International Journal of Infectious Diseases 34 (2015) 71–75

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

The usefulness of serum troponin levels to predict 1-year survival rates in infective endocarditis

Esra Gucuk Ipek *, Yesim Guray, Burak Acar, Habibe Kafes, Lale Dinc Asarcikli, Gizem Cabuk, Burcu Demirkan, Mevlut Serdar Kuyumcu, Umit Guray

Yuksek Ihtisas Education and Research Hospital, Department of Cardiology, Ankara, Turkey

ARTICLE INFO

Article history:
Received 2 January 2015
Received in revised form 23 February 2015
Accepted 3 March 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Infective endocarditis
outcome
troponin
biomarker

SUMMARY

Background and aim: Infective endocarditis (IE) is associated with increased mortality and morbidity. In this study, we aimed to evaluate the role of troponin levels in predicting long-term survival in patients with IE.

Methods: A retrospective analysis of the medical database of Yuksek Ihtisas Education and Research Hospital was performed to reach the patients that received the diagnosis of definite IE according to Duke criteria. Out of 84 definite IE cases, 48 patients (mean age 45.6±17.3, 39.6% female) that had troponin T levels measured upon hospital admission were included. The survival status of the study subjects was assessed during a follow-up period of 1 year.

Results: A total of 20 (41.7%) patients died during the follow-up. Baseline median troponin T levels were significantly higher in fatal cases (0.08 [0.02-0.24] ng/ml vs. 0.02 [0.01-0.04] ng/ml p=0.003). The optimal troponin T level to detect mortality was 0.05 ng/ml according to receiver operating characteristic curve (area under the curve 0.75, 95% Confidence Interval (CI) [0.61-0.9], p=0.003) with 70% sensitivity and 79% specificity. Patient with elevated troponin levels were older, were more likely to be male and tended to have enterococcal infection. These patients had also higher creatinine levels and increased systolic pulmonary pressures. In the multivariate Cox regression analysis, renal failure (hazards ratio (HR) 8.23, CI 95% 2.53-26.9, p<0.0001), heart failure (HR 4.48, CI 95% 1.73-11.61, p=0.002) and troponin T ≥ 0.05 ng/ml (HR 3.11, CI 95% 1.13-8.56, p=0.03) were associated with increased mortality rates.

Conclusions: IE has poor outcome and baseline troponin T levels may predict long-term survival rates in these patients.

1. Introduction

Infective endocarditis (IE) is associated with considerable mortality and morbidity rates despite recent improvements in the management of the cardiovascular diseases. In-hospital mortality rates range from 10% to 20%, while long-term mortality rates can be much higher [1–3].

IE has a broad range of course and identifying individuals who are at increased risk of adverse outcomes is challenging due to interaction of various factors. The immune status of the host, foreign body involvements, underlying heart disease, causative microorganism, and the region of the infection may all alter the course of this complex disease. Various clinical predictors have been proposed to estimate the outcome, but these parameters generally emerge overtime [1,4]. Indications and timing of the surgery, or duration of the antimicrobial therapy are still a matter of debate; therefore a powerful biomarker may facilitate risk stratification to make decision on these critical points, especially at the early stages of the disease.

Troponins are cardiac specific proteins that are released in case of myocardial injury. Besides well-known relationship with troponins and adverse outcome in acute coronary syndrome, similar associations have also been demonstrated in other cardiac and non-cardiac settings [5]. Recent studies have demonstrated that high troponin levels can be detected in IE and elevated troponin levels are associated with adverse outcome in patients with IE [6,7]. However, to date no study has evaluated the role of

* Corresponding author. Address: Gülbeng Sitesi G Blok No:21 Yaşamkent ANKARA / TURKEY, 06820. Tel.: +90 505 8956416; fax: +90 312 6213503.
E-mail address: esragucuk@hotmail.com (E. Gucuk Ipek).

http://dx.doi.org/10.1016/j.ijid.2015.03.004

cardiac troponins in predicting long-term outcome. In the present study, we aimed to investigate the relationship between troponin levels and 1-year survival status in patients with IE.

