THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Clinical Features and Mortality Rate of Infective Endocarditis in Intensive Care Unit: A Large-Scale Study and Literature Review

ORIGINAL INVESTIGATION

ABSTRACT

Background: Large-scale multicentric studies reported that, despite advances in diagnosis, antibiotics, and surgical treatment, infective endocarditis (IE) in-hospital mortality remains high. Most data have been obtained from patients treated in infective disease wards, internal medicine, cardiology, or cardiac surgery departments and are therefore heterogeneous. The few studies focused on complicated IE patients leading to intensive care unit (ICU) admission have reported different methodologies and results. The aim of our study was to describe the epidemiological, clinical, and microbial features of critically ill patients admitted to the ICU with a definite IE diagnosis.

Methods: We conducted a prospective case-series population study from January 1, 1998, to December 31, 2020. Patients were divided into 2 groups: "Ward" (group 1) and "ICU" patients (group 2), and a 1-year follow-up was performed.

Results: After performing a univariate and multivariate logistic regression analysis, we found that the independent predictors of ICU admission were vegetation diameter >10 mm, abnormal PaO_2/FiO_2 ratio, and acute heart failure. Five independent mortality risk factors were identified: SOFA score >14, not performing surgery, age >70 years, acute heart failure, and embolic complications.

Conclusions: Infective endocarditis in-hospital mortality remains high. ICU admission and mortality can be predicted by independent risk factors.

Keywords: Cardiac surgery, endocarditis, endocarditis prognosis, infective endocarditis, intensive care infections, valve disease

INTRODUCTION

Despite advances in diagnosis and treatment, infective endocarditis (IE) mortality remains high, and the incidence seems to be increasing.[1-3] Because of different populations and methodologies, a wide variability in mortality rate is reported in the literature, ranging from 8% to 40%.[4,5] Most case series are collected in referral cardiac surgery centers, and selection biases are frequent. Very serious cases are often excluded from trials and registries, and this often happens in critically ill patients admitted to resuscitation or intensive care units (ICUs). Recent large-scale multicentric studies report that in-hospital mortality remains high—17% in EUROENDO Registry[6]—and without a decreasing trend both in western[2] and less developed countries.[7] Infective endocarditis can present with a wide spectrum of possible clinical manifestations and complications. Different mortality rates should be analyzed among different subgroups. The most common infective microorganism is, nowadays, *Staphylococcus aureus,* which represents an independent variable correlated to higher mortality.[8] The new nosocomial or drug-intravenous-abuse pathogens, owing to the increased prevalence of *S. aureus* and enterococcus species often multiresistant to antibiotics and therefore more dangerous, are emerging.[9] Few studies have focused on critically ill patients[10] and whether the admission unit may affect survival is a rarely explored topic. Does the admission to the ICU play a protective role or is it just a variable correlated to the initial critical state and, therefore, an indicator of worse prognosis? The few studies focused on complicated IE patients leading to ICU admission[10-14] have reported

Alberto Cresti[1]
Pasquale Baratta[1]
Francesco De Sensi[1]
Elio Aloia[1]
Bruno Sposato[2]
Ugo Limbruno[1]

[1]*Department of Cardiology, Misericordia Hospital, Grosseto, Italy*
[2]*Department of Pneumology, Misericordia Hospital, Grosseto, Italy*

Corresponding author:
Alberto Cresti
alcresti@gmail.com

Received: May 18, 2023
Accepted: September 21, 2023
Available Online Date: January 01, 2024

Cite this article as: Cresti A, Baratta P, De Sensi F, Aloia E, Sposato B, Limbruno U. Clinical features and mortality rate of infective endocarditis in intensive care unit: A large-scale study and literature review. *Anatol J Cardiol.* 2024;28(1):44-54.

DOI:10.14744/AnatolJCardiol.2023.3463

different methodologies and results. Most of these data have been obtained from patients treated in infective disease wards, internal medicine, cardiology, or cardiac surgery departments and are therefore heterogeneous.

The aim of our study was to describe the epidemiological, clinical, and microbial features of critically ill patients admitted to the ICU with a definite IE diagnosis, to investigate in-hospital and 1-year mortality and, moreover, to investigate the mortality prognostic factors according to severity scores and variables registered at admittance in an ICU setting.

METHODS

Study Design and Patients

A prospective case-series population study was conducted among patients admitted in the hospital, with a definite IE diagnosis. From January 1, 1998, to December 31, 2020, all subjects referred to our center for a suspected IE were entered in a database if criteria for a definite diagnosis were fulfilled.[15] Patients were divided into 2 groups: "Ward" (group 1) and "ICU" patients (group 2).

Data Collection

1. Epidemiological data included clinical risk factors: underlying heart disease, heart failure at admission, renal insufficiency, diabetes, embolic events, septic shock, chronic obstructive pulmonary disease, peripheral vasculopathy, immunocompromised state, and intravenous drug abuse.
2. Microbiological features include blood cultures, serology, and valve/tissue cultures. Blood cultures were performed on at least 3 samples before the initiation of antibiotics. Additional cultures were analyzed in case of valve surgery or pacemaker device/lead extraction.
3. The largest vegetation length was measured. In the absence of vegetations, echographic criteria included new valvular insufficiencies, i.e., flail or prosthesis dehiscence, abscess, pseudoaneurysm, fistula, or new valvular perforation.
4. Univariate and multivariate analyses were performed on several clinical parameters: causative microorganism, persistent bacteremia, diabetes, renal insufficiency, heart failure, embolic events, neurological complications, septic shock, age, sex, chronic obstructive pulmonary disease, peripheral vasculopathy, presence of predisposing factors, community or health-acquired pathogenesis, valve involvement, prosthesis, native or catheter-related IE, indications for surgery, surgery indicated but not performed, and ICU admission risk score.
5. In-hospital and 1-year mortality were analyzed. Patients admitted to the ICU were separately analyzed, and their clinical features were compared to other IE cases in order to evaluate those responsible for a worse prognosis.

HIGHLIGHTS

- Mortality rate in infective endocarditis is still high.
- In patients admitted to the intensive care unit for infective endocarditis, mortality is very high and probably underestimated.
- Patients for whom surgery was indicated but not performed have very poor survival.

