largely reflect baseline risk and operative selection rather than pathogen-specific virulence.

Comparison of baseline characteristics, treatment strategies, and clinical outcomes in enterococcal, staphylococcal, and streptococcal infective endocarditis

Patients with enterococcal IE were significantly older (mean age 67.7 ans) than those with staphylococcal (59 ans) or streptococcal IE (61 ans) ($P < 0.001$). Diabetes (30%), cancer (19%), chronic kidney disease (23%), previous heart failure (29%), and previous endocarditis (13%) were all more common in enterococcal IE compared to the other groups ($P < 0.001$ for all except previous endocarditis, $P = 0.009$).

Staphylococcal IE showed higher rates of intravenous drug use (11%), device-related infection (15%), tricuspid valve involvement (18%), embolic events (31%), pulmonary embolism (10%), and septic shock (11%) compared to the other groups.

Aortic valve involvement (65%) and prosthetic valve endocarditis (41%) were most frequent in enterococcal IE ($P < 0.001$ for both).

Colonoscopy was performed more often in enterococcal (16%) and streptococcal IE (17%) than in staphylococcal IE (2%) ($P < 0.001$), with the highest rate of positive findings in the streptococcal group (71%, $P = 0.003$).

Prior antibiotic exposure was more common in enterococcal IE (45%, $P < 0.001$).

Surgical indications were slightly less frequent in enterococcal IE (67%) than in staphylococcal IE (72%, $P = 0.016$). However, surgery was performed less often in enterococcal IE (61%) compared to staphylococcal (79%) and streptococcal IE (75%, $P < 0.001$).

In summary, enterococcal IE affects an older and more comorbid population, with more frequent prosthetic involvement and prior antibiotic exposure; staphylococcal IE is associated with more intravenous drug use, device-related infections, and complications; while streptococcal IE stands out by the diagnostic yield of colonoscopy and aortic involvement. All significant differences are summarized in *Table 3*.

Comparison of baseline characteristics, treatment strategies, and clinical outcomes in healthcare-associated (including nosocomial) vs. community-acquired infective endocarditis

Healthcare-associated EIE represented 18% (60/326) of enterococcal endocarditis cases. Compared to community-acquired EIE, patients in the healthcare-associated group were significantly older (mean age 74 vs. 66 years, $P < 0.001$) and more frequently required dialysis (13% vs. 4%, $P = 0.012$). There was no significant difference regarding gender, diabetes, cancer, or chronic kidney disease. Prosthetic valve endocarditis was more frequent in healthcare-associated cases (57% vs. 33%, $P = 0.001$), and a prior intravenous catheter was more common (20% vs. 7%, $P = 0.005$).

Inflammatory markers were higher in healthcare-associated EIE, with a greater mean C-reactive protein (CRP) (106 vs. 70 mg/L, $P = 0.006$). There was a non-significant trend towards lower platelet counts (193 vs. 213 G/L, $P = 0.081$). The rate of septic shock was higher in the healthcare-associated group (13% vs. 4%, $P = 0.012$).

Regarding treatment and outcomes, vancomycin use was more frequent in healthcare-associated cases (18% vs. 6%, $P = 0.004$), but there were no significant differences in aminoglycoside, amoxicillin, or daptomycin use. Surgery was indicated and performed in 47% of patients in both groups ($P = 0.547$), with similar rates of surgery actually performed. In-hospital mortality was significantly higher in healthcare-associated EIE (32% vs. 12%, $P = 0.001$).

The main clinical and prognostic features are summarized in *Table 4*.

Comparison of baseline characteristics, treatment strategies, and clinical outcomes in native valve vs. prosthetic valve enterococcal infective endocarditis

Nearly half of all enterococcal IE cases occurred on a prosthetic valve. Patients with prosthetic valve EIE were older (mean age 73

Table 1 Comparison of baseline characteristics, treatment strategies, and clinical outcomes in enterococcal (EIE) vs. non-enterococcal infective endocarditis (NEIE)

