Infective Endocarditis: Two Years of Experience at Mansoura University

Original Article

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ABSTRACT

Background: Infective endocarditis (IE) remains a rare but serious condition associated with high morbidity and mortality. Its diagnosis and management are complicated by its diverse clinical manifestations and the lack of clear, evidence-based guidelines. Despite advancements, the in-hospital mortality rate has remained around 20% over the past three decades. Aim of the Work: To assess clinical characteristics, complications, and outcomes, with each IE patient followed-up for one

year post-discharge.

Patients and Methods: A prospective observational study was conducted at the Cardiology Department, Specialized Medical Hospital, Mansoura University, from August 2016 to August 2018. Fifty patients were diagnosed with definite IE based on modified Duke criteria. Clinical data were collected. Patients underwent electrocardiography, echocardiography, blood cultures, and laboratory tests. Multi-slice computed tomography (MSCT) was utilized to assess systemic complications.

Results: Fever and dizziness were universal symptoms present in 50 patients (100%). Vegetations were detected in 42 patients (84.5%), and embolic events occurred in 14 (28%). Staphylococcus aureus was the predominant pathogen in 26 patients out of 35 patients with positive growth (74.3%). In-hospital mortality was observed in 17 patients (34%), primarily due to sepsis/ multi-organ failure (11 out of 17 patients). At one-year follow-up, 8 patients (27.6%) had died, and recurrence of IE was rare observed in 1 out of 29 (3.4%).

Conclusion: IE presents with diverse clinical manifestations and significant mortality. Early diagnosis and appropriate management, including timely surgical intervention, are critical for improving outcomes. The study underscores the importance of tailored treatment strategies to address the multifaceted nature of IE.

Key Words: Clinical outcomes, echocardiography, infective endocarditis, mortality, valve replacement.

Received: 20 January 2025, Accepted: 16 February 2025.

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ISSN: 2735-3540, Vol. 76, No. 1, March 2025.

INTRODUCTION

The diagnostic challenges of infective endocarditis (IE), first noted by Sir William Osler in 1885, persist today due to the disease's rarity, unpredictable nature, and wide-ranging clinical manifestations^[1]. Research has been largely retrospective and reliant on registries, limiting progress and resulting in a lack of level A recommendations in current guidelines. A study emphasized the continued reliance on both art and science in managing IE, underscoring the need to enhance scientific approaches to improve patient care^[2].

IE remains a rare but serious condition linked to risk factors like rheumatic heart disease, artificial valves, and intravenous drug use, with significant complications such as heart failure, stroke, embolization, and sepsis. Despite advancements in diagnosis and treatment, the in-hospital mortality rate of IE has remained around 20% over the past three decades^[3]. Reducing risk factors, particularly rheumatic heart disease, may help lower the incidence of IE^[4].

In regions with a high incidence of streptococcal IE, prophylaxis before oral procedures is crucial^[5]. Prompt hospital referrals with echocardiography can reduce diagnostic delays and prevent complications, while access to urgent heart surgery is essential to lower early mortality in facilities without surgical capabilities. Additionally, a study indicates a 50% higher infection risk in biological prostheses than mechanical ones^[6].

AIM OF THE WORK

This study aims to describe the clinical characteristics, complications, treatment, and long-term outcomes of IE through a hospital-based prospective study.

PATIENTS AND METHODS

This observational, descriptive, prospective study was conducted on 50 patients at the Cardiology Department of the Specialized Medical Hospital, Faculty of Medicine, Mansoura University, from August 2016 to August 2018, with ethical committee approval. Consents were obtained from each patient per the department's research plan. Each surviving patient was followed-up for one year postdischarge.

ETHICAL CONSIDERATION

The study was done after being approved by the Institutional Review Board, Mansoura University, Faculty of Medicine (Approval code: MS/17.08.120).

Eligibility Criteria:

This study included patients diagnosed with definite IE according to the modified Duke criteria^[7], with no exclusion criteria.

Assessments:

Medical History Assessment: History taking focused on personal details and risk factors for IE, including hypertension, diabetes, chronic kidney disease, drug abuse, prosthetic valves, smoking, HIV, immunocompromised states, and prior dental or surgical procedures. Symptoms and signs such as fever, chest pain, dizziness, syncope, embolic complications, acute pulmonary edema, and vascular phenomena like splinter hemorrhages and Roth spots were also recorded.

