

Original article

Relationship Between *Enterococcus faecalis* Infective Endocarditis and Colorectal Neoplasm: Preliminary Results From a Cohort of 154 Patients[☆]



Juan M. Pericàs,^a Juan Corredoira,^b Asunción Moreno,^a M. José García-País,^b Carlos Falces,^c Ramón Rabuñal,^b Carlos A. Mestres,^{d,e} M. Pilar Alonso,^f Francesc Marco,^g Eduard Quintana,^h Manel Almela,ⁱ Juan C. Paré,^c Jaume Llopis,^j Antoni Castells,^k and José M. Miró^{a,*}, on behalf of the *Hospital Clínic* and *Hospital Lucus Augusti* Infective Endocarditis Investigators[◇]

^aServicio de Enfermedades Infecciosas, Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain

^bUnidad de Enfermedades Infecciosas, Hospital Lucus Augusti, Lugo, Spain

^cServicio de Cardiología, Hospital Clínic de Barcelona, IDIBAPS, Universitat de Barcelona, Barcelona, Spain

^dServicio de Cirugía Cardíaca, Hospital Clínic de Barcelona, Barcelona, Spain

^eServicio de Cirugía Cardíaca, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates

^fServicio de Microbiología, Hospital Lucus Augusti, Lugo, Spain

^gISGlobal, Fundació Privada Centre de Recerca en Salut Internacional de Barcelona (CRESIB), Servicio de Microbiología, Hospital Clínic de Barcelona, Universitat de Barcelona, Barcelona, Spain

^hServicio de Cirugía Cardíaca, Hospital Clínic de Barcelona, IDIBAPS, Universitat de Barcelona, Barcelona, Spain

ⁱServicio de Microbiología, Hospital Clínic de Barcelona, IDIBAPS, Universitat de Barcelona, Barcelona, Spain

^jDepartamento de Estadística, Facultad de Biología, Universitat de Barcelona, Barcelona, Spain

^kDepartamento de Gastroenterología, Hospital Clínic de Barcelona, IDIBAPS, Universitat de Barcelona, Barcelona, Spain

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ABSTRACT

Introduction and objectives: The association between *Streptococcus bovis* group infective endocarditis and colorectal neoplasm (CRN) is well-known. However, no studies have assessed the association between *Enterococcus faecalis* infective endocarditis (EFIE) and CRN. We aimed to determine whether the prevalence of CRN is higher in patients with EFIE and an unclear source of infection than in patients with EFIE and a known source of infection or in the general population.

Methods: Retrospective analysis of a cohort of 154 patients with definite EFIE (109 with an unclear source of infection and 45 with an identified source) from 2 Spanish teaching hospitals to determine the prevalence of CRN and other colorectal diseases.

Results: In the group with an unknown source of infection, 61 patients (56%) underwent colonoscopy; of these, 31 (50.8%) had CRN. Nonadvanced colorectal adenoma was detected in 22 patients (36%), advanced adenoma in 5 (8.2%), and colorectal carcinoma (CRC) in 4 (6.6%). Among patients who survived the EFIE episode with ≥ 2 years of follow-up, 1 case of CRC was subsequently diagnosed. Only 6 patients (13.3%) with an identified focus of infection underwent colonoscopy; 1 of these patients (16.7%) was diagnosed with CRN. The prevalence of adenomas was slightly higher than that of the Spanish population in the same age range, whereas that of CRC was 17-fold higher.

Conclusions: CRN was found in more than half of patients with EFIE and an unclear focus of infection who underwent colonoscopy. Colonoscopy should be recommended in patients with EFIE and an unclear source of infection.

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* Corresponding author: Servicio de Enfermedades Infecciosas, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain.

E-mail address: jmmiro@ub.edu (J.M. Miró).

◇ See [Appendix](#) for a complete list of the Hospital Clínic and Hospital Lucus Augusti Infective Endocarditis Investigators.

Asociación entre la endocarditis infecciosa por *Enterococcus faecalis* y la neoplasia de colon: resultados preliminares a partir de una cohorte de 154 pacientes

RESUMEN

Palabras clave:

Endocarditis
Epidemiología
Enterococcus faecalis
Cáncer colorrectal
Colonoscopia
Enfermedad colorrectal

Introducción y objetivos: Así como la asociación entre la endocarditis infecciosa por *Streptococcus bovis* y la neoplasia colorrectal (NCR) es bien conocida, no se han publicado hasta la fecha resultados de estudios que valoren dicha asociación con la endocarditis infecciosa por *Enterococcus faecalis* (EIEF). El objetivo de este estudio es determinar si la prevalencia de NCR es mayor en los pacientes con EIEF de foco desconocido que en la población general y en los pacientes con EIEF y foco conocido.

