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First year after surgery is the optimal period to define early prosthetic valve endocarditis: a cohort study

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ABSTRACT

Background The definition of early prosthetic valve endocarditis (PVE) remains controversial. This study aims to refine the definition of early PVE by analysing data from the Spanish endocarditis registry (Spanish Collaboration on Endocarditis).

Methods From 2008 to 2022, 1305 consecutive cases of PVE were included. The objective was to identify the time period that best defined early PVE by comparing the frequency of cases due to nosocomial micro-organisms and the frequency of intracardiac complications. For this purpose, the periods most frequently considered in the literature were selected: the first 4, 6 or 12 months after surgery. Each of these three periods was compared with a period immediately thereafter.

Results Most cases of PVE diagnosed within the first year were caused by nosocomial pathogens, such as coagulase-negative staphylococci (CoNS) (236 cases, 49.3 %) and *Candida* spp (23 cases, 4.8 %) and was associated with higher rates of intracardiac complications (252 cases 52.6%). In patients diagnosed after the first year, these figures were 197 cases (23.8%, p<0.001); 10 cases (1.2%, p<0.001) and 298 cases (36.1%, p<0.001), respectively. No significant differences were found between the first 4 months and the 5th–6th months. When comparing cases diagnosed in the first 6 months with those diagnosed during the 7th and 12th months, there was a higher prevalence of cases due to CoNS (186 cases, 52.1% vs 50 cases 41%; p=0.034). Hospital mortality among patients who did not undergo surgery due to lack of indication was similar in those diagnosed during or after the first 6 months (17.1% vs 13.8%; p=0.663, respectively).

Conclusions We consider that the first year after surgery is the most appropriate period for defining early PVE. Our results question whether cases diagnosed in the first 6 months after surgery constitute cases of early EVP and the need for valve replacement, as postulated by European guidelines.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early prosthetic valve endocarditis (PVE) is predominantly caused by nosocomial pathogens and has a high incidence of intracardiac complications. Current European guidelines define early PVE as occurring within the first 6 months after surgery and recommend that surgical treatment be considered in all cases.

WHAT THIS STUDY ADDS

⇒ Most microbiological and clinical features traditionally associated with early PVE persist throughout the first year after surgery. Mortality of patients diagnosed during the first 6 months who were not operated on, because they did not present complications that determined the surgical indication, presented a similar mortality to that of those diagnosed later.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Although empirical coverage of patients with PVE should be based on several variables in addition to time of onset, our study could result in a better empirical coverage of nosocomial pathogens. It also could lead to avoiding surgical intervention in patients diagnosed during the first 6 months without conventional surgical indication.

INTRODUCTION

Prosthetic valve endocarditis (PVE) represents 20%–30% of infective endocarditis (IE) cases.[1] This entity presents distinctive clinical features and a worse prognosis than IE on native valves.[2] Between 3% and 6% of prosthetic valve carriers will develop PVE during the first 5 years after surgery.[3] Its incidence is higher during the first months and decreases over time.[4 5] Invasive procedures such as the use of vascular catheters are risk factors for PVE in the first months after surgery in patients with recently implanted prosthetic material and without endothelial coverage.[5]

The classification of PVE into early and late PVE is relevant because it differentiates two

groups of patients with somewhat different pathogenesis and aetiology. Cases of early PVE are predominantly caused by coagulase-negative staphylococci (CoNS) and other nosocomially acquired bacteria, with substantial participation of yeasts such as *Candida* spp. This high incidence of cases due to CoNS, with high methicillin resistance (MTR), may justify a different empirical antibiotic treatment.[4] Intracardiac complications such as perivalvular abscess, pseudoaneurysm or destruction of valve prosthesis are also more frequent during the first months and usually require reintervention.[2 4 6] The period considered by various authors to define early PVE in recent years has shown great differences among them.[2 4 6–8] Thus, the current European endocarditis guidelines consider that early PVE is that which appears in the first 6 months.[2] However, other authors consider that the characteristics of early PVE are present throughout the first year.[5 6 9 10] Conversely, authors such as Siciliano *et al* suggest that the first 4 months is the period in which cases of PVE caused by nosocomial pathogens may occur.[4] Several characteristics of early PVE have prompted the authors of the current European guidelines to consider surgical intervention in all cases diagnosed during the first 6 months.[2] This recommendation, however, has been questioned by some authors and could be the subject of future research.[1]

This study aimed to contribute to a better definition of PVE using information from the Spanish endocarditis registry Spanish Collaboration on Endocarditis (GAMES). We consider this study provides a large, contemporary prospective cohort (2008–2022), facilitating the study of patient characteristics at each period considered after valve surgery. A meta-analysis might have been less appropriate considering the differences in methodology among the published studies.

METHODS

Study population

From 1 January 2008 to 31 December 2022, consecutive patients with a confirmed diagnosis of IE were prospectively included in the study to the modified Duke criteria. These patients received treatment at a group of Spanish hospitals serving approximately 30% of the nation's population. At each centre, a multidisciplinary team completed a standardised form detailing the IE episode, along with a follow-up form 1 year after the episode. The registry included sections for demographic, clinical, microbiological, echocardiographic, management and prognostic information.

Data collection

Clinical data from patients included in the medical records were accessed for research purposes. Access to medical records containing identifiable patient information was granted while ensuring privacy throughout data collection. The data were subsequently analysed in 2023 and 2024. The authors did not have access to identifiable participant information during or after data collection. The data on which this study is based are available on reasonable request through the technical office of the research network (GAMES), which can be contacted via the following email: games08@gmail.com.

