Infective Endocarditis – Characteristics and Prognosis according to the Affected Valves.

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Article

Infective Endocarditis—Characteristics and Prognosis According to the Affected Valves

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Abstract: Background: Infective endocarditis (IE) continues to be a disease with high mortality despite medical advances. **Objective:** To investigate the characteristics and prognosis of IE according to the affected valves. **Material and methods**: The study is retrospective, single-center, cross-sectional and includes 270 patients with diagnosis IE, for the period 2005 – 2021, who received treatment at the University Hospital "St. Georgi" in Plovdiv, Bulgaria. **Results**: Single-valve IE (SIE) was found in 82.6% (n-222), multivalvular IE (MIE) in 16.66% (n=45) and device IE (CDRIE) in 0.74% (n=2) patients. The most commonly affected valve was the aortic 44.8% (n=121). The predominant multivalvular involvement was aortic-mitral valves (AV-MV) – 13.7% (n=37). The patients with tricuspid valve (TV) IE were significantly younger – 39 (30) years and were more frequently male (80.8%). Mortality was higher in MIE than SIE (31.1% vs 23.8%) and highest in multivalve aortic-tricuspid (AV-TV) IE (75%). Early surgery was done most in AV-MV IE 29.7% (n=11). Charlson comorbidity index was significantly higher in MV 4 (4) and AV 3 (3) than TV IE 1 (5) (p=0.048 and p=0.011, respectively). Septic shock occurred most frequently in AV-TV involvement (75%; p=0.0001). The most common causative agent was Staphylococcus group. Staphylococcus aureus affected more often TV alone 46.2% (n=124) vs. AV 9.9% (n=14); p=0.0001 and vs. MV 22.6% (n=17), p=0.022; Staphylococcus coagulase-negative (CNG) was the prevalent cause of MV IE 22.7% (n=17) vs AV-MV 2.7% (n=1); p=0.007. Streptococci were represented in a low percentage and only in left-sided IE, and more frequently in AV-MV 18.9% (n=7); vs. AV 6.6% (n=8); (p=0.025). **Conclusion**: Aortic valve is the most frequently affected valve, as single valve IE or multivalve AV-MV, with the predominant causative agents Staphylococcus group. The AV-TV IE has the worst prognosis, with the most common complication of septic shock and the highest in-hospital mortality.

Keywords: infective endocarditis; affected valve; mortality

Introduction

IE is a disease with poor prognosis and has a changing profile over the past few decades. Despite advances in diagnosis, including new imaging modalities, in treatment with the use of new antibiotic molecules and early surgical treatment, mortality in IE remains high at 16-25% [1,2]. Characteristics of IE change over time and depend on geographical and socio-economic level of the country. IE usually affects one valve, less commonly two valves (10-18%) [2] and extremely rarely three or four valves. There is a lot of information about left-sided and right-sided IE. Some studies compared single and multivalve IE [3–5]. Whether there are specifics in characteristics and outcome of IE according to the affected valve is vaguely studied To the best of our knowledge, we didn't find a study that compare all types of valve involvement in IE. This information could serve for improving prognosis and outcomes in IE.

Material and Method

The study is retrospective, single-centered, cross-sectional, including 270 patients with a diagnosis of IE, according to the modified Duke criteria, treated at the University Hospital "St. Georgi", in the city of Plovdiv for the period January 2005 – December 2021. The hospital capacity is

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1500 beds, and the cardiology clinic is a reference center for the treatment of IE for a large part of southern Bulgaria. The medical records of treated patients with codes I33, I38, and I39 for the described period were used. Variables studied included demographics, risk group, presence of predisposing heart disease, comorbidities, Charlson comorbidity index (CCI), entry gate, predictors for transient bacteremia, clinical, echocardiographic findings, causative organisms, complications, and clinical outcome.

Ethical Considerations

The study was conducted with the consent of the Local Ethics Committee (decision #2/09.03.2023) and in accordance with the principles of the Declaration of Helsinki.