Métodos: Análisis retrospectivo de una cohorte de 154 pacientes con EIEF definitiva (109 con foco desconocido y 45 con foco definido) de 2 hospitales universitarios españoles. Estudio de la prevalencia de NCR y otras enfermedades colorrectales.

Resultados: Se realizó colonoscopia a 61 pacientes (56%) con foco desconocido, y se diagnosticó NCR a 31 (50,8%); adenoma colorrectal no avanzado en 22 casos (36%), adenoma avanzado en 5 (8,2%) y carcinoma colorrectal (CCR) en 4 (6,6%). Entre los supervivientes al episodio de endocarditis con seguimiento ≥ 2 años, se diagnosticó otro caso de CCR. Por otro lado, solo 6 colonoscopias (13,3%) se llevaron a cabo entre pacientes con foco claro de la EIEF, y se halló NCR en 1 (16,7%). La prevalencia de adenomas era ligeramente mayor que en la población general española de la misma franja de edad, mientras que la prevalencia del CCR resultó 17 veces mayor.

Conclusiones: Se diagnosticó NCR a más de la mitad de los pacientes con EIEF y foco desconocido a los que se realizó una colonoscopia. Estos resultados indican que se debe recomendar la realización de una colonoscopia a todo paciente con EIEF y foco no claro.

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Abbreviations

CRA: colorectal adenoma
CRC: colorectal carcinoma
CRN: colorectal neoplasm
EFIE: *Enterococcus faecalis* infective endocarditis
IE: infective endocarditis

INTRODUCTION

Enterococcus faecalis is the third leading cause of infective endocarditis (IE) worldwide. It is becoming increasingly relevant due to epidemiological changes among patients at risk.^{1,2} *E. faecalis* is one of the most relevant microorganisms of gut commensal flora involved in human disease. It is located in the colon wall, where it is involved in various processes, including translocation leading to systemic infection.³ However, the most commonly reported portal of entry in the literature on *E. faecalis* infective endocarditis (EFIE) is the genitourinary tract, followed by unknown origin.⁴ Some preliminary data indicate that *E. faecalis* might be involved in the mutagenesis of colonic cells⁵ and that the presence of lesions affecting the intestinal mucosa may lead to higher rates of translocation of *E. faecalis* into the bloodstream. However, whereas the relationship between IE caused by *Streptococcus bovis* group and colon malignancies has been widely studied,^{6–8} the relationship between EFIE and colorectal neoplasms (CRNs) has not been thoroughly explored to date.

Colonoscopy is the gold standard for CRN screening.⁹ In a study performed in asymptomatic patients with undiagnosed CRN undergoing colonoscopy for colorectal carcinoma (CRC) screening in Spain, the disease was detected in 27 of 5059 patients undergoing colonoscopy (0.5%) and in 30 patients (4.5%) with positive fecal immunochemical testing and colonoscopy findings (n = 663); advanced colorectal adenomas (CRAs) were found in 493 (9.7%) and 252 (38%) patients and nonadvanced CRA in 1116 (22.1%) and 112 (16.9%) patients, respectively.¹⁰ The global prevalence of CRA and CRC differs significantly between men and women (about 30% vs 20% for CRA and 1.4% vs 0.6% for CRC).^{11,12} More than 70% of EFIE patients are men, with a median

age of around 70 years.^{1,2} The prevalence of CRC among patients within the age range of standard EFIE patients (70–80 years) undergoing screening colonoscopy is 0.8%–3.2%.¹¹

Our aim was to assess the prevalence of CRN, and specifically that of CRC, in patients with EFIE undergoing colonoscopy due to an unclear origin of infection and to compare it with that of patients with an identified portal of entry. We compared this prevalence with that of the Spanish general population to determine whether colorectal examination to rule out neoplasm is necessary in these patients.

METHODS

Design

We performed a descriptive, retrospective analysis of 2 cohorts that were prospectively collected from 2 Spanish teaching hospitals (centers 1 and 2): *Hospital Clínic*, Barcelona, Spain, an 830-bed university reference center for cardiac surgery (1979 to 2015); and *Hospital Lucas Augusti*, Lugo, Spain, a 690-bed center (1988 to 2015). The inclusion criteria were definite EFIE according to the modified Duke criteria¹³ and available clinical and microbiological data. Patients with previous episodes of IE due to *S. bovis* were excluded due to a higher risk of CRN.