Definitions

General variables

The study analysed demographic, clinical, echocardiographic and treatment data for the included patients, along with morbidity and mortality rates at admission and during the first year of follow-up. General definitions align with those published in other studies on endocarditis.[11 12] Cases were considered community acquired if they were diagnosed within 48 hours of admission, in a patient without extensive out-of-hospital contact with healthcare systems. Cases were considered nosocomial if they occurred in a patient hospitalised for more than 48 hours prior to the onset of signs or symptoms or during the first month after hospital discharge. Cases were considered non-nosocomial health signs or symptoms consistent with IE developed prior to hospitalisation in patients with extensive out-of-hospital contact with healthcare systems (intravenous therapy, nursing care at home, haemodialysis in the 30 days before the onset of native valve endocarditis; hospitalisation in the 90 days before the onset of symptoms or residence in a long-term care facility).[13] Persistent bacteraemia was defined as the presence of positive blood cultures lasting more than 7 days after the initiation of appropriate antibiotic treatment. Systemic embolisation referred to embolism to any major arterial vessel, excluding stroke, which was characterised as an acute neurological deficit of vascular origin lasting more than 24 hours. Episodes with neurological symptoms lasting less than 24 hours but showing imaging scans suggestive of infarction were classified as strokes.[14] Patients with native valve endocarditis or device-related infections were only included if they also had a concurrently infected prosthetic valve. Patients who had undergone transcatheter aortic valve implantation were excluded due to distinct characteristics.

Exposures of interest

Surgical indications followed the latest current European guidelines available at the time of diagnosis.[2 15 16] Special attention was given to identifying patients with surgical indications, particularly those who did not undergo surgery.

Outcomes of interest

In-hospital mortality was defined as death from any cause occurring during hospital admission. Recurrent IE was defined as a new episode of IE caused by the same or a different micro-organism within the first year of follow-up.

Statistical analysis

The characteristics considered as typical of PVE were CoNS or *Candida* spp as causative pathogen, intracardiac complications, perivalvular abscess and pseudoaneurysm.[2 4 6] The aim was to identify the point in time when a

majority of these five variables were significantly different in relation to the subsequent period. The study periods considered were based on most previously published studies, that is, the first 4 months, first 6 months and first 12 months.[2 4 6–8] Two types of comparisons were made: The first comparison involved contrasting each of the three initial periods (first 4, 6 and 12 months) with a subsequent, distinct period (ie, the 5th–6th months were compared with the first 4 months; the 7th–12th months to the first 6 months and cases beyond 1 year to the first 12 months, respectively). The other comparison contrasted the characteristics of each of these three periods with those of patients diagnosed later (eg, first 4 months vs >4 months). Reduced periods of time were not considered in cases diagnosed after the first year.

Categorical variables are expressed as absolute numbers and percentages. Quantitative variables are expressed as medians and IQRs. Categorical variables were compared using the χ^2 test or Fisher's exact test when necessary. Quantitative variables were compared using Mann-Whitney U tests. The selection of the most appropriate period for defining early PVE was based on the differences observed in variables typically associated with early infections among the patient groups studied. All statistical analyses were performed using SPSS V.25 software (SPSS).

RESULTS

During the study period, a total of 4520 consecutive cases of definitive IE were identified. Among these, 1305 cases (28.9%) were classified as PVE (figure 1). As specified in previous sections, the time periods considered were selected according to the research conducted about PVE over the last decades. Of the PVE cases, 291 (22.3%) were diagnosed during the first 4 months, 68 cases (5.2%) between the 5th and 6th months, 122 cases (9.3%) between the 7th and 12th months, and 826 cases (63.3%) were diagnosed after the first year. The median time after valve implantation at diagnosis was 25 months (IQR 5–91 months).

Among the PVE cases, 935 patients (71.6%) had an infected prosthetic valve in the aortic position, while 501 patients (38.4%) had it in the mitral position. Simultaneous infection of both prosthetic valves occurred in 166 cases (12.7%). The percentage of PVE cases on biological valves was 63.6% (283 cases) during the first year, dropping to 42.7% (330 cases) after the first year (p<0.001, table 1). In-hospital mortality for patients who were not operated on due to lack of indication was 17.1% (12 patients) for those diagnosed in the first 6 months and 13.8% (37 patients) for those diagnosed after 6 months (p=0.663, figure 2).

Clinical characteristics of cases diagnosed in the first 4 months versus those diagnosed in the 5th and 6th months postsurgery

There were no significant differences in terms of underlying diseases, valve position or type of valve affected comparing cases diagnosed during the first 4 months after surgery with those diagnosed later. However, microbiological testing revealed more cases of *Enterococcus* (49 cases, 16.8% vs 4 cases, 6%; p=0.033) and fewer cases of *Streptococcus* spp (16 cases, 5.5% vs 9 cases, 13.6%; p=0.030) during the 5th–6th months period (table 2).

