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Early Outcome after Mitral Valve Replacement in Adult Patients with Infective Endocarditis

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ABSTRACT

Background: The mitral valve is frequently affected by the complicated illness known as active infective endocarditis (IE), which has significant rates of mortality and morbidity.

Objective: To evaluate early outcome after mitral valve replacement in adult patients with IE.

Patients and methods: This descriptive prospective study was carried out at cardio thoracic Department at Suez Canal University Hospitals, where 30 patients who have infective endocarditis and underwent operative mitral valve replacement were included and were followed up for 3 months after surgery. Patients were clinically assessed and managed as per the ABC protocol, after stabilizing the patient. Postoperative evaluation was performed during their intensive care unit stay, hospital stay, and through first 3 months postoperatively.

Results: A native infective endocarditis was present in 19 cases and a prosthetic infective endocarditis was in 11 cases. There were 9 cases with heart failure, 7 cases had risk of embolization, 9 cases had uncontrolled infection, and 5 cases had severe MR. There were 17 cases who needed inotropes for weaning from bypass. There was 1 case that had intraoperative mortality. Mean aortic cross clamp was 1.66 ±0.37. Mean intraoperative blood transfusion was 2.43±0.72. The mean hours of weaning from ventilator was 6.00 ±1.4 and of weaning from cardiac support was 25.84±16.5. Mean days of removal of med. drain was 3.46±0.50.

Conclusion: There was increasing risk of 3 months mortality with prosthetic IE and staphylococcus infection. There was increasing risk of 3 months recurrence and CONS with staphylococcus infection. There was increasing risk of operative mortality with prosthetic IF and large valve vegetation.

Keywords: Infective Endocarditis; Mitral Valve Replacement; Early Outcome.

INTRODUCTION

Infectious endocarditis (IE) was fatal in the days before antibiotics. The early mortality rate of IE remains rather high (14-31%) even after more than fifty years since the first successful valve replacement and more than thirty years since the introduction of antibiotic therapy. The use of CT-guided stereotactic surgery to treat deep-seated brain lesions [(1,2)].

The prevalence of mortality and morbidity is still high: one in five patients pass away during their initial hospital stay, even with improvements in therapeutic diagnosis and antibiotic choice. The type and virulence of the infecting organisms have advanced, as has the population at risk of developing IE, which are some of possible explanations for this increased mortality [(3)].

Patients with ESRD on HD who abuse intravenous drugs may develop native valve endocarditis. There are potential abnormalities with the tricuspid, mitral, and aortic valves. The predominant organism among intravenous drug abusers is usually Staphylococcus aureus. Usually, this is an indication of acute bacterial endocarditis. Infections from dental abscesses, tooth extractions, or oral surgery can cause valvular endocarditis in non-drug-abusing patients. Often streptococcal, the organism is indicative of subacute bacterial endocarditis [(4)].

A post-surgical infection of the heart valve results in prosthetic valve endocarditis. Gram-negative organisms and Staph epidermidis are the most prevalent in the early stages of the perioperative period and even up to one year. Streptococcal bacteria are mostly responsible for late prosthetic valve endocarditis [(5)]. Multiple presentation patterns are possible in patients with infective endocarditis. These can include evidence of hemodynamic compromise, heart failure, shortness of breath, chills, fever, and night sweats, among other symptoms of systemic bacteremia [(6)].

Echocardiography and blood culture should be performed on a patient suspected of suffering from infective endocarditis in order to confirm the diagnosis. Medical care was initially provided with an empirical broad-spectrum antibiotic, but as the culture result was acquired, the primary treatment shifted to sensitivity antibiotics [(7)]. To identify any septic foci that need to be treated before surgery, a CT scan of the brain and spleen is crucial. In order to minimise the risk of heart surgery, the patient should ideally get intravenous antibiotics for at least one week [(8)].

