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Frequency of clinical symptoms and para-clinical finding in patients with infective endocarditis

Manizheh Jozpanahi [1], Mehrnoush Rahnama [2], Ahmadreza Mobaien [1], Afsaneh Karami [1*]and Nooshin Jalili [3]

[1]Department of Infectious Diseases, Zanjan University of Medical Sciences, Zanjan, **Iran**
[2]MD, Zanjan University of Medical Sciences, Zanjan, **Iran**
[3]Pulmonologist, Department of Internal Medicine, Zanjan University of Medical Sciences, Zanjan, **Iran**

***Correspondence:** dr.akarami@yahoo.com **Received 09-11-2022, Revised: 30-12-2022, Accepted: 31-12-202 e-Published: 31-12-2022**

Infective endocarditis is one of the important causes of mortality and morbidity and is one of the important diseases that is diagnosed acutely or subacutely based on clinical manifestations, duration of illness and laboratory tests. Therefore, the aim of this study was to investigate the frequency of clinical and paraclinical symptoms in patients diagnosed with infective endocarditis. This descriptive study was performed on patients diagnosed with endocarditis admitted to the infectious department of the hospital. According to their history, clinical symptoms, tests and imaging findings, they were recorded in the relevant checklists. Information such as primary clinical symptoms at the time of visit (fever and skin and endovascular lesions) as well as aggressive and non-invasive paraclinical findings such as transthoracic echocardiography and valvular involvement or vegetation were recorded. In addition, laboratory findings such as blood culture, ESR and CRP levels, underlying diseases, demographic characteristics, disease course and response to treatment were recorded. Data analysis was done using SPSS version 22 software and descriptive statistics. A significance level of 0.05 was considered. A total of 45 patients were included in the study, 30 patients (66.7%) were male and 15 patients (33.3%) were female. The average age of the patients was 42.77 ± 18.98 years from a minimum of 13 to a maximum of 90 years. Also, the average duration of the onset of symptoms was 3.62 ± 2.19 days from a minimum of 0.14 to a maximum of 21.43 days. The number of systemic diseases showed 7 people (15.6 %) had IHD, followed by CVA (6.7%, 1 cases), and Parkinson's disease (2.2%, 1 cases). The frequency distribution of clinical symptoms showed that, out of 45 patients, 10 patients (22.2%) had weakness, followed by fever (71.1%, 32 cases), endovascular phenomenon (6.7%, 3 cases) (linear bleeding of nails, conjunctiva, clubbing and heart murmur) and mediastinal abscess (2.2%, 1 cases), while the rest of the patients were normal. Contrary to most studies that Staphylococcus aureus was the main bacteria found in blood culture, the microbial agent of blood culture was determined to be streptococcus. Considering the sub-acute nature of the disease, the main cause of which is streptococcus, the results of our study are consistent with reliable scientific sources. In addition, the high percentage of negative blood culture in the present study was consistent with the studies conducted in Asian and African countries.

Keywords: Infective endocarditis, clinical symptoms, para-clinical symptoms, hospitalized patients.

INTRODUCTION

Infective Endocarditis (IE) is an infection of the endocardial surface of the heart, by which one or more heart valves are affected (Thuny et al.2014). The existence of cardiovascular diseases, congenital heart diseases, artificial valves and previous episodes are some of the known risk factors of endocarditis. However, predisposing factors such as intracardiac devices, use of intravenous drugs, HIV virus, diabetes, hemodialysis, degenerative heart valve diseases and dental infections are some of the factors that have been mentioned more than other risk factors (Nunes et al.2018,Abdulhak et al.2014).

Clinical suspicion of IE is often delayed because early clinical signs are not properly evaluated and it presents as a subacute illness with symptoms such as fever and malaise that are not consistent with serious illness. Infective endocarditis can mimic the symptoms of many diseases, and its rapid diagnosis remains a major problem in terms of in-hospital morbidity and puts patients at risk of short-term outcomes (Hoen et al.2013). Delay in antibiotic treatment and inappropriate antibiotics in cases of suspected infective endocarditis have a negative effect on clinical outcomes in the acute phase (Holland et al.2016).

