A RETROSPECTIVE OBSERVATIONAL STUDY: CLINICAL AND PARACLINICAL ASPECTS OF INFECTIOUS ENDOCARDITIS

**G.L. ŞTEFĂNESCU[1,2]*   L.A. TUDOSE [1,2] N. COJOCARU[1,2]
V. BENZA[1,2]   H. RUS[1,2]   E. BOBESCU[1,2]   A. COVACIU[1,2]**

Abstract: *A multitude of data on infectious endocarditis has already been published so far. Nevertheless, the medical care of patients with infective endocarditis remains a significant challenge, and debates on this topic will continue. The diagnosis of this pathology can be difficult, and the treatment is prolonged and presents many challenges, as patients with infective endocarditis are susceptible to numerous both local and systemic complications. We correlated data from the medical records of patients hospitalized with infective endocarditis in order to analyze their predisposing conditions, clinical and biological parameters and treatment outcomes. We concluded that infective endocarditis most commonly affects patients over 60 years who already have structural valve changes, most often involving the aortic valve, with the course of patients being mostly burdened by perivalvular abscesses.*

Key words: *infective endocarditis, germs, blood cultures, heart failure, fever.*

1. Introduction

Infective endocarditis is a public health issue associated with increased morbidity and mortality, responsible for 66,300 deaths per year worldwide. Data from 2019 indicate an increase in incidence of 13.8 cases per 100,000 population per year [1].

Infective endocarditis remains a challenging pathology to diagnose due to the variability in clinical presentation. It should be considered in patients presenting with sepsis or persistent fever of unknown origin in the presence of risk factors. Fulminant forms with a fever -dominated clinical picture or paucisymptomatic forms that may mimic the clinical presentation of many diseases, such as autoimmune diseases or neoplasms, may be encountered.

The initial clinical assessment should include a thorough physical examination to identify portals of entry and predisposing cardiac or non-cardiac risk factors. The most commonly associated cardiac risk factors are a history of infective endocarditis,

[1] Faculty of Medicine, Transilvania University of Braşov
[2] Clinical County Emergency Hospital Braşov
* Corresponding author: stefanescugeorgianalaura@gmail.com

valvular heart disease, prosthetic heart valves, venous/arterial catheters, intracardiac devices and congenital heart disease. Associated non-cardiac risk factors are intravenous drug administration, immunosuppression, recent dental surgical procedures, recent hospitalisations and haemodialysis [2].

According to the latest data, the incidence of infective endocarditis has increased due to a growing population at risk and with diagnosis facilitated by the widespread use of imaging techniques [3]. The etiology of infective endocarditis has gradually changed over the years, now being more correlated with healthcare-associated infections, accounting for approximately 20-25% of the studied patient cohorts [4].

At the same time, with the rising number of COVID 19 cases during the pandemic, there have been reports of patients diagnosed more frequently with infective endocarditis. Many centers have reported an increase in the incidence of infective endocarditis, more likely as a consequence of immunosuppressive therapies, central venous or urinary catheterization [5].

Regarding the microorganisms involved in the etiology, over the years Staphylococcus has replaced Steptococcus as the most common cause of infective endocarditis in developed countries, while the etiology in developing countries is less clear due to lack of medical evidence [6].

The administration of antibiotics before establishing the diagnosis of infectious endocarditis is the most common reason for negative blood culture results, resulting in the difficulty of establishing a definitive diagnosis [7].

Infective endocarditis on cardiac implantable devices is difficult to diagnose and has an unfavorable prognosis, requiring device explantation and long-term antibiotic therapy. Additionally, the presence of conduction disorders (high-degree atrioventricular block) requires urgent cardiac pacemaker implantation if associated with any of the following conditions: Staphylococcus aureus infection, aortic root abscess, tricuspid valve involvement, or a history of valve surgery [8].

The treatment of infectious endocarditis should be initiated promptly after collecting 3 sets of blood cultures at a 30-minute interval [9].

The initial empiric treatment should take into account certain considerations:
- ✓ previous antibiotic therapy;
- ✓ whether the infection is on a native heart valve or a prosthetic heart valve;
- ✓ type of infection - nosocomial or community-acquired;
- ✓ knowledge of local epidemiology, antibiotic resistance, pathogens involved in negative blood cultures [10].

There are 3 main causes requiring surgery in the context of acute endocarditis: heart failure refractory to treatment, uncontrolled infection and prevention of remote embolization [11].