The following are the indications for valve endocarditis surgery: 1) Heart failure along with hemodynamic impairment. This usually manifests as a sudden and severe cardiac regurgitation, either of the aortic or mitral. 2) A resistant organism or persistent bacteremia following at least one week of appropriate antibiotic therapy. 3) Prosthetic valve malfunction or massive valve destruction due to an annular abscess or atrioventricular obstruction. 4) The vegetation's embolisation occurring repeatedly or continuously, with the potential to embolise at any time. 5) Fungal or brucella-induced infectious endocarditis. 6) Late-onset prosthetic endocarditis caused by S. aureus [(9,10)].

Surgery is a considerable survival improvement over medical therapy for prosthetic valve endocarditis. A periprosthetic leak is typically present in cases of

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prosthetic valve endocarditis. Before surgery, antibiotics are administered for a periprosthetic infection, and the valve is subsequently replaced. Antibiotics can be used to treat the infection in the absence of any further problems or periprosthetic leaks. The surgical procedure involves removing the contaminated tissue completely, closing fistulas and cavities, resecting the affected valve, and replacing it with a mechanical valve prosthesis [(11)].

The purpose of this study was to compare preoperative and postoperative echocardiography variables. In addition, to assess the risk factors for developing further complications after mitral valve replacement.

PATIENTS AND METHODS

This descriptive prospective study included patients with infective endocarditis who underwent operative mitral valve replacement and were attending at Cardio Thoracic Department, Suez Canal University Hospitals in the period from January 2017 and March 2019. Patients were followed up for 3 months after surgery.

Inclusion criteria:

Patient of both sexes, aged >18 years, who were diagnosed as infective endocarditis on mitral valve by echocardiography and blood culture.

Exclusion criteria:

Patients with significant aortic valve disease. Patients with coronary artery disease. Patients who refused to participate, patients presented initially with cardiopulmonary arrest, pregnant females, and patients with tricuspid valve endocarditis were excluded.

Sample size:

The sample size was calculated using the following formula [(11)]: $n = \left[\frac{Z_{\propto/2}}{E}\right]^2 * P(1-P)$

Where: ***(n** = sample size, **$Z_{\alpha/2}$** = 1.96; **P** = Prevalence/proportion in the study group = 7.6% [(13)]; **E** = Margin of error/Width of confidence interval = 6%*). Therefore, the sample size was equal to 27 subjects; a 10% drop-out rate makes the sample size total 30 subjects.

Preoperative evaluations:

The history and clinical examination, as well as the measurements of vital signs, regional and cardiac examination, were performed for all patients. The level of instability or stability in the patient's condition was established in order to determine the necessary investigations and management strategy. Laboratory testing included arterial blood gas (ABG), liver and kidney function tests, blood culture, blood type and cross matching, coagulation profile, serum electrolytes, and random blood sugar if necessary.

All patients had electrocardiogram (ECG) and radiographic studies, including plain chest X-ray, M mode, two-dimensional, and Doppler echocardiography. Patients with a positive history of ischemic vascular events, postmenopausal women, and males over 40 had coronary angiography. Ultrasound of the pelvis and abdomen, carotid duplex if necessary, and computed tomography of the chest and brain were also performed.

The cardiac medication dose for each patient was administered in the morning. Prior to being transferred to the operating room, every patient received a 10-mg intramuscular dose of morphine sulphate. Local anaesthetic was used to introduce a 14 gauge peripheral intravenous cannula once the patient arrived in the preparation room. The ideal dosage for sedation was 0.03-0.07 mg/kg of midazolam. Under local anaesthesia, a non-dominant radial artery cannula in the gauge of 20 was placed. Two arterial blood samples were taken: one for baseline arterial blood gas (ABG) analysis and the other for preoperative baseline activated clotting time (ACT). Preoperative monitoring included direct arterial blood pressure, pulse oximetry, and a five-lead ECG.

