Clinical predictors of mortality in hospitalized patients with infective endocarditis at a tertiary care center in Pakistan

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Abstract

Objective: To evaluate the clinical characteristics and predictors of in-hospital mortality in patients with infective endocarditis at a tertiary care centre in Pakistan.

Methods: The cross-sectional study was conducted at the Aga Khan University Hospital, Karachi, from January 1, 2002, to December 31, 2006, and comprised 84 consecutive patients hospitalised with infective endocarditis,. All patients underwent verification of the diagnosis according to the Modified Duke criterion. Data was collected through a questionnaire and analysed using Student's t test, Chi square and Fisher's exact test. Univariate and multivariate logistic regression analysis was performed to assess predictors of mortality.

Results: Of the total, 53(63%) patients were male and 31(37%) female. The mean age of the patients was 42±17 years. Overall, 34(41%) patients had rheumatic valve disease as a predisposing condition. The most commonly affected valve was mitral in 43(51%) patients, and the most commonly isolated organism was methicillin-resistant staphylococcus aureus in 12(14.3%).. Overall in-hospital mortality was 27(32.1%), while 18(21%) patients developed congestive cardiac failure, 15(18%) developed arrhythmias, 16(19%) developed peripheral embolism and renal failure was present in 38(54%). Besides, 17(20%) patients underwent surgical intervention.

The final multivariate model that can be used to predict mortality in this study consisted of the presence of neurological complications (p <0.001) Odds Ratio 7.26, Confidence Interval (2.27-23.18), congestive cardiac heart failure (p <0.023) Odds Ratio 5.39, Confidence Interval (1.26-23.04), and arrhythmias (p <0.034) Odds Ratio 4.21, Confidence Interval (1.11-15.88).

Conclusion: Significant predictors of mortality in hospitalised patients with infective endocarditis in our study were the presence of neurological complications, congestive cardiac heart failure, and the presence of arrhythmias.

Keywords: Infective, Endocarditis, Mortality. (JPMA 65: 3; 2015)

Introduction

Infective endocarditis (IE) is a rare infection which mostly afflicts patients with a predisposing cardiac condition. The characteristics of patients presenting with IE have changed with time even in developing countries.[1] A trend towards an increasing number of infections in degenerated and prosthetic valve disease as opposed to rheumatic and congenital heart disease has been observed. The incidence of nosocomial and procedure-related endocarditis also appears to be on the rise.[2]

Despite improvements in diagnostic modalities and clearly defined diagnostic criteria and management guidelines, case morbidity and fatality remain high. This is especially true for hospitalised patients with IE where reported mortality is as high as 20-25%.[3,4]

Many studies have attempted to delineate parameters on the basis of which we can identify those at highest risk of

mortality.[3] The results from these studies are fairly heterogenous, and no predictive model has been developed to date.

The current study was planned to evaluate the clinical characteristics and predictors of in-hospital mortality in IE patients at a tertiary care centre in Pakistan.

Patients and Methods

The cross-sectional study was conducted at the Aga Khan University Hospital, Karachi, from January 1, 2002, to December 31, 2006, and comprised 84 consecutive in-hospital IE patients enrolled through convenience sampling.

Only those patients in whom verification of the diagnosis according to the Modified Duke criterion was possible were included. Informed consent was obtained from all patients. At the time the study was conducted, chart reviews did not require clearance from the institutional ethics review committee.

All patient information pertained to events that occurred during hospitalisation. Data was primarily collected

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through chart review and a questionnaire was filled. Missing information, if any, was collected by the principal researcher through analysis of laboratory results and clinical assessment of the patient. This information was verified by the admitting physician. Information on demographic and laboratory parameters and pre-specified in-hospital outcomes was obtained.

These included details regarding the history and physical examination along with relevant laboratory tests and echocardiography. Clinical outcomes including death and significant morbidity such as congestive cardiac failure, peripheral embolisation and neurological complications were also documented.

SPSS 19 was used for data analysis. Continuous variables with normal and non-normal distributions were reported as mean ± standard deviation (SD) and median [inter-quartile range (IQR)], respectively, while frequency and percentage were calculated for qualitative variables. Student's t test was used to compare quantitative

variables and Chi square and Fisher's exact test for categorical variables.

Primary outcome of in-hospital mortality versus discharge was dichotomised. Clinical characteristics associated with mortality on univariate analysis were age, neurological complications, congestive cardiac failure, arrhythmias, coexisting infection, serum albumin and serum creatinine.