Clinical Examination: The full clinical examination included general assessment of blood pressure, temperature, heart rate, and consciousness level (Glasgow score), along with identifying vascular and immunological signs such as Osler nodules, Janeway lesions, and Roth spots. Local cardiac examination focused on auscultation for heart murmurs, extra heart sounds, and prosthetic valve clicks.

Electrocardiograms (ECG): A standard 12-lead electrocardiogram (ECG) was performed for all patients at a paper speed of 25 mm/s and standardization of 1 mV/10

mm. The ECG assessment focused on detecting rhythm abnormalities, chamber enlargement, and conduction disturbances. Special attention was given to atrial fibrillation, atrioventricular blocks, and ischemic changes.

Echocardiographicy: All patients underwent echocardiographic evaluation upon admission and were followed up weekly until discharge using a Vivid E9 ultrasound machine with M5S and TEE probes.

Transthoracic Echocardiography (TTE): TTE was the initial imaging modality for all patients, focusing on valvular involvement, vegetation presence, mobility, and size. Additionally, left ventricular function, pulmonary hypertension, and any congenital lesions were assessed.

Transesophageal Echocardiography (TEE): TEE was performed when TTE was inconclusive or when there was suspicion of prosthetic valve involvement, abscess formation, pseudo-aneurysm, or intracardiac fistula. Major echocardiographic diagnostic criteria included vegetation, abscess or pseudoaneurysm, and new prosthetic valve dehiscence.

Laboratory investigations: Three separate blood culture sets from distinct venipunctures were obtained at least one hour apart over 24 hours, with follow-up cultures every 10 days until negative results were obtained. Discharge or referral for elective surgery was considered after three negative cultures. Serum creatinine levels were monitored for potential elevations, which could indicate renal hypoperfusion due to sepsis or heart failure, embolic renal infarction, immune complex-mediated glomerulonephritis, or toxicity from antibiotics or contrast agents used in imaging.

Multi-slice computed tomography (MSCT): MSCT with contrast was performed in 35 patients based on clinical indications, primarily for the assessment of systemic embolization. Renal function (serum creatinine, estimated glomerular filtration rate) was monitored pre- and post-MSCT to assess potential contrast-induced nephropathy, particularly in patients receiving nephrotoxic antibiotics or those with preexisting kidney disease.

Statistical analysis

All statistical analyses were conducted using Statistical Package for the Social Sciences version 16 (SPSS v16 Inc., Chicago, Illinois, USA). Data were described using mean \pm standard deviation, median, interquartile range, or

frequencies and percentages as appropriate. Correlation between variables will be assessed using Pearson's correlation for normally distributed data and Spearman's rank correlation for non-normally distributed data, with *p*-values <0.05 considered statistically significant.

RESULTS

The study sample comprised 40 males (80%) and 10 females (20%). Regarding body mass index, 24 participants (63%) had normal weight, 9 (24%) were overweight, and 5 (13%) were obese. Regarding age, 34 participants (68%) were under 40, and 16 (32%) were 40 years or older, with a mean age of 36.4 ± 14.3 years. Hospital stay was under 25 days for 26 participants (53%) and 25 days or longer for 23 (47%), with a mean duration of 24 ± 14 days. The history of comorbidities and risk factors included smoking (50%), intravenous drug abuse (48%), hepatitis C virus (34.7%), chronic obstructive pulmonary disease (24.5%), prosthetic valve (18%), stroke or intracranial hemorrhage (18%), dental procedures (14.3%), diabetes mellitus (12%), atrial fibrillation (10%), dialysis (8%), previous infective endocarditis (6%), hypertension, chronic kidney disease, autoimmune conditions (6% each), pulmonary edema, HIV, and thyroid dysfunction (4% each), and pacemaker and cancer (2% each).