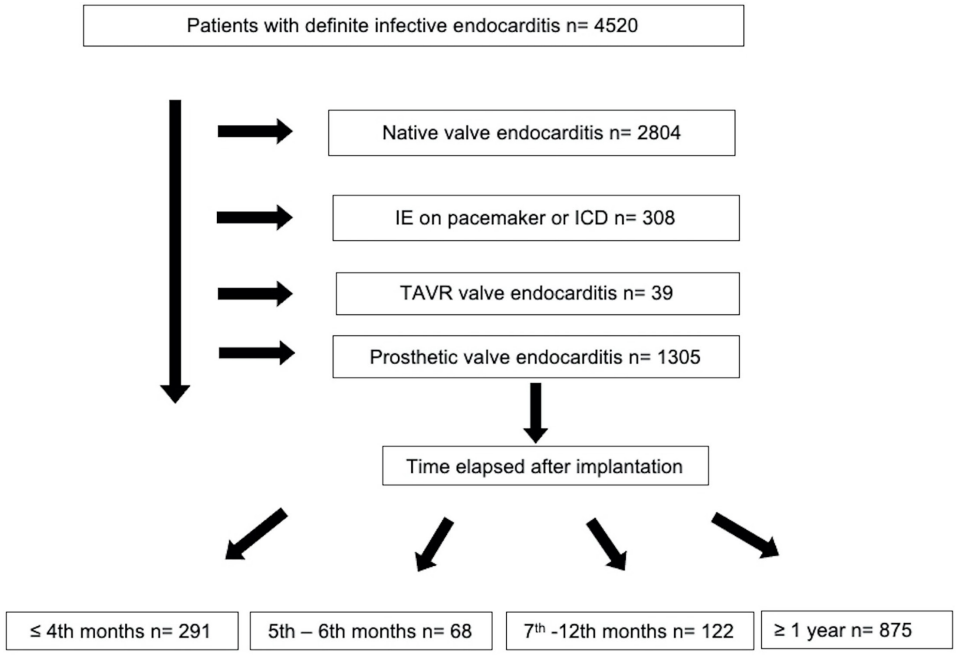

Figure 1 Flow chart of patients presenting with definite or possible infective endocarditis (IE) according to the type of affected valve (GAMES cohort 2008–2022). GAMES, Spanish Collaboration on Endocarditis; ICD, implantable cardioverter defibrillator; TAVR, transcatheter aortic valve replacement.

Table 1 Characteristics of patients with PVE diagnosed during the first year after surgery versus those diagnosed after the first year

	First year (n=479)	After first year (n=826)	P value
Age, years (IQR)	71 (63–76)	71 (63–78)	0.140
Male gender	330 (68.8)	544 (65.8)	0.261
Hospital acquired	313 (65.3)	187 (22.6)	<0.001
Non-nosocomial healthcare	145 (30.3)	574 (69.5)	<0.001
Community acquired	21 (4.4)	65 (7.9)	0.014
Site of infection			
Aortic	380 (79.3)	555 (67.2)	<0.001
Mitral	155 (32.4)	346 (41.9)	0.001
Biological prosthetic valve*	283 (63.6)	330 (42.7)	<0.001
Mechanical prosthetic valve*	162 (36.4)	443 (57.3)	<0.001
Tricuspid	7 (1.5)	8 (1.0)	0.421
Pulmonary	3 (0.6)	18 (2.2)	0.038
Implantable cardiac device†	1 (0.2)	22 (2.7)	0.001
Other locations	9 (1.9)	8 (1.0)	0.162
Comorbidity			
Chronic heart failure	222 (46.3)	361 (43.7)	0.355
Coronary disease	182 (37.9)	278 (33.6)	0.114
Chronic lung disease	95 (19.8)	150 (18.1)	0.456
Diabetes mellitus	137 (28.6)	259 (31.3)	0.297
Peripheral vascular disease	39 (8.1)	85 (10.3)	0.202
Cerebrovascular disease	75 (15.6)	150 (18.1)	0.249
Neoplasia	49 (10.2)	165 (19.9)	<0.001
Chronic renal failure	114 (23.8)	237 (28.7)	0.055
Chronic liver disease	26 (5.4)	67 (8.1)	0.069
Congenital heart disease	34 (7)	41 (4.9)	0.110
Age-adjusted Charlson index (IQR)	5 (3–6)	5 (3–7)	0.016
Microbiology			
Gram-positive bacteria			
Staphylococcus aureus	58 (12.1)	150 (18.2)	0.004
MRSA	17 (3.5)	26 (3.1)	0.801
CoNS	236 (49.3)	197 (23.8)	<0.001
MTR CoNS	146 (30.5)	93 (11.3)	<0.001
Enterococcus	74 (15.4)	141 (17.1)	0.447
Streptococcus	46 (9.6)	214 (25.9)	<0.001
Gram-negative bacilli	18 (3.8)	42 (5.1)	0.270
Anaerobic bacteria	3 (0.6)	27 (3.3)	0.002
Fungi			
Candida	23 (4.8)	10 (1.2)	<0.001
Polymicrobial	7 (1.5)	11 (1.3)	0.847
Other micro-organisms	9 (1.9)	26 (3.1)	0.171
Echocardiographic findings			
Vegetation	320 (66.8)	572 (69.2)	0.360
Intracardiac complications	252 (52.6)	298 (36.1)	<0.001
Valve perforation or rupture	23 (4.8)	25 (3)	0.101

Continued

Table 1 Continued

	First year (n=479)	After first year (n=826)	P value
Pseudoaneurysm	80 (16.7)	66 (7.9)	<0.001
Perivalvular abscess	196 (40.9)	249 (30.1)	<0.001
Intracardiac fistula	27 (5.6)	34 (4.1)	0.210
Clinical course			
Acute heart failure	194 (40.5)	327 (39.5)	0.746
Persistent bacteraemia	59 (12.3)	94 (11.3)	0.612
Stroke	113 (23.6)	199 (24.1)	0.838
Embolism‡	99 (20.6)	179 (21.6)	0.670
Acute renal failure	200 (41.7)	351 (42.5)	0.794
Septic shock	62 (12.9)	118 (14.2)	0.498
Surgery indicated	381 (79.5)	586 (70.9)	0.001
Surgery performed	247 (51.6)	378 (45.8)	0.043
Surgery indicated, not performed	134 (28)	215 (26)	0.444
In-hospital mortality	168 (35.1)	262 (31.7)	0.214
First year mortality	191 (39.8)	302 (36.5)	0.234
Recurrence	26 (5.4)	28 (3.4)	0.075

*Aortic or mitral position, in 87 patients (6.7%), information on the nature of the valve is missing.
†Patients with PVE and concomitant infection of an implantable electronic device.
‡Excluding central nervous system embolism.
CoNS, coagulase-negative staphylococci; MRSA, Methicillin-resistant *Staphylococcus aureus*; MTR, methicillin-resistant; PVE, prosthetic valve endocarditis.