Definitions

- Underlying conditions were evaluated by the Charlson comorbidity index (CCI) score.[16] Comorbidity severity was categorized into 3 grades: mild with CCI scores of 1-2, moderate with CCI scores of 3-4, and severe with CCI scores ≥5.
- Illness severity at ICU admission was assessed by the Sequential Organ Failure Assessment (SOFA) score.[8]
- Neurologic conditions were evaluated according to the Glasgow Coma Scale (GCS).[17]
- New York Heart Association (NYHA) Functional Class was classified at admission.
- Renal insufficiency was defined as the presence of a serum creatinine concentration >2 mg/dL within the first 24 hours of ICU admission and/or urine output <500 mL/24 h.
- Paravalvular abscess and pseudoaneurysm definitions were consistent with European Society of Cardiology guidelines[15] and were associated with the group named "perivalvular diffusion" of the infection.
- Septic shock was defined as an acute circulatory failure due to sepsis, with persistent systolic pressure <90 mm Hg, despite adequate volume resuscitation.[18]
- Cardiogenic shock was considered an acute circulatory failure due to myocardial dysfunction, with systolic pressure <90 mm Hg, tissue hypoperfusion, and low cardiac index.[19]
- Other definitions and timing of surgery were established according to current guidelines.[15]
- In-hospital mortality was defined as death occurring within the same hospitalization as ICU admission, regardless of its cause.

Statistical Analysis

The incidence rate per 100 000 inhabitants per year was calculated.

Continuous variables were expressed in mean ± SD in case of normal distribution or median (interquartile) with non-normal distribution. The comparison of normal continuous variables was performed by *t*-test for 2 samples. Non-normally distributed variables were compared by the Mann–Whitney *U*-test. The comparison between variables in frequencies was performed using the chi-square test.

The normality of continuous variables was tested by the Kolmogorov–Smirnov test for ICU admission (backward selection).

Actuarial survival analysis was performed using the Kaplan–Meier method, with the day of diagnosis as the starting point; in-hospital and 1-year survival was estimated. Survival curves were compared using the log-rank test. The Kaplan–Meier curve was also made for survival analysis stratified by non-surgery indication group, surgery performed group, and surgery indication/unperformed group. Significance was calculated by the log-rank test. Hazard ratios and CIs for death were based on the Cox proportional hazards model (backward selection). This multivariate model included the variables that were significant at the univariate analysis with $P <$ .1 and the most relevant clinical characteristics. A P-value of less than .05 was considered statistically significant. R Cran 3.3.0 for Windows 11 was used for all analyses.

RESULTS

Clinical Features of Infective Endocarditis Patients in Intensive Care Unit

During the study period, 325 patients with criteria for a definite IE diagnosis were consecutively enrolled. The average annual population of the province was 217 778 (99.8% Caucasian, average age 45.7 years). An incidence rate of 6.78/100 000/year was calculated. Among them, 94 were admitted in ICU. The reasons for ICU admission were shock (n = 47, 50%), acute heart failure (n = 46, 48.94%), or indication for invasive mechanical ventilation (n = 36, 38.3%). A 1-year follow-up was completed for all patients. The main populations' characteristics at ICU admission, underlying diseases, and predisposing factors are summarized in Table 1. Features associated to a higher risk of ICU admission at the univariate analysis were: embolic complications, IE perivalvular extension, vegetation diameter > 10 mm, chronic renal insufficiency, SOFA score ≥ 5, CCI ≥ 3, GCS ≤ 8, NYHA class at admission > 2, indication for surgery although unperformed, history of heart failure, and stroke. Among them, in the multivariate analysis, risk factors for ICU admission were the presence of vegetation >10 mm, renal insufficiency, acute heart failure, SOFA score, and IOT (Table 2). On the contrary,

Table 1. Comparisons of Baseline Characteristics Between Ward and Intensive Care Unit Groups

	Total	Ward	CCU/ICU	*P*
Patients, n (%)	325	231 (71.08)	94 (28.92)	
Male, n (%)	182 (56.00)	134 (58.00)	48 (51.06)	.253
Age median (interquartile)*	72.17 (18.57)	72.40 (20.11)	70.52 (17.71)	.523
CCU, n (%)	43 (13.23)		43 (45.74)	
OTI, n (%)	36 (11.08)	0 (0.00)	36 (38.30)	.000
IVDA, n (%)	29 (8.92)	17 (7.36)	12 (12.77)	.121
HIV infection, n (%)	5 (1.54)	3 (1.30)	2 (2.13)	.288
Cancer, n (%)	40 (12.31)	28 (12.12)	12 (12.77)	.789
Recent cardiac surgery, n (%)	9 (2.77)	5 (2.16)	4 (4.26)	.288
Congenital heart disease, n (%)	8 (2.46)	7 (3.03)	1 (1.06)	.300
Immunocompromised, n (%)	37 (11.38)	27 (11.69)	10 (10.64)	.288
Diabetes, n (%)	57 (17.54)	39 (16.88)	18 (19.15)	.633
Ischemic heart disease, n (%)	56 (17.23)	37 (16.02)	19 (20.21)	.285
Congenital heart valve disease, n (%)	96 (29.54)	68 (29.44)	28 (29.79)	.233
Bicuspid aortic valve, n (%)	*50 (15.38)*	*31 (13.42)*	*19 (20.21)*	.311
Mitral valve prolapse, n (%)	*46 (14.15)*	*37 (16.88)*	*9 (9.57)*	.311
Prothesis, n (%)	102 (31.38)	72 (31.17)	30 (31.91)	.017
CVC, n (%)	46 (14.15)	30 (12.99)	16 (17.02)	.910
COPD, n (%)	54 (16.62)	31 (13.42)	23 (24.47)	.015
History of HF, n (%)	99 (30.46)	59 (25.54)	40 (42.55)	.003
Previous stroke, n (%)	20 (6.15)	11 (4.76)	9 (9.57)	.080
Periferal arteropathy, n (%)	42 (12.92)	29 (12.55)	13 (13.87)	.756
SOFA score (points)	2 (0-17)	1 (0-11)	5 (1-17)	.000
Charlson Comorbidity Index (points)	2 (0-11)	2 (0-11)	3 (1-10)	.000
Previous endocarditis, n (%)	18 (5.54)	13 (5.63)	5 (5.32)	.912
Atrial fibrillation, n (%)	56 (17.23)	39 (16.88)	17 (18.09)	.795
GCS ≤ 8, n (%)	23 (7.08)	2 (0.87)	21 (22.34)	.000
NYHA class > 2 (points)	90 (27.69)	43 (18.61)	47 (50.00)	.000
LVEF (%), median (interquartile)*	60 (10)	60 (10)	60 (10)	.431
Creatinine mg/dL, median (interquartile)*	1.27 (0.86)	1.20 (0.7)	1.60 (1.88)	.000
Dialysis, n (%)	9 (2.77)	5 (2.16)	4 (4.36)	.298

Independent *t* test was performed for all normal variables. *Mann–Whitney *U*-test for non-normal variables.
CCU, cardiac care unit; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; GCS, Glasgow Coma Scale; HF, heart failure; HIV, human immunodeficiency virus; ICU, intensive care unit; IVDA, intravenous drug abuse; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SOFA, Sequential Organ Failure Assessment; OTI, Oro-tracheal intubation.