The clinical presentation of the study population showed that all patients (100%) presented with fever and dizziness, while 44% had cough, 30% had other symptoms, 8% had chest pain, and 4% experienced acute pulmonary edema. Regarding the New York Heart Association (NYHA) classification, 56% were in class I, 30% in class II, 8% in class III, and 6% in class IV. ECG findings revealed that 90% had sinus rhythm and 10% had atrial fibrillation, while 92% had normal conduction, 6% had atrioventricular block, and 2% were on a pacemaker. Glasgow score assessment showed that 92% had a score of 15 or higher, and 8% had a score below 15. Complications at admission included abscesses (71.2% no abscess, 15.4% pulmonary, 5.8% splenic and cardiac, and 1.9% femoral), inflammatory reactions (86.3% no inflammatory reaction, 7.8% spondylitis, and 5.9% arthritis), and embolic events (66.7% no embolic events, 11.8% pulmonary, 9.8% stroke, 5.9% peripheral, 3.9% renal, and 2% splenic). Other complications included hemorrhagic stroke (2%), acute kidney injury (18.4%), and septic shock (10%). (Table 1)

 Table 1: Clinical features and complications at admission of study population.

study population.	
Parameter	N (%)
Clinical Presentation	
Fever	50 (100%)
Dizziness	50 (100%)
Cough	22 (44%)
Others	15 (30%)
Chest pain	4 (8%)
Acute pulmonary edema	2 (4%)
NYHA Class	
Class I	28 (56%)
Class II	15 (30%)
Class III	4 (8%)
Class IV	3 (6%)
ECG Rhythm	
Sinus rhythm	45 (90%)
Atrial fibrillation (AF)	5 (10%)
Conduction Abnormality	
Normal	46 (92%)
AV block	3 (6%)
On pacemaker	1 (2%)
Glasgow Score	
< 15	4 (8%)
15	46 (92%)
Complications at Admission	
Abscess	
No	37 (71.2%)
Pulmonary	8 (15.4%)
Splenic	3 (5.8%)
Cardiac (aortic root abscess)	3 (5.8%)
Femoral	1 (1.9%)
Inflammatory Reactions	
No	44 (86.3%)
Spondylitis	4 (7.8%)
Arthritis	3 (5.9%)
Embolic Events	
No	36 (66.7%)
Pulmonary	6 (11.8%)
Stroke	5 (9.8%)
Peripheral	3 (5.9%)
Renal	2 (3.9%)
Splenic	1 (2%)
Hemorrhagic Stroke	1 (2%)
Other Complications	
AKI	9 (18.4%)
Septic Shock	5 (10%)

NYHA: New York Heart Association, ECG: Electrocardiogram, AF: Atrial Fibrillation, AV: Atrioventricular, AKI: Acute Kidney Injury.

Native valve infective endocarditis (NVIE) was observed in 15 cases (44.1%) on the right side and 19 cases (55.9%) on the left side. Among prosthetic valve infective endocarditis (PVIE), there were 9 left-sided cases (29.6%). Regarding intravenous drug abuse, 13 cases (68.4%) had right-sided infective endocarditis, and 6 cases (31.6%) had left-sided infective endocarditis (p < 0.001). Among NVIE cases, 18 cases (94.7%) were associated with intravenous drug abuse, whereas only 1 case (4.2%) of PVIE had a history of drug abuse (p = 0.024). (Table 2)

Table 2: Association between right and left sided infective endocarditis regarding valve type, IV drug abuse, and valve type in relation to IV drug addiction.

Parameter	Right-sided IE	Left-sided IE	Total	P value
Valve Type				
NVIE	15	19	34	0.035*
% within Native Valves	44.1%	55.9%	100%	
% within Valve Site	100%	70.4%		
PVIE	0	9	9	
% within Prosthetic Valves	0%	100%	100%	
% within Valve Site	0%	29.6%		
IV Drug Abuse				
IV Drug Abuse	13 (68.4%)	6 (31.6%)	19 (100%)	<0.001*
NVIE	18 (94.7%)			0.024*
PVIE	1 (4.	2%)		

IE: Infective Endocarditis, NVIE: Native Valve Infective Endocarditis, PVIE: Prosthetic Valve Infective Endocarditis, IV: Intravenous, *: Statistically Significant *p*-value as p < 0.05.

