An epidemiological study to define the recent clinical characteristics and outcomes of infective endocarditis in southern Turkey

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Abstract

Introduction: The aim of this study was to characterise the recent features of patients with infective endocarditis (IE) at one referral centre in southern Turkey, in order to be able to identify the high-risk subgroup and revise preventative measures and management strategies.

Methods: Medical records of patients 18 years and older, who had been diagnosed with IE according to the Duke criteria between January 2009 and October 2019, were retrospectively evaluated in a referral general hospital.

Results: The total of 139 IE cases comprised 59.7% males and 40.3% females, with a mean age of 55 ± 16 years. The most encountered symptom was fever (55.4%) and the mitral valve (54%) was the most frequently involved. The most common causative micro-organisms were coagulase-negative staphylococci (30.2%). The in-hospital mortality rate was 30.2%, with congestive heart failure, chronic renal disease and chronic dialysis found to be significantly associated with in-hospital mortality.

Conclusion: The study results demonstrate the recent epidemiological features of IE in southern Turkey that are important for clinicians to manage diagnostic and therapeutic processes successfully. Older age, the predominance of staphylococci and higher surgery rates are consistent with the changing trends of IE in some parts the world.

Keywords: infective endocarditis, epidemiology, dialysis, mortality

Submitted 10/5/20, accepted 21/3/21
Published online 7/4/21
Cardiovasc J Afr 2021; **32**: 188–192 www.cvja.co.za

DOI: 10.5830/CVJA-2021-009

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Infective endocarditis (IE) is an uncommon disease with an annual incidence of three to 10 per 100 000 people, but it remains a serious health problem, causing lengthy hospitalisation with high costs.[1]

Recently there have been some changes in the epidemiology of IE worldwide, with *Staphylococcus aureus* and coagulase-negative staphylococci replacing streptococci as the causative micro-organisms.[2] When the underlying predisposing factors were reviewed, a decrease was seen in the prevalence of rheumatic heart disease (RHD), and an increase in prosthetic heart material, intravenous catheters and immunosupression. IE patients tend to be older now than they were previously.[3] The epidemiology of IE also shows regional variation.

IE has a high mortality rate,[4] possibly because of late or missed diagnosis. Therefore, physicians should be fully aware of recent trends and developments for early diagnosis and optimal management of patients with IE.

This retrospective study was conducted to define recent trends in the epidemiology of IE over a 10-year period at a tertiary-care centre, which is a referral hospital in southern Turkey, and to evaluate clinical outcomes. We aim to guide clinicians in defining the high-risk population and choosing the right empirical antibiotic therapy.

Methods

Medical records of a referral general hospital were scanned to identify patients diagnosed with IE between January 2009 and October 2019. Modified Duke criteria were used to define IE, and definite IE cases were enrolled into the study.[5] The data of 139 IE patients, whose management was completed in our hospital, were included in this research. Patients who were under the age of 18 years or who left the hospital before treatment was completed were excluded from the study.

Basal characteristics (gender, age), symptoms on admission, echocardiographic features (structural heart disease, prosthetic heart valve), laboratory and microbiological examinations (culture results), co-morbidities (hypertension, chronic dialysis, diabetes mellitus), predisposing factors (invasive procedures, intravascular catheters), surgery and mortality outcomes were recorded. Echocardiographic examinations were also screened to identify the valve involved and vegetation size. Possible complications of IE were analysed from clinical course records, and embolic complications were determined from radiological studies.

Approval for the study was granted by the Institutional Ethics Committee (approval code: 43867).

Statistical analysis

Data obtained in the study were analysed statistically using SPSS for Windows version 21.0 (SPSS Inc, Chicago, IL, USA) software.

