U.PORTO

MESTRADO INTEGRADO EM MEDICINA

The Last Decade of Prosthetic Valve Endocarditis in a Tertiary Hospital

Adriana Raquel Rua Rafael

M

2021

The Last Decade of Prosthetic Valve Endocarditis in a Tertiary Hospital

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Estudante: Adriana Raquel Rua Rafael

Aluna do 6º ano profissionalizante de Mestrado Integrado em Medicina

Afiliação: Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Endereço: Rua de Jorge Viterbo Ferreira nº228, 4050-313 Porto

Endereço eletrónico: adrianarua_r@hotmail.com

Orientador: André Miguel Coimbra Luz

Assistente hospitalar graduado do serviço de Cardiologia no Hospital de Santo António - Centro Hospitalar Universitário do Porto

Professor associado convidado da unidade curricular Medicina I e Especialidades Médicas do Mestrado Integrado em Medicina no Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Endereço: Largo Prof. Abel Salazar 4099-001, Porto, Portugal

Porto, maio de 2021

The Last Decade of Prosthetic Valve Endocarditis in a Tertiary Hospital

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Estudante: Adriana Rafael

Orientador: A. Luz

Porto, maio de 2021

“É a vida que segue e não espera pela gente
Cada passo que dermos em frente
Caminhando sem medo de errar
E creio que noite sempre se tornará dia
E o brilho que o sol irradia há-de sempre nos iluminar
Sei que o melhor de mim está pra chegar”

AC Firmino

AGRADECIMENTOS

Ao Dr. André Luz, pela oportunidade de trabalho, pela motivação constante desde a primeira reunião, pela orientação e disponibilidade ao longo de todo este processo para a produção de conteúdo relevante e de excelência, muito obrigada.

À Alexandra, por me ouvir e guiar, por ser o meu raio de luz durante esta jornada, obrigada.

Aos meus pais, ao Nuno e às minhas avós, que me ajudaram a percorrer este caminho de uma forma tão mais agradável e confiante, nunca conseguirei agradecer o suficiente por todo o amor e estabilidade que me proporcionam diariamente, obrigada.

Ao Ricardo, por me apoiar incondicionalmente e estar ao meu lado, sempre, em todos os momentos, por nunca duvidar de mim e por ser o melhor companheiro de uma vida repleta de sonhos conjuntos, obrigada.

Ao João, por todos os ensinamentos e por partilhar comigo a sua visão da medicina, obrigada.

À Inês, Joana, Carla e Margarida, com quem foi um enorme prazer viver estes últimos 6 anos, por todas as experiências, momentos de partilha e compreensão, por esta linda amizade pura e duradoura, obrigada.

RESUMO

Introdução e objetivos: A endocardite de prótese valvular é uma complicação com risco de vida que ocorre após a substituição de válvulas cardíacas por uma prótese. Apesar de todos os avanços já efetuados na profilaxia, diagnóstico e tratamento, a endocardite de prótese valvular ainda é uma situação associada a um elevado risco de mortalidade. Ao longo dos anos, o perfil epidemiológico deste tipo de endocardite tem-se revelado diferente tendo em conta as populações selecionadas para os diversos estudos. O objetivo do nosso estudo foi fornecer mais informações sobre o perfil epidemiológico dos pacientes que apresentam endocardite de prótese valvular, incluindo a sua prevalência, características clínicas, tipo de abordagem e tratamento e *outcomes* intra-hospitalares e ao fim de um ano após o diagnóstico.

Métodos: Todos os pacientes com diagnóstico de endocardite de prótese valvular, entre 2009 e 2019, foram incluídos neste estudo retrospetivo. Os eventos cardiovasculares *major* foram avaliados um ano após o diagnóstico de endocardite de prótese.

Resultados: Um total de 32 pacientes foram incluídos. A média de idade foi de 71 anos e 62,5% eram do sexo masculino. A comorbilidade de base mais frequente foi a hipertensão arterial (81,3%). As próteses valvulares biológicas foram mais frequentemente afetadas e a posição aórtica foi o local mais comum de infeção. *Enterococcus* spp foi o agente etiológico isolado mais frequente, seguido pelo *Staphylococcus aureus*. O tratamento cirúrgico foi realizado em um terço de nossa coorte. Em relação à ocorrência de eventos cardiovasculares adversos major um ano após o diagnóstico, estes foram relatados em 43,8% dos pacientes. O tratamento cirúrgico encontrou-se associado a um menor risco de ocorrência destes eventos (HR = 0,249(IC95% 0,076 - 0,810).

Conclusões: Este estudo forneceu-nos mais informações sobre o perfil epidemiológico e microbiológico da endocardite de prótese no nosso hospital. Deve ser feito um esforço para a implantação de uma *Heart Team* no sentido de otimizar a abordagem destes pacientes e para uma avaliação multidisciplinar.

Palavras-chave: Endocardite infeciosa; Prótese cardíaca valvular; Epidemiologia; Prognóstico

ABSTRACT

Introduction and objectives: Prosthetic valve endocarditis (PVE) is a life-threatening complication of heart valve replacement procedures. Despite all advances in prophylaxis, diagnosis and treatment, PVE is still associated with a high mortality risk. Over the years, the epidemiological profile of PVE has been shown to differ according to the selected population for the study. The aim of our study was to provide further insight into the epidemiological profile of patients presenting with PVE, including its prevalence, clinical features, management, in-hospital and one-year outcomes.

Methods: All patients diagnosed with PVE between 2009 and 2019 were included in this retrospective study. Major adverse cardiovascular events (MACE) were evaluated at one-year after PVE diagnosis.

Results: A total of 32 patients were included. Mean age was 71 years and 62.5% were male. The most frequent underlying condition was hypertension (81.3%). Bioprosthetic valves were more often affected, and the aortic position was the most common site of infection. *Enterococcus* spp was the most frequent etiological agent isolated, followed by *Staphylococcus aureus*. Surgical treatment was performed in a third of the cohort. Regarding the occurrence of MACE one-year after diagnosis, events were reported in 43.8% of the patients. Surgery was associated with a lower risk for the occurrence of events (HR=0.249, 95%CI 0.076–0.810).