2. Materials and Methods

We conducted a retrospective observational study based on the analysis of data from medical records in the archive of the Clinical County Emergency Hospital Braşov. The study group consisted of 29 patients diagnosed with infective endocarditis admitted to the Cardiology Department of the Clinical County Emergency Hospital Braşov between 01.01.2021 and 31.12.2021.

Following the outbreak of COVID-19 disease, we noticed an increase in the number of patients with infective endocarditis hospitalized in our departament. Considering the fact that the SARS CoV2 pandemic took place between

March 2020 and April 2022, we selected for this study only patients hospitalized with infective endocarditis during the year 2021, this being the only year fully included in the pandemic.

The inclusion of patients in the study was done in the order of admission, and their data were extracted from the medical records existing in the hospital's archive. For each patient included in the study, medical parameters were analyzed by creating a database in Microsoft Excel, including the patient's gender and age, place of origin, personal medical history (infectious endocarditis, other infections, including SARS-CoV-2 infection), the presence of pre-existing predisposing factors, signs and symptoms at presentation, associated systemic diseases, and NYHA functional class at admission.

Subsequently, we analyzed and interpreted the monitored biological parameters during hospitalization, including complete blood count, C-reactive protein, erythrocyte sedimentation rate, markers of

myocardial cytolysis, and serum creatinine, along with repeated sets of blood cultures and bacteriological screening.

Additionally, we interpreted the information obtained from transthoracic and transesophageal echocardiography (affected valves, local complications), as well as data resulting from the analysis of therapeutic strategies. The results were statistically analyzed and expressed as percentages.

Statistical Analysis: Categorical variables were reported as counts and proportions, and Pearson Chi-square test were used to analyze the differences between the study groups. A value of $p < 0.05$ was considered statistically significant.

3. Results and discussion

The study group consisted of 29 patients, with a significantly higher incidence in urban areas 20 (69%) in comparison with rural areas 9 (31%) (p< 0.05) as illustrated in Figure 1.
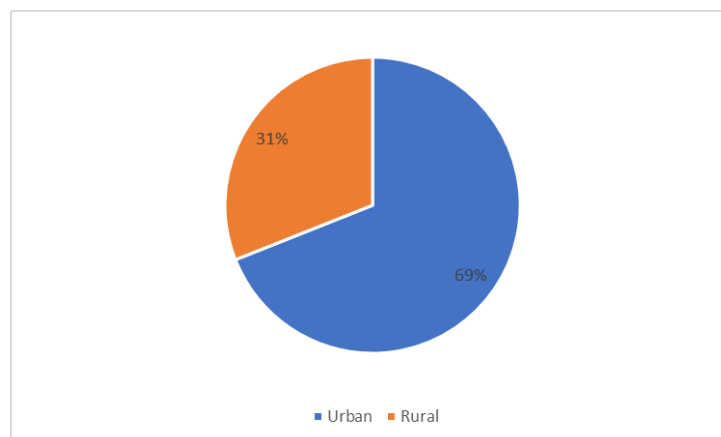

Fig. 1. *Incidence of endocarditis in urban and rural areas*

Studies conducted in various regions and on multiple subpopulations have demonstrated that infectious endocarditis is a pathology more frequently encountered in male subjects, accounting for two-thirds

of cases. The reason for the lower incidence of this pathology in females is unknown and requires further investigation [11]. From the analysis of our cohort of patients with infectious endocarditis, 8 (27.5%) male patients and 21 (72.5%) female patients

were identified, p=0.015. We can conclude that women had a higher predisposition to develop infectious endocarditis compared to men, contrary to data obtained in similar studies so far.

According to Forestier E. et al., infectious endocarditis is diagnosed in over one-third of cases in patients over 70 years old [12]. In our study, the entire patient cohort, divided into 2 categories, had ages ranging from 23 to 88 years. The peak incidence age for patients with infectious endocarditis was significantly higher over 60 years - 23 patients (80%), while only 6 patients (20%) were under 60 years old (p=0.001).

Although infectious endocarditis can affect both native and prosthetic valves, infection rarely occurs on a structurally normal heart, with the majority (60%) of patients having a predisposing heart

endocarditis cases can be cured either through medical therapy or combined medical and surgical therapy, recovering patients remain at risk for an additional episode of infectious endocarditis. The risk of developing a second episode of infectious endocarditis among survivors has been estimated to be between 2% and 22% [13]. Among the selected patients, only 2 patients (6.8%) had a personal history of endocarditis. In contrast, 9 patients (31%) in the entire cohort had other infectious foci, while 22 patients (75.8%) had no identifiable infectious pathology in their recent personal history.