Table 1. Baseline clinical characteristics of the patients

Variables	*Number (%)*
Gender, female	56 (40.3)
Hypertension	57 (41)
Diabetes mellitus	46 (33.1)
Ejection fraction < 55%	29 (20.9)
Chronic kidney disease	45 (32.4)
Immunosupression	5 (3.6)
Chronic dialysis	33 (23.7)
Active smoking	11 (7.9)
Pacemaker	10 (7.2)
Central venous catheter	23 (16.5)
Prior history of endocarditis	1 (0.7)
Intravascular drug abuse	1 (0.7)

Conformity of the data to normal distribution was assessed with the Kolmogorov–Smirnov test. Continuous data are presented as mean ± standard deviation (SD) or median [range, interquartile range (IQR)], and categorical data as number (*n*) and percentage. Categorical parameters were analysed with the chi-squared test, and continuous variables with a normal distribution with the unpaired *t*-test. The Mann–Whitney *U*-test was applied to continuous variables with a non-normal distribution. Multiple linear regression analysis was applied to determine independent determinants of mortality. A value of $p < 0.05$ was accepted as statistically significant.

Results

This retrospective epidemiological research on IE was conducted in a regional referral hospital. Evaluation was made of a total of 139 patients with IE, comprising 59.7% males and 40.3% females, with a mean age of 55 ± 16 years. The basal clinical characteristics of the subjects and predisposing conditions for IE are presented in Tables 1 and 2, respectively.

The primary symptom was fever in 77 (55.4%) patients, coagulase-negative staphylococci (30.2%) were the most frequent causative agents, and the mitral valve was the most commonly affected site (54%) in the study population. The frequency of IE-related symptoms and the site of endocarditis are listed in Table 3, and the causative micro-organisms are presented in Table 4. The median time between hospital admission and diagnosis was three (five) days.

Table 2. Predisposing risk factors of the patients

Underlying heart disease	*Number (%)*
Intracardiac prosthetic material	35 (25.2)
Prosthetic mitral valve	22 (15.8)
Prosthetic aortic valve	9 (6.5)
Prosthetic tricuspid valve	1 (0.7)
Valvular ring	2 (1.4)
Left ventricular assist device	1 (0.7)
Rheumatic valvular disease	5 (3.6)
Rheumatic mitral stenosis	3 (2.2)
Rheumatic mitral regurgitation	2 (1.4)
Mitral valve prolapse	4 (2.9)
Bicuspid aortic valve	7 (5)
Atrial or ventricular septal defect	7 (5)
Hypertrophic cardiomyopathy	4 (2.9)
Other	3 (2.1)
History of invasive procedure	
Percutaneous angiographic procedure	7 (5)
Catheter insertion	6 (4.3)
Valve replacement	3 (2.2)
Dental procedure	3 (2.2)
Endoscopy	2 (1.4)

Table 3. Clinical presentations and site of endocarditis in the study population

Clinical presentation	*Number (%)*
Fever	77 (55.4)
Shortness of breath	11 (7.9)
Weakness	16 (11.5)
Cerebral embolism	10 (7.2)
Back pain	5 (3.6)
Cough	3 (2.2)
Nausea, vomiting	3 (2.2)
Vegetation site	
Mitral	75 (54)
Aortic	36 (25.9)
Tricuspid	11 (7.9)
Pacemaker	3 (2.2)
Catheter tip	2 (1.4)
Pulmonary	1 (0.7)

Transthoracic echocardiography (TTE) displayed a vegetation or related formation (abscess, fistula, dehiscence) in 64.7% of the patients, and this rate increased to 99.3% with the use of transoesophageal echocardiography (TEE). In 44 patients (31.6%) a vegetation was determined on TEE and not on TTE. Echocardiographic examinations displayed moderate to severe mitral regurgitation in 63 patients (45.3%), aortic regurgitation in 40 (28.7%) and tricuspid regurgitation in 33 patients (23.7%).

The surgical treatment ratio was 65.5% in this study population. The most common reason for surgery was persistent infection (28.1%), and the median time between diagnosis and referral for surgery was seven (18) days. Systemic embolism (39.6%) was the most frequent complication encountered during the entire follow-up period in these patients with IE. Other common complications and reasons for surgery are listed in Table 5.