Despite advances in medical knowledge, technology, and antimicrobial therapy, infective endocarditis is still associated with devastating outcomes and has become a major problem where at least one in four people with

infective endocarditis usually die (Abdulhak et al.2014). Despite recent surgical treatments, the mortality rate of this disease in 1 and 5 years has been estimated at 40 and 70% (Juneau et al.2018). The most micro- organism involved in the pathology of this disease is Staphylococcus aureus, and it is also more associated with embolism and mortality (Selton-Suty et al.2012). In-hospital mortality (22%) and 5-year mortality (45%) in cases of infective endocarditis were significantly associated with higher mortality. Overall, it caused 48,300 deaths worldwide in 2010 (Abegaz et al.2017.Cancan et al.2016 and N'Guyen et al.2017). Among the common symptoms are fever and temperature above 38 degrees, Splinter Hemorrhage, Osler's nodes, Janeway lesions and Roth spots, thromboembolic events, Hepatosplenomegaly and increase of markers such as ESR, CRP, and rheumatoid factor (Vogkou et al.2016).

Diagnosis of endocarditis is based on Duke criteria (Pazdernik et al.2016), so knowing the frequency, amount of clinical symptoms of patients as well as their para-clinical symptoms can help in early diagnosis of the disease, appropriate treatment of the disease and prevention of its long-term and short-term complications in order to reduce mortality and morbidity. It can also assist in guessing the pathogen involved in endocarditis. Considering the relatively long course of the disease and the high possibility of its being missed, paying attention to the results of this study can help in diagnosis. Therefore, the aim of this study is to determine the frequency of clinical and para-clinical symptoms in hospitalized patients diagnosed with IE.

MATERIALS AND METHODS

This descriptive study was conducted on patients diagnosed with endocarditis admitted to the infectious department of valiasr Hospital in Zanjan-Iran during 10 years (2009-2019). Patients who met the inclusion and exclusion criteria were included in the study. Inclusion criteria included all hospitalized patients with a final diagnosis of infective endocarditis. Exclusion criteria included lack of informed consent.

Sample size

The sampling method was census and 45 patients were included in the study.

Procedure

During the years 2009-2019, the medical records of patients with the diagnosis of endocarditis were examined, and their history, clinical symptoms, tests and imaging findings were recorded and analyzed in the relevant checklists. Information such as initial clinical symptoms at the time of visit, such as fever and chills, skin lesions were entered into the checklist. Furthermore, invasive and non-invasive para-clinical cases such as thoracic echocardiography and esophageal echocardiography and valve involvement or vegetation, laboratory findings such as consecutive blood cultures and ESR, CRP levels, as well as underlying diseases, demographic characteristics, disease course, and response to treatment were all included in the desired checklists.

Data analysis

Quantitative variables were described using central and dispersion indices (mean, standard deviation). Qualitative data description was reported using frequency percentage as a frequency distribution table. Data analysis was done using SPSS version 22 software and descriptive statistics. A significance level of 0.05 was also considered.

Ethical considerations

The information of all patients was kept confidential. This research was conducted in accordance with relevant guidelines and regulations in the ethics research committees of the University of Medical Sciences and Declaration of Helsinki. Ethical approval was obtained from the Research Council of the Faculty of Medicine by receiving the code of ethics (IR.ZUMS.REC.1398.386).

RESULTS

A total of 45 patients were included in the study, among which 30 patients (66.7%) were male and 15 patients (33.3%) were female. The average age of the patients was 42.77 ± 18.98 years from a minimum of 13 to a maximum of 90 years. Furthermore, the average duration of the onset of symptoms was 3.62 ± 2.19 days from a minimum of 0.14 to a maximum of 21.43 days.

The frequency distribution of systemic diseases is shown in Table 1. In terms of systemic diseases, 7 people (15.6%) showed IHD, followed by CVA (3 people, 6.7%) and Parkinson's (1 person, 2.2%)

Table 1: Frequency distribution of systemic diseases

systemic diseases	No	Yes
	Frequency	**Frequency**
IHD	38 (84.4%)	7 (15.6%)
AF	42 (93.3%)	3 (6.7%)
CVA	42 (93.3%)	3 (6.7%)
HTN	44 (97.8%)	1 (2.2%)
Parkinson	44 (97.8%)	1 (2.2%)
Cancer	42 (93.3%)	3 (6.7%)
Unknown panceraticmass	44 (97.8%)	1 (2.2%)

The frequency distribution of clinical symptoms in the patients showed that, out of a total of 45 patients, 10 patients (22.2%) had weakness, 32 patients (71.1%) had fever, 3 patients (6.7%) had endovascular phenomenon (linear bleeding of the nail, conjunctiva, clubbing and heart murmur) and 1 patient (2.2%) had a mediastinal abscess and the rest of the patients were reported to be normal.