Conclusions: This study provides us further insight on the epidemiological and microbiological profile of PVE in a portuguese hospital. An effort should be made towards implementation of a Heart Team so that the management of these patients goes through a multidisciplinary evaluation.

Keywords: Infective endocarditis; Heart valve prosthesis; Epidemiology; Prognosis

LIST OF ABBREVIATIONS

CI – Confidence Interval

CKD - Chronic Kidney Disease

CRP - C-reactive protein

EuroSCORE - The European System for Cardiac Operative Risk Evaluation

ESC - European Society of Cardiology IE - Infective endocarditis

IQR - Interquartile Range

LVEF – Left Ventricle Ejection Fraction

MACE - Major adverse cardiovascular events

MSSA - Methicillin-sensitive *staphylococcus aureus* NVE - Native Valve Endocarditis

PVE – Prosthetic Valve Endocarditis

SCr – Serum Creatinine

SD - Standard Deviation

TTE - Transthoracic Echocardiography

TOE - Transesophageal Echocardiography

TAVI – Transcatheter Aortic Valve Implantation

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Infective endocarditis (IE) is defined as an infection of the endocardial lining of the heart and the presence of intra-cardiac prosthetic material is one of its major risk factors.[1,2] Prosthetic valve endocarditis (PVE) is a life-threatening complication of heart valve replacement procedures and it accounts for 10-30% of all infective endocarditis cases, with an increasing prevalence.[1,3] It has been estimated to occur in 5% of the patients who undergo a cardiac valve replacement procedure within the first 10 years.[1]

Prosthetic heart valves have been in use since the 1950s but still no ideal prosthetic valve has been created.[4] Both bioprosthetic and mechanical valves are at risk for PVE, however, in a recent meta-analysis, bioprosthetic valves have been associated with a 60% higher risk of PVE when compared to mechanical valves.[5]

Over the years, the epidemiological profile of PVE has been shown to differ in different international studies according to the selected population and time of study.[6,7] Despite all advances in prophylaxis, diagnosis and treatment, PVE is still associated with a high mortality risk.[6,8,9] A successful management of PVE depends on the early implementation of antimicrobial therapeutic and on every patient being promptly considered for surgery.[1]

Therefore, PVE must be continually characterized for a more accurate and appropriate management. Regarding the Portuguese population there are no published descriptive studies exclusively on this subject. With this study, we aimed to provide further insight into the epidemiological profile of patients presenting PVE in a tertiary hospital in Portugal, including its prevalence, clinical features, management, short- and long-term outcomes.

METHODS

Study design

This retrospective observational study was conducted at a tertiary hospital in Porto, Portugal, between 2009 and 2019. The study was approved by the local ethics committee (214-DEFI/223-CE). For personal data protection, a General Data Protection Regulation pseudonymization technique was used and no written consent was required since this study was conducted retrospectively, patients were not involved in its conduct and there was no impact on their care.

Patient selection

All patients diagnosed with IE (ICD9 codes 421.0; 421.1; 421.9 and ICD10 codes I33.0; I33.9; I39.0) were registered in a data base only accessible by the first author. Patients whose electronic medical records had insufficient information or improper coding, were excluded from the initial sample.

According to the infection site and the nature of the heart valves (native *vs* prosthetic), only PVE cases were selected, and their IDs were registered in a second data base for the following data collection.

Data collection

All data was collected from patients' electronic medical records presented in the *SClínico*® platform. Collected data included patients' demographics (age, gender), clinical background regarding conditions predisposing to IE (such as intra-cardiac devices, poor oral hygiene or dental disease and history of intravenous drug use), history of cardiac surgery, other medical comorbidities (including diabetes mellitus, hypertension, chronic kidney disease, ischemic heart disease, peripheral arterial disease and chronic immunosuppressive therapies), presence of fever at hospital admission, diagnostic work-up (including C-reactive protein (CRP), hemogram and biochemical parameters, blood cultures with microorganism identification and transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) data), complications during hospital stay (including paravalvular extension, embolization, sepsis and kidney failure), length of hospital stay, surgical treatment, echocardiographic data at 1 year follow-up and major outcomes. In cases with multiple PVE episodes during this study's 10-year timeline, the first PVE episode to occur after valve replacement was selected to be included in our study.

Creatinine clearance was calculated using the Cockcroft-Gault Equation[10] and chronic kidney disease was defined based on a creatinine clearance value <60ml/min. Acute renal failure was assessed using serum creatinine (SCr) values (increase of SCr by ≥0.3 mg/dl within 48 hours).[11]

Each admission was classified based on Modified Duke Criteria as definite or possible EI. Early PVE was defined as the diagnosis of PVE within 1 year after the prosthetic valve implantation.

PVE-infection acquisition mode was categorized as either health care-associated or community acquired. Health care-associated infections included infections developed in a hospital or other health care facility, that first appeared ≥48 hours after hospital admission or within 30 days after having received health care.[12]

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) II was determined in all patients and it was calculated retrospectively using an online calculator.[10]

The primary outcome was defined as the occurrence of a major adverse cardiovascular event (MACE) within a year after diagnosis. It included non-fatal myocardial infarction, non-fatal stroke and cardiovascular death. Secondary outcomes involved in-hospital complications and mortality, one-year mortality and one-year reinfection. Reinfection was defined as a second IE episode caused by a different agent.

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Normal distribution was verified using the Shapiro-Wilk test. Categorical variables were reported as absolute and relative frequencies. The association between categorical variables was tested using the Chi-Square test or Fisher's exact test. Unpaired samples t-test was performed to compare unpaired means for continuous variables normally distributed. Nonparametric Mann-Whitney U test was performed to compare unpaired means and medians for continuous variables not normally distributed. All reported *P* values were two-tailed, with a *P* value <0.05 indicating statistical significance. Survival curves and rates for the primary outcome were calculated using the Kaplan-Meier method and compared by the log-rank test, as appropriate. All statistical analysis was performed using IBM® SPSS Statistics, version 26 for Windows (IBM® SPSS, Inc., Chicago, IL, USA) and MedCalc® Statistical Software, version 19.7.4 (MedCalc® Software Ltd, Ostend, Belgium).