In-hospital mortality was seen in 42 patients (30.2%) with a diagnosis of IE. In logistic regression analyses, chronic renal disease, congestive heart failure and chronic dialysis were found to be associated with an increased mortality risk. A statistically significant correlation was determined between mortality and high C-reactive protein (CRP) and high creatinine levels. The association of mortality with selected variables is shown in Table 6.

Table 4. Micro-organisms isolated from blood cultures in the study

Micro-organisms	*Number (%)*
Coagulase-negative staphylococcus	42 (30.2)
Staphylococcus aureus	22 (15.8)
Viridans streptococcus	4 (2.9)
Streptococcus bovis	1 (0.7)
Other streptococci	15 (10.8)
Enterococci	9 (6.5)
Brucella species	5 (3.6)
Pseudomonas aeruginosa	1 (0.7)
Fungal	1 (0.7)
Culture negative	30 (21.6)

Discussion

In this study, the findings of 139 patients with IE were evaluated to determine recent epidemiological features in southern Turkey during a 10-year period. Compared with previous studies from Turkey, a shift can be seen over the years in terms of patient age, predisposing factors and causative micro-organisms.[6-9]

Consistent with recent trends in IE epidemiology, the median age of our study patients was higher compared with older data.[3,10] The mean age (55 ± 16 years) of this study population is the highest ever reported for IE in Turkey, although it remains below the mean age in European countries.[6-9,11,12] The older age of the IE population can be explained by a decrease in incidence of RHD, an increase in incidence of valvular degenerative disease due to longer life expectancy, and a larger number of patients with intracardiac prosthetic material.

The average diagnosis time of three (five) days was extremely short compared with a previous case series, where a period of 18 days (range, 1–30 days) was reported.[13] This indicates an improved IE diagnostic process.

Supporting previous data, fever was the most frequent symptom in the current study, detected in more than half of the patients.[6-9,14] Conflicting with medical teaching, Roth spots were detected in only one patient and membranoproliferative glomerulonephritis in one patient. However, in 2006, Leblebicioglu *et al.* reported a 50% incidence rate of immunological phenomenona.[11] The low rates in our series may have been due to prompt diagnosis of IE before the emergence of immunological signs.

Diagnostic imaging for IE should begin with TTE. However, in the case of intracardiac devices or prostheses, or unclear results with high clinical suspicion of IE, TEE should be performed. Moreover, even if the diagnosis is clear on TTE, TEE should also be applied to investigate complications such as abscess.[15]

While in the current study, TTE examinations had a sensitivity of 64.7%, which is lower than expected (75%), TEE examinations were more sensitive, supporting the findings of previous studies.[16] This high rate of sensitivity of TEE cannot be attributed to only the presence of prosthetic heart valves in one-third of the study population because 20 of 44 patients who showed a vegetation on TEE and not on TTE had prosthetic heart material. It must be kept in mind that TEE should be the modality of choice in cases with prosthetic heart valves, intracardiac devices, or if there are complications such as a fistula, abscess or leaflet perforation.

Table 5. Complications of IE and indications for surgery

Complications	*Number (%)*
Systemic embolism	
Brain	30 (21.6)
Spleen	22 (15.8)
Lungs	6 (4.3)
Renal	5 (3.5)
Multiple locations	8 (5.7)
Acute renal failure	11 (7.9)
Heart failure	31 (22.3)
Spondylodiscitis	10 (7.2)
Heart block	0
Cause of surgery	
Persistent infection	39 (28.1)
Valvular dysfunction with heart failure	32 (23)
Recurrent embolism on antibiotic therapy	13 (9.4)
Paravalvular invasion or abscess	7 (5)

RHD-related endocarditis was very rare in this study population, with an incidence of 3.5%, which is lower compared to previous reports from Turkey.[7-9,11,17] Elbey *et al.* reported RHD as the most common underlying heart disease, with a prevalence of 28%, in a study from 2005 to 2012 in 13 tertiary-care centres.[7] In a study by Yavuz *et al.* published in 2015, covering the previous 14 years, patients with RHD comprised 33.9% of the IE population.[9] Due to the successful treatment of streptococcal tonsillitis, there has been a decrease in patients with RHD over the years.