Variable	EIE ($n = 365$)	NEIE ($n = 2718$)	*P*-value
Age, mean ± SD (years)	67.7 ± 14.9	58.1 ± 18.2	<0.001
Male sex	222/365 (60.8%)	1862/2718 (68.5%)	<0.001
Weight, mean ± SD (kg)	76.0 ± 17.5	74.2 ± 17.9	0.094
Diabetes mellitus	110/365 (30.1%)	587/2714 (21.6%)	<0.001
Cancer	70/364 (19.2%)	287/2691 (10.7%)	<0.001
Chronic kidney disease	83/365 (22.7%)	462/2715 (17.0%)	0.007
Chronic heart failure	93/319 (29.2%)	557/2489 (22.4%)	0.007
Previous endocarditis	49/365 (13.4%)	223/2718 (8.2%)	<0.001
Prior surgical AVR	138/365 (38.1%)	636/2718 (23.4%)	<0.001
Prior TAVI	24/99 (24.2%)	45/374 (12.0%)	0.002
Prosthetic valve IE	125/304 (41.1%)	578/2198 (26.3%)	<0.001
Device-related IE (PM/ICD)	23/365 (6.3%)	277/2711 (10.2%)	0.018
Heart failure at admission	109/365 (29.9%)	728/2718 (26.8%)	0.007
Septic shock	14/365 (3.8%)	187/2717 (6.9%)	0.027
Aortic valve involvement	230/365 (63.0%)	1320/2711 (48.7%)	<0.001
Mitral valve involvement	164/365 (44.9%)	1289/2711 (47.5%)	0.347
Tricuspid valve involvement	46/365 (12.6%)	477/2711 (17.6%)	0.017
Abscess	32/365 (8.8%)	328/2718 (12.1%)	0.065
Embolic events	79/363 (21.8%)	552/2706 (20.4%)	0.546
Splenic emboli	33/363 (8.3%)	135/2706 (5.0%)	<0.001
Spondylodiscitis	28/363 (7.7%)	117/2706 (4.3%)	0.004
Colonic PET-CT uptake	14/45 (31.1%)	49/273 (17.9%)	0.040
Gastro or urinary suspected source	104/317 (33.2%)	197/2475 (8.0%)	<0.001
Healthcare-associated IE	60/326 (18.4%)	415/515 (16.5%)	0.386
CRP, mean ± SD (mg/L)	77.9 ± 71.2	94.2 ± 94.1	0.002
WBC, mean ± SD (G/L)	10.4 ± 5.1	11.9 ± 6.7	<0.001
Haemoglobin, mean ± SD (g/dL)	10.4 ± 1.9	11.0 ± 2.2	<0.001
Platelet count, mean ± SD (G/L)	210.2 ± 97.1	224.0 ± 112.3	0.019
Prior antibiotic exposure	124/274 (45.3%)	809/2112 (38.3%)	0.027
Colonoscopy performed	57/365 (15.6%)	158/2718 (5.8%)	<0.001
Aminoglycoside use	211/365 (57.8%)	1585/2718 (58.3%)	<0.001
Amoxicillin/ampicillin use	282/365 (77.2%)	699/2718 (25.7%)	<0.001
Ceftriaxone use	218/365 (59.7%)	802/2718 (29.5%)	<0.001
Surgery indicated	249/363 (68.6%)	1880/2704 (69.5%)	0.718
EUROSCORE II, mean ± SD	13.1 ± 15.4	11.3 ± 13.6	0.007
Haemodynamic surgical indication	132/363 (36.4%)	852/2704 (31.5%)	0.063
Infectious surgical indication	141/363 (38.8%)	1227/2704 (45.4%)	0.019
Embolic surgical indication	78/363 (21.5%)	609/2704 (22.5%)	0.657
Surgery performed	178/249 (71.5%)	1395/1879 (74.2%)	0.352
Definite IE at discharge	338/363 (92.6%)	2245/2704 (82.6%)	<0.001
In-hospital mortality	58/363 (16.0%)	465/2704 (17.1%)	0.579
1-year recurrence	12/195 (6.1%)	55/1379 (4.0%)	0.161
1-year recurrence to enterococci or GI streptococci	6/12 (50.0%)	8/55 (14.5%)	0.013

IE, infective endocarditis; EIE, enterococcal infective endocarditis; NEIE, non-enterococcal infective endocarditis; AVR, aortic valve replacement; TAVI, transcatheter aortic valve implantation; PM, pacemaker; ICD, implantable cardioverter-defibrillator; CRP, C-reactive protein; WBC, white blood cell count; SD, standard deviation; GI, gastrointestinal.

vs. 65 years) and more likely to have a prior history of endocarditis (22% vs. 5%) compared to those with native valve infection. Most prosthetic valve infections involved a bioprosthesis, while transcatheter aortic valve implantation (TAVI) and mechanical valves were also represented.

Table 2 Multivariable logistic regression for in-hospital mortality

Variable	Adjusted OR (95% CI)	*P*-value
Enterococcal IE	0.67 (0.42–1.04)	0.083
EuroSCORE II (per point)	1.05 (1.04–1.06)	<0.001
Chronic kidney disease	1.43 (0.99–2.04)	0.051
Heart failure	1.37 (0.97–1.93)	0.072
Cancer	1.54 (1.02–2.30)	0.038
Surgery performed	0.23 (0.17–0.31)	<0.001
Prosthetic valve	0.73 (0.52–1.01)	0.057

IE, infective endocarditis.

Clinically, prosthetic valve EIE was associated with a more severe presentation. Aortic abscess was identified in 20% of prosthetic cases compared to 7% in native valve infections, and severe prosthetic dysfunction—such as dehiscence or regurgitation—was observed only in the prosthetic group. Although heart failure at admission was common in both groups, cardiogenic shock was seen exclusively in patients with native valve EIE. Advanced imaging techniques, particularly PET/CT, were more frequently utilized in prosthetic valve EIE (28% vs. 8%), reflecting the greater diagnostic challenges in this subgroup. Management of prosthetic valve EIE often requires complex, multi-drug antibiotic regimens.

Surgical intervention was indicated in the majority of cases, though less frequently in prosthetic valve EIE (64% vs. 80%), and was performed in 65% of prosthetic and 74% of native valve cases, with no significant difference between groups ($P = 0.140$). In-hospital mortality rates were similar between groups (13% for prosthetic vs. 19% for native), but patients with prosthetic valve EIE had a substantially higher risk of 1-year recurrence (10% vs. 0%).