Variables Related to Infective Endocarditis

Demographic, microbiological, and clinical data were collected as defined in previous studies by our group.^{14,15} Antibiotic therapy and surgery were indicated according to American¹⁶ and European¹⁷ guidelines. Our working group on IE held multidisciplinary weekly meetings to evaluate the management of all suspected or confirmed IE cases during the last 30 years.¹⁸

Variables Related to Colorectal Neoplasms

Data from colonoscopies performed to investigate the origin of EFIE during admission were collected. Endoscopic findings as reported by gastroenterologists from the 2 centers and

histopathological reports of colorectal samples by pathologists were categorized as CRN as follows: nonadvanced CRA was defined as a tubular adenoma with a diameter of < 1 cm; advanced CRA was defined as an adenoma with a diameter of \geq 1 cm, or tubulovillous (25%-75% of villous component) or villous (> 75%) histology, or high-grade dysplasia. Carcinoma in situ was classified as an adenoma with high-grade dysplasia. The criterion for invasive cancer was the presence of malignant cells beyond the muscularis mucosa. Colorectal neoplasms included both CRA and CRC. The histological classifications of polyps and CRN were based on World Health Organization criteria.¹⁹ Nonneoplastic colonic diseases were also registered.

Performance of Colonoscopy or Other Digestive Tests During Admission for *Enterococcus faecalis* Infective Endocarditis

Colonoscopy and other tests to study the gastrointestinal tract have been systematically performed to identify the focus of EFIE in both centers since the late 1990s. Colonoscopy has been the test of choice in *Hospital Lucus Augusti* since 1998 and in *Hospital Clínic* only since 2010 (barium enema was previously used). None of the patients undergoing colonoscopy had a high pretest suspicion of CRN. Reasons for not performing colonoscopy were poor clinical status or prognosis irrespective of colonic disease or refusal of the patients or relatives. Thus, not all patients with EFIE and an unclear focus of infection diagnosed during the study period underwent colonoscopy. In some patients, the work-up to determine the focus of the infection could not be completed for various reasons during admission; therefore, we also included patients undergoing colonoscopy and other gastrointestinal tests during the first 3 months after admission.

Statistical Analysis

Categorical variables were compared using the chi-square test (or the Fisher exact test when necessary). Continuous variables were compared using the Kruskal-Wallis test. A 2-sided $P < .05$ was considered statistically significant. The statistical analysis was performed using SPSS version 16.0 (SPSS Inc.; Chicago, Illinois, United States).

RESULTS

We evaluated 170 patients to determine their eligibility for the study and excluded 16 (Figure): 8 had a previous episode of IE caused by *S. bovis* and were considered to be at higher risk for CRN at baseline, 5 had non-*E. faecalis* species enterococcal IE, and 3 lacked clinical data. The study population comprised 154 patients with EFIE: 109 had an unclear source of infection and 45 had an identified portal of entry (genitourinary tract, 34; catheter, 4; surgical wound, 4; biliary tract, 3).

The demographic data of the 154 cases of EFIE included in the analysis are shown in Table 1. The general characteristics correspond to that of a typical EFIE profile: elderly individuals with multiple comorbidities (median age-adjusted Charlson score \geq 5 in both groups), with a predominance of native and aortic endocarditis. Of note, patients with an unknown origin were more frequently male and had acquired their disease in the community. Patients with a known source had higher rates of cancer and hemodialysis. As for clinical characteristics, treatment details, and outcomes (Table 2), patients with an identified portal of entry had significantly longer symptom duration prior to diagnosis; however, no other significant differences were found between the 2 cohorts.