Definition and Classification of IE

The diagnosis was defined as definite IE or possible IE according to the modified Duke criteria [6]. Surgical treatment of IE was defined as early when the surgery was done during antibiotic treatment. Valvular involvement of IE is determined based on findings from echocardiography, other imaging studies, cardiac surgery, or in some cases by clinical presentation. The presence of septic emboli and an extracardiac focus of infection was defined as a focus of infection detected by imaging or based on typical clinical presentation. Complications were diagnosed according to the established diagnostic criteria and recommendations.

Statistical Methods

Quantitative data are presented as arithmetic mean±standard deviation (mean±SD) or median and interquartile range ((median (IQR)) according to the type of distribution of the variables (Kolmogorov-Smirnov test). Categorical variables were summarized using absolute (n) and relative (%) magnitudes. Man-Whitney test for independent samples was used to compare quantitative variables between two groups. A z-test was used to compare the relative shares of categorical variables between the studied groups. A p-value<0.05 (two-tailed test) was considered statistically significant for all tests. Statistical analysis was performed using SPSS, version 26.0 (IBM corp., NY, USA).

Results

Of all 270 patients, 75.9% (n=205) had definite IE, with 65% (n=133) of them having two major criteria and 35% (n=72) having one major and three minor criteria. There were 24.1% (n=65) diagnosed with possible IE, 95% (n=62) of them with one major and one minor criterion and three with three minor criteria.

Location

Transthoracic echocardiography was performed in 100% of patients, transesophageal echocardiography – in 35.9% of them. We found vegetation in 83.7% (n=226), perianular abscess – 3% (n=8), chordal rupture – 3.3% (n=5), valve obstruction – 11.9% (n=32). The distribution of valvular regurgitation according to severity was as follows: mild/moderate: AV – 29.3%; MV – 23.7%; TV – 6%. Severe regurgitation: AV – 24.8%; MV – 19.3%; TV – 7.4%.

Single-valve IE (SIE) was found in 82.6% (n=222), multivalvular IE (MIE) in 16.66% (n=45) and CDRIE in 0.74% (n=2). The most frequently affected valve was aortic (AV – 44.8%, n=121), followed by mitral valve (MV – 27.8%, n=75) and tricuspid valve (TK – 9.62%, (n=26). We had one case (0.37%) with pulmonary valve IE. Of the MIE, the most common was AV-MV IE – 13.7%, (n=37) (Table 1). There was no triple- or quadruple-valve endocarditis in our series.

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Table 1. Clinical characteristics—demographics, risk groups, outcome 30 days (died), EF, type of valves, early surgery, entry door, predisposing heart conditions, type of acquisition.

Variables	AV n=121 (44.81%) 1	MV n=75 (27.80 %) 2	TV n=26 (9.62 %) 3	PV n=1 (0.37%) 4	AV + MV n=37 (13.70 %) 5	AV+ TV n=4 (1.48 %) 6	MV + TV n=4 (1.48 %) 7	CDRIE n=2 (0.74 %) 8	p-value
	Single valves IE – 222 (82.60%)				Double valves IE – 45 (16,66%)			2 (0,74 %)	
Age in yrs., *median (IQR)*	65 (21)	66 (21)	39 (30)	45(-)	67 (16)	44 (30)	63.5 (45)	74(-)	**p=0.005[1-3]†** **p=0.002[2-3]†** **p=0.002[3-7]†**
Gender – male, *n (%)*	83 (68.6)	43 (57.3)	21 (80.8)	1(100)	23 (62.2)	4 (100)	1 (25)	1 (50)	**p=0.019[3-7]***
Risk groups, n (%)									
Low	52 (43)	42 (56)	15 (57.7)	1 (100)	20 (54.1)	3 (75)	1 (25)	2 (100)	p>0.05
Moderate	22 (18.2)	13 (17.3)	2 (7.7)	0	4 (10.8)	1 (25)	2 (50)	0	p>0.05
High	47 (38.8)	20 (26.7)	9 (34.6)	0	13 (35.1)	0	1 (25)	0	p>0.05
	Single valves IE – 53 (23.8)				Double valves IE – 14 (31.1)				p>0.05
Outcome 30 days – died, *n (%)*	28 (23.1)	19 (25)	5 (19.2)	1 (100)	10 (27)	3 (75)	1 (25)	2 (100)	**p=0.018[1-6]*** **p=0.029[2-6]*** **p=0.019[3-6]*** **p=0.012[1-8]*** **p=0.018[2-8]*** **p=0.011[3-8]*** **p=0.029[5-8]***
EF %, *median (IQR)*	60 (13)	60 (13)	61.5 (20)	0	64 (14)	56.5 (12)	65 (10)	61 (-)	p>0.05
Type of valves									
Native IE	74 (61.2)	56 (74.7)	21 (80.8)	1 (100)	24 (64.9)	4 (100)	3 (75)	0	p>0.05*
Prosthetic IE	47 (38.8)	19 (25.3)	5 (19.2)	0	13 (35.1)	0	1 (25)	0	p>0.05*
Late prosthetic	42 (34.7)	18 (24.0)	4 (15.4)	0	11 (29.7)	0	1 (25)	0	p>0.05*
Early prosthetic	5 (4.1)	1 (1.3)	1 (3.8)	0	2 (5.4)	0	0	0	p>0.05*