There were no significant differences in PVE caused by CoNS, *Candida* spp or intracardiac complications.

Comparison of cases diagnosed in the first 6 months with those diagnosed between the 7th and 12th months postsurgery

When comparing cases diagnosed in the first 6 months to those diagnosed in the latter half of the first year, there was a greater prevalence of CoNS (186 cases, 52.1% vs 50 cases, 41%; p=0.034), including MTR strains (119 cases, 33% vs 27 cases, 22.1%; p=0.019), and a lower incidence of infections caused by streptococci (25 cases, 7% vs 21 cases, 17.2%; p=0.001). There were no significant differences in PVE caused by *Candida* spp or intracardiac complications (table 3).

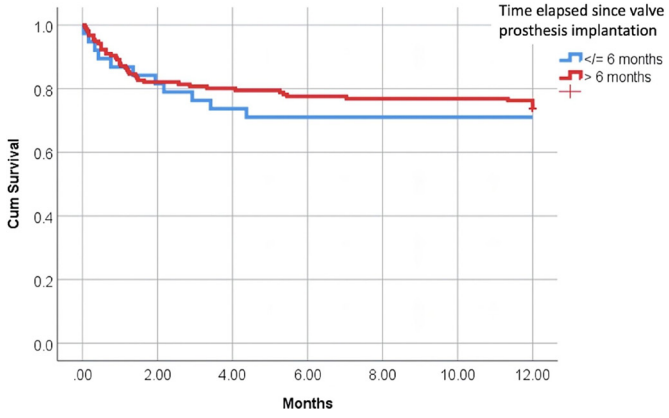

Figure 2 Survival of patients who were not operated on because there was no indication according to the time of diagnosis since surgery.

Comparison of cases diagnosed between the 7th and 12th months with those diagnosed after the first year

More cases diagnosed between the 7th and 12th months affected biological valves than cases diagnosed afterwards (64 cases, 52.4% vs 330 cases, 39.9%; p=0.009, table 4). In addition, more cases were due to CoNS (50 cases, 41% vs 197 cases, 23.8% after the first year; p<0.001) and *Candida* spp (6 cases, 4.9% vs 10 cases, 1.2%; p=0.003), along with fewer cases caused by *Staphylococcus aureus* (12 cases, 9.8% vs 150 cases, 18.2%; p=0.023) and *Streptococcus* spp (21 cases, 17.2 vs 214 cases, 25.9%; p=0.038), respectively. Moreover, more intracardiac complications were observed (56 cases, 45.9% vs 298 cases, 36.1%; p=0.036), including pseudoaneurysms (22 cases, 18% vs 66 cases, 7.9%; p<0.001, respectively). There were no significant differences regarding surgical treatment or mortality (table 4).

Comparison of cases diagnosed in the first year with those diagnosed after the first year

When comparing all cases diagnosed during the first year to those diagnosed after the first year, the differences became even more pronounced. In addition to confirming previous findings, more cases of PVE in the aortic position were identified (380 cases, 79.3% vs 555

Table 2 Characteristics of patients with PVE diagnosed during the first 4 months after surgery versus those diagnosed during 5th–6th months

	First 4 months (n=291)	5th–6th months (n=66)	P value
Age, years (IQR)	71 (63–77)	72 (63–76)	0.815
Male gender	194 (66.6)	47 (71.2)	0.477
Hospital acquired	238 (81.8)	30 (45.5)	<0.001
Non-nosocomial healthcare	6 (2)	6 (9.1)	0.012
Community acquired	47 (16.2)	30 (45.5)	<0.001
Site of infection			
Aortic	233 (80.1)	55 (83.3)	0.544
Mitral	99 (34)	16 (24.2)	0.125
Biological prosthetic valve*	177 (65.3)	42 (63.6)	0.672
Mechanical prosthetic valve*	94 (34.7)	21 (31.8)	0.939
Tricuspid	3 (1)	0	–
Pulmonary	1 (0.3)	0	–
Implantable cardiac device†	0	0	–
Other locations	4 (1.4)	0	–
Comorbidity			
Chronic heart failure	141 (48.4)	23 (34.8)	0.097
Coronary disease	112 (38.4)	23 (34.8)	0.399
Chronic lung disease	63 (21.6)	12 (18.1)	0.532
Diabetes mellitus	83 (28.5)	22 (33.3)	0.439
Peripheral vascular disease	19 (6.5)	6 (9.1)	0.390
Cerebrovascular disease	35 (12)	11 (16.6)	0.310
Neoplasia	33 (11.3)	8 (12.1)	0.857
Chronic renal failure	64 (22.0)	16 (24.2)	0.692
Chronic liver disease	14 (4.8)	0	–
Congenital heart disease	19 (6.5)	6 (9.1)	0.715
Age-adjusted Charlson index (IQR)	5 (3–6)	5 (3–6)	0.594
Microbiology			
Gram-positive bacteria			
Staphylococcus aureus	40 (13.7)	6 (9.1)	0.308
MRSA	12 (4.1)	3 (4.5)	0.877
CoNS	149 (51.2)	37 (56.1)	0.476
MTR CoNS	94 (32.3)	25 (37.9)	0.386
Enterococcus	49 (16.8)	4 (6)	0.033
Streptococcus	16 (5.5)	9 (13.6)	0.030
Gram-negative bacilli	10 (3.4)	3 (4.5)	0.664
Anaerobic bacteria	1 (0.3)	0	–
Fungi			
Candida	14 (4.8)	3 (4.5)	0.927
Polymicrobial	4 (1.4)	2 (3)	0.307
Other micro-organisms	4 (1.4)	1 (1.5)	0.930
Echocardiographic findings			
Vegetation	184 (63.2)	46 (69.7)	0.322
Intracardiac complications	155 (53.3)	41 (62.1)	0.192
Valve perforation or rupture	15 (5.1)	4 (6)	0.767