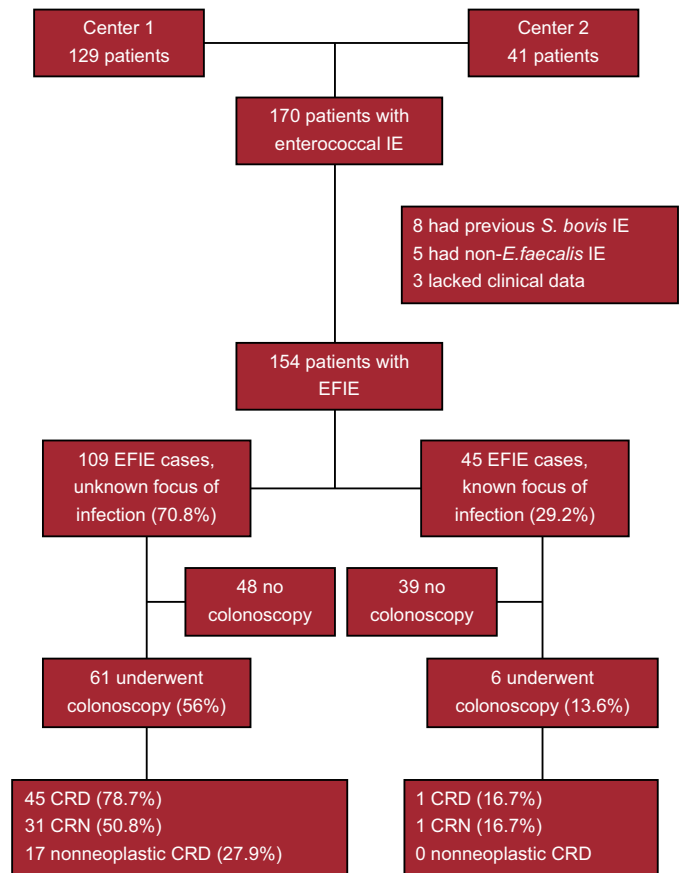


Figure. Patient disposition flowchart. CRD, colorectal disease; CRN, colorectal neoplasm; EFIE, *Enterococcus faecalis* infective endocarditis; IE, infective endocarditis.

Data on CRN diagnosis in the study cohort are shown in Table 3. Sixty-one patients with an unclear source of infection (56%; 44 men [72.1%] and 17 women [27.9%]; median age, 71 years [interquartile range, 46-68 years]) and 6 patients in those with an identified source underwent colonoscopy during the work-up (13.6%; 5 men [83.3%] and 1 woman [16.7%]; median age, 64.5 years [interquartile range, 63-79 years]). One patient diagnosed with CRC underwent colonoscopy more than 3 months after discharge (at 4 months) due to prolonged recovery in a rehabilitation center. Colorectal diseases were diagnosed in 48 of the 61 patients who underwent colonoscopy (78.7%, 95% confidence interval [95%CI], 68.20%-89.17%) in the group with an unknown source of infection. Colorectal neoplasm was identified in 31 patients who underwent colonoscopy in the group without a clear focus of infection (50.8%, 95%CI, 38.02%-63.62%) and in 1 of the 6 patients (16.7%, 95%CI, 0.00%-4.89%) with a known portal of entry. One male patient with an unknown source of infection and normal colonoscopy findings during the initial admission was diagnosed with CRC 4 months after discharge, giving a total of 5 cases of CRC in 109 patients with EFIE and an unknown source of infection (prevalence of 4.6%) and in 61 patients with colonoscopy results from the first admission (prevalence of 8.2%). The ages of the 5 patients with a diagnosis of CRC were 62, 68, 74, 77, and 81 years. Four of the 5 patients died within 2 years of receiving the CRC diagnosis (median survival time was 94 days), whereas 1 was still alive at the end of 2015 (2730 days of follow-up). Additionally, 12 patients in the unknown source group who did not undergo colonoscopy and 5 in the group with an identified source underwent a barium enema. One patient in the first group was diagnosed with CRA in a colonoscopy subsequent to

Table 1
Baseline Characteristics of 154 Patients With *Enterococcus faecalis* Infective Endocarditis According to the Source of Infection

Variable	Unknown origin	Known origin	P
Number of cases	109	45	
Median age in years	71 [63-78]	71 [62-76]	.445
Male sex	73 (62.4)	39 (86.7)	.002
Transferred patients	29 (26.6)	11 (25.0)	.838
Type of endocarditis			.083
Native	64 (58.7)	33 (73.3)	
Prosthetic	41 (37.6)	9 (20)	
Pacemaker/defibrillators	4 (3.7)	3 (6.7)	
Valve involvement			.726
Aortic	51 (46.8)	24 (53.3)	
Mitral	35 (32.1)	15 (33.3)	
Mitral + aortic	15 (13.8)	2 (4.4)	
Right	5 (4.6)	3 (6.7)	
Other	3 (2.8)	1 (2.2)	
Type of acquisition			<.001
Community	64 (58.7)	11 (24.4)	
Health care-related	45 (41.3)	34 (75.6)	
Strains of <i>E. faecalis</i> with high-level aminoglycoside resistance	32 (29.4)	15 (33.3)	.336
Comorbidities			
Diabetes mellitus	36 (33.0)	14 (31.1)	.120
Chronic renal failure	19 (17.4)	11 (24.4)	.318
Hemodialysis	2 (1.8)	6 (13.3)	.008
Cancer	16 (14.7)	14 (31.5)	.019
Human immunodeficiency virus	3 (2.8)	2 (4.4)	.630
Liver cirrhosis	15 (13.8)	4 (8.9)	.403
Chronic lung disease	25 (22.9)	4 (8.9)	.043
Transplant	2 (1.8)	0 (0.0)	1.000
Previous IE	8 (7.3)	1 (2.2)	.285
Age-adjusted Charlson score	5.0 [4-7]	6.0 [4-7]	.110