Intraoperative Assessment:

All patients received the same intraoperative anaesthetic strategy, which included fentanyl 5–10 micrograms per kilogramme and pancuronium 0.02 mg/kg in addition to 0.5–1 mg/kg of propofol as a supplement for hypnosis. 100–200 mic of fentanyl was administered as a further dose. An appropriate-sized endotracheal tube was used to intubate the trachea orally once the patient's muscles had fully relaxed. All patients were kept anaesthetized with isoflurane 0.5–1% inhalation. After induction, a single lumen catheter (Angio 16 gauge) and a triple lumen central venous catheter were placed into the right internal jugular vein. Furthermore, a urethral catheter, a nasogastric tube, and a nasopharyngeal temperature probe were implanted. This probe was used for transesophageal echocardiography, or TEE.

Aortic cross clamp time, total cardiopulmonary bypass time, weaning from cardiopulmonary bypass and the need for inotropic support were assessed.

Postoperative evaluation:

During their stay in the intensive care unit and five days after being discharged from the facility, all patients had comprehensive evaluations. Hemodynamics (blood pressure, heart rate and rhythm, central venous pressure, and peripheral temperature) of patients during an ICU stay. If necessary, ventilator support and inotropic weaning were provided.

Morbidity, mortality, and length of hospital stay were documented during the patient's stay. A follow-up echocardiogram was performed to evaluate the prosthetic mitral valve, the size and function of the left ventricle, and the pressure in the pulmonary artery.

Ethical Consideration:

An approval of the study was obtained from Suez Canal University Academic and Ethical Committee (IRB #3582/2018). Written informed

consent of all the participants was obtained. This work has been completed in compliance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis: IBM SPSS Statistics® 22 for Windows 10 was used. For continuous parametric variables, the descriptive data were stated as mean±standard deviation; for categorical and dichotomous variables, the expressions were count/total and percentages (%). The correlation coefficient was also calculated. A P value was deemed significant when it was less than 0.05.

RESULTS

During the study period, 30 patients were operated on (17 males and 13 females), their age ranged from 26 to 46 years. A native infective endocarditis was present in 19 cases and a prosthetic infective endocarditis in 11 **(Table 1)**.

Table (1): Distribution of the studied patients regarding their demographic data and clinical characteristics

Characteristic		n	%
Sex	Males	17	56.7%
	Females	13	43.3%
Mean Age (Years)		35.6 ±5.6	---
Diabetes Mellitus		7	23.3%
Hypertension		5	16.7%
Blood transfusion		9	30%
Dyspnea NYHA ≥ 3		17	56.7%
Mean Body Mass Index (Kg/m^2)		27.2±3.9	---
Lower limb edema		9	30%
Heart Rate	Regular sinus	16	53.3%
	AF	14	46.7%
Fever		14	46.7%
Pneumonia		7	23.3%
IV addict		17	56.7%
Previous dental proc.		20	66.7%
ESRD		12	40%
Duration of symptoms before diagnosis (days)		18±4.3	
Chronic obstructive pulmonary disease		13	43.3%
Duration of antibiotic before operation (days)		9±3.3	
Preoperative coronary arteriography		12	40%
Emergency surgery		8	26.7%
Preoperative stroke		3	10%

The mean blood hemoglobin level was 11.61 gm/dl and the white cell count was 12.3 thousands/mm^3. Serum albumin level ranged between 2.6 to 3.9 gm/dL for all cases. Mean serum total bilirubin was 1.2 mg/dL. Mean value for AST was 18.55 U/L and for ALT was 17.42 U/L. The mean serum creatinine level was 1.3 mg/Dl **(Table 2)**.

Table (2): Mean values of laboratory investigations

Laboratory test	Mean Value
Hemoglobin (gm/dl)	11.61 ± 1.54
White blood count (cells in thousands/mm^3)	12.3 ± 2.24
Albumin (gm/dL)	2.6 ± 0.37
Total bilirubin (mg/dL)	1.2 ± 0.30
AST (U/L)	18.55 ± 4.22
ALT (U/L)	17.42 ± 3.62
Creatinine (mg/dL)	1.3 ± 0.31

Left atrium diameter visualized echocardiographically mean value was 5.26. Mean left ventricular end diastolic dimensions (LVEDD) was 50.08 mm. While mean left ventricular end systolic dimensions (LVESD) were 32.60 mm. Ejection fraction ranged from 45 to 63% with a mean value of 61.20. Most of the cases (63.3%) had native mitral valve. 7 cases had vegetation more than 10 mm and 3 cases had vegetation 5-7mm. 8 cases had cordal rupture of the valve apparatus and 7 cases had annular abscesses (they had staphylococcus microorganism) **(Table 3)**.