Table 2. Binary Logistic Regression Analysis for Predictors of Intensive Care Unit Admission

	Univariate				Multivariate			
		95% CI				95% CI		
	Adjusted OR	Lower Limit	Upper Limit	*P*	Adjusted OR	Lower Limit	Upper Limit	*P*
Age (years)	1.000	0.984	1.015	.964				
Previous endocarditis	0.942	0.326	2.720	.912				
Embolic complication	1.854	1.129	3.046	.015				
Perivalvular extension	2.539	1.449	4.449	.001				
Prosthetic valve	1.145	0.681	1.927	.609				
Vegetation diameter >10 mm	2.371	1.447	3.882	.001	2.150	1.160	3.986	.015
Staphylococcus aureus infection	1.654	0.970	2.821	.064				
Creatinine >2 mg/dL	4.945	2.631	9.296	.000				
PaO_2/FiO_2 ratio (mm Hg) %	0.985	0.979	0.992	.000	1.689	1.470	1.940	.000
SOFA score (point)	1.711	1.492	1.962	.000				
AHF	2.346	1.431	3.845	.001	2.193	1.182	4.070	.013
Charlson comorbidity index (point)	1.310	1.166	1.471	.000				

Multivariate Model included: SOFA score, acute heart failure, creatinine > 2 mg/dL; 2, *Staphylococcus aureus* infection, vegetation dimension >10 mm, perivalvular extension, embolic complication, Charlson comorbidity index.
AHF, acute heart failure; OR, odds ratio; PaO_2, partial pressure of oxygen; FiO_2, inspired fraction of oxygen; SOFA, Sequential Organ Failure Assessment.

other clinical features, such as the presence and typology of a preexisting cardiac disease, diabetes, conditions of immunodepression, presence of a prosthetic valve, and ejection fraction (EF), were not significant risk factors for ICU admission. The mean value of left ventricular EF was 60 ± 11.6% in the 2 groups. The main results and parameters in the 2 groups of IE patients are summarized in Table 3. The most frequently affected valve was the aortic valve (n = 136, 41.85%) followed by the mitral, tricuspid, and pulmonary valves. No differences in the frequency of involvement in the 2 groups according to affected valve classification were found, except for a higher multivalvular compromise in ICU patients. A prosthetic IE was present in 102 patients (31.38%)—mechanical in 11.38% and biological in 20%—without differences in the 2 groups. The presence of a prosthetic valve did not increase the risk of ICU admission. The same result was found for device-related IE : 5.63% in group 1 and 5.32% in group 2**.** Negative blood cultures were found in 14.76%, with a nonsignificant trend toward a higher frequency in ICU. *Staphylococcus aureus* (SA) was the most frequent pathogen (24.92%) followed by coagulase-negative staphylococci (18.15%), *Streptococcus viridans* (13.84%), and enterococci (13.32%). A trend toward a higher SA incidence in ICU patients was present without reaching statistical significance (22.08% vs. 31.92%, *P* = .108). The frequency of community-acquired and health-care-associated did not present significant differences between the 2 groups (67.97% vs. 67.02% and 31.17% vs. 35.11%, respectively). Echocardiographic exams revealed valvular vegetations in 63% vs. 36% of ICU patients. In this last group, however, vegetations were larger (>10 mm), with higher embolic risk, in 62.77% vs. 41.56% of ward patients. Embolic complications were found in 109 subjects (33.54%): 29.94% of group 1 and in 56.38% of group 2. Brain was the most common target representing more than 50% of embolic events in both groups, followed by pulmonary embolism in right-sided IE. An embolic stroke was found in 37 subjects (16.01%) vs. 25 (26.60%), with a significant difference, thus representing a risk factor for ICU admission. Among ICU patients, the most common valvular dysfunction was severe mitral regurgitation, which was significantly associated with ICU admission (n = 39, 16.9% in group 1 vs. n = 28, 29.8% in group 2). Severe mitral insufficiency included cases with fail and/or leaflet perforation. A perivalvular extension of the infective process was diagnosed in 60 cases (18.15%): 14.71% ward and 24.47% ICU patients with a significant difference. A fistulization was found in 2 ICU subjects. A prosthesis dehiscence was diagnosed in 13 cases with no differences between the 2 groups. A prosthesis obstruction was found in 3 cases among ward patients. Right-sided IE cases were 47 (14.46%), and multivalvular (right- and left-sided) cases were 23. Right-sided IE was equally distributed in the 2 groups: 14.89% of ICU patients. An intra-cardiac device-related IE (CDRIE) was present in 18 subjects with neither incidence nor mortality differences between ward and ICU patients. The total number of pulmonary septic embolisms was 25 (7.69%), and cases requiring ICU admission were 7 (7.45%). No significant differences between the 2 groups were found. Surgery was indicated in 202 (62%) subjects: 128/231 (55.41%) in ward and 74/94 (78.72%) in ICU subjects. In cases with indication, surgery was performed in 134 patients (41.23%): 91/128 (71.09%) in group 1 and 43/74 (58.10%) in group 2, with a significant difference in favor of those admitted to ICU. Although with a surgical indication, 68 cases were not operated on: 37/128 (28.90%) and 31/74 (41.8%) in the 2 groups, respectively. Fifty-seven patients (17.54%), 28 (12.12%) in ward, and 29 (30.85%) in ICU were denied surgery because of a very high risk with a significant difference in the 2 groups. Among ICU patients**,** surgical intervention was not performed due to the absence of informed consent in 9 (3.90%) of group 1 vs. 2 (2.13%) of group 2, respectively. Among the others,

Table 3. Main Results and Parameters in the 2 groups of Infective Endocarditis Patients