IE, infective endocarditis.

Data are expressed as No. (%) or median [interquartile range].

the admission when the barium enema was carried out, whereas none in the second group were diagnosed with CRN.

Overall, 32 cases of CRN were diagnosed in the whole cohort during the time between admission and the 3-month follow-up; the overall prevalence of CRN was 20.8% (95%CI, 14.24%-27.32%), 23.6% in men and 14.6% in women ($P = .202$). If only CRA was taken into account, the overall prevalence was 19.8% in men and 14.6% in women ($P = .436$). When only patients with colonoscopy were taken into account, the prevalence of CRN was 51% in men and 38.9% in women ($P = .378$); in the case of CRA, the prevalence was 42.9% and 38.9% for men and women, respectively ($P = .770$). In-hospital mortality and 1-year mortality were significantly higher among patients not diagnosed with CRN than among those who were (27.9% vs 6.2%; $P = .009$; and 38.5% and 12.5%; $P = .006$, respectively), whereas relapses were not significantly more frequent among patients diagnosed with CRN (8.3% in patients without CRN and 3.1% in patients with CRN; $P = .460$). When patients with CRN were compared with those who did not have the disease, no significant differences were detected in the classic factors associated with poorer prognosis of IE (type of IE [native/pacemaker vs prosthetic], valve involvement, rates of cardiac surgery, systemic and central nervous system emboli, heart failure, renal failure, persistent bacteremia, periannular complications, and type of antibiotic treatment [ampicillin plus aminoglycoside vs ampicillin vs ceftriaxone]) or in baseline comorbidities (data not shown).

DISCUSSION

The prevalence of CRN in the group of EFIE patients with an unclear source of infection is substantially higher than that expected for similarly aged patients in the general population, approaching that reported in patients with *S. bovis* IE. The prevalence of CRN in patients with *S. bovis* undergoing colonoscopy is approximately 60%,³ and both American¹⁶ and European¹⁷ guidelines recommend systematic colonoscopy in these patients. Although the prevalence of CRN in the group of EFIE patients with an unknown source of infection was significantly higher than that in those with a clear focus (and this finding is reliable), the data from our study are not conclusive because only 6 of 45 patients with an identified focus underwent colonoscopy.

The prevalence of CRA in a cohort study based on an Austrian national screening colonoscopy program with 44 350 participants was 18.4% (95%CI, 16.7%-20.1%) for women and 32% (95%CI, 30%-34%) for men in the 70–74-year age group,¹¹ whereas it was 44.3% (95%CI, 31.54%-56.98%) in our cohort for patients undergoing colonoscopy (45.5% for men and 41.2% for women) in the group with an unknown source of infection. In the Austrian study, and within the same age group, the prevalence of CRC was 0.7% (95%CI, 0.4%-1.2%) in women and 1.9% (95%CI, 1.4%-2.6%) in men.¹¹ In contrast, it was 8.2% (95%CI, 1.17%-15.22%) in our cohort in patients with available colonoscopy results and 11.4% (95%CI, 1.79%-20.93%) in men. Because all patients with a diagnosis of CRC

Table 2Clinical and Treatment Characteristics and Outcomes of the 154 Patients With *Enterococcus faecalis* Infective Endocarditis According to the Source of Infection