2. Methods

2.1. Study Patients

The medical database of Yuksek Ihtisas Education and Research Hospital, Ankara, Turkey was reviewed retrospectively. Between January 2008 and January 2011, 84 consecutive patients diagnosed with definite IE according to the modified Duke criteria were enrolled [8]. Of all cases, 48 patients that had troponin T levels measured upon hospital admission (within 48 hours of initial admission) were included. Clinical, echocardiographic, and laboratory findings were recorded for each subject. Predisposing heart diseases including prosthetic valve, pre-existing valvular disease (rheumatic heart disease and degenerative valves), congenital heart disease, implantable cardiac device, nosocomial infection and previous history of IE were assessed. Hypertension was defined as blood pressure >140/90 mm Hg on >2 occasions during office measurements or use of antihypertensive treatment. Coronary artery disease was considered to be present when there was documented coronary stenosis of >50%.

Complications during hospitalization such as heart failure, renal failure, abscess formation, cerebrovascular events and surgical treatment for IE were recorded. Cerebrovascular events referred to the one of the following presentations: intracranial hemorrhage, ischemic stroke, and transient ischemic attacks. Renal failure was defined by serum creatinine concentration exceeding 2 mg/dl during hospital stay. The primary end point of the study was the incidence of all cause death within one year after the index hospitalization. Clinical event data were collected during the follow-up period for all patients by reviewing medical files and by telephone contacts. One-year follow-up was completed in all of the patients. The study was performed in accordance with the Declaration of Helsinki for human research and was approved by the local ethics committee.

2.2. Laboratory

Blood samples for troponin T were obtained upon admission and measured with an auto analyzer (Elecsys 2010) running commercial assays (Roche Diagnostics, Penzberg, Germany). This assay was reported in ng/ml and the upper reference limit (99th percentile) was < 0.01ng/ml in studies performed with healthy volunteers. Hemoglobin and white blood cell counts were measured using an automated hematology analyzer. C reactive protein (CRP), glucose and creatinine levels were measured accordingly. At least 3 sets of blood samples for cultures were obtained from each patient immediately after hospital admission. Any other available fluid, tissue (valves, vegetations or intracardiac abscesses removed at surgery) or foreign body samples (pacemaker leads, catheters) were used to isolate microorganisms.

2.3. Echocardiography

All patients underwent two-dimensional transthoracic echocardiography within 24 hours of admission. Echocardiographic examinations were performed with the Vivid 7 system (GE Healthcare, Wauwatosa, Wisconsin). Transesophageal echocardiography was performed when image quality with transthoracic echocardiography was not sufficient for an accurate diagnosis; or in cases of high clinical suspicion of IE, prosthetic valve involvement, and suspicion of complications. Vegetation, abscess formation, and valvular destruction (such as perforation of leaflet and chordal rupture) were noted. Vegetation size was measured by using different echocardiographic windows, and the maximal length was obtained. Existence of rocking motion of the prosthetic valve with an excursion of $> 15^{\circ}$ in at least one direction led to the diagnosis of dehiscence. Left ventricular ejection fraction was calculated by the modified Simpson method. Severe valvular regurgitation was identified according to guideline recommendations [9]. Continuous-wave Doppler of the tricuspid regurgitation jet signal using the Bernoulli equation estimated pulmonary artery systolic pressure [10].

2.4. Statistics

Continuous variables were expressed as mean ± SD or as median with interquartile range; and categorical variables were expressed as number and percentages. Categorical variables were compared with $\chi 2$ test or Fisher test; continuous variables were compared with Student's *t*-test or Mann-Whitney U test, as appropriate. Spearman correlation analysis was performed to evaluate the relation of troponin T with other variables. Receiver operating characteristic (ROC) curve was used to detect the optimal cut-off point of troponin T levels to estimate 1-year survival. Patients with IE were categorized into two groups on the basis of this cut-off value. Kaplan-Meier survival curves and log-rank values were used to assess survival in subgroups. Univariate Cox regression analysis was performed to assess the association of the variables with 1-year mortality. Variables that had $p<0.1$ in the univariate analysis were further analyzed with multivariate Cox regression model with conditional stepwise method. Results of the Cox regression analysis were reported with hazards ratios (HR) and 95% confidence intervals (CI). Statistical analysis was performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL). A p value of 0.05 was considered statistically significant.