	Total	Ward	CCU/ICU	*P**
Patients, n (%)	325	231 (71.08)	94 (28.92)	
Diagnosis				
1) Vegetations, n (%)	180 (55.38)	146 (63.20)	34 (36.17)	.000
Diameter > 10 mm, n (%)	155 (47.69)	96 (41.56)	59 (62.77)	.001
2) Complications, n (%)	145 (44.62)	85 (36.80)	60 (63.83)	.000
Perivalvular extension, n (%)	60 (18.15)	34 (14.71)	26 (27.6)	.006
Mitral flail/severe regurgitation/perforation, n (%)	67 (20.6)	39 (16.90)	28 (29.80)	.001
Proshetic dehiscence/leaks, n (%)	13 (4.00)	9 (3.90)	4 (4.26)	
Fistula, n (%)	2 (0.62)	0 (0.00)	2 (2.13)	
Prothesis obstruction, n (%)	3 (0.92)	3 (1.30)	0 (0.00)	
3) Endocarditis side				
Left heart, n (%)	272 (83.70)	196 (84.85)	76 (80.85)	.41
Right heart, n (%)	46 (14.15)	33 (14.29)	13 (13.82)	
Left/right heart, n (%)	7 (2.15)	2 (0.87)	5 (5.32)	
4) Valve				
Aortic, n (%)	136 (41.85)	96 (41.56)	40 (42.55)	.622
Mitral, n (%)	120 (36.92)	88 (38.10)	32 (34.04)	
Tricuspid, n (%)	26 (8.00)	19 (8.23)	7 (7.45)	
Pulmonary, n (%)	2 (0.62)	1 (0.43)	1 (1.06)	
Plurivalvular, n (%)	23 (7.07)	14 (6.06)	9 (9.57)	
5) Native/prosthetic, n (%)				
Native, n (%)	205 (63.04)	146 (62.20)	59 (62.76)	.868
Prothesis, n (%)	102 (31.38)	72 (31.17)	30 (31.92)	
Mechanical prosthesis, n (%)	37 (11.38)	25 (10.82)	12 (12.77)	
Biological prosthesis, n (%)	65 (20.00)	47 (20.35)	18 (19.15)	
TAVI, n (%)	5 (1.54)	4 (1.73)	1 (1.06)	.858
CDRIE, n (%)	18 (5.54)	13 (5.63)	5 (5.32)	
Emodynamic complications				
Acute heart failure, n (%)	113 (34.77)	67 (29.00)	46 (48.94)	.000
Septic shock, n (%)	68 (20.92)	21 (9.09)	47 (50.00)	.000
Creatinine > 2.00 mg/dL, n (%)	50 (15.38)	20 (8.66)	30 (31.91)	.000
Embolic complications				
None, n (%)	216 (66.46)	163 (70.56)	53 (56.38)	.014
Yes, n (%)	109 (33.54)	68 (29.44)	41 (43.62)	
Cerebral, n (%)	62 (19.07)	37 (6.01)	25 (26.60)	.093
Splenic, n (%)	7 (2.15)	4 (1.73)	3 (3.19)	
Pulmonary, n (%)	25 (7.69)	18 (7.79)	7 (7.45)	
Peripheral, n (%)	8 (2.46)	6 (2.60)	2 (2.13)	
Coronary, n (%)	1 (0.31)	0 (0.00)	1 (1.06)	
Renal, n (%)	5 (1.54)	3 (1.30)	2 (2.13)	
Intestinal, n (%)	1 (0.31)	0 (0.00)	1 (1.06)	
Surgery				
Yes, n (%)	134 (41.23)	91 (39.39)	43 (45.74)	.000
Elective, n (%)	49 (15.08)	41 (17.75)	8 (8.51)	.000
Urgent, n (%)	78 (24.00)	48 (20.78)	30 (31.91)	
Emergency, n (%)	7 (215)	2 (0.87)	5 (5.32)	
None, n (%)	191 (58.77)	140 (60.61)	51 (54.26)	

(*Continued*)

Table 3. Main Results and Parameters in the 2 groups of Infective Endocarditis Patients (*Continued*)

	Total	Ward	CCU/ICU	*P**
Reason				
No indication, n (%)	123 (37.85)	103 (44.59)	20 (21.28)	.000
High risk, n (%)	57 (17.54)	28 (12.12)	29 (30.85)	
Decline, n (%)	11 (3.38)	9 (3.90)	2 (2.13)	
Time to surgery (days)	17.50 (0.303)	19 (0.303)	16 (1.185)	.199
Early surgery (<7 days)	31 (9.54)	19 (8.23)	12 (12.77)	.226
Indication/performed, n (%)	134 (41.23)	91 (39.39)	43 (45.74)	.000
No indication, n (%)	123 (37.85)	103 (44.59)	20 (21.28)	
Indication/not performed, n (%)	68 (20.92)	37 (16.02)	31 (32.98)	
Blood cultures				
a) Sterile, n (%)	49 (15.10)	32 (13.85)	17 (18.09)	
b) Positive, n (%)	276 (84.90)	199 (86.15)	77 (81.91)	.482
Health-care acquired	105 (32.30)	72 (31.17)	33 (35.11)	.561
Community acquired	220 (67.70)	157 (67.97)	63 (67.02)	.784
Staphylocuccus aureus, n (%)	81 (24.92)	51 (22.08)	30 (31.92)	.155
Streptococcus viridans, n (%)	45 (13.84)	37 (16.01)	8 (8.51)	
Staphylococcus coagulase negative, n (%)	59 (1815)	42 (1818)	17 (1809)	
Other, n (%)	13 (4.00)	11 (4.76)	2 (2.12)	
Enterobacter, n (%)	23 (7.07)	18 (7.80)	5 (5.32)	
Enterococcus, n (%)	43 (13.23)	33 (14.28)	10 (10.63)	
Fungal, n (%)	2 (0.61)	2 (0.87)	0 (0.00)	
Polymicrobical, n (%)	9 (2.76)	4 (1.73)	5 (5.32)	
HACEK group, n (%)	1 (0.31)	1 (0.43)	0 (0.00)	
Mortality				
In-hospital death, n (%)	88 (27.07)	29 (12.55)	59 (62.77)	.000
30-days death, n (%)	68 (20.90)	21 (9.09)	47 (50.00)	.000
After 30 days death, n (%)	29 (8.92)	5 (2.16)	4 (10.25)	.043
1-year death, n (%)	97 (29.84)	34 (14.71)	63 (67.02)	.000
Cardiac death, n (%)	40 (45.54)	12 (41.38)	28 (47.45)	.000
Surgery-related death, n (%)	6 (6.82)	0 (0.00)	6 (10.16)	.000
Diagnosis to in-hospital death days, median (interquartile)	13 (0, 9)	13.5 (0, 72)	13.8 (1, 72)	.563
Aureus infection, n (%)	81 (24.92)	51 (22.08)	30 (31.91)	.108
No aureus infection, n (%)	244 (75.08)	180 (77.92)	64 (68.09)	

Independent *t* test was performed for all normal variables. *Mann–Whitney *U*-test for non-normal variables.
CCU, cardiac care unit; CDRIE, intracardiac device-related infective endocarditis; HACEK, *Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae;* ICU, intensive care unit; TAVI, transcatheter aortic valve implantation.

reasons for nonsurgical treatment included poor prognosis due to comorbidities (32%), death before surgery (22%), stroke (17%), and septic shock (29%). Patients denied surgery had poor survival with mortality of 16/37 (43.24%) of ward vs. 28/31 (90.03%) of the ICU group ($P < .001$). Surgical procedure timing was considered as an emergency in 2 (0.87%) and 5 (5.32%), respectively; urgent in 48 (20.76%) vs. 30 (31.91%); and elective in 41 (17.75%) vs. 8 (8.51%) in the 2 groups.