Among patients with prosthetic valve EIE, survival at 1 year was significantly higher in those who underwent surgery compared to those managed medically (*Figure 1*), underscoring the critical prognostic value of surgical management in this high-risk group.

Further details on clinical features, management, and outcomes are summarized in *Table 5*.

Table 3 Comparison of baseline characteristics, treatment strategies, and clinical outcomes in patients with enterococcal, staphylococcal, and streptococcal IE

Variable	Enterococcal	Staphylococcal	Streptococcal	*P*-value
Age, mean ± SD (years)	67.7 ± 14.9 ($n = 362$)	58.8 ± 17.8 ($n = 1016$)	60.6 ± 16.9 ($n = 436$)	<0.001
Male sex	222/365 (60.8%)	724/1025 (70.7%)	273/438 (62.3%)	<0.001
Chronic kidney disease	83/365 (22.7%)	234/1023 (22.9%)	36/438 (8.2%)	<0.001
Diabetes mellitus	110/365 (30.1%)	273/1021 (26.7%)	79/438 (18.0%)	<0.001
Cancer	70/364 (19.2%)	108/1017 (10.6%)	60/433 (13.9%)	<0.001
Previous heart failure	93/319 (29.2%)	243/934 (26.0%)	58/374 (15.5%)	<0.001
Previous endocarditis	49/365 (13.4%)	91/1025 (8.9%)	32/438 (7.3%)	0.009
Intravenous drug use	19/363 (5.2%)	113/1016 (11.1%)	8/433 (1.8%)	<0.001
Device-related IE (PM/ICD)	28/365 (7.7%)	155/1025 (15.1%)	17/430 (4.0%)	<0.001
Aortic valve involvement	229/355 (64.5%)	399/995 (40.1%)	240/429 (55.9%)	<0.001
Tricuspid valve involvement	21/355 (5.9%)	174/995 (17.5%)	19/429 (4.4%)	<0.001
Embolic events	81/365 (22.2%)	314/1025 (30.6%)	84/438 (19.2%)	<0.001
Pulmonary embolism	13/365 (3.6%)	99/1025 (9.7%)	9/438 (2.1%)	<0.001
Septic shock	14/365 (3.8%)	113/1025 (11.0%)	12/437 (2.7%)	<0.001
C-reactive protein, mean ± SD (mg/L)	77.9 ± 71.2 ($n = 334$)	121.6 ± 110.0 ($n = 927$)	67.8 ± 66.9 ($n = 396$)	<0.001
Prior antibiotic exposure	165/365 (45.3%)	396/1025 (38.6%)	128/438 (29.2%)	<0.001
Colonoscopy performed	57/365 (15.6%)	20/1025 (2.0%)	75/438 (17.1%)	<0.001
Positive colonoscopy	29/57 (50.9%)	10/20 (50.0%)	53/75 (70.7%)	0.003
Prosthetic valve endocarditis	125/304 (41.1%)	216/780 (27.7%)	86/388 (22.2%)	<0.001
Surgery indicated	242/362 (66.9%)	730/1012 (72.1%)	290/430 (67.4%)	0.016
Haemodynamic indication	104/362 (28.7%)	336/1012 (33.2%)	93/430 (21.6%)	<0.001
Infectious indication	93/362 (25.7%)	403/1012 (39.8%)	170/430 (39.5%)	<0.001
Embolic indication	50/362 (13.8%)	185/1012 (18.3%)	57/430 (13.3%)	0.038
Surgery performed	147/242 (60.7%)	575/730 (78.8%)	217/290 (74.8%)	<0.001
In-hospital mortality	58/363 (16.0%)	169/1025 (16.5%)	61/438 (13.9%)	0.488

IE, infective endocarditis; SD, standard deviation; PM, pacemaker; ICD, implantable cardioverter-defibrillator.

Table 4 Comparison of baseline characteristics, treatment strategies, and clinical outcomes in healthcare-associated (including nosocomial) vs. community-acquired EIE