Table (3): Mean echocardiographic findings preoperatively:

Echo findings	Mean Value
Left Atrial Size (cm)	5.26 ±0.85
PAP %	46.00 ±6.9
LVESD (mm)	32.60 ±4.4
LVEDD (mm)	50.08 ±5.3
Ejection Fraction %	61.20 ±6.0
Fractional Shortening %	32.68 ±3.5
Native valve	19 (63.3%)
Prosthetic valve	11(36.7%)
Vegetation	10(33.3%)
Cordal rupture	8(26.7%)
Annular abscesses	7(23.3%)
Leaflet perforation	5(16.7%)

Regarding preoperative blood culture, 9 cases were Staphylococcus, and 8 cases were coagulase negative staphylococcus **(Figure 1)**.

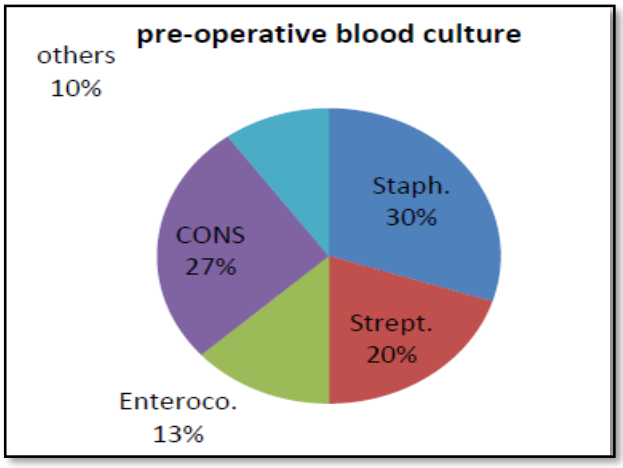

Figure (1): Pie chart of distribution of preoperative blood culture among the studied patients.

Concerning the indications for surgery; there were 9 cases had heart failure, and 9 cases had uncontrolled infection **(Figure 2)**.

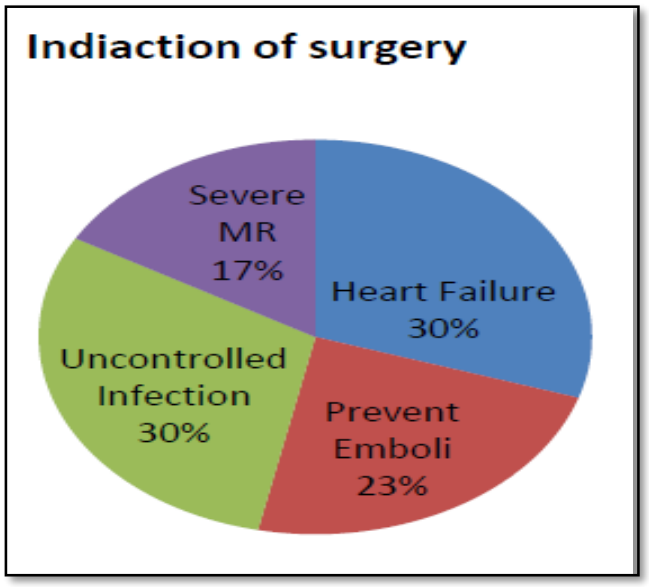

Figure (2): Pie chart of distribution of surgery indication among the studied patients.

There were 17 cases who needed inotropes for weaning from bypass while 1 case only had intraoperative mortality. Mean aortic cross clamp was 1.66. Mean intraoperative blood transfusion was 2.43. The mean hours of weaning from ventilator was 6.00 and of weaning from cardiac support was 25.84. Mean days of removal of med. drain was 3.46 **(Table 4)**.