In univariate analysis $p<0.25$ was used as the level of significance in order not to exclude important variables from the model. Multivariable models were then constructed, including variables that showed an effect in the prediction of mortality in the univariate analysis. Odds Ratios (OR) and their 95% Confidence Intervals (CI) were estimated using logistic regression analyses, with mortality as an outcome. All p values were 2-sided and $p<0.05$ was considered statistically significant.

Results

Of the 84 patients in the study 53(63%) patients were

Table-1: Comparison of clinical characteristics of study population by outcome.

	Total	In-hospital mortality group n=27	Alive at discharge group n=57	P value
Age (years)	42 ± 17	44 ± 17	41 ± 18	0.44
Male	53(63)	17(63)	36(63)	0.99
Female	31(37)	10(37)	21(37)	>0.999
Clinical Presentation				
Fever	82(98)	27(100)	55(96)	0.99
Murmur	74(88)	25(93)	49(86)	0.48
Splenomegaly	17(20)	4(15)	13(23)	0.56
Valve involved type and site				
Native valve IE	72(86)	23 (85)	49(86)	1.0
Prosthetic valve IE	6(7)	3(11)	3(5)	0.38
Isolated mitral valve	43(51)	15(56)	18(31)	0.64
Multiple valves	13(15)	7(26)	6(10)	0.10
Isolated aortic valve	18(21)	4(15)	14(25)	0.39
Microorganism isolated				
MRSA	12 (14)	5 (18)	7 (12)	0.51
Strep Viridans	10(12)	2(7)	8(14)	0.48
Culture negative	28 (33)	8 (30)	20 (35)	0.80
Complications & treatment				
Renal Failure	38(45)	17(63)	21(37)	0.03
Vegetations on echo	69(82)	23(85)	46(81)	0.76
Arrhythmias	15(18)	11(41)	4(7)	<0.001
Peripheral embolism	16(19)	11(41)	5(9)	0.001
Coexisting Infection	40(48)	19(70)	21(37)	0.005
Congestive heart failure	18(21)	12(44)	6(11)	0.001
Neurological complications	28(33)	18(67)	10(17)	<0.001
Presence of haemolysis	11(13)	4(15)	7(12)	0.74
Valve abscess	6(7)	3(11)	3(4)	0.38
Surgical intervention	17(20)	3(11)	14(25)	0.24

IE: Infective Endocarditis.
MRSA: Methicillin-Resistant Staphylococcus Aureus.

Table-2: Univariate and multivariate analysis.

Variable	Univariate OR (95% CI)	P-value
Age	2.33(0.912-5.96)	p=0.07
Neurological complications	9.4(3.28-26.9)	p=<0.005
Congestive cardiac failure	6.8(2.18-21.18)	p=0.001
Arrhythmias	9.10(2.54-32.5)	p=0.001
Coexisting Infection	4.071(1.51-10.91)	p=0.005
Serum albumin level	0.170(0.17-1.67)	p=0.13
Serum creatinine level	2.976(1.03-8.58)	p=0.04
Multivariate		
Neurological complications	7.26(2.27-23.18)	p=0.001
Congestive cardiac failure	5.39(1.26-23.04)	p=0.023
Arrhythmias	4.21(1.11-15.88)	p=0.034

OR: Odds Ratio.
CI: Confidence Interval.

male and 31(37%) female, with an overall mean age of 42±17 years. Predisposing condition in 34(41%) patients was prior rheumatic heart disease. Other predisposing conditions included congenital heart disease in 10 (12%), recent central venous catheter placement 9(11%), recent intravenous (IV) antibiotics treatment 8(10%), prosthetic valve 6(7%) and IV drug use in 4(5%) patients. In 8(9%) patients no risk factors could be identified.

The most commonly affected valve was mitral in 43 (51%), followed by multiple valve involvement in 13(15%), and isolated aortic valve involvement in 18(21%).

Mean duration of symptoms at the time of hospital presentation was 28±26 days, ranging from 2 to 90 days with a median of 15 days (IQR: 8, 45). Fever was present in all patients. Besides, 74(88%) patients had a murmur on auscultation, either on presentation or during subsequent examination. Splenomegaly was observed in 17(20%) patients. Classical signs of vasculitis or immunological phenomena associated with sub-acute IE were observed in only a few patients: Roth spots in 4(5%) patients, Osler nodes in 3(3.5%) and Janeway lesions in 9(10%).

Blood cultures were positive in 56 (66.6%) patients. The most commonly isolated organism was methicillin-resistant staphylococcus aureus in 12(14.3%) patients, followed by streptococcus viridians and enterococci in 10(12%) each (Table-1).