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Early surgery, *n (%)*	24 (19.8)	10 (13.3)	6 (23.1)	0	11 (29.7)	0	1 (25)	2 (100)	**p=0.036[2]** **-5*** **p=0.001[2]** **-8*** **p=0.006[1]** **-8*** **p=0.001[2]** **-8** **p=0.020[3]** **-8*** **p=0.040[5]** **-8***
Entry door									
Unknown	64 (52.9)	36 (48)	4 (15.4)	0	17 (46)	2 (50)	2 (50)	0	**p=0.001[1]** **-3*** **p=0.003[2]** **-3*** **p=0.011[3]** **-5***
Dental	15 (12.4)	8 (10.7)	0	0	7 (18.9)	0	0	0	p>0.05*
Skin	4 (3.3)	3 (4.0)	1 (3.8)	0	2 (5.4)	0	0	0	p>0.05*
Hemodialysis	4 (3.3)	6 (8.0)	0	0	1 (2.7)	1 (25)	1 (25)	0	**p=0.029[1]** **-6** **p=0.029[1]** **-7*** **p=0.049[5]** **-6*** **p=0.049[5]** **-7***
Urogenital	8 (6.6)	0	1 (3.8)	0	0	0	0	0	p>0.05
Gastrointestinal	1 (0.8)	0	0	0	3 (8.1)	0	1 (25)	0	**p=0.013[1]** **-5*** **p=0.000[1]** **-7***
Ear Nose Throat	1 (0.8)	3 (4.0)	0	0	0	0	0	0	p>0.05
IV drug users	5 (4.1)	2 (2.7)	16 (61.6)	0	0	1 (25)	0	0	**p<0.0001** **1-3*** **p<0.0001** **2-3*** **p=0.024[2]** **-6***
Manipulation/ procedures	17 (14)	15 (20)	4 (15.4)	1 (100)	6 (16.2)	0	0	2 (100)	**p=0.001[1]** **-8*** **p=0.007[2]** **-8*** **p=0.002[3]** **-8*** **P=0.004[5]** **-8***
Respirators	2 (1.7)	2 (2.7)	0	0	1 (2.7)	0	0	0	p>0.05*
Predisposing heart conditions									
Prosthetic valve	47 (38.8)	19 (25.3)	5 (19.3)	0	13 (35.1)	0	1 (25)	0	p>0.05*

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Rheumatic heart disease	2 (1.7)	4 (5.3)	0	0	2 (5.4)	1 (25)	0	0	**p=0.003[1–6]***
Congenital heart disease	1 (0.8)	0	1 (3.8)	0	0	0	0	0	p>0.05*
Degenerative valve	10 (8.3)	3 (4)	1 (3.8)	0	1 (2.7)	0	0	0	p>0.05*
Bicuspid Ao valve	9 (7.4)	0	0	0	1 (2.7)	0	0	0	p>0.05*
Mitral valve prolapse	0	5 (6.7)	0	0	0	0	1 (25)	0	p>0.05*
Without	52 (43)	44 (58.7)	19 (73.1)	1(100)	20 (54.1)	3 (75)	0	0	p>0.05*
Type of acquisition									
Community acquired IE	87 (71.9)	52 (69.3)	7 (26.9)	0	26 (70.3)	1 (25)	2 (50)	0	**p<0.0001[1–3]*** **p=0.0002[2–3]*** **p=0.0007[3–5]*** **p=0.043[1–6]*** **p=0.014[1–8]***
Health care–associated IE	29 (24)	22 (29.3)	4 (15.4)		11 (29.7)	1 (25)	2 (50)	2 (100)	**p=0.033[2–8]*** **p=0.005[3–8]*** **p=0.040[5–8]***
Intravenous drug use–related IE	5 (4.1)	1 (1.3)	15 (57.7)	0	0	2 (50)	0	0	**P<0.0001[1–3]***