Table (4): Intraoperative data and intensive care course among the studied patients

Intraoperative data	Mean Value
Aortic cross clamp	1.66±0.37
Blood product transfusion per unit	2.43±0.72
Weaning from bypass by Inotropes	17(56.6%)
Intraoperative mortality	1 (3.3%)
Intensive care course	
weaning from ventilator (hours)	6.00±1.4
weaning from cardiac support (hour)	25.84±16.5
Removal of med. drain (day)	3.46±0.50

During postoperative course, 5 cases were complicated with postoperative mediastinal bleeding and 8 cases with arrhythmia **(Table 5)**. The mean ICU stay was 4.16 days and hospital stay was 6.36 days **(Table 6)**.

Table (5): Postoperative course of the studied patients:

Complications	N (%)
Hemorrhage	5(16.7%)
Arrhythmia	8(26.7%)
Renal impairment	1(3.3%)
Liver impairment	2(6.7%)
CNS complications	2(6.7%)
Mortality	1(3.3%)
Sternal wound infection	4(13.3%)

Table (6): Distribution of ICU and hospital stay among the studied patients:

	Mean Value
ICU stay (day)	4.16±0.83
Hospital stay (day)	6.36±0.71

Concerning 3 months postoperative echocardiographic findings, left atrium diameter mean value was 4.43 cm. Mean LVEDD was 48.72 mm while mean LVESD was 31.52 mm. Mean ejection fraction was 58.68%. Mean pulmonary arterial pressure was 31.60 mmHg. 28 cases had good prosthetic mitral valve function **(Table 7)**.

Table (7): Distribution of 3 months postoperative echocardiography of the studied patients:

Echo findings	Mean Value
Left atrial size (cm)	4.43±0.76
PAP %	31.60±4.9
LVESD (mm)	31.52±4.1
LVEDD (mm)	48.72±4.8
Ejection fraction %	58.68±4.6
Good mitral valve function	28(93.3%)

Three months mortality were significantly and strongly positively correlated with both staphylococcus infection and prosthetic infective endocarditis. The three-month recurrence and CONS and staphylococcus infection showed a substantial positive connection. The incidence of prosthetic infective endocarditis and surgical mortality were significantly positively correlated **(Table 8)**.

Table (8): Correlations of 3 months mortality and recurrence with other variables:

	3 months mortality		3 months recurrence		Operative mortality	
	r value	P value	r value	P value	r value	P value
Staphylococcus	0.725	0.001	0.617	0.003	0.293	0.027
Streptococcus	0.167	0.003	0.134	0.502	0.224	0.145
Enterococcus	0.131	0.299	0.105	0.129	0.175	0.236
CONS	0.302	0.664	0.741	0.004	0.135	0.698
IV addict	0.157	0.100	0.436	0.100	0.030	0.108
ESRD	0.281	0.300	0.255	0.000	0.183	0.154
Dental	0.236	0. 200	0.194	0. 200	0.253	0. 009
Severe MR	0.249	0.002	0.120	0.103	0.200	0.002
Prevent emboli	0.179	0.100	0.117	0.130	0.579	0.109
Heart failure	0.124	0.299	0.196	0.229	0.198	0.002
Uncontrolled infection	0.144	0.100	0.178	0.300	0.098	0.167
Prosthetic valve infective endocarditis	0.736	0.002	0.294	0.202	0.716	0.003

DISCUSSION

This study reflects our experience managing patients with infected endocarditis (IE) surgically at Suez Canal University Hospital. These cases required not only hemodynamic repair but careful attention to the removal of the infectious focus to prevent early postoperative colonization of the prosthesis by residual microorganisms, despite our best efforts. As a result, there are still a number of diagnostic and management challenges.

Aggressive debridement of infected tissue and suitable and enough antibiotic treatment can be used to attain this goal; however, the overall early results are not favorable. Most of the time, it may seem obvious whether surgery is indicated; there are a few other clinical situations that create significant challenges for the surgeon [(5)].