Variable	Unknown origin	Known origin	P
Number of cases	109	45	
Length of symptoms of IE, days	24.9 ± 28.3	36.5 ± 45.5	.0158
Patients with ≥ 90 days of symptoms	3 (2.8)	5 (11.1)	.047
<i>Symptoms potentially related to colorectal cancer*</i>			
Fever	98 (89.9)	43 (95.6)	.348
Rectal bleeding	5 (4.6)	0 (0.0)	NA
Bowel obstruction	3 (2.6)	0 (0.0)	NA
Toxic syndrome	39 (36.4)	16 (38.1)	.851
Anemia at admission (haemoglobin < 11 g/L)	57 (53.3)	25 (67.6)	.130
<i>Echocardiographic findings</i>			
Vegetations	81 (74.3)	34 (75.6)	.872
Vegetation size in mm	8 [5-13]	10 [7-16]	.398
Periannular complications	17 (15.6)	3 (6.7)	.134
<i>Complications</i>			
Heart failure (≥ Killip II)	43 (39.4)	22 (48.9)	.281
Systemic emboli	31 (28.4)	15 (33.3)	.546
Acute renal failure	36 (33.3)	15 (33.3)	1.000
Persistent bacteremia	5 (7.9)	1 (5.3)	1.000
<i>Initial antibiotic therapy</i>			
Ampicillin + aminoglycoside	39 (35.8)	19 (42.2)	
Ampicillin + ceftriaxone	58 (53.2)	20 (44.4)	
Other	12 (11)	6 (13.3)	
Length of antibiotic treatment in survivors to initial admission, days	42 [28-42]	42 [28-42]	.859
Length of aminoglycosides in survivors to initial admission, days	28 [20-42]	28 [21-34]	.392
Switch to A + C in patients initially receiving A + G	10 (25.6)	4 (21.1)	1.000
Surgery during the episode (admission + first 3 months of follow-up)	36 (33)	19 (42.2)	.279
In-hospital mortality	24 (22)	12 (26.7)	.535
1-year mortality	34 (31.2)	17 (37.8)	.430
Relapses	9 (8.4)	2 (4.4)	.508
Follow-up in survivors to initial admission, days	839 [377-1876]	677 [188-2870]	.089

A + C, ampicillin plus ceftriaxone; A + G, ampicillin plus aminoglycoside.

Data are expressed as No. (%), mean ± standard deviation or median [interquartile range].

* Note that fever, toxic syndrome, and anemia can also be due to the infective endocarditis.

were men, our findings represent a 1.4-fold higher prevalence of CRA and 6-fold higher rate of CRC than in the Austrian cohort when only male sex is considered. In the case of female patients, the CRA rate was 2.2-fold higher.

Comparison with data on the prevalence of CRN diagnosed by colonoscopy in Spain reveals even greater differences. In the study by Quintero et al.,¹⁰ the prevalence of CRC in patients undergoing colonoscopy (with no previous fecal immunochemical testing) was

Table 3Gastrointestinal Diseases Among the 154 Patients With *Enterococcus faecalis* Infective Endocarditis According to the Source of Infection

Variable	Unknown origin	Known origin	P
Number of cases	109	45	
Patients with colonoscopy during the admission or within the first 90 days after diagnosis	61 (56)	6 (13.6)	<.001
Patients with colonoscopy and diagnosis of colonic disease	48 (78.7)	1 (16.7)	.004
Colorectal neoplasms diagnosed using colonoscopy^a			
Colorectal adenoma	31 (28.44)	1 (2.2)	<.001
Nonadvanced adenoma	27 (24.8)	1 (2.2)	<.001
Advanced adenoma	22 (20.2)	0 (0.0)	
Colorectal cancer	5 (4.6)	1 (2.2)	.193
Colorectal cancer	4 (3.7)	0 (0.0)	
Nonneoplastic diseases diagnosed using colonoscopy^b			
Nonneoplastic diseases diagnosed using colonoscopy ^b	17 (15.6)	0 (0.0)	.005
New diagnosis of adenocarcinoma during follow-up (after 90 days of admission)^c			
New diagnosis of adenocarcinoma during follow-up (after 90 days of admission) ^c	1/56 (1.8)	0/31 (0.0)	.560

Data are expressed as no./No. (%).

^a The percentages shown correspond to the prevalence in the whole group, including patients without colonoscopy.^b Diverticula (n = 9), ischemic colitis (n = 3), radiation colitis (n = 3), angiodysplasia (n = 5), and nonspecific ulcers (n = 1).^c After 90 days of admission in survivors with undiagnosed previous colorectal neoplasm, with the exception of 1 patient who underwent colonoscopy 4 months after discharge due to prolonged rehabilitation after cardiac surgery.

