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ORIGINAL ARTICLE

Cardiac Troponin T as a Prognostic Marker of Cardiovascular Morbidity and Mortality in Patients with End-stage Renal Disease

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ABSTRACT

Introduction: Cardiovascular disease is the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD), accounting for more than 50% of all deaths. High-sensitivity troponin T (hsTnT) assay is a sensitive and specific marker of myocardial injury and necrosis.

Objective: The objective of this study was to evaluate the prognostic role of elevated hsTnT levels in identifying ESRD patients with high risks of developing cardiovascular morbidity or mortality.

Materials and methods: The present study was a cross-sectional observational study conducted in 50 patients fulfilling the prespecified inclusion criteria. Patients were evaluated based on the history, clinical findings, lab investigations including hsTnT, two-dimensional echocardiogram, and duration and frequency of hemodialysis (HD).

Results: The study cohort showed significant correlation of elevated hsTnT levels with left ventricular hypertrophy ($p < 0.05$), diabetes mellitus ($p < 0.005$), duration of HD ($p < 0.01$), and mortality ($p < 0.05$).

Conclusion: Troponin T is a promising prognostic tool, since elevated levels identify a subset of ESRD patients who have poor survival and higher risk of death. Though sample size was small, this study corroborates previous postulates on this subject. However, being a small sample study, findings could not be subjected to a larger population.

Keywords: Cardiovascular disease, Diabetes, End-stage renal disease, Hemodialysis, High-sensitivity troponin T, Hypertension, Left ventricular hypertrophy.

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INTRODUCTION

End-stage renal disease (ESRD) is one of the most common health problems in both developed and developing countries.[1] A population-based study calculated the ESRD incidence to be 152 per million population in India.[2,3] Cardiovascular disease is the leading cause of morbidity and mortality in patients with ESRD, accounting for more than 50% of all deaths.[4] Early identification of patients with ESRD who are vulnerable to develop cardiovascular morbidity and mortality using newer prognostic serum markers may facilitate more aggressive and focused treatment in this group. Cardiac troponins are sensitive and specific biochemical markers of myocardial injury and necrosis.[5] The recently introduced high-sensitivity troponin T (hsTnT) assay allows detection of ~10-fold lower levels with less analytical variation compared with previous assays.[6,7] The aim of this study was to study the levels of serum cardiac troponin T in ESRD and thereby determine whether stable asymptomatic ESRD patients with elevated hsTnT levels had a greater prevalence of cardiovascular risk factor, comorbidity and mortality.

MATERIALS AND METHODS

The present study was a cross-sectional, observational study conducted at MGM Medical College & Hospital, Navi Mumbai, Maharashtra, India. Fifty inpatient and outpatient departments patients fulfilling the inclusion criteria were studied over a span of 2 years between November 2013 and October 2015.

Inclusion Criteria

- Patients between age group 20 and 80 years.
- Patients who were diagnosed cases of ESRD.

Exclusion Criteria

- Age more than 80 and less than 20 years.
- Patients having past history of myocardial infarction, unstable angina, heart failure, severe sepsis, myocarditis, cardiac surgery.

Methodology

Patients were evaluated based on history and clinical findings at the time of presentation. Lab investigations

(complete blood count, renal function test, urine routine, hsTnT), electrocardiography, and two-dimensional (2D) echocardiography (ECG) were performed and duration and frequency of hemodialysis (HD) was noted in all patients.

Study Group

The patients enrolled were classified as ESRD based on the glomerular filtration rate <15 mL/minute, or undergoing/advised HD/renal transplant. Serum hsTnT levels were measured by an automated chemiluminescent immunoassay using the Roche hsTnT assay. The assay had a detection limit of 5 ng/L and 99th percentile was 14 ng/L.

Statistical Methods

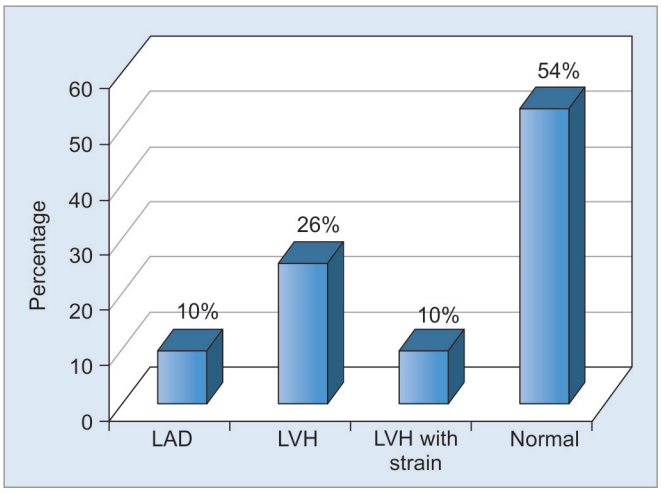
Data were tested first for normal distribution by Kolmogorov–Smirnov test. Comparison of quantitative variables was done using Student's t test and Mann–Whitney U test for normally and non-normally distributed data respectively. Multiple group comparison was done by Kruskal–Wallis test with *post hoc* Dunn's test. Spearman's correlation coefficient was used for computing correlation between quantitative (non-normally distributed) data. For comparing categorical data, chi-square test was performed. A probability value <0.05 was considered statistically significant.