The associated systemic pathology in patients with infectious endocarditis is most often directly related to advanced age, which frequently involves structural and functional valvular changes. Additionally,
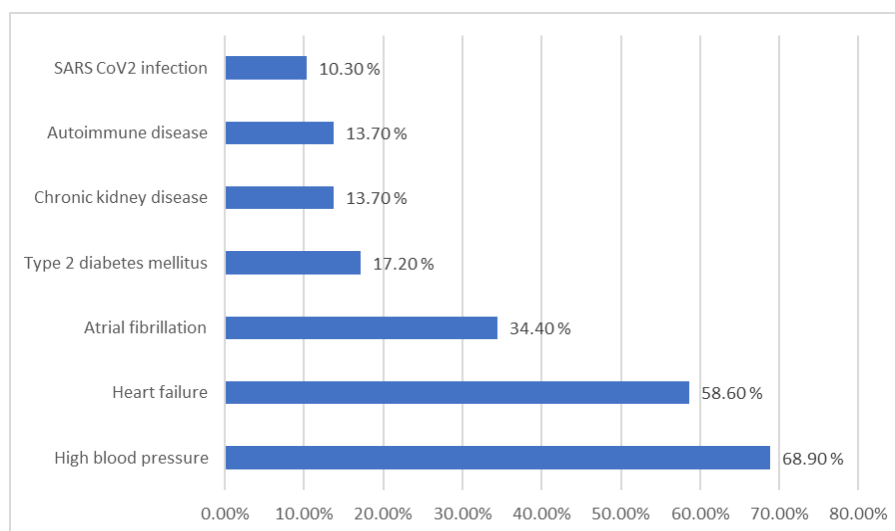

Fig. 2. *The prevalence of comorbidities in the patients with infectious endocarditis*

condition. It is well-known that valvular lesions represent a risk factor for this pathology, being included in the minor criteria for a positive diagnosis [11]. Similar to the data in the literature, in the present study, we identified 17 patients (58.6%) with pre-existing valve pathologies.

Although the majority of infectious

the high prevalence of comorbidities in the elderly explains why infectious endocarditis at advanced ages has an unfavorable prognosis [14]. From the patient cohort included in the study, the majority of patients - 20 patients (68.9%) had as can be seen in figure 2, arterial hypertension, 17 patients (58.6%) had associated heart

failure, 10 patients (34.4%) had atrial fibrillation, 5 patients (17.2%) had type 2 diabetes mellitus, 4 patients (13.7%) presented with chronic kidney disease, 4 patients (13.7%) had autoimmune diseases or were undergoing immunosuppressive treatment, while only 3 patients (10.3%) had a history of SARS-CoV-2 infection.

Heart failure is the most commonly encountered complication of infectious endocarditis and, at the same time, represents the most frequent indication for surgical intervention. Heart failure is observed in 42–60% of cases of infectious endocarditis on the native valves and is more common in aortic valve lesions compared to mitral valve lesions [15]. The entire patient cohort presented with symptoms of heart failure, with 5 patients (17.25%) in NYHA class I, 15 patients (51.72%) in NYHA class II, 7 patients (24.13%) in NYHA class III, and 2 patients (6.89%) in NYHA class IV, as illustrated in Figure 3. It is worth noting that none of the patients presented with cardiogenic shock.
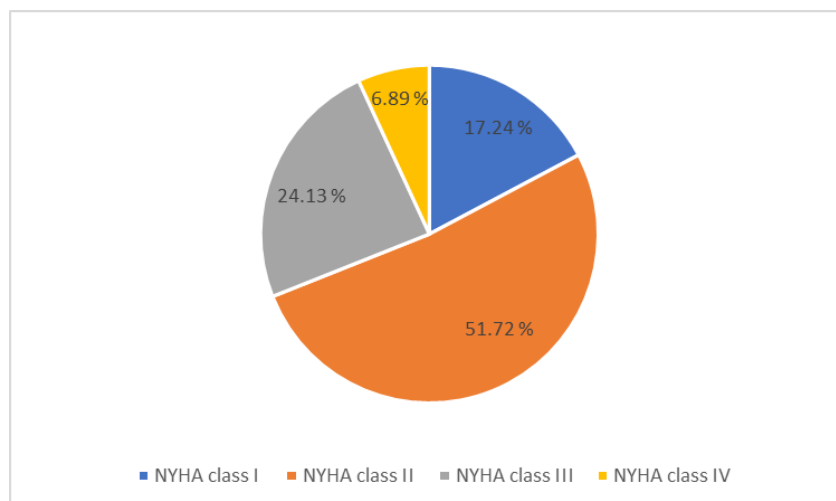