*ztest; †Man Whitney U test.

Demographic and Clinical Characteristics

The TV IE patients were youngest – 39 (30) years (statistically significant differences were presented in Table 1). The male gender predominated in all valvular involvements, with the highest proportion in TV IE 80.8% and AV-TV IE 100% (p=0.019) (Table 1).

Thirty days mortality was higher in MIE than in SIE (31.1% vs. 23.8%), without statistical difference (p>0.05). Mortality was significantly higher in AV-TV IE (75%), in PV IE (100%) and CDRIE (100%) (statistically significant differences were presented in Table 1).

The Charlson comorbidity index (CCI) was highest in MV IE 4 (4) and AV-MV IE 4 (3), and lowest in TV IE – 1 (5), (AV vs TV (p=0.048); MV vs TV (p=0.011). Early surgery was most often performed for CDRIE (100%) and multivalve AV-MV IE (29.7%) and statistically significantly higher compared to MV IE (13.3%) (p=0.036). Of the SIE, the most frequent early surgery was done in TV IE (23.1%).

Native IE predominated in all valvular involvements, more common in TV (80.8%), PV (100%) and AV-TV (100%). Prosthetic IE was nearly one third of all cases, most commonly in left side IE – AV (38.8%), MV (25.3%) and AV-MV (35.1%). Valvular prothesis was the most common cardiac predisposing condition, with no significant differences between types of valvular involvement. Degenerative valvular lesions were most often associated with AV IE (8.3%). Bicuspid AV occurred in 7.4% and MV prolapse in 6.7%. In about half of cases, there was no confirmed predisposing heart disease.

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The portal of entry of infection was unknown in about 50% of cases. In TV IE, the most common portal of entry was IV drug users (61.5%). The next known gateway was manipulations and procedures in all cases of SIE, in AV-MV IE and in device IE. The dental portal was a source of infection only in left-sided IE – most often in AV-MV (18.9%), followed by AV (12.4%) and MV (10.7%). Hemodialysis was a common cause of MIE (AV-TV 25%; MV-TV 25%), as well as single-valve involvement of AV and MV.

Community-acquired IE is most often in the left side IE – AV (71.9%), MV (69.3%) and AV-MV (70.3%). Healthcare-associated IE involved all valves, significantly more frequently in CDRIE (100%) and MV-TV IE (50%) ($p<0.05$). Intravenous drug-related IE most often affects TV (57.7%) and AV-TV (50%) ($p=0.0001$) (Table 1).

Charlson comorbidity index (CCI) was significantly higher in MV IE 4 (4) and AV IE 3 (3) vs TV IE 1 (5) ($p=0.048$ and $p=0.011$, respectively); and in AV-MV 3.5 (3). Arterial hypertension was the most common comorbidity in left side IE – AV (69.4%), MV (69.3%) and AV-MV IE (56.8%) vs TV IE (30.8%) ($p=0.0002$, $p=0.001$ and $p=0.041$, respectively). Coronary heart diseases were prevalent in AV IE (30.6%) vs TV (7.7%) ($p=0.016$). Hemodialysis is frequent in MIE – AV-TV (25%) and MV-TV (25%). Chronic liver diseases most often accompanied TV IE (19.2%) vs AV (5.8%) and vs MV (1.3%) ($p=0.024$ and $p=0.001$, respectively). The past IE was most common in TV (26.9%) vs AV (4.1%) and vs MV (4.0%) ($p=0.0001$ and $p=0.0008$, respectively). There were no significant statistical differences in the remaining comorbidities among various valvular involvements (Table 2).