Mortality in Infective Endocarditis Patients in Intensive Care Unit

During hospitalization, 88 patients died with a total mortality rate of 27.07%; 29 of them (12.55%) died in the ward and 59 (62.77%) in the ICU, with a highly significant difference in the 2 groups. The global 1-year mortality rate was 29.84%: 14.71 vs. 67.02, showing that a significant difference was still present between the 2 groups. In most cases, cardiac death was reported, while, in other cases, septic shock, multiorgan failure, or neurological complications were the main causes of death. None of the ward patients presented a surgery-related death, whereas it happened in 6 ICU cases, representing 10.16% of the deaths in this group. Figure 1 shows Kaplan–Meier mortality curves in ward vs. ICU patients (Panel A) and according to surgery (Panel B). Median survival time was >100 days in the ward group and 26 days (95% CI, 7.95- 44.04) in the ICU group. Main

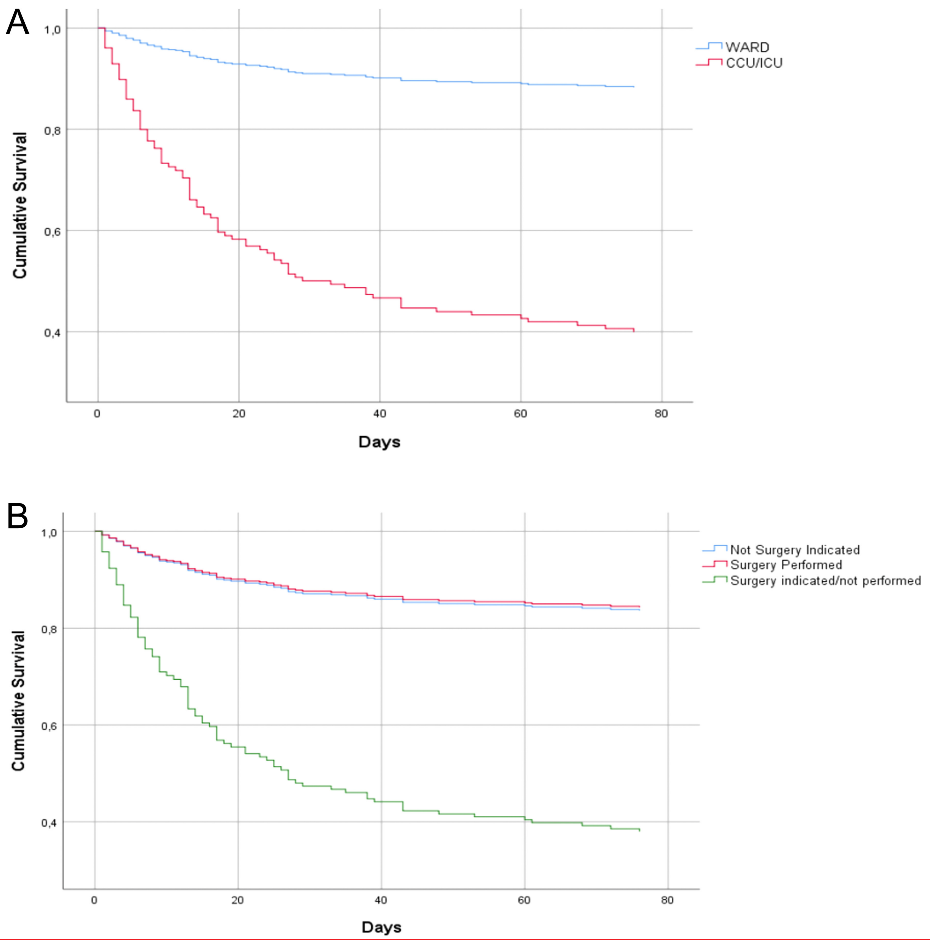

Figure 1. Kaplan–Meier mortality curves in ward vs. intensive care unit patients (A) and according to surgery (B). CCU, cardiac care unit; ICU, intensive care unit.

significant factors associated with in-hospital mortality at univariate analysis are reported in Table 4: embolic complications, vegetation dimensions >10 mm, renal failure, female sex, acute heart failure, *Staphylococcus aureus* sepsis, abscess formation, age > 70 years, SOFA score > 6, CCI, and unperformed although indicated surgery. Admission in ICU was another factor clearly associated with a higher mortality (Table 4). Health-care-associated did not present a higher mortality compared to community-acquired IE. Multivariate analysis, including all significant variables found at univariate analysis ($P < .05$), identified 5 independent mortality risk factors. They were SOFA score >14, not performing surgery although indicated, age > 70 years, acute heart failure, and embolic complications. Hazard ratio, upper and lower limits, and P-values are reported in Table 4.

DISCUSSION

We report an increased global incidence rate (6.78/100 000/year) with respect to our previous data (4.6/100 000/year in 2015).[2] This is in line with a recent meta-analysis performed by Talha et al[3] reporting a yearly increase in IE incidence of 0.24 cases per 100 000 per annum. Reasons for this trend may include increased risk factors, improvements in diagnosis, restrictions in antibiotic prophylaxis due to new guidelines, and improvements in the International Classification of Disease coding in discharge sheets.

Risk factors for ICU admission in the multivariate analysis were the need for mechanical ventilation, SOFA score > 5, GCS ≤ 8, renal insufficiency, septic shock, cerebral embolism, and surgical indication.