RESULTS

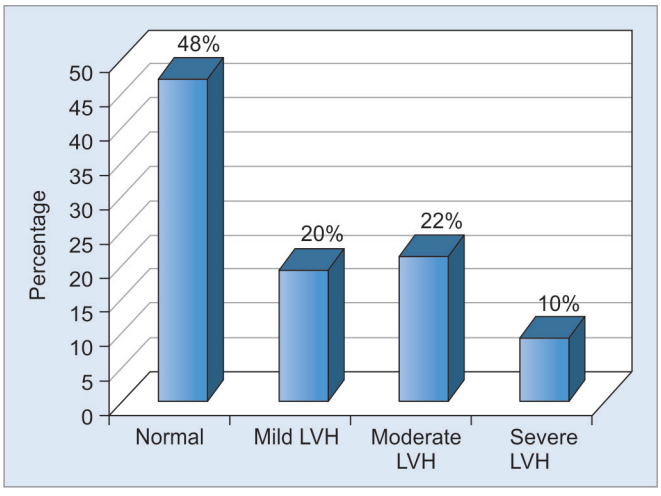
Maximum number of patients were in the age group of 51 to 70 years, and the mean age of the population being 55.18 ± 12.34 years with a male predominance (72%). Hypertension alone was the prevalent morbidity in 30% of patients followed by combined hypertension and diabetes (26%). As depicted in Graph 1, ECG was normal in most of the patients. The most common finding was left ventricular hypertrophy (LVH) without strain in 13 (26%) patients, followed by LVH with strain and left axis deviation (LAD) in 5 patients each. More than half of the population (52%) showed LVH on 2D Echo which was graded as mild (20%), moderate (22%), and severe (10%) respectively as shown in Graph 2. Graph 3 portrays that maximum number of patients had troponin T in the range of 15 to 50 ng/L, while only four patients had troponin T levels <14 ng/L which was normal. The median of the troponin T levels was 57 ng/L. Maximum number of patients (64%) were undergoing HD for less than 1 year and mean HD duration of the study cohort was 10.9 ± 5.6 months as shown in Graph 4. Patients having diabetes had a greater mean value of troponin T (142.43 ng/L) as compared with the rest of the population. Mean level of troponin T in patients who died was 210 ng/L, which was significantly higher as compared with the values in those who were alive. Troponin T levels were significantly raised with increasing duration of HD. Out of 50 patients in study group 15 (30%) died. It was observed that out of 13 patients who were having troponin levels more than 100 ng/L, 9 (69%) died during the study period, whereas only 6 out of 37 patients (16%), who died during study period, had troponin T levels less than 100 ng/L. There was statistical correlation of high antemortem troponin T levels with death (Table 1).

DISCUSSION

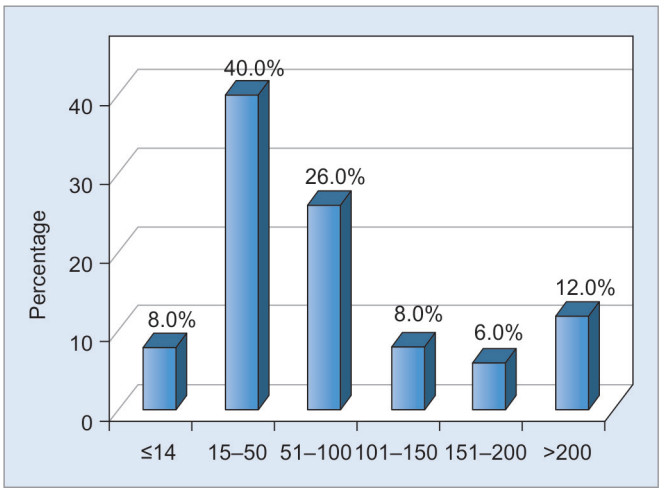
End-stage renal disease is a clinical syndrome caused by varied underlying pathology. Cardiovascular disease is the leading cause of death in ESRD.[4] The pathogenesis predominantly involves uremia induced intermyocytic fibrosis, which further leads to myocardial diastolic dysfunction and various cardiac arrhythmias.[8] End-stage renal disease patients are prone to variations in fluid and humeral homeostasis leading to an elevation in both