3. Results

Out of 84 definite IE cases, 48 patients had troponin T levels available. Supplement 1 shows baseline characteristics of the study subjects, and comparison of patients regarding the presence of troponin measurement. There were differences in various parameters of patients with and without troponin T levels, including presence of coronary artery disease, severe valvular regurgitation or enteroccocal infection, but these differences were not statistically significant.

Staphylococci species were the most common microorganisms. Presence of a prosthetic valve was the most common predisposing factor in the study cohort. Median duration of hospital stay was 31 days. A total of 20 (41.7%) patients died during the follow-up. Supplement 2 shows the differences between survivors and non-survivors. Renal failure, heart failure, and severe valvular regurgitation were significantly higher among non-survivors, whereas having a surgery due to IE was associated with lower mortality.

Baseline median troponin T levels were significantly high in fatal cases (0.08 [0.02-0.24] ng/ml vs. 0.02 [0.01-0.04] ng/ml, p=0.003). There was a modest correlation between troponin levels and age (r=0.38, p=0.008), CRP (r=0.32, p=0.03), creatinine (r=0.33, p=0.02), and systolic pulmonary artery pressure (r=0.49, $p<0.001$). The optimal troponin T level to detect mortality was 0.05 ng/ml according to ROC curve (area under the curve 0.75, 95% CI [0.61-0.9], p=0.003) with 70% sensitivity and 79% specifity (Figure 1). Of all patients, 19 (40%) had troponin T ≥ 0.05 mg/dl. To evaluate the association between troponin T and clinical outcome, patients were divided into 2 groups based on this cut-off value. Table 1

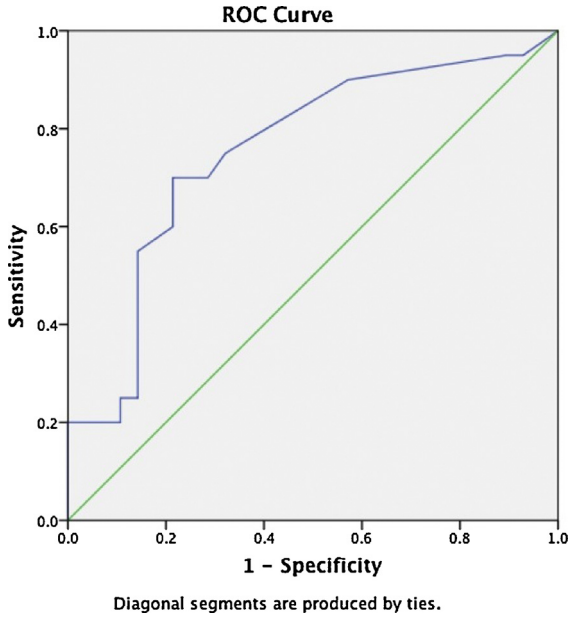

Figure 1. ROC curve for troponin levels to detect 1-year mortality. The optimal cut-off level was 0.05 ng/ml.

shows the differences between the subgroups (troponin T ≥ 0.05 ng/ml vs. < 0.05 ng/ml) regarding their demographic, clinical and echocardiographic properties. Patients with elevated troponin levels were older, more likely to be male, tend to have Enterococci infection, and had higher creatinine levels as well as increased systolic pulmonary artery pressures. There were no significant differences in cardiac abscess, heart failure, cerebrovascular event or renal failure between groups.