Culture-negative endocarditis was seen in this study at the rate of 21.6%, which is in the expected range of 20.6 to 36.1% in Turkey, and five to 34% worldwide.[3,6-8,18] Culture-negative endocarditis could have been a result of previous antibiotic therapy because 17 (12.2%) patients had been referred to our hospital from other peripheral centres where empirical antibiotic therapy had possibly been given.

It was confirmed in this study that staphylococci seem to have replaced streptococci as the major cause of IE. This could be attributed to the fact that the incidence of dialysis and other intravascular access is increasing, and the number of patients with RHD is decreasing throughout the world.[3,19-21]

In the current series, the surgery rate (65.5%) is higher than previously reported (40–50%).[22] It is also higher than rates (27.8–60%) in previous reports from Turkey.[6-8] This may be a result of the study being done in a tertiary referral centre and the high incidence of prosthetic valve endocarditis in the study population.

Unlike recent data, the most common indication for surgery in the current study population was persistent infection (enlarging vegetation or persistent bacteraemia despite appropriate antibiotic therapy), whereas previous reports have shown valvular dysfunction causing heart failure.[1,23] This may be a result of antibiotic-resistant micro-organisms. Therefore, early surgical management should be kept in mind, because antibiotics alone may not be sufficient to eradicate the disease.[24] Consequently, postponing surgery until after the completion of a course of antibiotics is not recommended.[25]

Tugcu *et al.* reported in 2007 that the median time between diagnosis and surgery was 11 days.[8] In our study population, the median time from diagnosis to surgery was seven (18) days. This trend is consistent with recent recommendations supporting early surgery in IE.[19,22]

In the current study, the most frequent complication was systemic embolism (39.6%), which is in the expected range reported by recent guidelines (20–50%).[5] It should be kept in mind that a cerebral embolic event can be a presenting symptom of IE on admission.

Table 6. Regression analysis of co-morbidities for mortality

Co-morbidities	β	*p-value*
Hypertension	–0.069	0.450
Diabetes mellitus	0.111	0.175
Chronic renal disease	0.239	0.008
Smoking	0.022	0.789
Congestive heart failure	0.198	0.017
Chronic dialysis	0.222	0.009
White blood cell level	0.095	0.266
C-reactive protein	0.222	0.009
Creatinine	0.201	0.018

The mortality rate of IE has been reported to vary between 14 and 37% in various studies, and in Turkey, from 15.3 to 33%.[6,9,26] The mortality rate in our study of 30.2% was higher than the most recently reported rate from Turkey of 27.8%.[9] This may have been due to the high number of dialysis patients and those with prosthetic heart material, and the referral of severely ill patients or those with more complications. However, it is striking that the mortality rate of IE has not decreased over the years.

Consistent with previous reports, this study showed that end-stage renal disease and heart failure were associated with increased risk of death.[9,14] This indicates the high-risk population.

A strength of this research, compared with previous reports from Turkey, is the high number of dialysis patients in the study population. They comprised 23.7% of the series, with a mortality rate of 48.5%. The most encountered micro-organisms in these patients were coagulase-negative staphylococci (39.4%). Our results are also consistent with those of a previous study performed on 52 dialysis patients with IE, which reported a 37% in-hospital mortality rate and a prevalence of 87% gram-positive micro-organisms in the aetiology.[27]

Mostaghim *et al*. reported on a study population of IE that included 26.7% dialysis patients, and the most frequently detected micro-organisms were coagulase-negative staphylococci.[26] Consistent with the current study results, Leblebicioglu *et al*. reported that haemodialysis was a risk factor for mortality.[11] The above data demonstrate that attention must be paid and strategies must be developed to prevent healthcare-related bacteraemia in order to reduce the seriously poor outcomes in dialysis patients. In addition, an arteriovenous fistula should be preferred over vascular catheters.