0.5%, whereas CRA was found in 31.8%. Thus, CRC was almost 17 times more frequent in our cohort (0.5% vs 8.2%) in patients with colonoscopy, whereas CRA was only slightly more frequent (31.8% vs 44.3%). However, the mean age of the participants in the study by Quintero et al. was significantly lower than that of patients in our cohort (59.2 ± 5.5 years vs 69 ± 12.4 years in patients undergoing colonoscopy in our study).

A more recent study showed that the CRC rate among patients undergoing surveillance colonoscopy (follow-up colonoscopy in individuals with abnormal results in the baseline colonoscopy) was 9.5 cases per 10 000 persons-years in patients aged 70 to 74 years.²⁰ Thus, even if we considered only the CRC cases diagnosed during follow-up, the incidence of CRC would still be considerably higher in our cohort of EFIE patients with an unknown source of infection undergoing colonoscopy than in patients at higher baseline risk of CRC due to a previous abnormal colonoscopy result within the same age range.

The diagnosis of CRN was not associated with poorer outcomes during admission and at 1 year or with a higher relapse rate. In contrast, mortality was significantly higher in the group without CRN, likely because a relevant percentage of patients presenting with severe courses of IE or poor baseline status did not undergo colonoscopy and thus were not diagnosed with CRN. The absence of an impact of EFIE on the prognosis of CRN is consistent with data from patients with IE due to the *S. bovis* group, who rarely die of CRN-related complications.¹⁵ On the other hand, EFIE and the *S. bovis* group IE might constitute, respectively, late and early markers of CRC due to the different temporal patterns of presentation. However, the differences between both entities could be due to a wide variety of reasons (eg, the epidemiology of our centers; the recent switch of EFIE from a subacute, community-acquired entity to an acute, health care-associated infection; and nonsystematic performance of colonoscopy in EFIE until recent years). These findings require confirmation in further studies. In this regard, we found a shorter duration of symptoms in patients with EFIE with unknown origin than in those with an identified focus of infection; community acquisition was more frequent in the former, and health care-associated acquisition was more frequent in the latter. We hypothesize that the diagnosis of IE was reached later in patients with health care-associated acquisition and an identified focus because they were mainly patients with invasive urinary procedures or a chronic urinary catheter with recurrent urinary infections. These cases of EFIE were partially treated as urinary infections, thus hindering the early detection of *E. faecalis* in blood cultures and suspicion of IE.

In our cohort, 17 patients with EFIE and an unknown source of infection underwent barium enema, and none were diagnosed with colorectal diseases. Given the high prevalence of colorectal diseases found in these patients using colonoscopy, we conclude that the sensitivity of barium enema is very low. Even though barium enema is no longer used as a screening tool for CRN in most countries, it remains crucial to highlight that the test of choice for ruling out CRN in patients with EFIE should always be colonoscopy.

Our findings could have a considerable impact not only on the diagnostic assessment of EFIE, but also on its management. If possible, colonoscopy should be performed early after the diagnosis of EFIE because the presence of an advanced neoplasm might change the performance or timing of invasive procedures (namely, cardiac surgery, which could be cancelled despite being indicated or postponed until after the initial treatment of the CRC). However, due to the risk of fluid overload in frail patients with valve regurgitation, as well as the difficulties of performing colonoscopy in critically ill patients, it is unlikely that all patients with EFIE will undergo colonoscopy in an early stage of the episode. In 3 of the patients of our cohort undergoing ¹⁸F-FDG positron emission tomography/computed tomography (PET/CT)

(performed in most patients with possible or definite IE in *Hospital Clínic* since 2013) in the initial phase of the diagnostic process, focal colonic uptake aroused early suspicion of CRN, which was later confirmed by colonoscopy and histopathological findings ([Supplementary material](#)). ¹⁸F-FDG PET/CT is efficacious in IE, not only for diagnosis of prosthetic valve endocarditis, but also for early detection of septic embolisms and neoplasms.^{21,22} However, ¹⁸F-FDG PET/CT cannot replace colonoscopy as a diagnostic tool for CRN in these patients but can only act as an additional approach for confirmation and detection of metastases from the neoplasm. This is especially relevant when treating patients with a high risk of CRN and comorbidities, such as patients with EFIE, because it might determine operability and timing in patients with an indication for cardiac surgery. These “special situations” in IE have not been addressed by recent American¹⁶ and European¹⁷ guidelines or in the comments of the Spanish Society of Cardiology on the European guidelines.²³ As stated elsewhere, we advocate including these considerations in future guidelines and recommendations.²⁴