In Kaplan Meier survival analysis, 1-year mortality rates were significantly higher in patients with elevated troponin T levels (p=0.002) (Figure 2). Results of the univariate and multivariate Cox regression analysis are listed in Table 2. In the multivariate Cox regression analysis, renal failure (HR 8.23, CI 95% 2.53-26.9, p<0.0001), heart failure (HR 4.48, CI 95% 1.73-11.61, P=0.002) and troponin T ≥ 0.05 ng/ml (HR 3.11, CI 95% 1.13-8.56, p=0.03) were associated with increased mortality rates.

4. Discussion

In our study cohort, 20 (41.7%) patients died during the follow-up period of 1 year. There was an independent association between troponin T levels and poor outcome, suggesting that baseline troponin T may become a valuable biomarker to estimate poor outcome in patients with IE. To the best of our knowledge, this is the first study that evaluated the association of troponin levels with long-term mortality in IE.

Table 1
Comparison of clinical characteristics of the study patients with low vs. high troponin levels

	All Patients (n=48)	Troponin ≥ 0.05 ng/ml (n=19)	Troponin < 0.05 ng/ml (n=29)	p value
Demographics, comorbidities and predisposing conditions				
Female gender	39.6% (19)	21.1% (4)	51.7% (15)	**0.03**
Age (years)	45.6±17.3	53.4±16.9	40.5±15.8	**0.01**
Coronary artery disease	10% (5)	15.8% (3)	6.9% (2)	0.37
Hypertension	16.7% (8)	15.8% (3)	17.2% (5)	1
Prosthetic valve	45.8% (22)	31.6% (6)	55.2% (16)	0.11
Pre-existing valvular disease	39.6% (19)	57.9% (11)	27.6% (8)	**0.04**
Congenital cardiac disease	12.5% (6)	5.3% (1)	17.2% (5)	0.38
Cardiac device	8.3% (4)	15.8% (3)	3.4% (1)	0.29
Nosocomial infection	16.7% (8)	31.6% (6)	6.9% (2)	0.05
Previous infective endocarditis	6.3% (3)	5.3% (1)	6.9% (2)	1
Affected valve				
Aortic	47.9% (23)	52.6% (10)	44.8% (13)	0.59
Mitral	35.4 (17)	26.3% (5)	41.4% (12)	0.29
Tricuspid	8.3% (4)	15.8% (3)	3.4% (1)	0.29
Echocardiography				
Cardiac abscess	10.4% (5)	21.1% (4)	3.4% (1)	0.07
Severe valvular regurgitation	27.1% (13)	36.8% (7)	20.7% (6)	0.22
Vegetation ≥10 mm	50% (24)	57.9% (11)	44.8% (13)	0.38
Valvular destruction/dehiscence	14.6% (7)	15.8% (3)	13.8% (4)	1
Pulmonary artery pressure (mm Hg)	45 (36.3-50)	48 (40-65)	42 (35-45)	**0.008**
Left ventricular ejection fraction (%)	58 (50-60)	59 (45-60)	58 (50-60)	0.93
Laboratory parameters on admission				
Hemoglobin (g/dl)	10.8±2.2	10.3±2.2	11.1±2.1	0.22
C reactive protein (mg/dl)	16 (4.2-63.6)	30.4 (12-126)	9.7 (3.2-41.4)	0.07
Creatinine (mg/dl)	0.9 (0.66-1.39)	1.09 (0.76-1.6)	0.85 (0.63-1.17)	**0.03**
Glucose (mg/dl)	100 (88-126.8)	106 (87-127)	98 (88.5-126.5)	0.9
White blood cell count (x10^3/uL)	10.4 (7.9-14.5)	10.5 (9.7-14.8)	12 (7.4-13.9)	0.5
In-hospital outcome				
Renal failure	47.9% (23)	57.9% (11)	41.4% (12)	0.26
Cerebrovascular events	16.7% (8)	26.3% (5)	10.3% (3)	0.24
Heart failure	25% (12)	36.8% (7)	17.2% (5)	0.18
Surgery	27.1% (13)	26.3% (5)	27.6% (8)	0.92
Outcome at 1 year follow-up				
Mortality	20 (41.7%)	13 (68.4%)	7 (21.4%)	0.002
Microorganism				
Staphylococcus Aureus	20.8% (10)	21.1% (4)	20.7% (6)	1
Coagulase-negative Staphylococcus	14.6% (7)	26.3% (5)	6.9% (2)	0.1
Streptococci	14.6% (7)	10.5% (2)	17.2% (5)	0.69
Brucella spp	4.2% (2)	0% (0)	6.9% (2)	0.51
Enterococci	12.5% (6)	26.3% (5)	3.4% (1)	**0.03**