Vegetations were present in 69(82%) patients on echocardiography and valve abscess in 6(7%). Besides, 52(62%) patients were diagnosed with IE on transthoracic echo only, 26(31%) required additional transesophageal

study, while transesophageal echo (TEE) was the initial imaging modality in 6(7%) patients.

All patients received antibiotic therapy. Mean antibiotic duration was noted during in-hospital stay only, and was found to be 3.74±1.8 weeks. The mean antibiotic duration in those patients who underwent surgery was 4.17±1.5 weeks. Five (5.9%) patients received one antibiotic, while 27(32%) received three antibiotics. The remaining 52(62%) patients received two antibiotics.

Seventeen (20%) patients underwent surgical intervention. Surgical indications included embolic complications (including stroke) in 5(6%) patients, congestive heart failure in 4(5%), large vegetations in 4(5%) and perivalvular abcess in 1(1.1%). The remaining 3(3.5%) patients required surgery for persistent bacteraemia.

Overall in-hospital mortality was 27(32.1%) at the end of the 5-year study period. In-hospital mortality occurred within a range of 1 to 53 days, with a median of 14 (mean: 17±14 days) from the time of hospitalisation.

Eighteen (21%) patients developed congestive cardiac failure, 15(18%) developed arrhythmias (predominantly complete heart block) and valve abscess formation was observed in 6(7%). Besides, 28(33%) patients developed neurological complications, while 16(19%) developed peripheral embolism. Renal failure was present in 46(54%) patients with an observed median serum creatinine value of 2.3 and median 1.2 (IQR: 0.9, 2.5) mg/dl.

Univariate analysis found the following factors to be significant: age >50 (p <0.007), arrhythmias (p <0.017), neurological complications (p <0.001), congestive cardiac failure (p <0.001), renal failure (p <0.027), other coexisting infection (p <0.005) and serum creatinine level ≥1.4 (p <0.04) (Table-2).

The final multivariate model to predict mortality consisted of the presence of neurological complications (p <0.001) OR 7.26, CI (2.27-23.18), congestive cardiac heart failure (p <0.023) OR 5.39 CI (1.26-23.04), and arrhythmias (p <0.034) OR 4.21, CI (1.11-15.88).

Discussion

A review of initial South Asian literature describing the demographics and outcomes of hospitalised IE patients revealed a spectrum similar to that of the West of about 40 years previously.[5]

Patients were younger, had rheumatic valvular heart

disease or congenital heart disease as a predisposing condition, predominantly grew streptococci or were culture-negative and were less likely to undergo surgery.

Two studies[5,6] had found a mean age of 27.6 and 29 years respectively. In contrast, two others[4,7] found it to be 58 and 57 years. A study from Turkey[1] revealed a mean age of 45±19 years, which is similar to our findings. However, one study[8] reported a mean age of 23±8.9 years. This may reflect differences in populations who present at various tertiary care hospitals. However, the same authors found a higher proportion of staphylococcal endocarditis. This may imply that some aspects of the clinical spectrum in developing countries may be changing and may now more closely reflect Western trends.

Regional studies showed a higher frequency of endocarditis in men.[9] However, female gender has been found to be associated with a worse prognosis, though this has not been unequivocally proven. In our study, gender was not a significant predictor of mortality.

Rheumatic heart disease was the most prevalent risk factor in our cohort, which has remained a consistent feature in most studies published from the region.[5,6,8]

The majority of our patients had native valve endocarditis. Congenital heart disease was present in 12 per cent patients of which the most common condition was a ventricular septal defect. Seven per cent patients presented with prosthetic valve endocarditis (PVE). A study[10] in 1981 reported that 13% of its subjects had PVE6. Since then the incidence has been steadily increasing. A review[11] of 4106 patients admitted to the ICU found 21% to have PVE. And two other studies[3,7] found that 32% and 26% of their study population had PVE respectively.

In 8 study patients, no predisposing factor was identified except the administration of IV antibiotics for an unrelated infection prior to the development of endocarditis. An increasing trend of invasive medical procedures has been associated with the risk of nosocomial endocarditis.[12] It is possible that these patients developed endocarditis due to haematogenous introduction of pathogens through this route.

In the Euro heart study,[7] and a 15-year review,[13] the most commonly affected valve was aortic. However, local and regional studies[1,5,8] reported predominantly mitral valve endocarditis, either alone or in combination with another valve.