Variable	Healthcare-associated ($n = 60$)	Community-acquired ($n = 266$)	*P*-value
Age, mean ± SD (years)	73.7 ± 11.0 ($n = 60$)	66.3 ± 15.5 ($n = 266$)	<0.001
Male sex	35/60 (58.3%)	167/266 (62.8%)	0.500
Diabetes mellitus	23/60 (38.3%)	77/266 (28.9%)	0.126
Cancer	13/60 (21.7%)	50/266 (18.8%)	0.670
Chronic kidney disease	17/60 (28.3%)	58/266 (21.8%)	0.282
Dialysis	8/60 (13.3%)	10/266 (3.8%)	0.012
Previous heart failure	17/51 (33.3%)	76/266 (28.6%)	0.522
Prior intravenous catheter	12/60 (20.0%)	18/266 (6.8%)	0.005
Prosthetic valve endocarditis	34/60 (56.7%)	88/266 (33.1%)	0.001
Device-related IE (PM/ICD)	6/57 (10.5%)	16/262 (6.1%)	0.270
Aortic valve involvement	30/60 (50.0%)	133/266 (50.0%)	1.000
Mitral valve involvement	31/60 (51.7%)	111/266 (41.7%)	0.170
Tricuspid valve involvement	5/60 (8.3%)	10/266 (3.8%)	0.184
Vegetation size, mean ± SD (mm)	13.1 ± 7.6 ($n = 54$)	13.4 ± 7.5 ($n = 228$)	0.835
Embolic events	11/60 (18.3%)	61/266 (22.9%)	0.456
Splenic emboli	3/60 (5.0%)	23/266 (8.6%)	0.480
Spondylodiscitis	6/60 (10.0%)	19/266 (7.1%)	0.483
CRP, mean ± SD (mg/L)	105.7 ± 91.4 ($n = 55$)	70.2 ± 65.9 ($n = 242$)	0.006
White blood cell count, mean ± SD (G/L)	11.1 ± 6.1 ($n = 60$)	10.1 ± 4.7 ($n = 259$)	0.190
Haemoglobin, mean ± SD (g/dL)	10.2 ± 1.7 ($n = 60$)	10.4 ± 2.0 ($n = 263$)	0.369
Platelet count, mean ± SD (G/L)	193.0 ± 88.1 ($n = 60$)	212.5 ± 98.1 ($n = 257$)	0.081
Septic shock	8/60 (13.3%)	10/266 (3.8%)	0.012
Colonoscopy performed	5/60 (8.3%)	41/266 (15.4%)	0.166
Positive colonoscopy	1/5 (20.0%)	26/41 (63.4%)	0.085
Vancomycin use	11/60 (18.3%)	16/266 (6.0%)	0.004
Daptomycin use	2/60 (3.3%)	2/266 (0.8%)	0.164
Aminoglycoside use	34/60 (56.7%)	142/266 (53.4%)	0.711
Amoxicillin-based regimen	38/60 (63.3%)	182/266 (68.4%)	0.482
Surgery indicated	28/60 (46.7%)	137/266 (51.5%)	0.547
Surgery performed	28/60 (46.7%)	137/266 (51.5%)	0.547
Death before surgery	3/28 (10.7%)	9/137 (6.6%)	0.435
In-hospital mortality	19/60 (31.7%)	32/266 (12.0%)	0.001

IE, infective endocarditis; EIE, enterococcal infective endocarditis; CRP, C-reactive protein; SD, standard deviation; PM, pacemaker; ICD, implantable cardioverter-defibrillator.

Comparison of baseline characteristics, treatment strategies, and clinical outcomes in recurrent vs. non-recurrent enterococcal infective endocarditis

Recurrence of enterococcal endocarditis within 1 year was observed in a minority of patients (6%). There were no significant differences between patients with and without recurrence regarding age (63 vs. 68 years, $P = 0.398$), male sex (83% vs. 74%, $P = 0.734$), diabetes (17% vs. 34%, $P = 0.343$), chronic kidney disease (8% vs. 6%, $P > 0.999$), or healthcare-associated acquisition (58% vs. 36%, $P = 0.094$).

Rates of surgery indication (50% vs. 70%, $P = 0.198$) and surgery performed (67% vs. 79%, $P = 0.610$) were not statistically different between groups, nor were inflammatory markers at presentation (CRP 68 vs. 76 mg/L, $P = 0.794$). The only variable significantly associated with recurrence was the use of a higher number of antibiotics during treatment (mean 4.7 vs. 3.5, $P = 0.011$).

In-hospital mortality tended to be higher in patients with recurrence (33% vs. 25%, $P = 0.477$), but this difference did not reach statistical significance. Full details are provided in *Table 6*.

Discussion

Key findings and clinical implications

This study represents the largest dedicated analysis of EIE within a contemporary, multicentre, prospective registry.[7,22] Our study confirms that EIE is a distinct clinical entity, predominantly affecting older and comorbid patients, with frequent prosthetic valve involvement. Compared to staphylococcal IE, clinical presentation was less frequently associated with acute complications such as septic shock or embolic