In Table 2, the frequency distribution of some blood indicators in the studied patients was examined and the results showed that 18 patients had WBC more than 10

microliters, 31 patients had Hb less than 12g/dl, 2 patients had ESR more than (mm/ hr) 100 and 2 people had PLT more than 450 µL.

Table 2: Frequency distribution of blood indices

Available		Frequency
WBC	4<	3 (6.7%)
	4-10	24 (53.3%)
	10>	18 (40%)
HB	12<	31 (68.9%)
	12>	14 (31.1%)
ESR	20<	25 (55.6%)
	20-100	18 (40%)
	100>	2 (4.4%)
PLT	150<	16 (35.6%)
	150-450	27 (60%)
	450>	2 (4.4%)

Laboratory findings of blood and urine in the studied patients showed that 1 out of 5 tested samples (20%) was FANA positive. Furthermore, out of 27 samples, 7 samples (26%) were positive for Hematuri. In the case of brucellosis, 3 samples (20%) out of 15 examined samples were also positive. In addition, Out of 5 tested samples, 1 sample (20%) was positive for RF. Additionally, in terms of blood culture, out of 18 tested samples, 3 samples (16.66%) were positive (Table 3).

Table 3: Frequency of laboratory results of some blood and urine indicators

Tested indicators	**Not requested**	Negative	Positive
	Frequency	**Frequency**	**Frequency**
FANA	40 (88.9%)	4 (8.9%)	1 (2.2%)
RF	40 (88.9%)	4 (8.9%)	1 (2.2%)
Hematuria	18 (40%)	20 (44.4%)	7 (15.6%)
Proteinuria	19 (42.2%)	25 (55.6%)	1 (2.2%)
Brocelose	30 (66.7%)	12 (26.6%)	3 (6.7%)
Urine culture	28 (62.2%)	17 (37.8%)	0 (0%)
Blood culture	27 (60%)	15 (33.3%)	3 (6.7%)

The frequency of risk factors investigated in patients showed that 38 injection drug addicts (84.4%) had artificial valves. Also, 43 patients (95.6%) had dental procedures and 42 patients (93.3%) had previous endocarditis, while the rest were normal.

The frequency distribution of echo findings and its location showed that 27 people (60%) had vegetation and 8 people (17.8%) had MVR. The vegetation of mitral was found in 17.8% (8 cases), followed by Aorta (8.9%, 4 cases) and tricuspid (6.7%, 3 cases). In addition, 4 out of 27 patients who had vegetation (14.8%) had mitral valve replacement (MVR). There were 3 cases of transesophageal echocardiography, 3 of which had reported vegetations. The diagnosis of endocarditis in these patients was confirmed by minor findings and blood culture.

Blood cultures of male patients were positive for streptococcus in 2 out of 10 tests. Among women, 1 out of 8 tests were positive. Of the 18 samples tested in men, one case was positive for proteinuria (++), while 8 samples of women did not show proteinuria (Table 4).

Table 4: Frequency of urine and blood culture results in patients according to gender

Gender / **urine and blood culture**		Male	Female
		Frequency	**Frequency**
Blood culture	Not requested	20 (66.6%)	7 (46.6%)
	Negative	8 (26.7%)	7 (46.6%)
	streptococcus	2 (6.7%)	1 (6.7%)
Proteinuria	Not requested	12 (40%)	7 (46.6%)
	Negative	17 (56.7%)	8 (53.3%)
	2 PLUS	1 (3.3%)	0 (0%)
Urine culture	Not requested	19 (63.3%)	9 (60%)
	Negative	11 (36.7%)	6 (40%)

The results of blood culture in the age group of 25 to 65 years showed that 2 out of 3 cases of positive blood culture belonged to this age group, while the age group below 25 years did not show any cases. Regarding proteinuria, only 1 positive case was observed, which belonged to the age group of 25 to 65 years. The rate of weakness and lethargy in the group with the onset of symptoms less than three weeks was recorded at 25.7%, while no case was observed in the group with the onset of symptoms 3-6 weeks. 85.7% of the group with symptom onset time of 3-6 weeks showed fever, and this was 100% in the group of more than 6 weeks.

Table 5 shows the distribution of the frequency of systemic diseases in the studied patients. The blood culture results showed 2 positive cases in the group with the onset of symptoms less than three weeks, while 1 case was observed in the group with the onset of symptoms 3-6 weeks. Moreover, only 1 positive case of proteinuria was seen, which belonged to the group with the onset of symptoms under three weeks.