Echo findings revealed vegetation in 84.5% of cases, abscesses in 6.9%, pseudo-aneurysms in 3.4%, and new prosthetic dehiscence in 5.2%. A total of 35 cases underwent MSCT, with 68.6% showing lesions and 31.4% with no lesions. The lesions were located in the lungs in 12 patients (50%), brain in 5 patients (20.81%), spleen in 4 patients (20.8%), kidneys in 2 patients (8.3%), and 1 in the heart (4.1%). Blood cultures from 50 cases showed

negative results in 30% and positive growth in 70%. The most common organisms identified in positive growth were Staphylococcus aureus (74.3%), followed by the HACEK group (17.1%), Streptococcus viridans (5.7%), and enterococci (2.9%). The sources of infection included intravenous drug abuse (47.1%), healthcare-associated infections (23.5%), unknown sources (15.7%), and community-acquired infections (13.7%). (Table 3)

infection in the study population.	NT (0/)
Finding	N (%)
Echo Findings	N=50
Vegetation	42 (84.5%)
Abscess	3 (6.9%)
Pseudo-aneurysm	2 (3.4%)
New Prosthetic Dehiscence	3 (5.2%)
MSCT Cases	N=35
Finding Lesions	24 (68.6%)
No Lesions	11 (31.4%)
Location of Lesions	N=24
Lung	12 (50%)
Brain	5 (20.83%)
Spleen	4 (16.67%)
Kidney	2 (8.3%)
Cardiac	1 (4.1%)
Blood Culture Results	N=50
Negative Culture	15 (30%)
Positive Growth	35 (70%)
Organisms Identified	N=35
Staphylococcus aureus	26 (74.3%)
HACEK Group	6 (17.1%)
Streptococcus viridans	2 (5.7%)
Enterococci	1 (2.9%)
Source of Infection	N=50
IV Drug Abuse	24 (47.1%)
Healthcare Associated	12 (23.5%)
Unknown	8 (15.7%)
Community Acquired	7 (13.7%)

Table 3: Imaging findings, blood culture results, and source of infection in the study population.

 Table 4: In-hospital mortality among the study population.

Cause of death (N=17)	N (%)
Cardiovascular	4 (23.5%)
non cardiovascular	4 (23.5%)
Cardiovascular + non cardiovascular	8 (47.1%)
Unknown	1 (5.9%)
Cardiovascular causes	
HF	8 (44.4%)
Arrhythmia	5 (27.8%)
Pulmonary Embolism	2 (11.1%)
Cerebral embolism	1 (5.6%)
Peripheral embolism	1 (5.6%)
Stuck valve	1 (5.6%)
Non cardiovascular causes	
Sepsis / multi-organ failure	11 (91.7%)
others	1 (8.3%)

N: Number, HF: Heart Failure.

At the one-year follow-up, 21 patients (72.4%) were alive, 8 (27.6%) had died, and 4 were lost to follow-up. Among the deceased, 25% died from cardiovascular causes, 25% from non-cardiovascular causes, 25% from both, and 25% from unknown causes. Of the 29 patients who underwent cardiac surgery, 13 (44.8%) had valve replacements, 1 (3.4%) had a percutaneous lead change, and 15 (51.7%) did not undergo surgery. Recurrent infective endocarditis was rare, occurring in 1 patient (3.4%). Among the 21 survivors, 81% were in NYHA Class I, 14.3% in Class II, and 4.8% in Class III. Valve assessment showed that 92.3% of those with valve replacements had no new dysfunction, while among those without valve replacement, 37.5% had healed vegetation, and 62.5% had valve or prosthetic dysfunction. (Table 5)

N: Number, MSCT: Multi-Slice Computed Tomography

In-hospital mortality (N=17) was observed with 23.5% of deaths attributed to cardiovascular causes, 23.5% to non-cardiovascular causes, and 47.1% to a combination of both, with 5.9% being of unknown origin. Cardiovascular causes included heart failure (44.4%), arrhythmia (27.8%), pulmonary embolism (11.1%), cerebral embolism (5.6%), peripheral embolism (5.6%), and a stuck valve (5.6%). Non-cardiovascular causes were primarily sepsis or multiorgan failure (91.7%), with others comprising 8.3%. (Table 4)