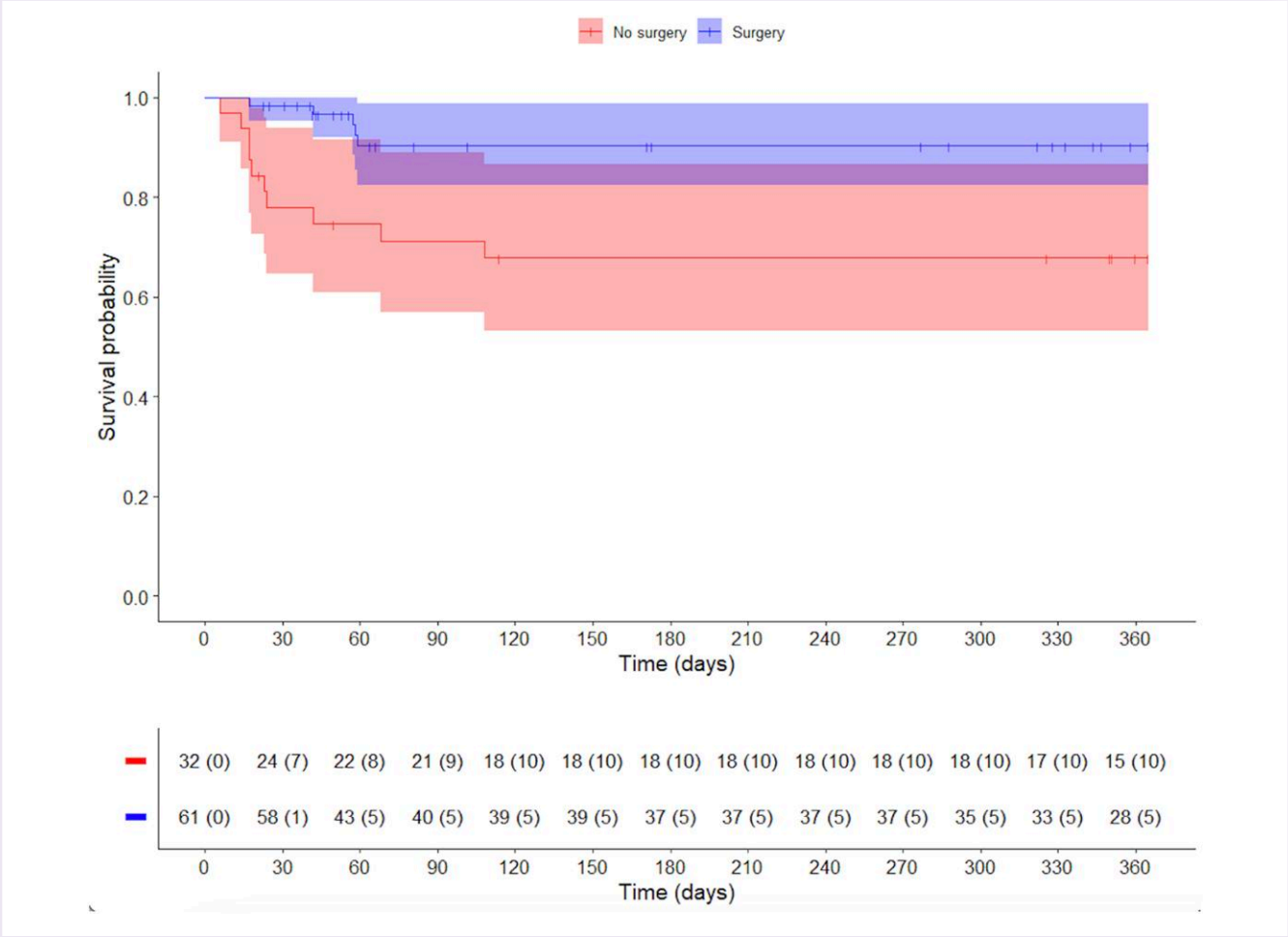


Figure 1 Kaplan–Meier survival estimates at 1 year in patients with enterococcal prosthetic valve endocarditis, according to surgical management. Survival was significantly higher in patients who underwent surgery compared to those managed medically (log-rank test, $P < 0.05$). The shaded areas represent 95% confidence intervals. The number at risk and cumulative events are displayed below the *x*-axis for each group.

events. Although EIE was associated with fewer acute complications than staphylococcal IE, overall outcomes remain suboptimal—possibly due to the high comorbidity burden, frequent prosthetic involvement, and a significantly lower rate of surgery performed compared to other major aetiologies. While a trend towards higher 1-year recurrence was observed in EIE, this difference was not statistically significant. Compared to earlier large-scale studies such as that by Pericàs *et al.*,[7] our dataset offers a more contemporary and geographically diverse perspective, with detailed information on healthcare-associated cases and 1-year follow-up. These findings highlight the need for improved strategies in the prevention, diagnosis, and management of EIE in this high-risk population.[9-11,28] After adjustment for EuroSCORE II and valve status, EIE was not independently associated with higher in-hospital mortality. This finding suggests that the crude similarity in outcomes between enterococcal and non-enterococcal IE primarily reflects differences in baseline comorbidity and operative risk, rather than pathogen-related virulence. In this elderly, high-risk population, prognosis appears largely determined by frailty and the feasibility of surgical management.

A distinct clinical and microbiological phenotype

Patients with EIE were significantly older and had a greater burden of comorbidities compared to those with staphylococcal or streptococcal IE. This clinical profile is consistent with previous cohorts,[3-5,7,13] which have linked *E. faecalis* infection to degenerative valvular substrates, particularly in the elderly. Our study not only confirms but extends these observations by demonstrating a markedly higher prevalence of prosthetic valve and TAVI involvement in EIE. Notably, TAVI-related EIE accounted for over one-fifth of all prosthetic valve infections in our series, highlighting the emerging challenge of enterococcal infection in this rapidly expanding patient population.[6,29-31]

These findings align with recent multicentre studies that report a high proportion of enterococcal IE after TAVI, often associated with adverse outcomes and complex management with infrequent surgical intervention. Given the ageing demographic of TAVI recipients and the increased risk of nosocomial acquisition, EIE is likely to become an increasingly important clinical problem in the coming years.