Table 5: Frequency distribution of systemic diseases in patients

Time of onset of symptoms	**3<**	**3-6**	**6>**

(weeks) / urine and blood culture		Frequency	Frequency	Frequency
Blood Culture	Not requested	21 (60%)	4 (57.1%)	2 (66.7%)
	Negative	12 (34.3%)	2 (28.6%)	1 (33.3%)
	streptococcus	2 (5.7%)	1 (14.3%)	0 (0%)
Proteinuria	Not requested	15 (42.9%)	2 (28.6%)	2 (66.75)
	Negative	19 (54.3)	5 (71.4%)	1 (33.3%)
	2 PLUS	1 (2.9%)	0 (0%)	0 (0%)
Urine Culture	Not requested	22 (62.9%)	4 (57.1%)	2 (66.7%)
	Negative	13 (37.1%)	3 (42.9%)	1 (33.3%)

DISCUSSION

IE is one of the important causes of mortality and morbidity and is one of the important diseases that is diagnosed acutely or subacutely based on clinical manifestations, duration of illness and laboratory tests (Weli, et al.2020). Therefore, the aim of this study is to investigate the frequency of clinical and para-clinical symptoms in patients diagnosed with IE.

The findings of the present study showed that the average age of the patients was 42.77 ± 18.98 years. In the study conducted by (Motaghi et al.2015), at the Rajaee Heart Center and Imam Khomeini Hospital in Tehran, the average age of the patients was 42.9 ± 16.8 years. Jingushi et al.'s study was conducted over 10 years on 42 patients with clinical manifestations of IE, the average age was 27.5 years (Jingushi et al. 2017). In two studies conducted in Africa, the average age of patients was 30.6 and 32.6 years, respectively (Nebie et al. 2008 Ikama et al.2013), which was lower compared to this study. While in a study conducted in Europe, patients with IE were usually older and their average age was around 60 years (Tamirat et al.2015), which was higher than the present study.

The difference in the average age in these continents can be explained to the health care situation, better care and medical services in Europe compared to Asia and the better situation of Asia compared to Africa. In addition, genetic factors, compliance with personal hygiene and oral hygiene are also very important in this matter. On the other hand, the age of endocarditis is increasing because less cases of rheumatic fever have been observed in developed countries than in developing countries (Carinci et al.2018).

Also, in the present study, 30 patients (66.7%) were male and 15 patients (33.3%) were female, and it showed that the number of male patients was twice as high as female patients. In Moghadam's study (Motaghi et al.2015), 51.7% of patients were men and 48.3% were women. In another study in Iran, 66.21% were men and 33.79% were women (Ryahian et al.2014). Other studies have shown that in African countries, the prevalence of IE is usually higher in women than in men. The studies conducted regarding the cause of this phenomenon have considered it to be related to the higher prevalence of rheumatic fever in women in this continent (Ikama et al.2013). While in Europe and America, men were affected more than women with a gender ratio up to 2 times (Habib et al.2009), which was largely similar to the results of the present study. This difference can be related to more care and prevention by women than men in some Asian and European countries. Other results of this study showed that 22.2% of patients had physical weakness and 71.1% had fever. In other studies, fever was usually high. In Bashart et al.'s study, 79% of patients had fever (Bashart et al.2011) and in Jingushi et al.'s study (Jingushi et al. 2017), 90% of IE patients had fever, which was seen in a number of other studies (Letaief et al.2007 and Day et al.2009). Also, Ryahian et al found that the most common reason for referral was fever with a ratio of 80% (Ryahian et al.2014). These findings show the agreement of this study regarding fever with other studies.

Regarding the microbial agent in the current study, out of the 18 samples that were requested to be cultured, 3 positive cases were seen, all of which were streptococcus. While in the study of (Jingushi et al. 2017), the main microbial agent was *Staphylococcus aureus*, as *Staphylococcus aureus* was observed in 50% of cases, followed by *Enterococcus faecalis* and *Klebsiella Pneumoniae* in 25% of positive cases.

The greater role of Staphylococcus aureus in blood culture positivity has been observed in a number of other studies (Yaméogo et al.2015 and Maharaj et al.2012). In Heydari et al.'s study (27), Staphylococcus aureus played the most important role, followed by *Staphylococcus Epidermidis* and *Streptococcus*. In another study conducted by Pazdernik et al regarding the clinical symptoms related to the etiological factor of IE, they concluded that episodes of endocarditis caused by *Staphylococcus aureus* were associated with an increase in short-term and long-term mortality (Pazdernik et al.2016). These findings show that Staphylococcus aureus was the main cause of positive blood cultures and deaths in IE patients. As mentioned in the findings of this study, streptococcus was the known microbial agent in microbial culture, which is acceptable considering the sub-acuteness of the disease.