Continued

Table 2 Continued

	First 4 months (n=291)	5th–6th months (n=66)	P value
Pseudoaneurysm	44 (15.1)	14 (21.2)	0.226
Perivalvular abscess	123 (42.3)	30 (45.5)	0.637
Intracardiac fistula	15 (5.1)	4 (6)	0.767
Clinical course			
Acute heart failure	121 (41.5)	22 (33.3)	0.217
Persistent bacteraemia	39 (13.4)	5 (7.5)	0.194
Stroke	69 (23.7)	19 (28.7)	0.388
Embolism‡	52 (17.8)	15 (22.7)	0.361
Acute renal failure	121 (41.5)	24 (36.3)	0.436
Septic shock	43 (14.7)	7 (10.6)	0.378
Surgery indicated	232 (79.7)	55 (83.3)	0.779
Surgery performed	148 (50.9)	34 (51.5)	0.923
Surgery indicated, not performed	84 (28.9)	21 (31.8)	0.635
In-hospital mortality	114 (39.2)	16 (24.2)	0.023
First year mortality	129 (44.3)	21 (31.8)	0.063
Recurrence	15 (5.2)	6 (9.1)	0.220

*Aortic or mitral position, in 23 patients (6.4%), information on the nature of the valve is missing.
†Patients with PVE and concomitant infection of an implantable electronic device.
‡Excluding central nervous system embolism.
CoNS, coagulase-negative staphylococci; MRSA, Methicillin-resistant *Staphylococcus aureus*; MTR, methicillin-resistant; PVE, prosthetic valve endocarditis.

cases, 67.2%; p<0.001; table 1), as well as fewer cases of pulmonary PVE (3 cases, 0.6% vs 18 cases, 2.2%; p=0.038). It was also observed that the first group had more cases due to CoNS (236 cases, 49.3% vs 197 cases, 23.8%; p<0.001, respectively), MTR CoNS (146 cases, 30.5% vs 93 cases, 11.3%; p<0.001) and *Candida* spp (23 cases, 4.8% vs 10 cases, 1.2%; p<0.001) and fewer cases due to *S. aureus* (58 cases, 12.1% vs 150 cases, 18.2%; p=0.004) and streptococci (46 cases, 9.6% vs 214 cases, 25.9%; p<0.001). Regarding echocardiographic findings, more cases were detected with intracardiac complications (252 cases, 52.6% vs 298 cases, 36.1%; p<0.001, respectively), perivalvular abscess (196 cases, 40.9% vs 249 cases, 30.1%; p<0.001), pseudoaneurysm (80 cases, 16.7% vs 66 cases, 7.9%; p<0.001), surgical indication (381 cases, 79.5% vs 586 cases, 70.9%; p=0.001) and surgery performed (247 cases, 51.6% vs 378 cases, 45.8%, p=0.043). Despite these differences, the comparison of mortality rates showed no significant variations (168 cases, 35.1% vs 262 cases, 31.7%; p=0.214).

Comparison of the cases diagnosed in the first 4 and 6 months with cases diagnosed later

When comparing the first 4 and 6 months with the rest, it was observed that in each of these early periods, there were more cases affecting the aortic valve, fewer cases with neoplastic diseases and comorbidity, and more cases due to CoNS and *Candida* spp and fewer cases due to *Streptococcus* spp, and more intracardiac complications such as abscess and pseudoaneurysm and more cases with a surgical indication (online supplemental tables 1S and 2S).

DISCUSSION

PVE diagnosed shortly after implantation surgery presents peculiar microbiological, clinical and prognostic characteristics that may lead to some differences in patient management. Infection by micro-organisms considered nosocomial and the appearance of intracardiac complications are more frequent in these patients than in late PVE. In this article, we present an extensive case series of PVE showing some typical features of early PVE (more cases due to CoNS and Candida as causative pathogens and intracardiac complications such as perivalvular abscess and pseudoaneurysm) that remained for a considerable time after surgery. All the periods considered (first 4, 6 or 12 months) showed very marked differences when compared with the period of more than 1 year. The absence of a clear turning point in the characteristics of patients diagnosed during the first 4 or 6 months with respect to a limited period immediately after (ie, 5th–6th months and 7th–12th months, respectively) has conditioned our selection of the first year as the most appropriate to define early PVE.

Periods considered in determining early PVE

The periods considered for defining early PVE have been diverse in the different investigations carried out to

Table 3 Characteristics of patients with PVE diagnosed during the first 6 months after surgery versus those diagnosed during the 7th–12th months