Diagnostic work-up and the role of advanced imaging

PET/CT imaging proved valuable for detecting both prosthetic involvement and extracardiac infectious foci in EIE.[1] Although the sensitivity of PET/CT for detecting native valve infection is lower than for prosthetic or device-related IE, the technique provides important complementary diagnostic information in *E. faecalis* IE. PET/CT can reveal peripheral septic emboli or metastatic infectious foci, thus contributing to the

Table 5 Comparison of baseline characteristics, treatment strategies, and clinical outcomes in native vs. prosthetic valve EIE

Variable	Native valve IE ($n = 170$)	Prosthetic valve IE ($n = 149$)	*P*-value
Age, mean ± SD (years)	65.0 ± 15.0 ($n = 168$)	72.5 ± 11.7 ($n = 148$)	<0.001
Male sex	104/170 (61.2%)	95/149 (63.8%)	0.671
Prior endocarditis	8/170 (4.7%)	33/149 (22.1%)	<0.001
Diabetes mellitus	52/170 (30.6%)	44/149 (29.5%)	0.837
Cancer	37/170 (21.8%)	26/148 (17.6%)	0.349
Chronic kidney disease	33/170 (19.4%)	39/149 (26.2%)	0.149
Intravenous drug use	12/168 (7.1%)	4/149 (2.7%)	0.048
Heart failure at presentation	40/150 (26.7%)	39/133 (29.3%)	0.619
Cardiogenic shock	11/150 (7.3%)	0/133 (0.0%)	0.001
Previous cardiac surgery (any)	0/170 (0.0%)	149/149 (100.0%)	<0.001
Bioprosthesis (within PVE)	—	86/149 (57.7%)	—
TAVI (within PVE)	—	33/149 (22.2%)	—
Mechanical valve (within PVE)	—	30/149 (20.1%)	—
Platelet count (G/L), mean ± SD	226.2 ± 105.0 ($n = 164$)	202.4 ± 87.4 ($n = 145$)	0.033
Mitral involvement	95/170 (55.9%)	66/149 (44.3%)	0.039
Aortic abscess	12/167 (7.2%)	30/148 (20.3%)	<0.001
Severe regurgitation/stenosis	0/170 (0.0%)	11–13/149 (7.5–8.8%)	<0.001
PET/CT performed	13/170 (7.6%)	41/149 (27.5%)	<0.001
Splenic emboli	18/170 (10.6%)	5/149 (3.4%)	0.013
Number of antibiotics (mean ± SD)	4.0 ± 2.4 ($n = 169$)	3.3 ± 1.4 ($n = 149$)	0.004
Surgery indicated	136/170 (80.0%)	95/149 (63.8%)	0.001
Haemodynamic indication	98/170 (57.6%)	29/149 (19.5%)	<0.001
Surgery performed	126/170 (74.1%)	97/149 (65.1%)	0.140
In-hospital mortality	33/170 (19.4%)	19/149 (12.8%)	0.108
1-year recurrence	0/170 (0.0%)	15/146 (10.3%)	0.003

IE, infective endocarditis; PVE, prosthetic valve endocarditis; TAVI, transcatheter aortic valve implantation; SD, standard deviation.

Duke minor criteria, and enabled the identification of colonic uptake suggestive of underlying malignancy, further supporting the systematic evaluation of the colon in patients with EIE.[23,24] Colonoscopy was performed more frequently in enterococcal IE (15.6%) than in staphylococcal IE (2.0%, $P < 0.001$), while rates were comparable to those observed in streptococcal IE (17.1%). Despite this, overall use of colonoscopy remained suboptimal relative to current ESC guideline recommendations. With over 50% of colonoscopies yielding positive findings in enterococcal IE, our results support previous evidence linking *E. faecalis* bacteraemia to occult colorectal neoplasia and underscore the relevance of systematic PET/CT and endoscopic screening. Although the strongest association between IE and colorectal cancer has historically been described for *Streptococcus gallolyticus*, several recent studies have demonstrated that *Enterococcus faecalis* IE is also associated with a high prevalence of colonic lesions. In the GAMES cohort,[23] nearly 70% of patients with *E. faecalis* IE who underwent colonoscopy had significant colorectal abnormalities, including advanced adenomas or carcinomas in ~15%. Our findings are consistent with this evidence, suggesting that systematic colorectal assessment should be considered in patients with enterococcal IE, not because of a pathogen-specific association, but rather due to the frequent detection of occult digestive pathology revealed by PET/CT or colonoscopy in this population.[24]

Beyond imaging, clinical scores such as the DENOVA score have been developed to help identify patients with *E. faecalis* bacteraemia at high risk for endocarditis, thereby optimizing the use of advanced investigations such as TEE or PET/CT.[9-12]

Surgical management aligned with indications, but disparities persist

Surgical indications were frequent in patients with enterococcal IE, particularly in native valve infections, where 80% of patients were deemed surgical candidates. Among them, 74% ultimately underwent surgery. In prosthetic valve IE, surgical indication was less common (64%), and surgery was performed in 65% of all patients. While this may suggest high adherence to surgical recommendations,[1] the near equivalence between the number of procedures and the number of formal indications in prosthetic cases likely reflects re-evaluation of operability during the hospital course or late decision-making. After adjustment for EuroSCORE II, enterococcal aetiology was not independently associated with higher in-hospital mortality, indicating that surgical decisions in this population were largely driven by operative risk and patient selection rather than by infection severity or pathogen virulence. The lower surgical rate observed in EIE compared with staphylococcal or