Tuble et elle year tellen ap 1	saits of the stady population.		
Follow up	N (%)		
Died	8 (27.6%)		
Alive	21 (72.4%)		
Cause of death follow	N=8		
Cardiovascular causes	2 (25%)		
Non- Cardiovascular causes	2 (25%)		
Both	2 (25%)		
Unknown	2 (25%)		
Cardiac surgery performed	N=29		
No	15 (51.7%)		
Valve replacement	13 (44.8%)		
Percutaneous lead changing	1 (3.4%)		
Recurrent IE on follow up	N=29		
No	28 (96.6%)		
Yes	1 (3.4%)		
Follow up NYHA	N=21		
Class I	17 (81%)		
Calss II	3 (14.3%)		
Class III	1 (4.8%)		
Class IV	8 (27%)		
Valve status at follow up			
Post valve replacement	N=13		
No new dysfunction	12 (92.3%)		
No valve replacement	N=8		
Healed vegetation	3 (37.3%)		
No vegetation	1 (12.5%)		
Valve/ prosthetic dysfunction	5 (62.5%)		
IE: Infective Endocarditis,	NYHA: New York Heart		

 Table 5: One-year follow-up results of the study population.

IE: Infective Endocarditis, NYHA: New York Heart Association.

DISCUSSION

This study was part of the ESC-EORP EURO-ENDO registry, focusing on patients with definite or possible IE. The study observed the clinical characteristics, investigations, treatment, and outcomes of enrolled patients both at discharge and during a one-year follow-up.

In this study, males were significantly more prevalent than females, which aligns with the findings of *Sambola et al.*^[8] and *Sevilla et al.*^[9]. The mean age of the study group was lower compared to the ESC-EORP EURO-ENDO registry, where the mean age was recorded as much higher, possibly due to the larger sample size. In comparison to the EURO-ENDO results, which indicate that IE more frequently affects men around 60 years of age, our study found a higher incidence in men under 40, potentially due

to the commonality of intravenous drug addiction in Egypt and effective geriatric healthcare.

Regarding risk factors, smoking and intravenous drug addiction were the most prevalent, consistent with the findings of *Rudasill et al.*^[10], who reported a lower percentage of intravenous drug users, which could be attributed to socioeconomic and hygiene differences.

Embolic events were the most frequent complication in our study, which aligns with the ESC-EORP EURO-ENDO registry^[11], showing a similar trend in prevalence. Acute renal failure was also a notable complication, with its prevalence being comparable to that recorded in the EURO-ENDO registry, where it ranked as the second most prevalent complication.

Staphylococcus aureus was the most prevalent organism in positive blood cultures in our study, a finding consistent with the reports by *Camou et al.*^[12] and *Habib et al.*^[11], which also showed high prevalence. Additionally, BCNIE patients constituted 30% of the study population, a relatively high percentage compared to the findings of *Camou et al.*^[12], which may be attributed to the previous misuse of antibiotics.

In our results, intravenous drug addiction was identified as a significant route of infection in native valve IE patients, with a strong association to right-sided IE, consistent with findings from *Lomas et al.*^[13] and the ESC-EORP EURO-ENDO registry^[11]. Community-acquired IE, including those related to intravenous drug addiction, represented a notable portion of the study population, aligning with the prevalence reported in these previous studies.

Echocardiography was performed in all patients, with more than one-third undergoing both transthoracic and transesophageal echocardiography, a higher incidence than reported by *Murdoch et al.*^[3], likely due to the increased prevalence of right-sided IE, which is more effectively diagnosed by transthoracic echocardiography. Vegetation was observed in the majority of patients, while abscesses were the most common paravalvular complication, findings that align with those of *Murdoch et al.*^[3] and the ESC-EORP EURO-ENDO registry^[11].

Patients with prosthetic valve IE showed a significant incidence of prosthetic valve complications, including dehiscence or new paravalvular regurgitation, a finding consistent with the results of *Murdoch et al.*^[3].

In this study, in-hospital complications were relatively high, likely influenced by delayed diagnosis, antibiotic resistance, and the complexity of patient conditions. Persistent fever and embolic events were the most frequent complications, aligning with findings from the ESC-EORP EURO-ENDO registry. Acute renal failure was also a significant complication, with its prevalence comparable to that recorded in the EURO-ENDO registry, where it ranked as the second most common complication.

The in-hospital mortality rate was notably higher compared to the findings of *Camou et al.*^[12] and *Habib et al.*^[11], possibly due to delayed patient care and high surgical risk preventing surgery. Sepsis and heart failure were the leading causes of death, followed by arrhythmia, consistent with the results of *Chu et al.*^[14] and *Habib et al.*^[11].