This study had several limitations, primarily the retrospective design. Previous antibiotic use could not be identified completely, and some statistical analyses according to risk factor and causative organism could not be performed because of the low number of patients. Furthermore, as the study was conducted in a referral centre, there may have been a selection bias towards severely ill patients or those with more complications.

Conclusion

The results of this study are of value for helping in the revision of preventative, diagnostic and management strategies for IE. The important aspects of IE epidemiology in southern Turkey were older age, increased prevalence of staphylococci and high mortality rates. TEE was found to be better than TTE for the diagnosis of IE, even in patients without prosthetic heart valves, and should be performed in all patients with suspected IE.

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Above-normal blood pressure in midlife linked to increased brain damage in later life

Higher-than-normal blood pressure, especially diastolic, is linked to more extensive brain damage in later life, according to a study in the *European Heart Journal*. In particular, the study found that there was a strong association between diastolic blood pressure before the age of 50 years and brain damage in later life, even if the diastolic blood pressure was within what is normally considered to be a healthy range.

The findings come from a study of 37 041 participants enrolled in UK Biobank, a large group of people recruited from the general population aged between 40 and 69 years, and for whom medical information, including MRI brain scans was available.

The research, carried out by Dr Karolina Wartolowska, a clinical research fellow at the Centre for Prevention of Stroke and Dementia, University of Oxford, UK, looked for damage in the brain called 'white matter hyperintensities' (WMH). These show up on MRI brain scans as brighter regions and they indicate damage to the small blood vessels in the brain that increases with age and blood pressure. WMH are associated with an increased risk of stroke, dementia, physical disabilities, depression and a decline in thinking abilities.

Dr Wartolowska said: 'Not all people develop these changes as they age, but they are present in more than 50% of patients over the age of 65 years and most people over the age of 80 years even without high blood pressure, but it is more likely to develop with higher blood pressure and more likely to become severe.'

Information on the participants was collected when they enrolled in UK Biobank between March 2006 and October 2010, and follow-up data, including MRI scans, were acquired between August 2014 and October 2019. The researchers adjusted the information to take account of factors such as age, gender, risk factors such as smoking and diabetes, and diastolic as well as systolic blood pressure. Systolic blood pressure is the maximum blood pressure reached each time the heart beats and is the top number in blood pressure measurements.

'To compare the volume of white matter WMH between people and to adjust the analysis for the fact that people's brains vary slightly in size, we divided the volume of WMH by the total volume of white matter in the brain. In that way, we could analyse the WMH load, which is the proportion of the WMH volume to the total volume of white matter,' said Dr Wartolowska.

The researchers found that a higher load of WMH was strongly associated with current systolic blood pressure, but the strongest association was for past diastolic blood pressure, particularly when under the age of 50 years. Any increase in blood pressure, even below the usual treatment threshold of 140 mmHg for systolic and below 90 mmHg for diastolic, was linked to increased WMH, especially when people were taking medication to treat high blood pressure.

For every 10-mmHg increase in systolic blood pressure above the normal range, the proportion of WMH load increased by an average (median) of 1.126-fold and by 1.106-fold for every 5-mmHg increase in diastolic blood pressure. Among the top 10% of people with the greatest WMH load, 24% of the load could be attributed to having a systolic blood pressure above 120 mmHg, and 7% could be attributed to having diastolic blood pressure above 70 mmHg, which reflects the fact that there is a greater incidence of elevated systolic rather than diastolic blood pressure in older patients.

Dr Wartolowska said: 'We made two important findings. Firstly, the study showed that diastolic blood pressure in people in their 40s and 50s is associated with more extensive brain damage years later. This means that it is not just the systolic blood pressure, the first, higher number, but the

continued on page 197 …