Limitations

The present study has several limitations. First, because it is retrospective and colonoscopy was not systematically indicated throughout the study period, endoscopic findings are not available for all patients. Second, the frequency of colonoscopy in our inner control group (patients with an identified focus of infection other than the digestive tract) was very small; therefore, findings in this group could be due to chance and are not conclusive. Third, the prevalence of CRN in our study is compared with that of a historical series of Spanish individuals undergoing colonoscopy for CRC screening. Fourth, the low rate of events related to CRC and mortality precludes any generalization of our results until new studies provide larger and better-controlled data. Fifth, the study period was very long. Consequently, because the rate of EFIE varied throughout and the exact rates of EFIE are unknown in our setting, we were unable to calculate the incidence density of CRN and adjust risk for age groups. Sixth, the availability and development of the different techniques and the expertise necessary to perform them (eg, diagnosis of IE or colonoscopy) have changed over time. Finally, because autopsy was performed in very few cases (CRC was not found in any of them), we cannot provide data on the cause of death (IE, CRN, or other) in patients without colonoscopy results.

CONCLUSIONS

In conclusion, the prevalence of CRN in EFIE with unknown origin was 50.8% in patients undergoing colonoscopy. When compared with patients with EFIE and an identified focus of infection, the CRN rate was significantly higher in the group of patients with an unclear source of infection. The prevalence of CRN was also higher than in the general population. Colorectal adenoma was only slightly higher than in the Spanish population, whereas CRC was 17-fold higher. In light of these preliminary data, colonoscopy should be recommended in all patients with EFIE and an unclear source of infection until further studies on the relationship between EFIE and CRC are available.

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CONFLICTS OF INTEREST

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WHAT IS KNOWN ABOUT THE ISSUE?

- Although the relationship between *Streptococcus bovis* group IE and colorectal cancer is well known, the interplay between EFIE and CRNs has not been thoroughly assessed to date.
- The epidemiology of EFIE has changed dramatically during the last 20 years and is now mainly health care-acquired when it is linked to a clear focus.
- *E. faecalis* IE mostly occurs in elderly patients with no identified origin. In these cases, the infection likely has a colorectal origin, although it is seldom identified.
- In this clinical setting, colonoscopy is an essential tool for work-up and colorectal cancer screening.

WHAT DOES THIS STUDY ADD?

- Although preliminary, our findings draw attention to several aspects of the relationship between EFIE and colorectal diseases that have not been previously assessed.
- First, there was a predominance of patients with an unclear focus of infection. Second, CRNs were found in more than half of all patients undergoing colonoscopy. Third, the prevalence of CRC was 17 times higher than in the general population of the same age.
- This is the first study to provide evidence that colonoscopy should be systematically performed in patients with EFIE and an unclear focus of infection.

APPENDIX

Members of the *Hospital Clínic* Endocarditis Study Group Barcelona, Spain: José M. Miró, Juan M. Pericàs, Asunción Moreno, Carlos Cervera, Adrián Téllez, Juan Ambrosioni, Ximena Castañeda, José M. Gatell (Infectious Diseases Service), Cristina García de la Mària, Yolanda Armero, Javier García-González (Experimental Endocarditis Laboratory), Francesc Marco, Manel Almela

(Microbiology Service), Carlos Falces, José M. Tolosana, Bàrbara Vidal, J. Carlos Paré, Manel Azqueta, Marta Sitges (Cardiology), Eduard Quintana, Elena Sandoval, Carlos A. Mestres, Ramón Cartañá, Salvador Ninot, Daniel Pereda, M. Castellà, José L. Pomar (Cardiovascular Surgery), José Ramírez, Teresa Ribalta (Department of Pathology), Mercè Brunet (Toxicology Service), Dolors Soy (Pharmacy Service), David Fuster, Ulises Granados (Nuclear Medicine Service), Jaume Llopis (Statistician from the *Departament de Estadística, Facultat de Biologia, Universitat de Barcelona*), and Antoni Castells (Gastroenterology Service).

Investigators from *Hospital Lucus Augusti*, Lugo, Spain: M. José García País, Ramón Rabuñal, M. José Perez Álvarez, Juan Corredoira (Infectious Diseases Service), Julia Pita, Amparo Coira, Ana Rodríguez Macías, Fernando García Garrote, M. Pilar Alonso (Microbiology Service), and Eva Martí, David Dacal, Beatriz Álvarez (Gastroenterology Service).

SUPPLEMENTARY MATERIAL



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