Fig. 3. *Prevalence of heart failure classes in patients with infective endocarditis*

Infectious endocarditis remains a diagnostic challenge due to its variable clinical presentation. Generally, the diagnosis should be considered in all patients with sepsis or fever of unknown origin, especially in the presence of risk factors. In the European Registry of Infective Endocarditis (EURO-ENDO), fever (77.7%) was one of the most common clinical manifestations [11]. The majority of patients - 17 patients (58.6%) in our study cohort had fever/chills as the main symptom, and only one of them presented with septic shock at the time of admission.

Investigations such as laboratory tests and biological markers usually yield nonspecific results in infectious endocarditis. The degree of anemia, leukocytosis/leukopenia, concentrations of C-reactive protein and procalcitonin, erythrocyte sedimentation rate, and markers of organ dysfunction (serum creatinine, thrombocytopenia, cardiac troponin, and brain natriuretic peptides) can be used to estimate the severity of the infection, but none are specific for diagnosis [11]. For each patient included in the study, we analyzed biological parameters to assess the infectious status, as illustrated in Figure 4.
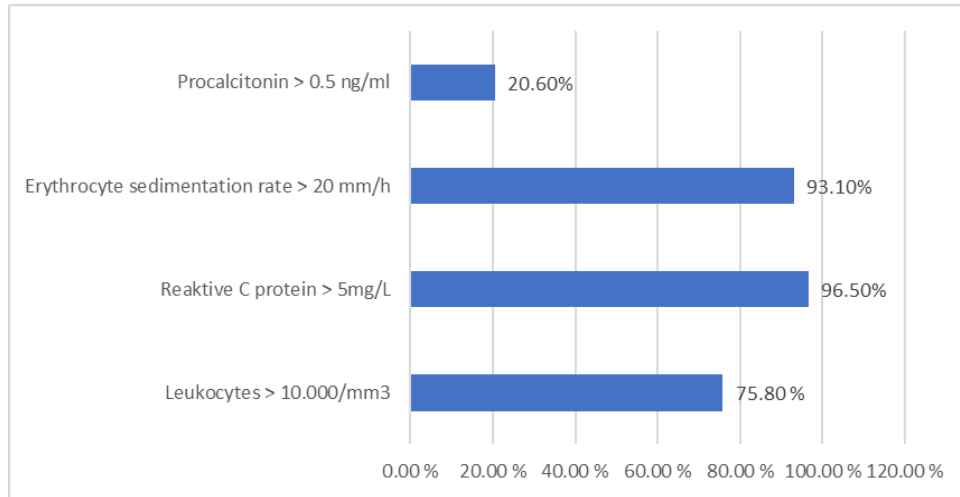
Fig. 4. *The biological parameters analyzed to evaluate the infectious status*

Thus, we observed that the majority of patients had leukocytosis at the time of admission - 22 patients (75.8%), while one patient had leukopenia. The inflammatory biological syndrome was observed in the vast majority of patients: elevated C-reactive protein in 28 of patients (96.5%), erythrocyte sedimentation rate in 27 of patients (93.1%), and procalcitonin in 6 of patients (20.6%). Subsequently, we interpreted the data resulting from the analysis of biomarker parameters with prognostic value in infectious endocarditis: anemia was present in 22 of patients (75.8%), while only 11 patients (37.9%) had thrombocytopenia. Renal function was impaired in 11 of patients (37.9%), as can be seen in Figure 5.
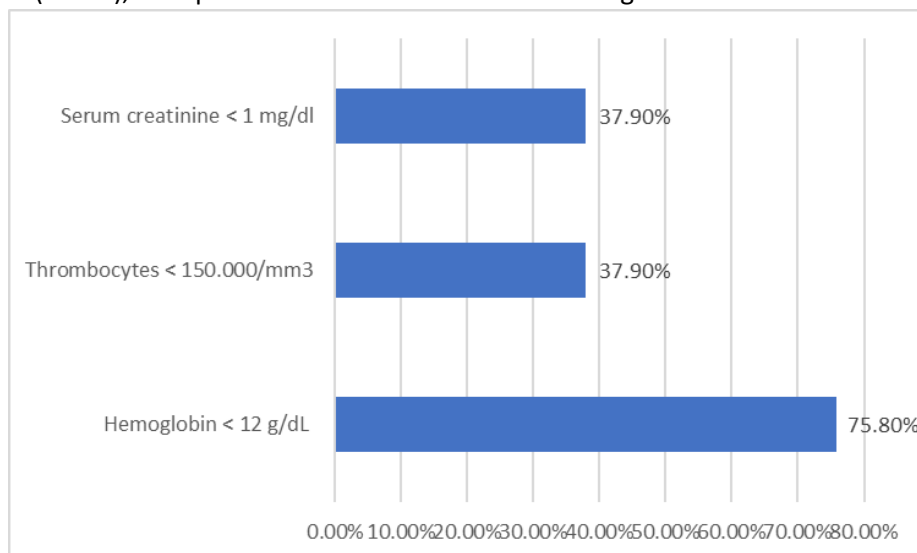