RESULTS

The initial screening from the hospital records database identified 245 patients with the corresponding code for IE diagnosis between 2009 and 2019. All clinical reports were analyzed and the presence of IE in 217 patients was confirmed, excluding the remaining for insufficient information, no echocardiogram available and improper coding. There were 180 cases (82.95%) related to native valves endocarditis (NVE) and 5 cases of IE (2.3%) originated in pacemaker leads. The remaining 32 cases were PVE (14,75%) and, therefore, included in the present study.

Baseline characteristics, clinical background and clinical/echocardiographic findings on admission/in-hospital are summarized in **Table I**. The mean age was 71 years (SD 9.08), minimum and maximum age values were 44 and 84, respectively. The male gender constituted 62.5% of our sample (n=20).

The most frequent underlying condition was hypertension (81.3%). Dyslipidemia and chronic kidney disease (CKD) were present in half of the sample (n=16) and 5 of the CKD patients were on hemodialysis. Also, nearly half of the patients had ischemic coronary disease (n=15) and a quarter had a history of stroke (n=8). Eight patients (25%) had a previous history of IE.

Early PVE was documented in 5 patients (15.6%) while late PVE accounted for 27 cases (84.4%). Community-acquired was the most frequent acquisition mode, observed in 17 patients (53.1%).

Bioprosthetic valves were double the site of infection compared to mechanical valves (n=21[65.6%] *vs* n=11[34.4%]). Left-sided heart valves constituted all PVE cases and no right-sided PVE was

observed in this study. The aortic valve was the most often infected valve, in 25 cases (78.1%), followed by the mitral valve.

According to the modified Duke criteria, 22 PVE cases (68.8%) were considered definite IE and 10 as possible IE (31.3%). Regarding clinical features, 71.9% of the sample (n=23) presented with fever at hospital admission. Transthoracic and transesophageal echocardiography was performed in all patients. Vegetations were reported in more than two thirds of the sample (n=22), of which 1/3 had vegetations larger than 10mm. Other intra-cardiac complications were present such as abscess, fistula or pseudoaneurysm and moderate perivalvular leak. Laboratory parameters related to admission and during hospital stay are summarized in **Table II**.

Detailed microbiological findings regarding causative microorganisms categorized by total and early *vs* late PVE, are stated in **Table III**. Microbiological diagnostics revealed positive blood cultures in a total of 31 patients (96.9%), with *Enterococcus* spp (n=10, 31.3%) being the most frequent etiological agent, followed by Methicillin-Sensitive *Staphylococcus aureus* (MSSA) (n=4, 12.5%). In the early PVE group of patients, infection was most frequently caused by MSSA (n=3, 60%), followed by *Enterococcus* spp (n=2, 40%). In the late PVE group, the most common infective agent was *Enterococcus* spp (n=8, 29.6%), followed by *Staphylococcus epidermidis* (n=3, 11.1%).

The median hospital length of stay was 47 days (IQR 19.25-61) with 2/3 of our sample (n=21) staying in the hospital for more than 30 days. Regarding treatment, valvular surgery was performed in 10 patients (31.3%), with the majority being urgent surgeries (n=7[21.9%]) and only 2 elective surgeries (6.3%). In the patients who underwent surgery, the median EuroSCORE was 15.73% (IQR 8.73-18.7). (**Table I**) There was no statistically significant difference in EuroSCORE medians between the groups of patients who did and who did not undergo surgery (p=0.072). (**Table IV**)

Outcomes are summarized in **Table V**. Acute renal failure was the most frequent complication during hospital stay (n=23[71.9%]), sepsis was observed in half of the sample (n=16) and embolic events occurred in 11 patients (34.4%). Five patients died in hospital (15.6%).

Occurrence of MACE within the first year after diagnosis was reported in nearly half the sample (n=14[43.8%]). The comparison analysis revealed an association between the type of treatment and the occurrence of MACE (p=0.021), suggesting that patients who underwent surgery did not have as much MACE as patients who were treated only with medical therapy. (**Table VI**)

Furthermore, Kaplan-Meier survival curves and the comparison analysis by log-rank test revealed a statistically significant difference on survival between the group of patients who underwent surgery and those who were treated only with medical therapy (p=0.021). Median survival time for patients who did not undergo surgery was 12 months (95% CI 1.83-22.17). In the group that underwent

surgery, at 12 months after diagnosis, the survival rate was nearly 90%. The estimated risk of an event occurring during the first year after PVE diagnosis in patients who did not undergo surgery was reported to be 4.02 (95% CI 1.235 – 13.088) times higher than patients treated with surgery. (**Figures 1** and **2**)

DISCUSSION

The main findings of this 10-year retrospective study can be summarized as follows: (i) PVE constituted 14.75% of all IE; (ii) mean age was 71 years and the most common underlying disease was hypertension; (iii) bioprosthetic valves were more often affected than mechanic valves and the aortic position was the most common site; (iv) *Enterococcus* spp was the most frequent etiological agent, followed by MSSA; (v) surgical treatment was performed in a third of the sample; (vi) MACE at one-year were 43.8% and surgery was associated to a lower risk of events.

In this study, PVE accounted for 14.75% of all IE cases. The observed rate of PVE in our center is in agreement with the 10-30% rate reported in literature.[1,3] Two recent portuguese cohorts showed rates of around 13%.[13,14]

As expected, mean age was higher than what is reported in other IE studies that included younger patients with native heart valves.[13–15] Along with other PVE studies, this result suggests that PVE patients have grown progressively older over time. [16–18]

The demographic and clinical characterization, as well as echocardiographic findings observed in our population, were similar to those described in other studies.[13,17,19–22] Something to contrast with previous studies' population, including some IE Portuguese cohorts, is that diabetes *mellitus* was not found to be such a common underlying disease in our sample.