Patients in the ICU present complications, such as acute heart failure or shock, and often need mechanical ventilation. The more complicated patients, with higher mortality risk, or who die within few days/hours from diagnosis, may be excluded thus causing a selection bias. This seems to have happened in large registries such as EUROENDO,[6] which reported a relatively low mortality rate (17.1%). Moreover, the frequency of ICU admissions is rarely reported in papers. It is not easy to estimate as many patients become critical during hospitalization and are subsequently transferred from a medical ward to ICU. Guidelines[15] do not report an agreement on which IE complications require an ICU setting, due to a broad spectrum of different scenarios, suffice to remember the wide spectrum of consequences due to embolic events. Infective endocarditis may initially present as a systemic inflammatory response syndrome or sepsis which can get complicated with shock, and these conditions are often rapidly evolving. The incidence of IE in ICU patients affected

Table 4. Mortality in Infective Endocarditis Cox Proportional Hazards Model

	Univariate Analysis				Multivariate Analysis			
	HR	Lower 95% CI	Upper 95% CI	*P*	HR	Lower 95% CI	Upper 95% CI	*P*
Embolic complication	2.129	1.429	3.173	.000	1.676	1.035	2.715	.036
Vegetation dimension > 10 mm	1.452	0.970	2.173	.069				
Serum creatinine > 2 mg/dL	3.635	2.364	5.589	.000				
Female sex	1.488	0.999	2.217	.050				
Acute heart failure	1.652	1.108	2.462	.013	1.583	10.140	2.473	.043
Aureus sepsis	1.646	1.074	2.523	.022				
Perivalvular extension	1.944	1.253	3.018	.003				
IVDA	0.972	0.471	2.004	.939				
Dialysis	2.068	0.759	5.634	.155				
Prosthetic valve	1.173	0.769	1.789	.458				
Previous endocarditis	0.505	0.160	1.595	0.244				
Age 70-85 years	2.953	1.453	6.004	.000	3.424	1.517	7.727	.003
Age > 85 years	2.784	1.465	5.293	.010	2.257	1.088	4.680	.029
Charlson comorbility index	1.189	1.059	1.335	.003				
Surgery performed	0.934	0.529	1.649	.810	0.576	0.296	1.126	.107
Surgery indicated/not performed	5.350	3.225	8.875	.000	3.096	1.746	5.491	.000
ICU admission	6.683	4.374	10.210	.000	3.771	2.202	6.457	.000
SOFA 7-9 points	4.675	2.236	9.776	.000	1.464	0.657	3.260	.351
SOFA 9-14 points	4.675	2.236	9.776	.000	1.331	0.684	2.589	.399
SOFA >14 points	4.392	2.425	7.955	.000	5.833	1.710	19.900	.005

Multivariate logistic regression model shows that acute heart failure ($P = .043$), SOFA score ($P = .013$), vegetation dimension >10 mm ($P = .015$), and SOFA score ($P = .000$) were the most important independent predictors of ICU admission.
HR, hazard ratio; ICU, intensive care unit; IVDA, intravenous drug abuse; SOFA, Sequential Organ Failure Assessment.

by severe sepsis is probably underestimated. Our data show that it is not the type of valve, the underlying heart disease, the presence of a device, nor the causative germ, but the clinical parameters influencing prognosis: at the multivariate analysis, independent factors associated with mortality were SOFA score > 14, unperformed surgery although indicated, age > 70 years, acute heart failure, and embolic complications.

Previous studies focusing on ICU IE patients are summarized in Table 5. In recent years, SOFA score seems to be the most used, and consequently, in our study, we evaluated its prognostic value together with CCI and GCS at ICU admission. In the ENDOREA study,[12] Mirabel et al[12] reported the SOFA score as a major mortality predictor even before surgery. Our data are in line with this paper, as the SOFA score was a major prognostic factor in both studies. This score includes several parameters describing organ failure, such as cardiac, respiratory, liver, renal, and neurological. Organ failure severity is measured with a 0-to-4-point scale for each organ. We found that a cutoff value >14 for SOFA was a major predictive parameter for higher mortality at multivariate analysis, similar to data reported by Mirabel et al,[12] whereas Asai et al,[8] in a small series, reported a cutoff value >6 as significant. Although previous studies used different severity scores and/or organ failure assessment in IE cases admitted in ICU, they all agree that these scores are independent mortality prognostic factors (Table 5). This is not surprising as are well-recognized mortality predictors scores in ICU patients.[17,21-29] We did not confirm the protective role of IE native valves; this may be surprising since prosthetic IE is commonly associated with a worse prognosis.[12,27,28] In the ICU setting, our data reveal that clinical parameters, expression of severe complications, and/or organ damage are the key prognostic factors. The presence of a known underlying heart disease, particularly a prosthesis, facilitates the suspicion and may lead to a quicker IE diagnosis, thus increasing survival. Therefore, even if prosthetic valves are more prone to complications, they often receive quicker attention and therapies. A wide range of frequencies of right-sided IE is reported as 4%-31%.[10,14] In our study, they represented 14.89% of ICU patients and those affected by a CDRIE were 18%. We did not find any differences either in incidence or in mortality between ward (5.32%) and ICU patients (5.36%). Consequently, the presence of an intracardiac device did not result a significant mortality risk factor. Even pulmonary septic embolism, which required ICU admission in 7.45% of the cases, did not result in a risk factor for ICU admission and did not increase mortality risk in the multivariate analysis. On the contrary, patients with septic pulmonary emboli and septic shock had poor survival, but it was only the variable septic shock impacting on prognosis. These data are similar to those described by Chou et al[29] in a series of 20 patients affected by pulmonary septic embolism and shock. The presence of intracardiac catheters increases the suspicion of a possible IE, thus permitting a more rapid diagnosis and treatment that have a favorable impact on prognosis. Health-care-associated did not present a higher mortality rate

Table 5. Studies Focusing on Intensive Care Unit Infective Endocarditis Population

Author	Year	n	Mortality %	Surgery %	Prognostic Score	Type of Study	Reference
Gouello	2000	22	68 (overall)	22.7	SAPS II	R	28
Delle Karth	2002	33	54 (in hospital)	60	APACHE-II GCS	R	29
Morvilliers	2004	228	45 (in hospital)	50	SAPS2 ODIN	R	21
Soneville	2011	188	44 (3 months)	63	SOFA CHARLSON SAPS2 GCS	P	13
Miranda-Montero	2012	102	42.1 (in hospital)	45.8	SOFA SAPS2 APACHE2	P	20
Mirabel	2013	198	59.5 months	52	SOFA GCS	P	12
Samol	2014	216	25 (30 days)	57	SAPS2	R	10
Leroy	2015	248	41.5 (in hospital)	50	SOFA SAPS2	R	21
Joffre	2018	4405	30 (in hospital)	34	SAPS2	R	14
Asai	2019	66	24 (in hospital)	29	SOFA	R	8
Nguyen	2021	110	35 (in hospital)	38	APACHE-II	R	22