The most common complication was acute heart failure, followed by impaired renal function, embolic events, and acute stroke, with no significant differences among valve locations. Septic shock was significantly more frequent in AV-TV involvement 75% vs AV 9.1% and vs MV (6.7%), ($p<0.0001$ and $p<0.0001$, respectively); also compared to both TV (7.7%) ($p=0.001$) and AV-MV (5.4%) ($p<0.0002$) (Table 2).

Table 2. Comorbidity and complications.

Variables	AV n=1211 n (%)	MV n=752 n (%)	TV n=263 n (%)	PV n=14 n (%)	AV + MV n=375 n (%)	AV+ TV n=46 n (%)	MV + TV n=47 n (%)	CDRIE n=28 n (%)	p-value
Comorbidity									
CCI, *median (IQR)*	3 (3)	4 (4)	1 (5)	1(-)	4 (3)	2.5 (3)	3.5 (3)	3 (-)	**p=0.048[1-3]†** **p=0.011[2-3]†**
AH	84 (69.4)	52 (69.3)	8 (30.8)	1(100)	21 (56.8)	1 (25)	3 (75)	1 (50)	**p=0.0002[1–3]*** **p=0.001[2–3]*** **p=0.041[3–5]***
CAD	37 (30.6)	17 (22.7)	2 (7.7)	0	6 (16.2)	0	1 (25)	1 (50)	**p=0.016[1–3]***
Heart surgery	48 (39.7)	25 (33.3)	9 (34.6)	0	12 (32.4)	0	1 (25)	0	p>0.05*
CHF	59 (48.8)	32 (42.7)	17 (65.4)	0	14 (37.8)	1 (25)	1 (25)	0	p>0.05*
Diabetes	22 (18.2)	17 (22.7)	3 (11.5)	0	8 (21.6)	1 (25)	0	0	p>0.05*

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Atrial fibrillation	22 (18.2)	14 (18.7)	4(15.4)	0	7 (18.9)	0	1 (25)	1 (50)	p>0.05*
Gastrointestinal	16 (13.2)	6 (8)	2 (7.7)	0	7 (18.9)	0	1 (25)	0	p>0.05*
Malignancy	11 (9.1)	10 (13.3)	2 (7.7)	0	7 (18.9)	0	0	0	p>0.05*
Systemic disease	1 (0.8)	3 (4.0)	0	0	0	0	0	0	p>0.05*
CKD	35 (28.9)	24 (32)	3 (11.5)	0	5 (13.5)	2 (50)	1 (25)	0	p>0.05*
Hemodialysis	5 (4.1)	6 (8.0)	0	0	1 (2.7)	1 (25)	1 (25)	0	**p=0.0495–6*** **p=0.0495–7***
Chronic liver disease	7 (5.8)	1 (1.3)	5 (19.2)	0	0	0	0	0	**p=0.0241–3*** **p=0.0012–3***
Past stroke	20 (16.5)	13 (17.3)	3 (11.5)	0	4 (10.8)	0	0	0	p>0.05*
Past IE	5 (4.1)	3 (4.0)	7 (26.9)	0	4 (10.8)	0	1 (25)	0	**p=0.00011–3*** **p=0.00082–3***
Complications									
AHF	57 (47)	31 (41.3)	10 (38.5)	1 (100)	13 (35.1)	2 (50)	2 (50)	1 (50)	p>0.05* **p<0.00011–6***
Septic shock	11 (9.1)	5 (6.7)	2 (7.7)	0	2 (5.4)	3 (75)	0	0	**p<0.00012–6*** **p=0.0013–6*** **p<0.00025–6***
Embolism	31 (20.7)	14 (18.7)	6 (15.4)	0	12 (32.4)	1 (25)	0	0	p>0.05*
Brain	15 (12.4)	7 (9.3)	0	0	6 (16.2)	1 (25)	0	0	p>0.05*
Lang	0	0	3 (11.5)	0	0	1(25)	1(25)	0	p>0.05*
Spleen	3 (2.5)	3 (4.0)	0	0	2 (5.4)	1(25)	1(25)	0	**p=0.0121–6*** **p=0.0121–7***
Other	5 (4.1)	3 (4.0)	1 (3.8)	0	3 (8.1)	0	0	0	p>0.05*
Worsening kidney function	54 (44.6)	28 (37.3)	11 (42.3)	0	14 (37.8)	3 (75)	1 (25)	0	p>0.05*