Fig. 5. *Some of the biomarkers with prognostic value in infectious endocarditis*

Elevation of myocardial injury markers above the 99th percentile in patients with infectious endocarditis may indicate myocardial injury, most commonly through septic embolism. However, high-sensitive troponin T was not reacted in any of the patients in the study cohort.

Most retrospective studies incriminate Staphylococcus spp. as the main etiological agent of infectious endocarditis, being responsible for up to 56% of cases, with the highest rates of complications and mortality. Streptococcus spp., Enterococcus spp., Gram-negative bacilli, and Candida spp. are less commonly reported. Identifying the infecting microorganism remains the cornerstone of effective therapy in complicated cases of infectious endocarditis. Therefore, in patients with negative blood cultures, serological or molecular testing via polymerase chain reaction should be considered [16].
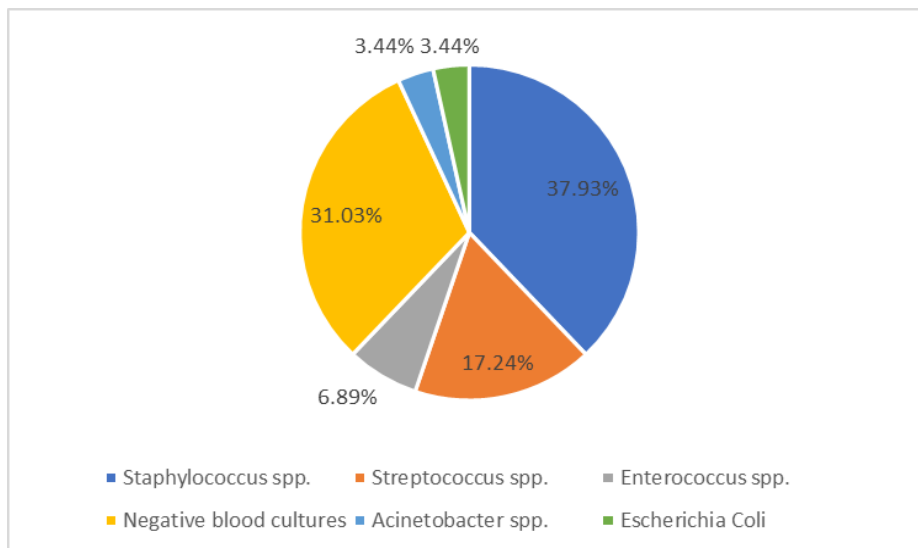
Registry of Infective Endocarditis (EURO-

Fig. 6. *The etiological agents identified in patients with infective endocarditis*

In our patient cohort, among the responsible pathogens identified through serial blood cultures, as shown in Figure 6, Staphylococcus spp was detected in 11 of patients (37.93%) , Streptococcus spp in 5 of patients (17.24%), Enterococcus spp. in 2 of patients (6.89%), Acinetobacter spp in 1 patient (3.44%), and Escherichia coli in 1 patient (3.44%), p=0.001. In a significant percentage of cases - 9 patients (31.03%), the blood cultures were negative, compared to the results from the European ENDO), where 16.8% of patients had negative blood cultures [11].