Table 6 Comparison of baseline characteristics, treatment strategies, and clinical outcomes in recurrent vs. non-recurrent EIE at 1-year follow-up

Variable	Recurrence ($n = 12$)	No recurrence ($n = 183$)	*P*-value
Age, mean ± SD (years)	62.8 ± 17.9 ($n = 12$)	67.5 ± 14.9 ($n = 183$)	0.398
Male sex	10/12 (83.3%)	135/183 (73.8%)	0.734
Diabetes mellitus	2/12 (16.7%)	63/183 (34.4%)	0.343
Chronic kidney disease	1/12 (8.3%)	10/183 (5.5%)	>0.999
Dialysis	0/12 (0.0%)	10/183 (5.5%)	>0.999
Healthcare-associated IE	7/12 (58.3%)	65/183 (35.5%)	0.094
Prior intravenous catheter	0/12 (0.0%)	13/183 (7.1%)	>0.999
CRP (mg/L), mean ± SD	68.2 ± 71.4 ($n = 12$)	75.5 ± 69.9 ($n = 183$)	0.794
Device-related IE (PM/ICD)	2/12 (16.7%)	10/183 (5.5%)	0.195
Surgery indicated	6/12 (50.0%)	128/183 (69.9%)	0.198
Surgery performed	4/6 (66.7%)	101/128 (78.9%)	0.610
Number of antibiotics (mean ± SD)	4.7 ± 1.7 ($n = 12$)	3.5 ± 1.7 ($n = 183$)	0.011
Third-line regimen used	6/12 (50.0%)	70/183 (38.3%)	0.543
Vancomycin use	3/12 (25.0%)	57/183 (31.1%)	0.728
Daptomycin use	0/12 (0.0%)	14/183 (7.7%)	>0.999
Amoxicillin-based regimen	10/12 (83.3%)	120/183 (65.6%)	0.320
EuroSCORE II (mean ± SD)	8.7 ± 6.7 ($n = 12$)	10.8 ± 13.3 ($n = 183$)	0.751
Heart failure	1/12 (8.3%)	47/183 (25.7%)	0.300
Death before surgery (if indicated)	2/6 (33.3%)	21/128 (16.4%)	0.350
In-hospital mortality	4/12 (33.3%)	45/183 (24.6%)	0.477

EIE, enterococcal infective endocarditis; SD, standard deviation.

streptococcal IE therefore reflects the older age, frailty, and comorbidity burden of these patients, rather than undertreatment.

Importantly, despite the availability of multidisciplinary teams in expert centres, surgery was performed in only 65% of prosthetic and 74% of native valve EIE cases, highlighting persistent disparities in access to surgery at the population level. These disparities may be driven by advanced age, frailty, comorbidities, or perceived surgical risk, which frequently affect this older, multimorbid population.[32]

Importantly, recurrence and late mortality remained higher in non-operated patients,[33] emphasizing the ongoing importance of patient selection and timely intervention. This is illustrated by the Kaplan–Meier survival analysis, which demonstrates significantly better 1-year survival in operated patients, including those with prosthetic valve IE. These findings reinforce the need for continued efforts to optimize surgical referral and management pathways in this high-risk population, in line with recent meta-analyses supporting the benefit of surgery when appropriate selection criteria are applied.[34]

High recurrence rates and therapeutic challenges

Although the initial clinical presentation of EIE was often less aggressive than in other forms of IE, therapeutic management remains particularly challenging. Previous studies have suggested higher recurrence rates in EIE, notably in the Spanish cohort by Pericàs *et al.*,[7] which reported a 1-year recurrence of 13% compared to 9% in non-enterococcal IE. In our study, the observed 1-year recurrence rate was lower, at 6%. However, this figure must be interpreted with caution: among the 365 patients with EIE, only 195 had available follow-up data at 1 year, and just 12 experienced documented recurrence. This small number of events raises the possibility of underestimating the true recurrence rate and severely limits the power of comparative analyses. Thus, while our results are in line with prior reports suggesting a trend towards increased recurrence in EIE,[14,16,33] the absolute numbers should be interpreted in light of this limitation.

In this small subgroup, no clinical or prognostic factor was significantly associated with recurrence, except for the higher number of antibiotics received during treatment. Unlike previous studies, we did not observe a significant association with prosthetic material, dialysis, healthcare-associated acquisition, or omission of surgery. This discrepancy may reflect limited statistical power or selection bias due to incomplete follow-up data.