PVE was observed to occur more frequently in bioprosthetic valves in the aortic position, supporting the results obtained in the most recent studies.[16,18,19,22–24] In a recent meta-analysis, bioprosthetic valves were found to have a higher risk of IE when compared to mechanical valves. Bioprosthetic valves are expected to degenerate over the years and this gradual process makes them more susceptible to organisms' adherence, implantation and infection.[5] Additionally, the present results differ from the European Society of Cardiology (ESC) guidelines which state that PVE affects biological and mechanical valves equally, possibly indicating outdated information.[25]

Concerning causative agents, identification through blood cultures was positive in 31 out of 32 patients, representing a higher rate than what other studies report.[14,15,17] This finding could be explained by a high clinical suspicion and early referral of patients to the hospital leading to a prompt PVE diagnosis, along with a decrease in incorrect using of antibiotics that could delay the microorganism identification. Most epidemiologic studies report *Staphylococcus aureus* as the

leading cause of PVE and its association with a worse prognosis.[17,20,26] Nevertheless, this study revealed opposite findings and confirmed the decrease in prevalence of *Staphylococcus aureus* and increase of *Enterococcus* spp that recent studies had already started to show.[18,20,21] Regarding time of infection, the most frequent organism underlying early PVE was *Staphylococcus aureus*, whereas in late PVE, *Enterococcus* spp was the most causative agent, in agreement with published literature.[16,20,25,27]

A correct application of ESC guidelines recommendations was observed since both transthoracic and transesophageal echocardiography were performed in all PVE patients.[25]

Regarding management and treatment, achieving the optimal therapeutic strategy in PVE patients is still a challenge for health-care professionals. International guidelines' indications on this topic are not specific for PVE as they follow the general principles outlined for NVE. Despite this, both literature and recent studies agree that an early implementation of antibiotic therapy and promptly consideration for surgery are key points for a successful management. Indications for surgical treatment include: complications unlikely to be treated effectively by medical therapy alone, such as prosthetic valve dysfunction or uncontrolled infection with intracardiac abscess formation; prevention of embolism; and to avoid progression of heart failure.[23,25,28] As confirmed with the present study, these are common conditions in PVE patients, however, only about a third of the sample underwent surgical treatment, which represents a much lower surgical rate than in the majority of other studies (40-50%).[15,16,23,26,29] This can be understood by taking into consideration that the sampled population was older, carrying a higher surgical risk and, therefore, explaining in part why surgery was not performed in those patients. However, we have no understanding about the reasons to why surgery was not performed in these patients.

Although the EusoSCORE was not different between patients who underwent surgery and those who did not, some variables prohibiting surgery as well as surgeon experience are not easily captured by a risk score. Several studies have demonstrated a survival benefit after surgical treatment compared to medical treatment alone.[22,26] Furthermore, at one year follow-up, the present study revealed a survival rate close to 90% in the group of patients that underwent surgery against 50% for those who were on medical treatment only. Our results support the hypothesis that surgical treatment is associated with a longer period free of major cardiovascular events after a PVE episode. However, since a formal comparison between groups taken risk factors into consideration, was not made, these results should be informative at best.

In this study, in-hospital mortality was observed in 15.6%, a lower rate when compared to PVE registries by Wang A. *et al* (2007)[16] and Habib G. *et al* (2005)[29], of 22,8% and 21%, respectively.

Although comparisons cannot be easily made, we risk admitting that better hospital management in the last decade could be the reason behind the present results.

The current study had some limitations that should be considered when interpreting the results. It is a single center study with a small sample of patients, features that limited our statistical analysis and may have influenced the results. Thus, these results may not be generalized to the national population. The study's retrospective nature limited the present study in terms of data collection, as the information available on medical records was sometimes incomplete or missing. A larger multicenter study on PVE or a comparative study between PVE and NVE would increase the external validity of results and would be of best interest to update epidemiological information and improve medical practice in Portugal regarding infective endocarditis.

CONCLUSION

As far as we are aware, this seems to be the first Portuguese study exclusively on prosthetic valve endocarditis. It provided us important insight on the epidemiological profile of these patients and microbiological trends in a tertiary hospital. Infection by *Enterococcus* spp was shown to be increasing while the prevalence of *Staphylococcus aureus*, which was considered the most common IE agent in previous studies, is decreasing. A lower surgical rate than expected was found. PVE remains associated with high mortality and risk of MACE. Moreover, it could be concluded that patients undergoing surgery experienced less events during the year following PVE than patients treated with medical therapy alone. As a final observation, an effort should be made towards implementation of a Heart Team so that management of these patients goes through a multidisciplinary evaluation in order to optimize their prognosis.

Ethical disclosures Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Conflicts of interest. The authors have no conflicts of interest to declare.