Additionally, microbiological screening of patients was conducted through culture collection: urine culture (3 patients positive for E. Coli, 1 patient positive for Pseudomonas spp., 1 patient positive for Klebsiella spp.), negative pharyngeal exudate for all patients, and nasal exudate (1 patient positive for Staphylococcus aureus, 1 patient positive for Klebsiella spp.).
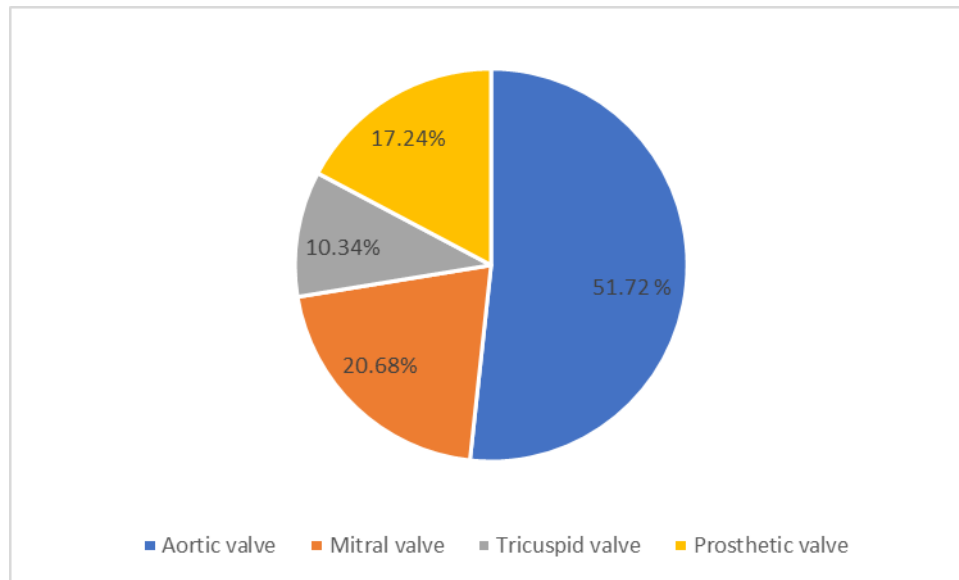
Fig. 7. *The percentage of affected valves in patients with infective endocarditis*

Even so, a causal relationship between the microorganism involved in the infection and the subsequent results of the collected blood culture sets could be established only in one of the patients included in the study.

Upon admission, all patients were evaluated through transthoracic echocardiography, and subsequently, those with prosthetic heart valves and suboptimal transthoracic images were further assessed through transesophageal echocardiography. Vegetations localizations were significantly more identified at the level of the aortic valve in 15 of patients (51.72%), followed by involvement of the mitral valve in 6 of patients (20.68%); less frequent locations were at the level of prosthetic heart valves - 5 of patients (17.24%), and the tricuspid valve - 3 of patients (10.34%), (p=0.008).

Complications of infective endocarditis   Table 1

Item No.	Complications of infective endocarditis	No. of patients	%
1	Valve abscesses	6	20,6%
2	Valve ruptures	5	17,2%
3	Septic embolisms	4	13,7%
4	Acute renal injury	3	10,3%
5	Valvular pseudoaneurysms	2	6,8 %

Among valvular and peripheral complications (Table 1), we most frequently observed valve abscesses - 6 of patients (20.6%), followed by valve ruptures - 5 of patients (17.2%), septic embolisms - 4 of patients (13.7%), acute renal injury - 3 of patients (10.3%), and valvular pseudoaneurysms - 2 of patients 6.8%).

4. Conclusions

After interpreting the analyzed data, the following conclusions can be drawn:
- ✓ The majority of patients diagnosed with infectious endocarditis were from urban areas.
- ✓ Women were more frequently diagnosed with infectious endocarditis compared to men.
- ✓ The age group most often affected was over 60 years.
- ✓ Pre-existing valvular lesions were found in a significant percentage of patients.
- ✓ Personal history of infectious endocarditis was very rarely present; furthermore, in the majority of cases, an incriminated infectious pathological agent could not be identified in establishing the etiology.
- ✓ The number of cases of infectious endocarditis has increased during the SARS-CoV-2 pandemic, possibly as a consequence of social isolation measures, reduced access to medical care, and the immunosuppression associated with this condition; at the same time, the large-scale use of empiric antibiotic therapy during this period led to the selection of much more resistant strains and brought challenges in terms of treatment.
- ✓ The majority of patients presented with symptoms of heart failure at the time of hospitalization.
- ✓ The inflammation marker with the highest sensitivity in assessing the severity of the infection was RCP, and among the prognostic biomarkers, the most relevant were hemoglobin, followed by platelet count and serum creatinine.
- ✓ Recognition of the pathology required complex analyses, with the diagnosis often being challenging in the presence of a significant percentage of patients with negative blood cultures. Staphylococcus spp. was the most frequently incriminated microorganism.
- ✓ The most common location was at the level of the native aortic valve, followed by the native mitral valve.
- ✓ The most frequent local complications were valve abscesses, followed by valve ruptures.

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