	First 6 months (n=357)	7th–12th months (n=122)	P value
Age, years (IQR)	71 (63–77)	70 (60–75)	0.201
Male gender	241 (67.5)	89 (72.9)	0.262
Hospital acquired	268 (75.1)	45 (36.9)	<0.001
Non-nosocomial healthcare	12 (3.4)	9 (7.4)	0.062
Community acquired	77 (21.6)	68 (55.7)	<0.001
Site of infection			
Aortic	288 (80.7)	92 (75.4)	0.215
Mitral	115 (32.2)	40 (32.8)	0.907
Biological prosthetic valve*	219 (61.3)	64 (52.4)	0.085
Mechanical prosthetic valve*	115 (32.2)	47 (38.5)	0.203
Tricuspid	3 (0.8)	4 (3.3)	0.073
Pulmonary	1 (0.3)	2 (1.6)	0.100
Implantable cardiac device†	0	1 (0.8)	0.255
Other locations	4 (1.1)	5 (4.1)	0.051
Comorbidity			
Chronic heart failure	164 (45.9)	20 (16.3)	0.270
Coronary disease	135 (37.8)	47 (38.5)	0.789
Chronic lung disease	75 (21.0)	20 (16.3)	0.270
Diabetes mellitus	105 (29.4)	32 (26.2)	0.502
Peripheral vascular disease	25 (7)	14 (11.5)	0.283
Cerebrovascular disease	46 (12.8)	29 (23.8)	0.004
Neoplasia	41 (11.4)	8 (6.6)	0.119
Chronic renal failure	80 (22.4)	34 (27.9)	0.221
Chronic liver disease	14 (3.9)	12 (9.8)	0.013
Congenital heart disease	25 (7)	9 (7.3)	0.889
Age-adjusted Charlson index (IQR)	5 (3–6)	5 (3–7)	0.616
Microbiology			
Gram-positive bacteria			
Staphylococcus aureus	46 (12.9)	12 (9.8)	0.373
MRSA	15 (4.2)	2 (1.6)	0.023
CoNS	186 (52.1)	50 (41)	0.034
MTR CoNS	119 (33.3)	27 (22.1)	0.019
Enterococcus	53 (14.8)	21 (17.2)	0.532
Streptococcus	25 (7.0)	21 (17.2)	0.001
Gram-negative bacilli	13 (3.6)	5 (4.1)	0.819
Anaerobic bacteria	1 (0.3)	2 (1.6)	0.100
Fungi			
Candida	17 (4.8)	6 (4.9)	0.944
Polymicrobial	6 (1.7)	1 (0.8)	0.494
Other micro-organisms	5 (1.4)	4 (3.3)	0.242
Echocardiographic findings			
Vegetation	230 (64.4)	90 (73.8)	0.058
Intracardiac complications	196 (54.9)	56 (45.9)	0.086
Valve perforation or rupture	19 (5.3)	4 (3.3)	0.467

Continued

Table 3 Continued

	First 6 months (n=357)	7th–12th months (n=122)	P value
Pseudoaneurysm	58 (16.2)	22 (18)	0.648
Perivalvular abscess	153 (42.9)	43 (35.2)	0.140
Intracardiac fistula	19 (5.3)	8 (6.6)	0.610
Clinical course			
Acute heart failure	143 (40)	51 (41.8)	0.734
Persistent bacteraemia	44 (12.3)	15 (12.3)	0.993
Stroke	88 (24.6)	25 (20.5)	0.350
Embolism‡	67 (18.7)	32 (26.2)	0.079
Acute renal failure	145 (40.6)	55 (45)	0.388
Septic shock	50 (14.0)	12 (9.8)	0.236
Surgery indicated	287 (80.4)	94 (77)	0.697
Surgery performed	182 (51.0)	65 (53.3)	0.661
Surgery indicated, not performed	105 (29.4)	29 (23.8)	0.231
In-hospital mortality	130 (36.4)	38 (31.1)	0.293
First year mortality	150 (42)	41 (33.6)	0.101
Recurrence	21 (5.9)	5 (4.1)	0.643

*Aortic or mitral position, in 34 patients (7.1%), information on the nature of the valve is missing
†Patients with PVE and concomitant infection of an implantable electronic device.
‡Excluding central nervous system embolism.
CoNS, coagulase-negative staphylococci; MRSA, Methicillin-resistant *Staphylococcus aureus*; MTR, methicillin-resistant; PVE, prosthetic valve endocarditis.

date for this purpose. The fundamental variables taken into account for this definition have been the causative microbiology and the rate of intracardiac complications.[2 4 6–8] Thus, some authors have considered the first 4 months in this definition as reported by Siciliano *et al*, while other research groups have considered 6 months as a more adequate period.[1 4 17] Chu *et al* found a high frequency of PVE cases due to CoNS with a slow decline in incidence over time. Therefore, they considered not 2 but 3 periods: a very early one comprising the first 2 months, an intermediate one from the 3rd to the 12th month, and a late PVE from the first year onwards.[7] In our series, we also observed that changes in aetiology and intracardiac complications evolved gradually over time (figure 3). Regardless of their debatable clinical significance, we consider that the most appropriate period to consider a case as early PVE is the first year after surgery, as suggested by other authors.[5 6 9 18 19]

In our opinion, comparing the first 4 or 6 months with the remaining patients diagnosed after each of these two periods (online supplemental tables 1S and 2S respectively) was not very useful. This may be because most of the cases included in this series were diagnosed after 1 year, which may have favoured significant differences in the variables typically associated with PVE (microbiological and related to intracardiac complications) when comparing any relatively small group of patients with PVE detected shortly after surgery with a large group of PVE cases detected much later after surgery. We believe that this result does not lead us to consider a period of less than 1 year as the definition of early PVE

Characteristics of the affected valve prostheses in early PVE

There was a greater involvement of prostheses in the aortic position during the first year, which has been related to greater exposure to high-pressure and turbulent blood flow that would facilitate endothelial damage and the adherence of micro-organisms in the first weeks after valve implantation.[20] There was also evidence of a higher percentage of infection of biological prostheses during the first year and of mechanical prostheses in later cases. Although a higher risk of endocarditis has been described in biological PVE compared with mechanical ones, to date, there has been no evidence of an earlier presentation in PVE on biological valves. Therefore, it is advisable to pay special attention to these patients during the first months after surgery.[21 22] On a merely theoretical basis, biological valve prostheses could become infected earlier because they lack their natural endothelium and because of the chemical treatments used to preserve the biological tissue that could interfere with re-endothelialisation, which could facilitate bacterial adhesion. [23] In any case, the above comments should be treated with great caution because we do not know the number of prostheses of each type (biological or mechanical) that have been implanted, so we do not know the actual percentage of PVE of each type over time.