At the one-year follow-up, the survival rate was similar to that reported by *Heiro et al.*^[15] and *Amodeo et al.*^[16]. Among the survivors, only one case of recurrent IE was observed in an IV drug addict, which is significantly lower than the findings of *Welton et al.*^[17], who reported a higher recurrence rate in drug abusers. This may be attributed to increased awareness and better psychological and medical support for IV drug users after valve surgery.

This study had several limitations, including a small sample size that hindered subgroup analysis, the reliance on blood cultures without PCR or serology for negative results, and the potential for misleading cultures due to prior antibiotic use. Additionally, the impact of new imaging techniques, such as 18 F-FDG PET/CT, on diagnosing and following up PVIE was not considered.

CONCLUSION

Significant morbidity and mortality was associated with IE, with sepsis and multi-organ failure being the leading causes of in-hospital death. Staphylococcus aureus was the most common pathogen, and intravenous drug use was a major risk factor, particularly for right-sided IE. Embolic events were frequent, and vegetation was a predominant echocardiographic finding. Despite surgical intervention in some cases, mortality remained high at one-year follow-up.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) received no financial support for the research, authorship, and/or publication of this article.

CONTRIBUTION

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

CONFLICT OF INTERESTS

There is no conflicts of interest.

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التهاب الشُّغاف المعدي: خبرة عامان في مستشفى جامعة المنصورة

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الخلفية: التهاب الشُّغاف المعدي لا يز ال حالة نادرة ولكن خطيرة ترتبط بمعدلات مراضة ووفيات عالية. يشكل تشخيصه و علاجه تحديًا بسبب تنوع مظاهره السريرية ونقص الإرشادات الواضحة المستندة إلى الأدلة. على الرغم من التقدم في العلاج، فإن معدل الوفيات داخل المستشفى بقي عند حوالي ٢٠٪ على مدار العقود الثلاثة الماضية.

هدف الدراسة: تقييم الخصائص السريرية والمضاعفات والنتائج، مع متابعة كل مريض لمدة سنة بعد الخروج من المستشفى.

المرضى والطرق: تم إجراء دراسة استباقية ملاحظة في قسم أمراض القلب بمستشفى الطب المتخصص بجامعة المنصورة من أغسطس ٢٠١٦ حتى أغسطس ٢٠١٨، شملت ٥٠ مريضًا تم تشخيصهم بالتهاب الشُّغاف المعدي بناءً على معايير Duke المعدلة. تم جمع البيانات السريرية، وأجريت للمرضى تخطيط كهربائية القلب، وفحوصات الإيكو، ومزرعة الدم، والاختبارات المعملية. تم استخدام التصوير المقطعي متعدد الشرائح لتقييم المضاعفات الجهازية.

النتائج: تكونت العينة من ٨٠٪ من الذكور، بمتوسط عمر ٣٦.٤ ± ١٤.٣ سنة. شملت الأمراض المصاحبة التدخين (٥٠٪) وإدمان المخدرات عن طريق الوريد (٤٨٪). كانت الأعراض السريرية تتمثل في الحمى والدوار (١٠٠٪)، مع ٤٤٪ يعانون من السعال و٣٠ من أعراض أخرى. أظهرت نتائج الإيكو وجود التورمات في ٨٤.٥٪ من الحالات، وكانت زراعة الدم إيجابية في ٧٠٪. كان المكورات العنقودية الذهبية هو المسبب الأكثر شيوعًا (٧٤.٣٪). بلغ معدل الوفيات داخل المستشفى ٣٠٠٪، حيث تم عزو معظم الوفيات إلى أسباب قلبية وعائية. عند المتابعة لمدة سنة، توفي ٢٢.٦٪ من المرضى، مع ظهور تحسن في الحالة الوظيفية لمعظم المرضى المتبقين (٨٠٪) في الفئة الأولى حسب تصنيف NYHA.

الخلاصة: يظهر التهاب الشُّغاف المعدي بتنوع في المظاهر السريرية ويتميز بارتفاع معدل الوفيات. التشخيص المبكر والإدارة المناسبة، بما في ذلك التدخل الجراحي في الوقت المناسب، أمر حاسم لتحسين النتائج. تبرز الدراسة أهمية استراتيجيات العلاج المخصصة للتعامل مع الطبيعة متعددة الأوجه لهذا المرض.