In this prospective study, we included thirty patients with infective endocarditis undergoing mitral valve replacement at the Cardio Thoracic Surgery Department, Suez Canal University Hospital. It was conducted to assess early outcome after mitral valve replacement in patients with mitral valve infective endocarditis.

Our study showed that 1 case (3.3%) died intraoperatively, 1 case (3.3%) died postoperatively, 2 cases (7%) died during 3 months postoperatively). Similar to our findings, **Tomšic *et al.*[(1)]** conducted a study on 83 individuals who received surgery for isolated active native mitral valve IE between January 2000 and March 2016, with an early death rate of 13% in this prospective analysis. The follow-up period lasted an average of 3.7 years. 8-year overall survival rates for hospital survivors were 74.2%.

Moreover, our findings were supported by **Kim *et al.*[(11)]** who studied 78 consecutive patients who received mitral valve replacement (MVR), and to assess the short- and long-term effects of MAR with pericardium during the surgery, a prospective study was carried out. The group with endocarditis had a 16% mortality rate.

In addition, **Aagaard and Andersen [(12)]** identified 21 patients with isolated mitral valve infective endocarditis. The patients received radical removal of all contaminated tissue as treatment, and the death rate was 13%. If feasible, direct suture was used to repair the annular flaws. With a median follow-up period of 45 months, 100% of the follow-up was completed.

In contrast to our findings**, Greason *et al.* [(13)]** carried out a retrospective analysis on 39 patients with isolated nonnative mitral valve infective endocarditis, with a 21% mortality rate. The study population was older on average, and 22 patients (56%) had Staphylococcus. Valve dysfunction was identified as an operational indication in 26 individuals (67%), while heart failure was identified in 22 patients (56%).

In contrast to our findings, **Pang *et al.* [(14)]** studied prosthetic valve endocarditis (PVE) and native valve endocarditis that were surgically treated in 139 patients. Surgical outcomes, including survival and postoperative complications, were evaluated over a mean follow-up of 6.6 ± 3.7 years. Diabetes mellitus represented 13%, renal function impairment was 29.8%, IV drug abusers was 9.9%, and early death rate was 6.8%.

In contrast to our findings, **Said *et al.* [(15)]** reported 159 patients with mitral infective endocarditis. A mean follow-up duration of 4.6 years revealed an early mortality rate of 11%, with 8% of patients receiving dialysis prior to surgery.

Our study showed that there were 2 cases (7%) of recurrence; 3 months postoperatively. Similar to our findings, **Manne *et al.* [(16)]** who studied 428 patients who received IE surgery: 248 (58%) had native valve endocarditis and 180 (42%), prosthetic valve endocarditis. Early recurrence occurred in 7% of patients after surgery.

In contrast to our findings, **Murashita *et al.*** [17] involved 57 patients who underwent surgery and had a mean follow-up of 5.7 years. They had clinical signs of ongoing endocarditis. 13 percent had staphylococcus aureus, 28 percent had streptococcus species, and the remaining 28 percent had postoperative recurrences of 18.4 percent. Culture-negative endocarditis was marginally significant, although Staphylococcus infection was not a significant variable.

In contrast to our findings, **Pang *et al.*** [14] reviewed the surgical outcomes to include survival and postoperative complications, Staph. aureus was found in 9.7% of recurrences, whereas IVDUs accounted for 9.9% of cases. The study included a mean follow-up of 6.6 ± 3.7 years.

Our study showed that there was significant strong positive correlation between 3 months mortality and prosthetic infective endocarditis and staphylococcus infection. Similar to our findings, **Suzuki *et al.*** [18] revealed that 585 patients received valve surgery for definitive left-sided IE, resulting in a 13% rise in the staphylococcus group death rate.

Similar to our findings, **Manne *et al.*** [16] included 428 patients who had IE surgery: 248 (58%) had endocarditis of the native valve and 180 (42%), patients with endocarditis of the prosthetic valve. Patients with endocarditis of the prosthetic valve had a considerably greater 30-day mortality.