Blood cultures were positive in 67% of our patients. This was in contrast to earlier findings in Pakistan[9] that had lower yield on blood cultures and had postulated prior antibiotic administration as a reason. Another study[6] had reported 52% culture-positive endocarditis. The most recent local data[9] found 53.3% culture yield. Western literature reports higher microbiological yield. An American Heart Association (AHA) consensus statement[14] on the subject reports up to 20% culture negativity. However, the same authors submitted that most series reported up to 95% culture positivity. Lower yields in our part of the world likely reflect the increased frequency of prior antibiotic use as well as unavailability or limited use of culture media and methods for fastidious organisms as well as immunological methods for microbiological identification. The AHA document emphasises that these conditions may reduce recovery rate of bacteria by 35-40%.[14]

Altogether, 62 per cent of our patients were reliably diagnosed with endocarditis on a transthoracic echocardiogram. The remaining 38% underwent both transthoracic and transesophageal echo, or TEE alone. In our cohort, only 6(7%) patients had PVE. At our institute, the use of echo in patients with endocarditis is in accordance with international guidelines. The AHA consensus statement[14] advocates that TEE should be utilised early if there is high initial patient risk, moderate or high suspicion of endocarditis or poor echocardiographic windows.

The most commonly isolated pathogen in our study was methicillin-resistant staphylococcus aureus. Since this was a hospital-based study, there was a higher proportion of patients who had undergone invasive procedures such as central venous catheter placement. The microbiology is probably reflective of this trend. This trend has also been borne out in similar hospital-based studies[15,16] The presence of staphylococcus on culture was found to be a predictor of in-house mortality in a cohort by several authors.[4,17]

IE poses many challenges because myriad complications may occur, which may impact morbidity and mortality from the disease. Neurological complications occurred in about a third of our patients, which was similar to earlier findings.[18] A review of available literature states a figure of 20-40%.[5,6,9]

Congestive cardiac failure occurred in 21% of our patients, which is slightly lower than in some other studies.[4-7] This was nevertheless a predictor in the final model for in-hospital mortality, similar to previous findings.[13]

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We found a higher proportion (51%) of patients with renal failure in our study, while most series have reported between 12-29%[5,6,9,13] and recognised it as a poor prognostic marker.[11]

Surgery was performed in one-fifth of our cohort, which is slightly lower than in other series in which 12-27% had received surgical intervention.[4-6,13] European data[7] revealed a surgical intervention rate of 52%. Surgical intervention has been proven to confer a better prognosis in many series[13] and increased mortality in others[19] but was not significant in our model.

The mortality in our study is comparable to data from developing countries who have reported in-hospital mortality rates ranging from 19% to 31%. This data is taken from series from India,[5] Saudi Arabia,[20] Tunisia[21] and Brazil.[15]

These figures are higher than previous data[3,4,7] that ranged from 12% to 19% with slightly higher six-month mortality (22-27%).

Our study had several limitations. Firstly, the sample size was small and thus factors which may be associated with increased mortality may have failed to reach statistical significance. Only in-patients admitted to a tertiary care hospital were recruited and adverse outcomes as well as complication rates were quite high as could be expected. Therefore, these results may not be generalisable to the whole population.

Since a significant number of patients had undergone recent interventions, and the predominant isolated micro-organism was staphylococcus aureus, the clinical outcomes may reflect those of patients presenting with acute endocarditis. Staphylococcus aureus endocarditis itself is associated with worse outcomes. The microbiology may also reflect that of patients with nosocomial or acute endocarditis rather than community acquired infection.

Microbiological yield was lower than that in the West, but the highest of all local studies published thus far. The reasons for this have already been discussed.

Surgical intervention was performed in 20% of our patients and was not found to be associated with outcomes. This is in contrast to Western data where surgical intervention confers better prognosis. However, their intervention rates are much higher. The lower rates of surgical intervention may have resulted in an erroneous lack of association and may also reflect the poor medical condition of patients who were deemed to be at prohibitively high risk for surgery.

Conclusion

Over time the range of indications for in-dwelling central venous catheters, pacemaker leads and prosthetic material are expected to become more extensive. This may lead to an increasing incidence of nosocomial and procedure-related endocarditis. This necessitates the development of validated models for predicting adverse outcomes in patients with endocarditis. Significant predictors of mortality in this study were the presence of neurological complications (primarily cardio embolic stroke), congestive cardiac failure, and arrhythmias. Further studies are needed to devise prediction models for both in-patients and out-patients with infective endocarditis.

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