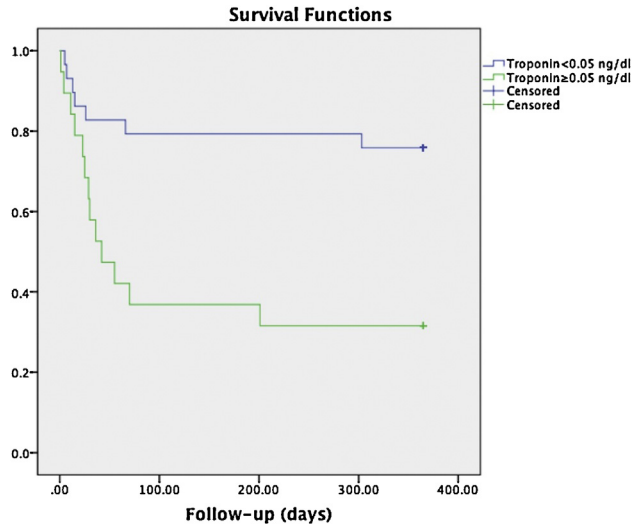

Figure 2. Kaplan Meier survival curves in patient subgroups.

A pilot study demonstrated high proportions of elevated troponin levels in 15 IE cases [11]. Although no correlation was found between poor outcome and troponin levels, two patients with increased troponin levels died during the hospital stay. Following this study, Purcell et al. found elevated troponin I levels in 65% of the 51 IE patients [7]. Composite outcome of death, cerebrovascular events, and abscess formation were correlated with troponin levels. Similarly, Tsenovoy et al. reported elevated troponin I levels in 57% of 62 IE patients who also had significantly higher mortality and surgery rates [12]. Finally, in a study with 42 IE patients, Stancoven et al. demonstrated that patients with a troponin I level of ≥0.08 ng/ml (n=16, 38%) were more likely to experience composite outcome of death, central nervous system event, and cardiac abscess [13]. Furthermore, troponin measurements improved the prognostic value of N-terminal pro-B-type natriuretic peptide levels in previous studies conducted in patients with IE [6,14]. In these studies, patients with elevated troponin and N-terminal pro-B-type natriuretic peptide levels were found to be at high risk for poor outcome.

Although our results confirm the previous work that demonstrated inverse relationship between increased troponin levels and survival, the mechanism behind this association remains unclear. Elevated troponin levels reflect myocardial injury and there are potential explanations of this in the absence of obstructive coronary artery disease. Local invasion of the myocardium may be a possible mechanism [7,13,15]. In our study, patients with elevated troponin levels tended to have more cardiac abscess and higher valvular or paravalvular complication rates. Moreover, enterococci species were common in these patients. These findings were consistent with previous studies [11,12]. Enterococci infection is more common in patients with prosthetic IE, device related IE or nosocomial infection. In our cohort, the rates of device infection (15.8% vs. 3.4%) and nosocomial infection (31.6% vs. 6.9%) were higher in patients with elevated troponin levels, but prosthetic valve was less common in this group (31.6% vs. 55.2%). Although the rate of enterococci infection was higher in troponin available group (12.5% vs. 2.8%) it was not statistically significant and we could not exclude the presence of selection bias in these patients. Another potential explanation of the increased troponin levels may be coronary embolism, which may be observed in the course of IE, although many cases may remain asymptomatic according to necropsy findings [15–17]. In our cohort, no patient presented with ischemic changes on electrocardiograms or had overt myocardial infarction. Increased myocardial stress in the setting of oxidative stress and inflammatory response may cause the myocardial damage, similar to troponin increase seen in sepsis [18]. Troponin elevation in IE may also represent a more extensive infection. In our cohort, a modest correlation between troponin and CRP levels was present, similar to association reported by Watkins et al. [11].