The complexity of antibiotic management in EIE has been well documented. There has been a shift from the classic ampicillin–gentamicin regimen towards dual β-lactam therapy (ampicillin–ceftriaxone), particularly in elderly and renally impaired patients.[17-20,35,36] Our data reflect this trend, although prospective comparative studies remain limited. Real-world experience suggests that outpatient parenteral antibiotic therapy, including dual β-lactam regimens, may be feasible and safe in selected patients.[37,38] Importantly, recurrence in our cohort appeared more closely related to incomplete source control than to the specific antimicrobial regimen, highlighting the crucial role of optimal surgical management in improving long-term outcomes. In high-risk or inoperable patients, long-term suppressive antibiotic therapy may be considered, as supported by recent case series.[39]

Strengths and limitations

The principal strengths of this study include its prospective, multicentre design; the large, well-characterized EIE cohort; and the

integration of detailed microbiological and imaging data.[22] Compared to earlier reports, our analysis encompasses a broader range of healthcare systems and clinical practices, enhancing the external validity of the findings. However, several limitations must be acknowledged. The observational nature of the registry precludes causal inference, and microbiological characterization was incomplete in some cases, with limited data on species and resistance profiles. Antibiotic regimens were not standardized across centres, reflecting real-world heterogeneity in clinical management. In this large multinational registry, follow-up data at 1 year were not systematically completed in all participating centres, resulting in limited availability of long-term information for approximately half of the cohort. Consequently, the true recurrence rate may have been underestimated due to incomplete long-term follow-up in some centres. Furthermore, patients with polymicrobial endocarditis were excluded, which may limit the generalizability of our results to all-comers with EIE. Finally, the EURO-ENDO registry reflects data collected between January 2016 and March 2018, which may not capture the most recent epidemiological trends or evolutions in management practices. These limitations are consistent with concerns raised in recent critical appraisals, which emphasize the ongoing need for standardized management protocols and robust prospective studies in EIE.

Conclusion

EIE is a distinct and increasingly frequent form of endocarditis, predominantly affecting elderly and comorbid patients, with frequent prosthetic involvement. Despite a generally subacute presentation, outcomes remain suboptimal, reflecting the challenges of timely diagnosis, surgical decision-making, and complex antimicrobial management. In this large multicentre registry, EIE was not independently associated with higher in-hospital mortality after adjustment for operative risk (EuroSCORE II) and valve status, suggesting that poor outcomes are largely driven by patient profile and surgical selection rather than pathogen-specific virulence. Surgery, when indicated, appears to improve prognosis even in high-risk patients, underscoring the importance of early referral to dedicated heart teams. Our findings further support the systematic use of PET/CT and colorectal evaluation to identify extracardiac foci and guide tailored management strategies. Future prospective studies should refine surgical indications, assess the role of long-term suppressive antibiotic therapy, and develop preventive approaches—particularly in patients with prosthetic valves or transcatheter implants.

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Acknowledgements

The EORP Oversight Committee, Registry Executive, and Steering Committees. The Data collection was conducted by the EORP department of the ESC: Emanuela Fiorucci and Gabrielle Bonneville as Project Officers; Viviane Missiamenou and Florian Larras as Data Managers, and Rachid Mir Hassaine, Clara Berlé, and Emmanuelle Mouraux as Clinical Project Managers.

Funding

Abbott Cardiovascular. (2011–21), Amgen Cardiovascular (2009–18), AstraZeneca (2014–21), Bayer AG (2009–18), Boehringer Ingelheim (2009–19), Boston Scientific Corporation (2009–12), The Bristol Myers Squibb and Pfizer Alliance (2011–19), Daiichi Sankyo Europe GmbH (2011–20), The Alliance Daiichi Sankyo Europe GmbH and Eli Lilly and Company (2014–17), Edwards (2016–19), Gedeon Richter Plc. (2014–16), Menarini Int. Op. (2009–12), MSD Sharp and Dohme-Merck & Co. (2011–14), Novartis Pharma AG (2014–20), ResMed (2014–16), Sanofi (2009–11), SERVIER (2009–21), and Vifor (2019–22).

Conflict of interest: B.P. declares Speaker fees Edwards Lifesciences and Polares Medical (<£5K); Participation on a Data Safety Monitoring Board or Advisory Board as Chair of Valvosoft DSMB (Personal payments <£5K); Shareholder in CERC. B.P. declares Speaker fee from GE Healthcare and Hitachi-Aloka; research support from GE Healthcare and Hitachi-Aloka. A.S. declares Consulting fees from Novartis; Payment or honoraria from Organon, AstraZeneca, and Daiichi-Sankyo. A.T. declares Leadership or fiduciary role (unpaid) from European Association of Cardiovascular Imaging (EACVI)—member of the Board 2024–26 (Echocardiography Councillor) and Chair of the EACVI Education Committee 2024–26. J.P.V.M. declares honoraria for academic activities (lectures, teaching, seminars) in the field of echocardiography and congenital heart disease. P.A.E. declares Royalties from Springer; Payment or honoraria from GE Healthcare, ITM; Leadership or fiduciary role (EANM Board; RLT Angels Board; ECO Women and Cancer). E.D. declares Consulting fees from General Electric Healthcare, Abbott, Pfizer, Alnylam. All other co-authors have nothing to declare.

Data availability

Data, research materials, and analytical methods supporting this study are available through the corresponding author upon reasonable request

Appendix

European Infective Endocarditis registry (EURO-ENDO): the EURO-ENDO Investigator Group

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