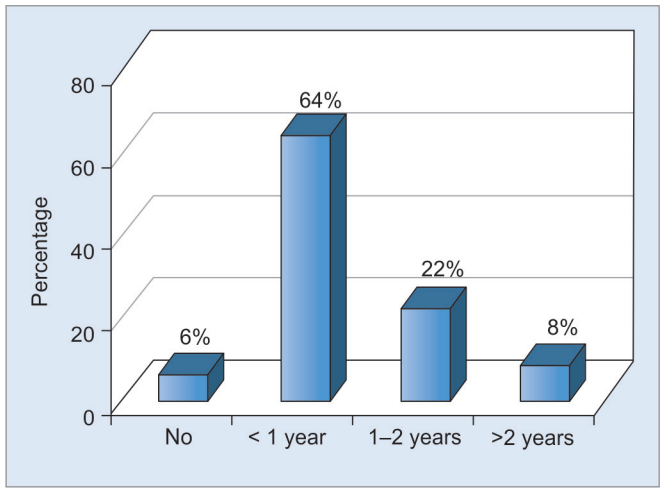
Graph 1: Electrocardiogram findings in study group



Graph 2: Two-dimensional echo findings in study group



Graph 3: Troponin T levels in study group



Graph 4: Duration of dialysis in study group

Table 1: Correlation of variables with troponin T

Troponin T		*n*	*Mean*	*SD*	*p-value*
2D echo	Normal	24	31.53	21.17	<0.05 (severe LVH *vs* others)
	Mild LVH	10	88.46	63.50	
	Moderate LVH	11	132.05	134.77	
	Severe LVH	5	323.54	296.15	
Diabetes mellitus	Yes	19	142.43	145.40	<0.05
	No	31	64.70	93.50	
HT	Yes	28	100.20	157.75	0.74
	No	22	86.60	115.10	
Outcome	Death	15	210.33	200.80	<0.01
	Alive	35	39.59	30.30	

SD: Standard deviation

Table 2: Comparison of variable with similar studies

Variables	*Present study*	*Wolley et al*[29]	*Dierkes*[30]	*Pianta et al*[11]	*Deegan et al*[31]
Age	55.18±12.34 years	63 years	64±13 years	73 years	64 years
DM	38%	58.2%	48%	47%	16.4%
HTN	56%	8%	–	56%	–
LVH	52%	–	–	56%	42.4%
Troponin T	92% positive	98% positive	83% positive	99% positive	27.3% positive
Troponin T median	57 ng/L	63 ng/L	–	69 ng/L	–
Mortality	30%	11.2%	27.4%	–	28.7%

preload and after-load on the myocardium. This subsequently leads to LVH which in the later stages becomes maladaptive, manifesting as clinical heart failure.[9] Coronary artery disease is highly prevalent in ESRD population owing to similar demographic profile and underlying disease states, such as diabetes and hypertension.[10] The most common cause of chronic kidney disease worldwide is diabetes. In our study, it was the second most common cause (38%) preceded by hypertension (56%). A similar dominance of hypertension over diabetes was also observed by Pianta et al in their study group (56 and 47%). Echocardiography showed LVH in majority of our patients (52%) corroborating with findings of the study conducted by Pianta et al[11] with 56% showing LVH in their study group. The presence of LVH is significantly correlated with increased TnT in patients with ESRD without acute myocardial ischemia.[12-15] In patients with ESRD, the prevalence of elevated hsTnT concentrations is 100% and these are highly prognostic of adverse events.[16-19] It is hypothesized that uremia-induced skeletal myopathy leading to reexpression of cardiac TnT from injured or regenerating skeletal muscle fibres may be responsible for increased troponins in renal failure.[19-23] It is also possible that patients with ESRD are more likely to sustain repeated episodes of clinically silent microinfarctions secondary to their high incidence of coronary artery disease. There are data indicating that serum TnT and TnI are increased in patients with heart failure in the absence of acute ischemia.[24] However, it is unlikely that elevated serum troponin is the result of decreased clearance by the failing kidney. Unlike previous studies, troponin T was measured by new generation high-sensitivity assay,[25-28] and was greater than the 99th percentile for normal in 92% of patients in our study group, which was in concordance with the studies conducted by Martin Wolley[29] (98%) and Pianta[11] (99%) (Table 2). Hypertension (56%) being the most prevalent comorbidity among our study population, showed no significant difference between the mean troponin T levels when compared to rest of the nonhypertensive population. However, 38% of study group having diabetes showed statistically significant higher positive troponin T levels when compared with rest of the population. The association between elevated hs-TnT and mortality is consistent with previous studies in ESRD population like those conducted by Dierkes et al[30] and a meta-analysis done by Nadia A Khan et al; however, they used earlier generation troponin assays. Fred S Apple concluded in his study that increases in

cTnT in ESRD patients show a two- to five-fold increase in mortality. To summarize the results, the study cohort showed significant correlation of elevated troponin T with LVH ($p < 0.05$), diabetes mellitus (DM) ($p < 0.005$), duration of HD ($p < 0.01$), and mortality ($p < 0.05$).

CONCLUSION

It is often difficult to risk-stratify stable, asymptomatic ESRD patients. Troponin T is a promising prognostic tool, because elevated levels identify a subset of ESRD patients who have poor survival and higher risk of death. Furthermore, the assay is standardized and readily available. This analysis corroborates previous postulates that a single elevated troponin T value is strongly predictive of long-term mortality irrespective of cause of death. However, being a small sample study, findings cannot be extrapolated to larger population. Further studies on larger sample sizes are required.

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