The patient's condition at intensive care unit admission was assessed using different risk scores: APACHE, Acute Physiologic Assessment and Chronic Health Evaluation score; GCS, Glasgow Coma Scale; P, prospective; R, retrospective; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

than community-acquired IE, according to previous data.[13] Consistent with consolidated literature data, mortality was significantly lower in patients surgically treated.[12,14] In our ICU subjects, surgery was indicated in 74/94 (78.72%) of ICU patients and performed in 43 (45.74%) of them. These data are similar to previous studies that reported a range of 35% to 54% of ICU patients who underwent surgery.[10,14,30,31] Although indicated, 31/94 (32.98%) of our ICU patients did not undergo surgery. Most of these cases were judged by a multidisciplinary endocarditis team as "too sick" to survive the surgical procedure. Among patients denied for surgery, mortality was very high: 43.24% in ward and 90% in ICU subjects, a percentage comparable to the one previously reported by Mirabel et al[12] (95% in-hospital mortality). The ICU patients raise difficult considerations on surgical indication and timing, and, in very critical cases, the surgical option may be "futile." The concept of "futility" has recently become central in modern "value-based" health-care evaluation of the benefit—risk and benefit—cost trade-offs as well as in shared informed decision-making with patients and their families.[32] Common reasons to declare surgery as futile are severe stroke or recent intracranial hemorrhage: these patients are denied by the surgeon at least for 3 weeks.[33] A consensus has been reached in recent guidelines on the surgical indication for vegetation larger than 10 mm, as they carry a high embolization risk.[16,33] This is confirmed by our experience, as in ICU patients, vegetations were significantly larger, with a higher embolic risk, in 62.77% in ICU vs. 41.56% of ward patients, representing a mortality risk factor even after multivariate analysis adjustment. Some cases are not accepted for the surgical solution: 30.85% of our ICU and in 12.12% of the "ward" patients (Table 2). The same percentage of individuals denied surgery was reported by Mirabell et al[12] (30%) with "clinical choice somehow validated by the extremely poor outcomes in those with high SOFA scores, regardless of treatment."[12] In a study performed by Leroy et al,[21] 75% of ICU-admitted IE patients should have been operated on, but 50% of them had contraindications: very severe co-pathologies, multiple organ failure, or intracranial bleeding. Reasons for nonsurgical treatment in our series were similar to those reported by Chu et al[34] and included poor prognosis due to comorbidities (32%), septic shock (29%), death before surgery (22%), and stroke (17%). In a meta-analysis, performed by Varela-Barca et al,[35] several factors associated with surgical mortality in IE were reported and cardiogenic shock showed the strongest association with mortality. Commonly used Surgical Risk Scores in IE patients have a suboptimal prognostic ability, therefore several IE-specific risk scores have been developed. Varela-Barca et al[35] using the area under the receiver operating characteristic curve, found that the STS-IE score[36] had a higher discrimination value: 0.76 (95% CI, 0.68-0.82), and its use should be advocated especially in the ICU setting.[37,38] Surgeons frequently ask for a possible operation delay preferring hemodynamic and septic stabilization of the patient, whenever possible. A difficult topic, unclear in guidelines, is the surgical timing for embolism prevention in high-risk vegetation. Early surgery is defined as performed within 7 days from diagnosis: in our series 19 (8.4%) ward and 12 (27.9%) ICU. A delay compared to the timing recommended by guidelines is frequent in clinical practice when dealing with complicated critically ill patients. On the other hand, a survival benefit from early surgical intervention is not supported by sufficient evidence as derived from a limited number of studies.[33] Surgical therapy is generally associated with improved early and late survival, and our study confirms that this is true even in IE patients admitted to ICU.[10,39]

Study Limitations

This was a single-center study; nevertheless, our data were prospectively collected on all consecutive cases included from the mildest IE forms to the most severe admitted in ICU. A multidisciplinary approach has always been performed, but early referral to tertiary surgical centers may have been delayed by the transfer difficulties in extremely ill patients.

The impact on mortality of the new imaging technologies, such as total body positron emission tomography and their indication in the diagnosis of secondary embolic localizations and in the port-of-entry evaluation, was not the aim of our study and has not been investigated. An increase in their use may reduce the long-term mortality, but further studies are needed.

Another unresolved issue is when to suspect and perform an echocardiographic exam in patients admitted to the ICU for a septic shock. In our experience, a transesophageal echo (TEE) was performed in all ICU patients except 1 intravenous drug abuse with a tricuspid valve IE. This topic deserves further investigation as the real incidence of IE among these patients, who present very high mortality within a few days, is probably under-estimated and has not investigated yet.

CONCLUSION

Despite modern diagnostic tools and medical and surgical therapies, the mortality rate in IE is still high and, in patients admitted to the ICU for IE, it is very high and probably underestimated. Most severe critical cases are underreported in the literature. Intensive care unit severity scores are useful for prognostic evaluation. Organ failures and patients denied surgery when indicated have very poor survival. Further studies focusing on the most critically ill patients admitted to the ICU are needed to define the best therapeutic and surgical strategies.

Ethics Committee Approval: This research study was conducted retrospectively using data obtained for clinical purposes. All the procedures being performed were part of the routine clinical care. The study was conducted according to the 1964 Declaration of Helsinki, and authors are complying with the specific requirements of their institution and their countries. Our local hospital's ethical board gave written consent to the study.