Table 4 Characteristics of patients with PVE diagnosed during the 7th–12th months versus those diagnosed after the first year

	7th–12th monts (n=122)	More than 1 year (n=826)	P value
Age, years (IQR)	70 (60–75)	71 (63–78)	0.066
Male gender	89 (72.9)	544 (65.8)	0.121
Hospital acquired	45 (36.9)	187 (22.6)	0.001
Non-nosocomial healthcare	9 (7.4)	65 (7.9)	0.85
Community acquired	68 (55.7)	574 (69.5)	0.002
Site of infection			
Aortic	92 (75.4)	555 (67.2)	0.069
Mitral	40 (32.8)	346 (41.9)	0.056
Biological prosthetic valve*	64 (52.4)	330 (39.9)	0.009
Mechanical prosthetic valve*	47 (38.5)	443 (53.6)	0.002
Tricuspid	4 (3.3)	8 (1.0)	0.033
Pulmonary	2 (1.6)	18 (2.2)	0.518
Implantable cardiac device†	1 (0.8)	22 (2.7)	0.217
Other locations	5 (4.1)	8 (1)	0.006
Comorbidity			
Chronic heart failure	58 (47.5)	361 (43.7)	0.426
Coronary disease	20 (16.3)	150 (18.1)	0.635
Chronic lung disease	47 (38.5)	278 (33.6)	0.290
Diabetes mellitus	32 (26.2)	259 (31.3)	0.252
Peripheral vascular disease	14 (11.5)	85 (10.3)	0.690
Cerebrovascular disease	29 (23.8)	150 (18.1)	0.139
Neoplasia	8 (6.6)	165 (19.9)	<0.001
Chronic renal failure	34 (27.9)	237 (28.7)	0.851
Chronic liver disease	12 (9.8)	67 (8.1)	0.520
Congenital heart disease	9 (7.3)	41 (4.9)	0.266
Age-adjusted Charlson index (IQR)	5 (3–7)	5 (3–7)	0.323
Microbiology			
Gram-positive bacteria			
Staphylococcus aureus	12 (9.8)	150 (18.2)	0.023
MRSA	2 (1.6)	26 (3.1)	0.301
CoNS	50 (41)	197 (23.8)	<0.001
MTR CoNS	27 (22.1)	93 (11.3)	<0.001
Enterococcus	21 (17.2)	141 (17.1)	0.969
Streptococcus	21 (17.2)	214 (25.9)	0.038
Gram-negative bacilli	5 (4.1)	42 (5.1)	0.639
Anaerobic bacteria	2 (1.6)	27 (3.3)	0.329
Fungi			
Candida	6 (4.9)	10 (1.2)	0.003
Polymicrobial	1 (0.8)	11 (1.3)	0.637
Other micro-organisms	4 (3.3)	26 (3.1)	0.939
Echocardiographic findings			
Vegetation	90 (73.8)	572 (69.2)	0.310
Intracardiac complications	56 (45.9)	298 (36.1)	0.036
Valve perforation or rupture	4 (3.3)	25 (3)	0.880

Continued

Table 4 Continued

	7th–12th monts (n=122)	More than 1 year (n=826)	P value
Pseudoaneurysm	22 (18)	66 (7.9)	<0.001
Perivalvular abscess	43 (35.2)	249 (30.1)	0.255
Intracardiac fistula	8 (6.6)	34 (4.1)	0.221
Clinical course			
Acute heart failure	51 (41.8)	327 (39.5)	0.641
Persistent bacteraemia	15 (12.3)	94 (11.3)	0.767
Stroke	25 (20.5)	199 (24.1)	0.382
Embolism‡	32 (26.2)	179 (21.6)	0.259
Acute renal failure	55 (45)	351 (42.5)	0.590
Septic shock	12 (9.8)	118 (14.2)	0.182
Surgery indicated	94 (77)	586 (70.9)	0.162
Surgery performed	65 (53.3)	378 (45.8)	0.120
Surgery indicated, not performed	29 (23.8)	215 (26)	0.594
In-hospital mortality	38 (31.1)	262 (31.7)	0.899
First year mortality	41 (33.6)	302 (36.5)	0.526
Recurrence	5 (4.1)	28 (3.4)	0.690

*Aortic or mitral position, in 64 patients (6.8%), information on the nature of the valve is missing.
†Patients with PVE and concomitant infection of an implantable electronic device.
‡Excluding central nervous system embolism.
CoNS, coagulase-negative staphylococci; MRSA, Methicillin-resistant *Staphylococcus aureus*; MTR, methicillin-resistant; PVE, prosthetic valve endocarditis.