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Stroke	14 (11.6)	8 (10.7)	1 (3.8)	0	6 (16.2)	1 (25)	0	0	p>0.05*

*z test; †Man Whitney U test; CCI – Charlson comorbidity index; AH – Arterial hypertension; CAD – Coronary arterial diseases; CHF – Chronic heart failure; CKD – Chronic kidney disease; AHF – Acute heart failure.

Negative blood cultures were prevalent in AV IE (50.4%) compared to TV IE (23.1%) (p=0.011). Staphylococcus group was the predominant cause of IE – (TV 53.8%, MV 45.3% and AV-TV 50%). Staphylococcus aureus significantly more often affected TV (46.2%) compared to AV (9.9%) (p=0.0001) and compared to MV (22.6%) (p=0.022); Staphylococcus CNG was the considerable part of the etiology of MV IE (22.7%) compared to AV-MV (2.7%) (p=0.007); and CDRIE (50%), compared to AV-MV (2.7%) (p=0.003). Streptococci were represented in a low percentage and were the causative agent only of the left-sided IE, being significantly more frequent in AV-MV IE (18.9%) compared to AV (6.6%) (p=0.025). Enterococci were found in all valvular involvement, but most often in MIE – MV-TV (50%), AV-TV (25%), PV (100%) and CDRIE (50%) than SIE – (vs AV 7.4%, p=0.003; vs MV 6.7%, p=0.003; vs TV 7.7%, p=0.021). Enterococcus faecalis was the most widespread agent of this group. Gram-negative (non-HASEK) bacteria were the most frequent causative agent of single-valve involvement, with Escherichia coli being the most common representative (14%). Klebsiella pneumoniae affected only AV (1.7%) and MV (1.3%) (Table 3).

Table 3. Microbiological agent.

Microbiological agent	**AV** **n=1211** **n (%)**	**MV** **n=752** **n (%)**	**TV** **n=263** **n (%)**	**PV** **n=14** **n (%)**	**AV + MV** **n=375** **n (%)**	**AV+ TV** **n=46** **n (%)**	**MV + TV** **n=47** **n (%)**	**CDRIE** **n=28** **n (%)**	**p-value**
Negative blood cultures	61 (50.4)	26 (34.7)	6 (23.1)	0	13(35.1)	1 (25)	1 (25)	0	**p=0.011[1–3]***
Staphylococci	**30 (24.8)**	**34 (45.3)**	**14 (53.8)**	**0**	**7 (18.9)**	**2 (50)**	**1 (25)**	**1 (50)**	**p=0.003[1–2]*** **p=0.003[1–3]*** **p=0.006[2–5]*** **p=0.004[3–5]***
Staphylococcus aureus	14 (9.9)	17 (22.6)	12 (46.2)	0	6 (16.2)	1 (25)	1 (25)	0	**p<0.0001[1–3]*** **p=0.022[2–3]*** **p=0.009[3–5]***
Staphylococcus CoNS	16 (13.2)	17 (22.7)	2 (7.7)	0	1 (2.7)	1 (25)	0	1 (50)	**p=0.015[1–2]*** **p=0.007[2–5]*** **p=0.003[5–8]***
Streptococci	**8 (6.6)**	**6 (8.0)**	**0**	0	**7 (18.9)**	0	0	0	**p=0.025[1–5]***
Streptococcus viridans	3 (2.5)	3 (4.0)	0	0	3 (8.1)	0	0	0	p>0.05*
Streptococcus beta-hemolytic	1 (0.8)	1 (1.3)	0	0	0	0	0	0	p>0.05*
Streptococcus alfa hemolyt	2 (1.7)	1 (1.3)	0	0	3 (8.1)	0	0	0	p>0.05*
Streptococci –other	2 (1.7)	1 (1.3)	0	0	1 (12.7)	0	0	0	**p=0.004[1–5]*** **p=0.010[2–5]***
Enterococci	**9 (7.4)**	**5 (6.7)**	**2 (7.7)**	**1 (100)**	**4 (10.8)**	**1 (25)**	**2 (50)**	**1 (50)**	**p=0.003[1–7]*** **p=0.003[2–7]*** **p=0.021[3–7]***