Informed Consent: Consent to participate was obtained from each patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.C., P.B.; Design – A.C., B.S.; Supervision – U.L.; Resources – P. B., B.S.; Materials – E. A., F.D.S.; Data Collection and/or Processing – B. S., P. B.; Analysis and/or Interpretation – P. B., U. L.; Literature Search – P. B., A.C.; Writing – A.C., P. B.; Critical Review – U.L., A.C.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. An increase in the incidence of infective endocarditis in England since 2008: a secular trend interrupted time series analysis. *Lancet*. 2015;385(9974):1219-1228. [CrossRef]
2. Cresti A, Chiavarelli M, Scalese M, et al. Epidemiological and mortality trends in infective endocarditis, a 17-year population-based prospective study. *Cardiovasc Diagn Ther*. 2017;7(1):27-35. [CrossRef]
3. Talha KM, Baddour LM, Thornhill MH, et al. Escalating incidence of infective endocarditis in Europe in the 21st century. *Open Heart*. 2021;8(2). [CrossRef].
4. Morelli S, De Marzio P, Voci P, Troisi G. Infective endocarditis. Recent progress in its epidemiology, clinical picture and therapy. Comments on cases. *Recenti Prog Med*. 1994;85(7-8):368-374.
5. Khanal B, Harish BN, Sethuraman KR, Srinivasan S. Infective endocarditis: report of a prospective study in an Indian hospital. *Trop Doct*. 2002;32(2):83-85. [CrossRef].
6. Habib G, Lancellotti P, Erba PA, et al. The ESC-EORP EURO-ENDO (European Infective Endocarditis) registry. *Eur Heart J Qual Care Clin Outcomes*. 2019;5(3):202-207. [CrossRef]
7. Angsutararux T, Angkasekwinai N. Cumulative incidence and mortality of infective endocarditis in Siriraj Hospital-Thailand: a 10-year retrospective study. *BMC Infect Dis*. 2019;19(1):1062. [CrossRef]
8. Asai N, Shiota A, Ohashi W, et al. The SOFA score could predict the severity and prognosis of infective endocarditis. *J Infect Chemother*. 2019;25(12):965-971. [CrossRef]
9. Talha KM, DeSimone DC, Sohail MR, Baddour LM. Pathogen influence on epidemiology, diagnostic evaluation and management of infective endocarditis. *Heart*. 2020;106(24):1878-1882. [CrossRef]
10. Samol A, Kaese S, Bloch J, et al. Infective endocarditis on ICU: risk factors, outcome and long-term follow-up. *Infection*. 2015;43(3):287-295. [CrossRef]
11. Mourvillier B, Trouillet JL, Timsit JF, et al. Infective endocarditis in the intensive care unit: clinical spectrum and prognostic factors in 228 consecutive patients. *Intensive Care Med*. 2004;30(11):2046-2052. [CrossRef]
12. Mirabel M, Sonneville R, Hajage D, et al. Long-term outcomes and cardiac surgery in critically ill patients with infective endocarditis. *Eur Heart J*. 2014;35(18):1195-1204. [CrossRef]
13. Sonneville R, Mirabel M, Hajage D, et al. Neurologic complications and outcomes of infective endocarditis in critically ill patients: the ENDOcardite en REAnimation prospective multicenter study. *Crit Care Med*. 2011;39(6):1474-1481. [CrossRef]
14. Joffre J, Dumas G, Aegerter P, et al. Epidemiology of infective endocarditis in French intensive care units over the 1997-2014 period-from Cub-Réa Network. *Crit Care*. 2019;23(1):143. [CrossRef]
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383. [CrossRef]
16. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC) Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European association of nuclear medicine (EANM) *Eur Heart J*. 2015;36(44):3075-3128. [CrossRef]
17. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. 1974;2(7872):81-84. [CrossRef]

18. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3) *JAMA*. 2016;315(8):801-810. [CrossRef]
19. Hollenberg SM, Kavinsky CJ, Parrillo JE. Cardiogenic shock. *Ann Intern Med*. 1999;131(1):47-59. [CrossRef]
20. Miranda-Montero S, Rodríguez-Esteban M, Alvarez-Acosta L, Lubillo-Montenegro S, Pérez-Hernández H, Llorens-León R. Endocarditis infecciosa en la Unidad de Medicina Intensiva. *Med Intensiva*. 2012;36(7):460-466. [CrossRef]
21. Leroy O, Georges H, Devos P, et al. Infective endocarditis requiring ICU admission: epidemiology and prognosis. *Ann Intensive Care*. 2015;5(1):45. [CrossRef]
22. Nguyen J, Baradi A, Reid D, et al. Characteristics, outcomes and prognostic factors of infective endocarditis in the Intensive Care Unit. *Heart Lung Circ*. 2021;30:S216. [CrossRef]
23. Fagon JY, Chastre J, Novara A, Medioni P, Gibert C. Characterization of intensive care unit patients using a model based on the presence or absence of organ dysfunctions and/or infection: the Odin model. *Intensive Care Med*. 1993;19(3):137-144. [CrossRef]
24. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Apache II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-829. [CrossRef]
25. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA*. 1993;270(24):2957-2963. [CrossRef]
26. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707-710. [CrossRef]
27. Hoen B, Duval X. Infective endocarditis. *N Engl J Med*. 2013;369(8):785. [CrossRef]
28. Gouëllo JP, Asfar P, Brenet O, Kouatchet A, Berthelot G, Alquier P. Nosocomial endocarditis in the intensive care unit: an analysis of 22 cases. *Crit Care Med*. 2000;28(2):377-382. [CrossRef]
29. Karth G, Koreny M, Binder T, et al. Complicated infective endocarditis necessitating ICU admission: clinical course and prognosis. *Crit Care*. 2002;6(2):149-154. [CrossRef]
30. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med*. 2009;169(5):463-473. [CrossRef]
31. Chou DW, Wu SL, Chung KM, Han SC, Cheung BM. Septic pulmonary embolism requiring critical care: clinicoradiological spectrum, causative pathogens and outcomes. *Clinics (Sao Paulo)*. 2016;71(10):562-569. [CrossRef]
32. van Mourik MS, Vendrik J, Abdelghani M, et al. Guideline-defined futility or patient-reported outcomes to assess treatment success after TAVI: what to use? Results from a prospective cohort study with long-term follow-up. *Open Heart*. 2018;5(2):e000879. [CrossRef]
33. Pettersson GB, Hussain ST. Current aATs guidelines on surgical treatment of infective endocarditis. *Ann Cardiothorac Surg*. 2019;8(6):630-644. [CrossRef]
34. Chu VH, Park LP, Athan E, et al. Association between surgical indications, operative risk, and clinical outcome in infective endocarditis: a prospective study from the International Collaboration on Endocarditis. *Circulation*. 2015;131(2):131-140. [CrossRef]
35. Varela Barca L, Navas Elorza E, Fernández-Hidalgo N, et al. Prognostic factors of mortality after surgery in infective endocarditis: systematic review and meta-analysis. *Infection*. 2019;47(6):879-895. [CrossRef]
36. Gaca JG, Sheng S, Daneshmand MA, et al. Outcomes for endocarditis surgery in North America: a simplified risk scoring system. *J Thorac Cardiovasc Surg*. 2011;141(1):98-106.e1. [CrossRef]
37. Varela L, López-Menéndez J, Redondo A, et al. Mortality risk prediction in infective endocarditis surgery: reliability analysis of specific scores. *Eur J Cardiothorac Surg*. 2018;53(5):1049-1054. [CrossRef]
38. Anantha-Narayanan M, Reddy YNV, Sundaram V, et al. Endocarditis risk with bioprosthetic and mechanical valves: systematic review and meta-analysis. *Heart*. 2020;106(18):1413-1419. [CrossRef]
39. Bannay A, Hoen B, Duval X, et al. The impact of valve surgery on short- and long-term mortality in left-sided infective endocarditis: do differences in methodological approaches explain previous conflicting results? *Eur Heart J*. 2011;32(16):2003-2015. [CrossRef]