REFERENCES

1. O'Connor CT, Kiernan TJ. Contemporary management of prosthetic valve endocarditis: principals and future outlook. *Expert Rev Cardiovasc Ther* 2015 [cited 2021 Feb 22];13(5):501–510. https://doi.org/10.1586/14779072.2015.1035648
2. Thuny F, Grisoli D, Cautela J, Riberi A, Raoult D, Habib G. Infective endocarditis: Prevention, diagnosis, and management [Internet]. Can. J. Cardiol. 2014 [cited 2021 Feb 22];30(9):1046–1057. https://doi.org/10.1016/j.cjca.2014.03.042
3. Vincent LL, Otto CM. Infective Endocarditis: Update on Epidemiology, Outcomes, and Management [Internet]. Curr. Cardiol. Rep. 2018 [cited 2021 Feb 22];20(10). https://doi.org/10.1007/s11886-018-1043-2
4. Basir A, Loncq De Jong M, Gründeman PF, Her Waarden JA van, Kluin J, Moll FL. The early days of vascular and heart valve prostheses: A historical review [Internet]. J. Cardiovasc. Surg. (Torino). 2020 [cited 2021 Feb 22];61(5):528–537. https://doi.org/10.23736/S0021-9509.19.11011-7
5. Anantha-Narayanan M, Reddy YNV, Sundaram V, et al. Endocarditis risk with bioprosthetic and mechanical valves: Systematic review and meta-analysis [Internet]. Heart. 2020 [cited 2021 Feb 22];106(18):1413–1419. https://doi.org/10.1136/heartjnl-2020-316718
6. Palo M De, Scicchitano P, Malvindi PG, Paparella D. Endocarditis in patients with aortic valve prosthesis: Comparison between surgical and transcatheter prosthesis [Internet]. Antibiotics. 2021 [cited 2021 Feb 22];10(1):1–21. https://doi.org/10.3390/antibiotics10010050
7. Thuny F, Grisoli D, Collart F, Habib G, Raoult D. Management of infective endocarditis: Challenges and perspectives [Internet]. Lancet. 2012 [cited 2021 Feb 22];379(9819):965–975. https://doi.org/10.1016/S0140-6736(11)60755-1
8. Habib G, Thuny F, Avierinos JF. Prosthetic Valve Endocarditis: Current Approach and Therapeutic Options. *Prog Cardiovasc Dis* 2008 [cited 2021 Feb 22];50(4):274–281. https://doi.org/10.1016/j.pcad.2007.10.007
9. Vongpatanasin W, Hillis LD, Lange RA. Prosthetic Heart Valves. *N Engl J Med* 1996 [cited 2021 Feb 22];335(6):407–416. https://doi.org/10.1056/NEJM199608083350607
10. New EuroSCORE II (2011) [Internet]. [cited 2021 Mar 13];
11. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury [Internet]. Nephron - Clin. Pract. 2012 [cited 2021 Mar 4];120(4). https://doi.org/10.1159/000339789
12. Haque M, Sartelli M, McKimm J, Bakar MA. Health care-associated infections – An overview [Internet]. Infect. Drug Resist. 2018 [cited 2021 Mar 13];11:2321–2333. https://doi.org/10.2147/IDR.S177247
13. Melo LP, Duarte J, Roque D, et al. Endocardite Infecciosa: Casuística do Departamento de Medicina Interna de um Hospital. *undefined* 2017;
14. Ferreira JP, Gomes F, Rodrigues P, et al. Left-sided infective endocarditis: Analysis of in-hospital and medium-term outcome and predictors of mortality. *Rev Port Cardiol* 2013 [cited 2021 Mar 21];32(10):777–784. https://doi.org/10.1016/j.repc.2012.11.015
15. Ilhão Moreira R, Coutinho Cruz M, Moura Branco L, et al. Infective endocarditis: Surgical management and prognostic predictors. *Rev Port Cardiol* 2018 [cited 2021 Mar 21];37(5):387–394. https://doi.org/10.1016/j.repc.2017.08.007
16. Wang A, Athan E, Pappas PA, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *J Am Med Assoc* 2007 [cited 2021 Mar 21];297(12):1354–1361. https://doi.org/10.1001/jama.297.12.1354
17. Fauchier L, Pericart L, Bourguignon T, et al. Comparison of Outcome of Possible Versus Definite Infective Endocarditis Involving Prosthetic or Bioprosthetic Heart Valves. *Am J Cardiol* 2017 [cited 2021 Mar 21];120(10):1884–1890. https://doi.org/10.1016/j.amjcard.2017.07.100
18. Weber C, Petrov G, Luehr M, et al. Surgical results for prosthetic versus native valve

endocarditis: A multicenter analysis. In: Journal of Thoracic and Cardiovascular Surgery. Mosby Inc.; 2021. p. 609-619.e10.https://doi.org/10.1016/j.jtcvs.2019.09.186
19. Østergaard L, Valeur N, Ihlemann N, et al. Incidence and factors associated with infective endocarditis in patients undergoing left-sided heart valve replacement. *Eur Heart J* 2018 [cited 2021 Mar 21];39(28):2668–2675. https://doi.org/10.1093/eurheartj/ehy153
20. Bezak B, Artemiou P, Hulman M. Valve-related factors and incidence of prosthetic valve endocarditis. *Kardiochirurgia i Torakochirurgia Pol* 2021 [cited 2021 Mar 21];17(4):178–182. https://doi.org/10.5114/kitp.2020.102341
21. Corte A Della, Mauro M Di, Actis Dato G, et al. Surgery for prosthetic valve endocarditis: a retrospective study of a national registry†. *Eur J Cardio-Thoracic Surg* 2017 [cited 2021 Mar 26];52(1):105–111. https://doi.org/10.1093/ejcts/ezx045
22. Tugtekin S, Matschke K, Daubner D, et al. Prosthetic valve endocarditis: Importance of surgical treatment. *Thorac Cardiovasc Surg* 2007 [cited 2021 Mar 21];55(2):94–98. https://doi.org/10.1055/s-2006-924569
23. Lalani T, Chu VH, Park LP, et al. In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis. *JAMA Intern Med* 2013;173(16):1495–1504. https://doi.org/10.1001/jamainternmed.2013.8203
24. Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Prosthetic valve endocarditis after surgical aortic valve replacement [Internet]. Circulation. 2017 [cited 2021 Mar 21];136(3):329–331. https://doi.org/10.1161/CIRCULATIONAHA.117.028783
25. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis [Internet]. Eur. Heart J. 2015 [cited 2021 Feb 24];36(44):3075–3123. https://doi.org/10.1093/eurheartj/ehv319
26. Mihos CG, Capoulade R, Yucel E, Picard MH, Santana O. Surgical Versus Medical Therapy for Prosthetic Valve Endocarditis: A Meta-Analysis of 32 Studies [Internet]. Ann. Thorac. Surg. 2017 [cited 2021 Mar 21];103(3):991–1004. https://doi.org/10.1016/j.athoracsur.2016.09.083
27. López J, Revilla A, Vilacosta I, et al. Definition, clinical profile, microbiological spectrum, and prognostic factors of early-onset prosthetic valve endocarditis. *Eur Heart J* 2007 [cited 2021 Mar 21];28(6):760–765. https://doi.org/10.1093/eurheartj/ehl486
28. Mostaghim AS, Lo HYA, Khardori N. A retrospective epidemiologic study to define risk factors, microbiology, and clinical outcomes of infective endocarditis in a large tertiary-care teaching hospital. *SAGE Open Med* 2017 [cited 2021 Mar 21];5:1–9. https://doi.org/10.1177/2050312117741772
29. Habib G, Tribouilloy C, Thuny F, et al. Prosthetic valve endocarditis: Who needs surgery? A multicentre study of 104 cases. *Heart* 2005 [cited 2021 Mar 21];91(7):954–959. https://doi.org/10.1136/hrt.2004.046177