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									p=0.035[5–7]* **p=0.028[1–8]*** **p=0.025[2–8]***
Enterococcus species	0	0	0	0	1 (2.7)	0	0	0	
Enterococcus faecalis	9 (7.4)	5 (6.7)	2 (7.7)	1 (100)	2 (5.4)	1 (25)	2 (50)	1 (100)	**p=0.003[1–7]*** **p=0.003[2–7]*** **p=0.021[3–7]*** **p=0.004[5–7]*** **p<0.0001[1–8]*** **p<0.0001[2–8]*** **p=0.0003[3–8]*** **p<0.0001[5–8]***
Enterococcus durans	0	0	0	0	1 (2.7)	0	0	0	
Gram negative (non HASEK)	**12 (9.9)**	**3 (4.0)**	**3 (11.5)**	0	**1 (2.7)**	0	0	0	p>0.05*
Pseudomonas aeruginosa	0	1 (1.3)	0	0	1 (2.7)	0	0	0	p>0.05*
Escherichia coli	6 (5.0)	1 (1.3)	2 (7.7)	0	0	0	0	0	p>0.05*
Enterobacter cloacae	1 (0.8)	0	0	0	0	0	0	0	-
Klebsiella pneumoniae	2 (1.7)	1 (1.3)	0	0	0	0	0	0	p>0.05*
Serratia marcescens	3 (2.5)	0	1 (3.8)	0	0	0	0	0	p>0.05*
Others	**1 (0.8)**	**0**	**0**	0	**3 (8.1)**	0	0	0	**p=0.013[1–5]***
Candida spp	0	0	0	0	3 (8.1)	0	0	0	-
Erysipelothix rhusiopathiae	0	1 (1.3)	0	0	0	0	0	0	-
Brevibacterium casei	1 (0.8)	0	0	0	0	0	0	0	-
Missing	0	0	1 (3.8)	0	2 (5.4)	0	0	0	-

*z-test.

Discussion

Our data presents a prevalent single valve IE, with predominant involvement of the aortic valve. The results of EURO-ENDO – 49.5% [2], Latin America – 42.4% [7] and Canada – 40% [8] are similar. The most frequent infection of MV was reported in ICI-PCS – 41% [1] , Africa – 54.7% [9] , South Korea – 61.3% [10], Japan – 42.2% [11], Turkey – 43.3% [12], Vietnam – 41.3% [13]. The distribution of affected valves is associated with the heart valve predisposition, entry door and causative microorganism. Predisposing cardiac conditions are an important part of IE pathogenesis. Their spectrum and distribution have undergone a substantial change over the last few decades, with significant differences in the geographical and socio-economic status of the countries also observed. Rheumatic heart disease (RHD) was the most common underlying lesion in the past, and the mitral valve was the most affected [14], with Streptococcus etiology. In developed countries, the proportion of cases associated with RHD has declined to 5% or less over the past two decades [1]. Nowadays the most affected valve is aortic as a result of degenerative valve disorders. [15]. However, in developing countries, RHD remains the most common predisposing risk factor for IE. For example, a meta-analysis for Africa published in 2022 reported 52% cases with predisposition of RHD [9], India

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– 19% [16], Saudi Arabia – 15% [17], and Latin America – 13% [7]. For comparison, in the International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) cases with RHD were registered to be 3% [1].

Most often IE involved tricuspid valve in India – 30.2% [16] and in a high percentage in Iran – 20.7% [18] and Canada – 15% [8], because of the widespread distribution of intravenous drug addiction. The pulmonary valve IE is a rare entity, 1-2% of all cases [19], which is in accordance with our results.