Also, **Delay *et al.*** [19] reported seventy-seven patients (57 men and 20 women, mean age 48 ± 16 years) with acute infective endocarditis who had valve replacement in a retrospective examination of the experience with prosthetic valve replacement following acute NVE and PVE at the Montreal Heart Institute. Artificial valve replacement for NVE resulted in high long-term patient survival with a minimal risk of reoperation compared with patients who received valve replacement for PVE. Of the patients, 50 had NVE and 27 had PVE.

Similar to our findings, **Mullany *et al.*** [20] included 151 patients who had been diagnosed with culture-positive active endocarditis. The results indicated a tendency towards a greater mortality rate associated with PVE and staphylococcal infection; 48% of patients were receiving regular hemodialysate, 39% had staphylococcal infection, and 30% had streptococcus infection.

Similar to our findings, **Murashita *et al.*** [17] whose mean follow-up in their study was 5.7 years, found that there were staphylococcus aureus in 13 %, streptococcus species in 28%, and others in 28%, which were the risk of mortality from prosthetic valve endocarditis 13-33% in comparison to native valve endocarditis which was less than 10%.

In contrast to our findings, **Said *et al.*** [15] showed increased incidence of mortality in patients had previous CABG, postoperative renal hemodialysis, during follow-up period with a mean of 4.6 years.

Also, **Jault *et al.*** [21] conducted a study on 247 patients who underwent surgery for active native valve endocarditis. Patients who were older, had neurologic problems before to surgery, experienced cardiogenic shock during the treatment, had shorter sickness durations, and had subtler illnesses before the procedure, had a higher mortality risk.

In contrast to our findings, **Tomšic *et al.*** [1] investigated the characteristics and results of individuals with active infective prosthetic valve endocarditis (PVE) who underwent surgery over a 20-year period. They revealed that septic multi-organ failure in 44 (44.4%) and cardiac failure in 27 (27.2%) of the 99 patients were the primary reasons of the early deaths.

Our study showed a significant strong positive correlation between 3 months recurrence and CONS and staphylococcus infection. This is similar to findings **Suzuki *et al.*** [18] who reported that staphylococcus group exhibits a 5% higher recurrence rate.

Similar to our study, **Tomšic *et al.*** [1] showed that Staph. Aureus was the most frequent causative microorganism of recurrence. However, **Said *et al.*** [15] showed increase incidence of recurrence in patients had previous CABG, pre- and postoperative renal hemodialysis.

Our study showed that there was significant strong positive correlation between operative mortality and prosthetic infective endocarditis. Similar to our findings, **Manne *et al.*** [16] revealed a higher rate of operational death in cases of infective endocarditis in prosthetic.

In contrast to our findings, **Mullany *et al.*** [20] revealed that the rate of surgical death increased in cases of renal failure and abscess during the procedure; 48% of patients had ESRD on regular hemodialyser, 39% had staphylococcus infections, and 30% had streptococcus infections.

In contrast to our findings, **Tomšic *et al.*** [1] indicated that there was a high operative death rate linked with surgery for active endocarditis with para-valvular abscess, especially in patients who were in shock and had formed an abscess.

CONCLUSION

There is still a high early fatality rate and a poor early term prognosis after surgery for IE. These cases nonetheless present a variety of diagnostic and therapeutic problems in addition to typically having negative early results.

Our study concluded that there is increased risk of 3 months mortality with prosthetic infective endocarditis and staphylococcus infection, there is increased the risk of 3 months recurrence and CONS with staphylococcus infection, there is increased the risk of operative mortality with prosthetic infective endocarditis and large valve vegetation.

From the current study, we recommend:

To lower the risk of prosthetic valve infective endocarditis and its recurrence, the operation room should only be used for open heart procedures.

We recommend conducting more studies on the long-term effects of mitral valve replacement surgery on a larger number of patients who have infective endocarditis.

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