ATTACHMENTS

Table I - Demographic and clinical characterization

Variable	Total (n=32)
Baseline characteristics – n(%)	
Age (years) - Mean(SD)	71.41(9.08)
Gender, male (female)	20(62.5)
Clinical background – n(%)	
Smoker	2(6.3)
Alcoholism	9(28.1)
Intravenous drug use	1(3.1)
Poor dental	2(6.3)
Hypertension	26(81.3)
Dyslipidemia	16(50)
Diabetes *mellitus*	7(21.9)
Chronic kidney disease	16(50)
Hemodialysis dependent	5(15.6)
Chronic obstructive pulmonary disease	3(9.4)
Stroke	8(25)
Active cancer	3(9.4)
Chronic immunosuppression therapy	2(6.3)
Cirrhosis	3(9.4)
Ischemic coronary disease	15(46.9)
Coronary artery revascularization	13(40.6)
Intra-cardiac devices	6(18.8)
Peripheral artery disease	5(15.6)
Previous IE	8(25)
Valve replacement procedure - Cardiac surgery (TAVI)	26(81.3)
Preserved left ventricle ejection fraction	28(87.5)
Admission and in-hospital findings – n(%)	
Valve prothesis type - Bioprosthetic (Mechanical)	21(65.6)
Acquisition – Community (Health care-associated)	17(53.1)
Affected Valve - Aortic valve (Mitral valve)	25(78.1)
Early PVE (Late PVE)	5(15.6)
Fever at admission	23(71.9)
Acute presentation	18(56.3)
Echography findings –	
Vegetations ≥10mm	10(31.3)
Vegetations <10mm	12(37.5)
Abscess	11(34.4)
Fistula	7(21.9)
Pseudoaneurysm	2(6.3)
Peri-valvular leak – normal/mild (moderate)	25(78.1)
Valvular regurgitation - normal/mild	32(100)
Definite IE (Possible IE)	22(68.8)
Hospital length of stay (≥30 days)	21(65.6)

Hospital length of stay (days) – Median(IQR)	47(19-62)
EuroSCORE (%) – Median(IQR)	18,3(12.81-23.37)
Surgery	10(31.3)
Elective	2(6.3)
Urgent	7(21.9)
Emergent	1(3.1)

IE: Infective Endocarditis Implantation; PVE: Prosthetic Valve Endocarditis; TAVI: Transcatheter Aortic Valve Implantation

Table II - Laboratory parameters

Parameter	Total (n=32)
Hemoglobin at admission (g/dL) – Mean(SD)	10.2(1.7)
White blood cells at admission (x10^{3}/µL) – Median(IQR)	11.9(7.57-17.66)
Platelets at admission (x10^{3}/µL) – Median(IQR)	163(103-207)
C-reactive protein (CRP) at admission (mg/L) – Mean(SD)	129.3(81.8)
Serum creatinine at admission (mg/dL) – Median(IQR)	1.3(1.02-2.69)
Maximum serum creatinine (mg/dL) – Median(IQR)	2.3(1.34-3.53)

Table III - Isolated microorganisms (total, early and late PVE)

Microorganism – n(%)	Total (n=32)	Early PVE (n=5)	Late PVE (n=27)
Methicillin-sensitive *staphylococcus aureus*	4(12.5)	3(60)	1(3.7)
Staphylococcus epidermidis	3(9.4)	0(0)	3(11.1)
Streptococcus gallolyticus/bovis	2(6.3)	0(0)	2(7.4)
Coagulase-negative staphylococcus	2(6.3)	0(0)	2(7.4)
Enterococcus spp	10(31.3)	2(40)	8(29.6)
HACEK group	1(3.1)	0(0)	1(3.7)
Others	9(28.1)	0(0)	9(33.3)
No microorganism isolated	1(3.1)	0(0)	1(3.7)

HACEK: *Haemophilus* species, *Actinobacillus* species, *Cardiobacterium hominis*, *Eikenella corrodens, Kingella kingae*; PVE: Prosthetic Valve Endocarditis

Table IV - Comparison of EuroSCORE between treatment with surgery and no surgery

Variable	Total (n =32)	Surgery		
		Yes (n=10)	No (n=22)	*P*
EuroSCORE (%) – Median(IQR)	18.3(12.81-23.37)	15.73(8.73-18.7)	19.9(13.2-30.1)	0.072

Table V - Follow-up and outcomes

Variable	Total (n=32)
Follow-up – n(%)	
Follow-up echocardiogram	18(56.3)
Preserved LVEF	17(53.1)
Impaired LVEF	1(3.1)
Valvular regurgitation	
Normal / Mild	15(46.9)
Moderate	2(6.3)
Severe	1(3.1)
Outcomes – n(%)	
Surgery complications	1(10)
In-hospital sepsis	16(50)
In-hospital embolic events	11(34.4)
In-hospital cardiac arrhythmias	10(31.3)
In-hospital acute renal failure	23(71.9)
In-hospital mortality	5(15.6)
One-year MACE	
Non-fatal myocardial infarction	1(3.1)
Non-fatal stroke	3(9.4)
Cardiovascular death	10(31.3)
One-year mortality	12(37.5)
One-year reinfection	2(6.3)

LVEF: left ventricle ejection fraction; MACE: major adverse cardiovascular events

Table VI - Comparison of clinical characteristics between occurrence of events and no events within the first year after diagnosis