It should be noted that prosthetic pulmonary valve endocarditis was less frequent during the first year. This phenomenon has been observed previously and may be due to lower pressure in the right heart with less endothelial damage and a distinct risk of more prolonged PVE over time.[24 25]

Microbiology of PVE

The percentage of cases of PVE due to CoNS (most of which were MTR) during months 1st–4th, 5th–6th and 7th–12th was 51%, 56%, and 41%, respectively. These high figures may challenge the validity of defining early PVE using a cut-off shorter than 1 year. The incidence of cases due to CoNS after the first year remained quite high at 24%, which is more striking and could suggest a change in the recommendation for empirical treatment in cases diagnosed even after the first year. A pending issue is to consider including coverage against MTR staphylococci in surgical antibiotic prophylaxis, a recommendation

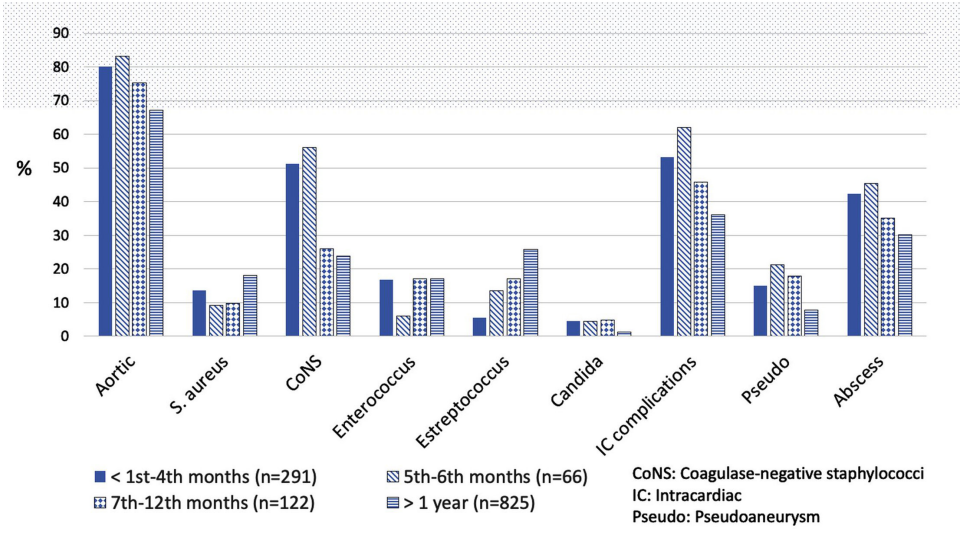

Figure 3 Clinical and microbiological characteristics of patients with prosthetic valve endocarditis according to the time of diagnosis.

proposed by Chu *et al*.[7] The high proportion of cases of endocarditis due to *Candida* spp (5% during the first year) is a concerning aspect also detected in previous investigations.[4] The delay in initiating correct treatment of *Candida* endocarditis is associated with increased mortality.[26] Therefore, PVE due to Candida spp should be considered when the patient presents risk factors for this infection such as immunosuppression, history of previous bacterial endocarditis, chronic renal insufficiency, use of central venous catheters, prolonged antibiotic therapy or candidaemia, especially in cases detected during the first 12 months.[27–29] It should also be noted that the incidence of PVE due to gram-negative bacilli was not higher during the first year, in contrast to what has been observed in previous studies, perhaps because these series are older than those presented in this article.[6 29]

Regarding the changes observed in the clinical characteristics of the patients (aetiology and proportion of intracardiac complications), it should be noted that these changes occur very gradually and progressively over time (figure 3). Therefore, when it comes to prescribing empirical treatment, it may be more useful to focus on the characteristics of each patient, especially their contact with healthcare facilities and the presence of other risk factors for PVE such as persistent bacteraemia or bacterial growth in all bottles of blood culture rather than on just the time elapsed since surgery.[30,31]. In this sense, we consider that empirical coverage of MTR staphylococci would be justified in all cases of PVE, regardless of the time of onset of the disease.

Intracardiac complications in patients with PVE

During the first year, there was a high frequency of perivalvular abscess (41%) and pseudoaneurysm (17%). These figures were significantly higher than those detected in cases diagnosed later (30% and 8%, respectively (table 1). Similar findings have been described previously.[7] It is worth noting that while the proportion of cases with perivalvular abscess showed a decreasing profile, in the case of pseudoaneurysm, the high incidence remained at similar values during that first year. Despite these differences, at all stages, it is recommended to have close clinical surveillance and a low threshold for transoesophageal echocardiography, positron emission tomography/CT (PET/CT) and cardiac to allow timely diagnosis of intracardiac complications.[32 33] Similarly, it should also be emphasised that frequent close contact should be maintained between the patient and the institution where the surgery was performed to detect the need for reintervention at any stage.[32]

Although recent European guidelines indicate that the first 6 months is the period to be considered to define early PVE, the information obtained in our series suggests that this period should be the first year. In addition, it should be noted that their recommendation to consider surgical treatment in PVE in cases diagnosed during the first 6 months could be questioned, taking into account the relatively low in-hospital mortality of patients without complications determining surgical indication who were not operated on regardless of the time of onset.[1 2]

LIMITATIONS

First, the long duration of the study must be acknowledged, which could have resulted in differences in patient characteristics over time. It should also be noted that the hospitals that have contributed a higher number of cases are tertiary hospitals that usually treat more complicated patients and can perform explorations (such as cardiac CT or PET/CT) which may have influenced the detection rate of perivalvular complications. Finally, we would like to acknowledge that we were unable to calculate the incidence of PVE according to the type of prosthesis, which would have been desirable, because the total number of patients in whom a prosthetic valve was implanted in the hospitals participating in the study was not available. In any case, we consider that the information analysed in this study has allowed us to outline the most appropriate defining period for early PVE with reasonable accuracy.

CONCLUSIONS

Although the peculiar characteristics of PVE gradually evolve over time, we consider the first year after prosthetic valve implantation to be the most appropriate period for defining early PVE. The high incidence of nosocomial pathogens, particularly CoNS and Candida spp, and the increased risk of intracardiac complications during this period justify this extended time frame. The findings suggest that current European guidelines may need revision, extending the risk period for early PVE to the first year postsurgery. Additionally, we think that the recommendation for surgery should be based on the presence of complications that have traditionally been accepted as indicating surgery and not solely on the time of PVE appearance since valve implantation.

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