Multivalve IEs were found in 16.7% of our patients, which is similar to the findings reported by EURO-ENDO – 18.2% [2], Iran – 17% [18], South Korea – 16.7 % [10], Latin America – 13.2% [7], India – 13.2% [16]. Controversial, other countries data includes fewer cases: Japan – 6.1% [11], Turkey – 7.7% [12], Vietnam – 9.5% [20]. This difference may be due to the different level of diagnostic techniques, frequency of use of TEE and other new diagnostic modalities. In our study, TEE was performed in 35.9% of patients. The outcomes from Canada are comparable – 29.4% [8]. TEE was used more often in Japan – 73.3%[11]; Latin America – 59.6%[7] ; ICE-PCS – 59% [1]; EURO-ENDO – 58.1% [2]; Iran – 54.4% [18]. TEE was performed significantly less frequently in India – 18.1% [16]. Insufficient data exists regarding the distribution of MIE. We found the most frequent involvement of AV-MV and with the worst prognosis were AV-TV IE.

The age of patients with IE increased over the past decades and our results is like the EURO-ENDO registry – mean age 59.25±18.03 years (46.3% > 65 years and 12.0% ≥ 80 years) and was higher in European than in non-European countries (60.97±17.36 vs. 52.66±19.01, $p<0.0001$) [2]. The data from other economically developed countries currently exhibit similarities: France – 69 years [21], Japan – 69.1 years [11], Canada – 56 years [8], Spain – 61.8 years [22] , Portugal – 47.1% between 60 and 79 years old [23], Netherlands – 67.5 years [24], South Korea – 56 years [10]. Only the patients with tricuspid valve IE were significantly younger, as a results of drugs abuses. Male gender remains the predominant gender. This has not changed over the years. We found predominant male in TV IE due to I.V. drugs users.

Prosthetic valve is the prevalent cardiac predisposition, nearly one third of all cases, without significant difference according to the valve location. These results are consistent with those of European and other economically developed countries and suggest an increase in prosthetic valves IE (PVIE) cases. In comparison, cases with PVIE in ICE-PCS was 21% [1]; France – 25% [21]; Euro Heart Survey – 26% [25]; EURO-ENDO – 30% [2].

We found higher 30 days mortality in multi-valves IE versus single valves IE, without significant difference. Kim and all also reported higher 30 days mortality in MIE [3]. Only in AV-TV and CDRIE, our results revealed significant differences, despite the small number of patients in these groups. We found no difference in complication rates according to the valve involvement, except the septic shock. The significantly higher rate of septic shock in TV-AV correlates with higher mortality in this group. The septic shock is associated with high mortality in IE [26,27]. We did not register 30 days mortality regarding different tape of MIE.

CCI is higher in the left side IE, due to high age, most common arterial hypertension and coronary heart disease, and extensive contact with the health care system. Hemodialysis is a predominant comorbidity and predisposition in MIE – AV-TV and MV-TV, with mostly staphylococcus and enterococcus etiology, because of health care acquired IE [28]. The chronic liver disease is most common in TV IE, due to I.V. drugs users with hepatitis C. Hepatitis C virus infection is frequent (36–82%) among these patients [29].

The entry door of infection is related to the affected valves, causative microorganisms, and tape of acquisition. In half of all cases the portal of entry is unknown. The portal of entry was dental only in left side IE, in low frequency – AV, MV and AV-MV, most often with streptococcal etiology and community acquired IE. The streptococcal etiology decreased over the past decades and this study produced results which corroborate the findings of a great deal of the previous work in this field EURO-ECHO registry. The most common causative agent was Staphylococcus group. Staphylococcus aureus affected more often TV alone, Staphylococcus coagulase negative (CNG) was the prevalent cause of MV IE. Manipulations and procedures are presented as a portal of entry in all

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tapes of valve involvement and are predisposition for health care associated IE. This type of IE presented with the most common staphylococcal etiology and the increasing proportion of enterococcus bacteria as a causative agent [30].

Conclusion

In patients with IE in our region the most affected valve is aortic, either as a single or multivalve location, in older patients, with high CCI, and with mostly staphylococcus or enterococcus etiology. The multivalve aorto-tricuspid IE has the worst prognosis, with a significantly high rate of septic shock and highest in-hospital mortality. Knowing the specificities of IE according to the affected valve would help in more accurate selection of initial empiric antibiotic treatment. More aggressive therapeutic behavior and the decision for early surgical treatment in poor prognostic features would improve the prognosis of patients.

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