Variable	Total (n =32)	1-year MACE		
		Yes (n=14)	No (n=17)	*P*
Baseline characteristics				
Age (years) - Mean(SD)	71.4(9.08)	72,86(7.14)	69,94(10.62)	0.388
Gender, male – n(%) (female)	20(62.5)	9(64.3)	10(58.8)	0.756
Clinical background – n(%)				
Smoker	2(6.3)	1(7.1)	1(5.9)	1.000
Alcoholism	9(28.1)	5(35.7)	4(23.5)	0.693
Intravenous drug use	1(3.1)	0(0)	1(5.9)	1.000
Poor Dental	2(6.3)	0(0)	2(11.8)	0.488
Hypertension	26(81.3)	13(92.9)	12(70.6)	0.185
Dyslipidemia	16(50)	6(42.9)	9(52.9)	0.576
Diabetes Mellitus	7(21.9)	4(28.6)	3(17.6)	0.671
Chronic Kidney Disease	16(50)	8(61.5)	7(41.2)	0.269
Hemodialysis dependent	5(15.6)	2(14.3)	3(17.6)	1.000
Chronic obstructive pulmonary disease	3(9.4)	2(14.2)	1(5.9)	0.576
Stroke	8(25)	3(21.4)	5(29.4)	0.698
Active cancer	3(9.4)	1(7.1)	2(11.8)	1.000
Chronic immunosuppression therapy	2(6.3)	1(7.1)	1(5.9)	1.000
Cirrhosis	3(9.4)	3(21.4)	0(0)	0.081
Ischemic coronary disease	15(46.9)	5(35.7)	9(52.9)	0.337
Coronary artery revascularization	13(40.6)	4(28.6)	8(47.1)	0.293
Intra-cardiac devices	6(18.8)	3(21.4)	3(17.6)	1.000
Peripheral artery disease	5(15.6)	2(14.3)	3(17.6)	1.000
Previous IE	8(25)	2(14.3)	6(35.3)	0.240
Valve replacement procedure - Cardiac surgery (TAVI)	26(81.3)	12(85.7)	13(92.9)	0.500
Preserved LVEF prior to PVE	28(87,5)	11(91,7)	16(100)	0.429
Admission and in-hospital findings – n(%)				
Valve prothesis type- Bioprosthetic (Mechanical)	21(65.6)	11(78.6)	9(52.9)	0.258
Acquisition – Community (Health care-associated)	17(53.1)	5(35.7)	11(64.7)	0.108
Affected Valve - Aortic valve (Mitral valve)	25(78.1)	10(71.4)	15(88.2)	0.370
Early PVE (Late PVE)	5(15.6)	2(14.3)	3(17.6)	1.000
Fever at admission	23(71.9)	10(43.5)	13(76.5)	0.119
Acute presentation (Sub-acute)	18(56.3)	6(42.9)	12(70.6)	0.712
Echography findings				
Vegetations ≥10mm	10(31.3)	5(35.7)	4(23.5)	0.693
Vegetations <10mm	12(37.5)	6(42.9)	6(35.3)	0.667
Abscess	11(34.4)	4(28.6)	7(41.2)	0.707
Fistula	7(21.9)	3(21.4)	4(23.5)	1.000
Pseudoaneurysm	2(6.3)	1(7.1)	1(5.9)	1.000
Peri-valvular leak – normal/mild	25(78.1)	10(71.4)	14(82.4)	0.671

(moderate)				
Valvular regurgitation - normal/ mild	32(100)	14(100)	17(100)	-
Definite IE (possible)	22(68,8)	9(64,3)	12(70,6)	1.000
Hospital length of stay (≥30 days) (<30 days)	21(65.6)	8(61.5)	13(76.5)	0.443
EuroSCORE (%) – Median(IQR)	18.3(12.81-23.37)	19.9(14.91-44.46)	15.85(10.61-23)	0.103
Surgery	10(31.3)	1(7.1)	8(47.1)	**0.021**
Timing of surgery				
Elective	2(6.3)	0(0)	2(11.8)	0.488
Urgent	7(21.9)	1(7.1)	5(29.4)	0.185
Emergent	1(3.1)	1(7.1)	0(0)	0.452
Laboratory parameters				
Hemoglobin at admission (g/dL) – Mean(SD)	10.2(1.7)	10.01(1.77)	10.33(1.71)	0.331
White blood cells at admission ($x10^{3}/\mu L$) – Median(IQR)	11.9(7.57-17.66)	16.2(10.54-23.92)	9.7(6.32-15.35)	0.084
Platelets at admission ($x10^{3}/\mu L$) – Median(IQR)	163(103-207)	148(94-196)	163(103.5-246-5)	0.544
CRP at admission (mg/L) – Mean(SD)	129.3(81,8)	140.1(96.91)	123.3(72.6)	0.436
Serum creatinine at admission (mg/dL) – Median(IQR)	1.28(1.02-2.69)	2.29(1.09-2.97)	1.25(0.91-1.48)	0.161
Maximum serum creatinine (mg/dL) – Median(IQR)	2.33(1.34-3.53)	3.21(2.24-4.82)	1.62(1.18-3)	0.084
Causative organism – n(%)				
Methicillin-sensitive *staphylococcus aureus*	4(12.5)	2(14.3)	2(11.8)	1.000
Staphylococcus epidermidis	3(9.4)	1(7.1)	2(11.8)	1.000
Streptococcus gallalyticus/bovis	2(6.3)	0(0)	2(11.8)	0.488
Coagulase-negative staphylococcus	2(6.3)	0(0)	2(11.8)	0.488
Enterococcus spp	10(31.3)	4(28.6)	5(29.4)	1.000
HACEK group	1(3.1)	1(7.1)	0(0)	0.452
Others	9(28.1)	5(35.7)	4(23.5)	0.693
No microorganism isolated	1(3.1)	1(7.1)	0(0)	0.452
Outcomes – n(%)				
In-hospital sepsis	16(50)	9(64.3)	7(41.2)	0.200
In-hospital embolic events	11(34.4)	7(50)	4(23.5)	0.153
In-hospital cardiac arrhythmias	10(31.3)	6(42.9)	4(23.5)	0.441
In-hospital acute renal failure	23(71.9)	12(85.7)	10(58.8)	0.132
Surgery complications	1(10)	0(0)	1(14.3)	1.000
One-year reinfection	2(6.3)	0(0)	2(11.8)	0.488

HACEK: *Haemophilus* species, *Actinobacillus* species, *Cardiobacterium hominis*, *Eikenella corrodens, Kingella kingae;* IE: Infective Endocarditis; LVEF: left ventricle ejection fraction; MACE: major adverse cardiovascular events; PVE: Prosthetic Valve Endocarditis; TAVI: Transcatheter Aortic Valve Implantation