Several years ago Saphir et al. and Perry et al. examined myocardial lesions in a substantial number of the postmortem IE patients [19,20]. Following these studies, Buchbinder et al. described necropsy findings in patients with left-sided IE [15]. Multiple histologic sections were examined in 38 patients and 87% of the cases had myocardial lesions including necrosis, myocardial inflammation and fibrosis. Of the examined cases, 21 patients had interstitial myocardial fibrosis, 22 had papillary muscle necrosis, and 3 had left ventricular free wall necrosis. Despite papillary muscle necrosis, no patient had overt mitral regurgitation and only 3 cases with papillary muscle necrosis had coronary artery involvement. Except for papillary muscle necrosis, other myocardial lesions did not correlate with the clinical heart failure. These observations may explain the prevalence of troponin elevation in patients with IE and the role of IE in predicting poor prognosis, as many cases with the myocardial involvement remained asymptomatic [13].

In our study cohort, patients with elevated troponin levels had higher creatinine levels and systolic pulmonary artery pressures. Troponin elevation is common in patients with renal disease [21]. Increased pulmonary pressure may reflect valvular

Table 2
Results of the univariate and multivariate Cox regression analysis to predict 1-year mortality

	Univariate Analysis			Multivariate Analysis		
	HR	(95% CI)	p value	HR	(95% CI)	p value
Age	1.01	(0.99-1.04)	0.44			
Female gender	0.55	(0.21-1.42)	0.22			
Troponin ≥ 0.05 ng/ml	3.83	(1.52-9.67)	0.005	3.11	(1.13-8.56)	0.028
Hemoglobin	0.81	(0.66-1.01)	0.06			
Pulmonary artery pressure	1.03	(1.007-1.06)	0.014			
Nosocomial infection	3.01	(1.13-7.99)	0.03			
Surgery	0.23	(0.05-0.99)	0.05			
S. Aureus infection	2.72	(1.07-6.89)	0.04			
Valvular destruction/dehiscence	3.18	(1.14-8.86)	0.03			
Severe valvular regurgitation	3.47	(1.43-8.41)	0.006			
Heart failure	5.63	(2.31-13.73)	<0.0001	4.48	(1.73-11.61)	0.002
Renal failure	7.09	(2.35-21.44)	0.001	8.23	(2.53-26.9)	<0.0001
Cardiac abscess	2.73	(0.9-8.23)	0.08			

regurgitation and heart failure. In our cohort, these complications were common in patients with elevated troponin levels but the difference was not statistically significant.

5. Conclusion

In conclusion, baseline troponin T levels may provide valuable information regarding the long-term outcome of the IE and potentially identify high-risk patients that need more aggressive treatment. Without an evidence of such a myocardial injury, IE may have a benign course.

Limitations

This is a single center study and the results may not reflect the properties of the general population. The mean age of the study subjects was lower and prosthetic valve was more common than that of western countries [22]. This is probably due to high prevalence of rheumatic valve disease in our country [23].

Retrospective design and small sample size are other main limitations. IE related complications and mortality rates were high. Our institution is a tertiary care center and the patient group may have had more co-morbid conditions as more severe or complicated cases referred from other institutions. Even though troponin T levels were measured upon hospital admission, patients may have presented in different stages of the disease. Serial measurements of troponin were not performed and most cases were already on treatment; therefore we may have underestimated the troponin positive cases. Since troponin T levels were measured only in some of the admitted IE patients for clinical reasons, sampling strategy may have led a selection bias. The unavailability of the troponin measurements in all subjects may have had a significant impact on our findings. Finally, small sample size and limited number of outcome events may have caused wider confidence intervals in the regression analysis.

Conflict of interest: None declared

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2015.03.004.

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