Another finding of this study showed that 2 patients had recent dental procedures. Studies have been conducted on the impact of dental interventions and oral

and dental infections with IE. Jingushi et al.'s study (Jingushi et al. 2017) showed that tooth decay was seen in 26.2% of these patients. In Nakatani et al.'s research, 18% of patients with endocarditis had recently undergone dental procedures (Nakatani et al.2003). Furthermore, Moghadam et al. (Motaghi et al.2015) reported that 16.7% of patients had undergone dental procedures requiring antibiotic prophylaxis in the last 6 months, which indicates that dental interventions can be a factor in IE. In the study of Olaya-Sánchez et al. 35.2% of IE patients had undergone invasive medical procedures in the last three months, including dental interventions (Olaya-Sánchez et al.2019). Other results of the present study showed that 3 patients (6.7%) had previous endocarditis and 7 patients (15.6%) had artificial valves. In Ryahian et al.'s study, 42.4% of patients had a history of mitral valve replacement (Ryahian et al.2014). In Swart et al.'s study (30), 14.3% of patients previously had endocarditis and 9.5% of patients had artificial valves. In a study, it was mentioned that endocarditis with artificial valve accounted for about 7-25% of IE cases in most developed countries. However, probably the increasing availability of medical facilities and the increasing number of heart valve replacements may indicate the proportion and importance of artificial valves in the development of IE in the near future. The percentage of artificial valve use in different studies varies according to the characteristics of the patients, including age, sex, access to healthcare services, stage of disease diagnosis and *Staphylococcus aureus* positivity (Sucu et al.2010). Another result of the current study was the echocardiography findings that 60% had vegetation and 17.8% had MVR. Regarding the location of vegetation, 17.8% was in the mitral valve, 8.9% in the aorta, and 6.7% in the tricospid. Also, out of 5 tested samples, one person was positive for rheumatic factor. In Ryahian et al.'s study, the share of tricuspid valve involvement was 67.5% (Ryahian et al.2014). In another study conducted on patients under 18 years of age by Motaghi Moghadam et al., 90% of patients had vegetation (Ryahian et al.2014). In Swart et al.'s study (Swart et al.2018), mitral and aortic valves were the most common sites involved in 23 and 8 patients, respectively. Also, 2.5% had tricuspid valve endocarditis and 2.5% had bicuspid valve. Also, 64.3% of patients were affected by rheumatic valve disease. In most studies conducted in Africa on the occurrence of IE, rheumatic valve is the predominant underlying disease (Ikama et al.2013). Currently, in high-income countries, patients with valvular heart disease and patients with congenital heart disease account for more cases of IE than patients with rheumatic heart disease due to the use of nonstandard implantable devices and the Illegal use of intravenous drugs (Habib et al.2009 and Elbey et al.2013).

Echocardiography is very important in the evaluation process of IE. In Swart's study (Swart et al.2018), vegetation was observed in 95.2% of cases. This percentage was close to that found in Africa and Japan (Yaméogo et al.2015 and Ikama et al.2013). In many studies in Africa (Ikama et al.2013), the mitral valve was the most affected site (57.5%), while some studies also considered the aortic valve as the most affected organ (Sucu et al.2010). Also, among the 18 patients who did not have vegetations and whose thoracic echocardiography was negative, the diagnosis of endocarditis was confirmed by examining minor findings, blood culture and other related symptoms by an infectious specialist.

CONCLUSION

The microbial agent in the blood culture was determined to be Streptococcus, which contradicted most similar studies in which Staphylococcus aureus was the main bacterium in the positive blood culture. Considering the sub-acute nature of the disease, the main cause of which is streptococcus, the results of our study are consistent with reliable scientific sources. In addition, the high percentage of negative blood culture in the present study was consistent with the studies conducted in Asian and African countries. It is recommended that tests such as blood culture be performed before starting antibiotic therapy, and in patients who are more suspected of endocarditis, it must be done three times and double the blood volume compared to the usual blood cultures.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

AUTHOR CONTRIBUTIONS

MJ and AK designed and performleed the experiments and also wrote the manuscript. MR and AM Data collections and analysis. NJ designed experiments and reviewed the manuscript. All authors read and approved the final version.

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