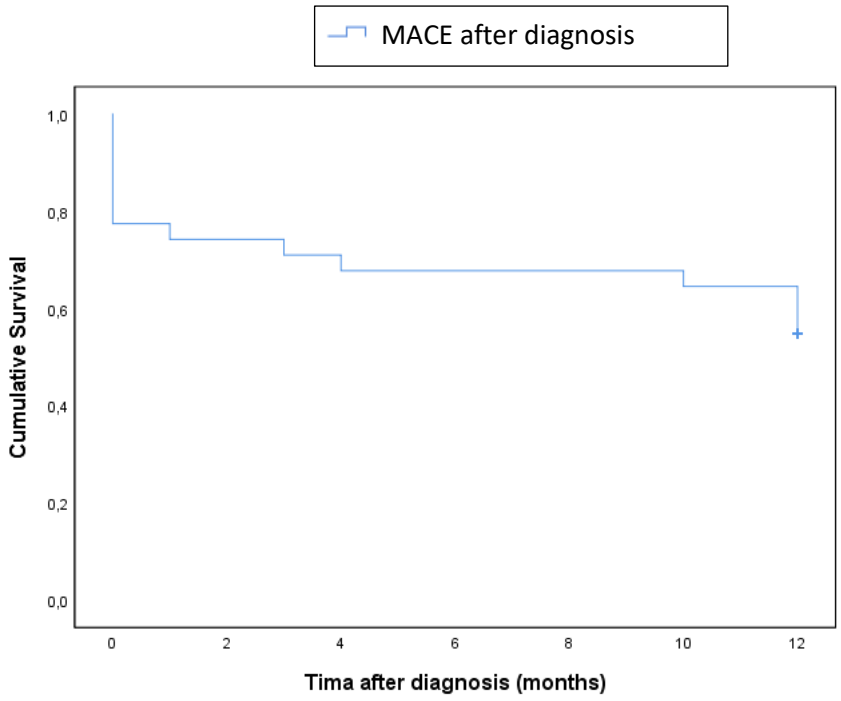

Figure 1 - Kaplan-Meier survival curve for primary outcome (occurrence of MACE within the first year after PVE diagnosis)

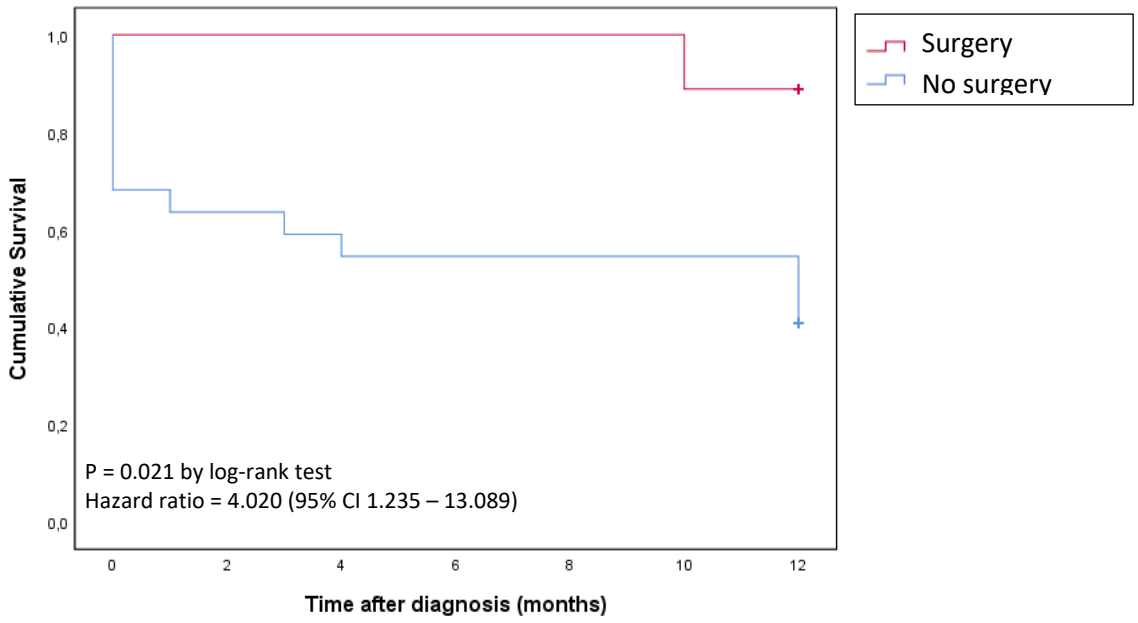

Figure 2 - Kaplan-Meier survival curves for primary outcome (occurrence of MACE within the first year after PVE diagnosis) in patients who underwent surgery and patients only treated with medical therapy

Exma. Sra. Adriana Rafael

Estudante do ICBAS

ASSUNTO: Trabalho Académico - MIM - **"Endocardite de Prótese Valvular nos últimos 10 anos"** – N/ REF.ª 2020.278(214-DEFI/223-CE)

O Conselho de Administração do CHUPorto autoriza a realização do estudo acima mencionado, a realizar no Serviço de Cardiologia Instituição e tendo como Investigador Principal Adriana Rafael, estudante do ICBAS.

O estudo foi previamente analisado pela Comissão de Ética do CHUPorto|ICBAS, pelo Serviço de Investigação Clínica, pela Direção do Departamento de Ensino, Formação e Investigação do CHUPorto e pelo Presidente do Conselho de Administração, tendo obtido parecer favorável.

Cumprimentos,

CONSELHO DE ADMINISTRAÇÃO
13/5/2021
Dr. PAULO BARBOSA
Presidente
Dr.ª RITA MOREIRA
Vogal Executiva
Prof. Doutor JOSÉ BARROS
Diretor Clínico
Dr.ª RITA VELOSO
Vogal Executiva
Enf.º EDUARDO ALVES
Enfermeiro Diretor

* Em todas as eventuais comunicações posteriores sobre este estudo é indispensável indicar a nossa ref.ª.