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Research Article

Implication for Myocarditis Diagnosis Using Troponin Test -Long-Term Outcomes in a Real-Life Experience Study

Ela Giladi[1,3]; Reut Ratzon[2,3]; Ranin Hilu[1,3]; Ziad Arow[1,3]; Ilya Losin[1,3]; David Pereg[1,3]; Abid Assali[1,3]; Yoav Arnson[1,3]

[1]Department of Cardiology, Meir Medical Center, Tel Aviv University, Tel Aviv, Israel

[2]Department of Emergency Medicine, Meir Medical Center, Kfar Saba, Israel

[3]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

***Corresponding author: Giladi E**

Department of Cardiology, Meir Medical Center, 59 Tshernichovsky, Kfar Saba, Israel

Tel: +972-9-7472587; Fax: +972-9-7472812

Email: ellafirst36@gmail.com

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Abstract

Background: The diagnosis of myocarditis is challenging, and typically relies on clinical presentation, non-invasive imaging, and serum biomarkers. While myocarditis generally has a generally good prognosis, it may be complicated by heart failure and malignant arrythmias. Despite reported recurrences, the overall recurrence rate of acute myocarditis is undisclosed. This study aims to uncover long-term prognosis and recurrence rates in myocarditis diagnoses using hsTnT, and whether the implementation of hsTnT has affected recognition of myocarditis

Methods: A retrospective analysis was conducted on patients aged 18 and above diagnosed with myocarditis at Meir Medical Center from January 2000 to the end of April 2020. Patients were categorized based on their diagnosis date: up to January 2014, with a regular troponin test (REG group), and from February 2014 onward, with a hsTnT test (HS group). An extended follow-up was conducted on patients diagnosed with acute myocarditis using hsTnT to assess mortality and recurrence events.

Results: We identified 262 patients who were diagnosed with myocarditis. There were no significant differences between the groups. After the implementation of hsTnT there was a two-fold increase in the diagnosis rate (0.0366 vs. 0.0625 cases per day; P<0.0001). There was no significant difference in mortality (8 deaths in the HS group vs. 7; p=0.62). Myocarditis recurred in 8.4% of patients during long-term follow-up.

Conclusions: Employing hsTnT testing in suspected myocarditis cases can improve diagnostic acuity and detect milder cases. Extended follow-up findings suggest a generally favourable prognosis for myocarditis recovery, with a relatively higher recurrence rate.

Keywords: Myocarditis; Troponin; Diagnosis; Prognosis; Long-term; Recurrence

Introduction

Myocarditis is an inflammatory condition of the myocardium, most often secondary to a viral infection, but it can also be immune-mediated due to eosinophilic reaction, exposure to chemotherapy or to toxic substances. Myocarditis is an uncommon and likely underdiagnosed potentially life threatening condition which may present with a wide range of cardiac and extra-cardiac symptoms [1,2]. The incidence of myocarditis is difficult to determine as the diagnostic gold standard, endomyocardial biopsy, is seldom used [3,4]. The Global Burden of Disease study reported an incidence of 22 cases of myocarditis per 100,000 patients based on International Classification of Diseases (ICD) codes on hospital discharge documentation between 1990 and 2013 [5].

Cardiac troponins are sensitive biomarkers for myocyte injury in patients with clinically suspected myocarditis. However, they are non-specific and when normal do not exclude myocarditis [6,7]. In the past few years, highly sensitive troponin tests allow detection of minimal increase in serum troponin levels and can possibly identify more patients with myocarditis. A small study demonstrated that high sensitive troponin-T (hsTnT) is a predictive marker for the diagnosis of acute myocarditis with a sensitivity of 83% and specificity of 80% using a cutoff of 50 ng/L [8].

Prognosis is generally good with recovery of most cases. However, when complicated by left ventricular (LV) dysfunction, Heart Failure (HF) or arrhythmia it is associated with up to a

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12% rate of either in-hospital mortality or need for heart transplant [9,10]. While literature has reported occurrence of myocarditis recurrences in significant proportion of patients [11,12], the overall recurrence rate of acute myocarditis has remained undisclosed.

The aims of this study were to uncover the long-term prognosis of myocarditis and the recurrence rate in a diagnosis with the use of hsTnT.

Methods

Study Design

This is an extended follow-up of a retrospective single center cohort study consisting of patients recently diagnosed with acute myocarditis at Meir Medical Center between January 1, 2000 and April 30, 2020. Data was sourced from Meir Medical Center's electronic medical records, including imaging studies, ER visits, hospital admissions, and outpatient follow-up at cardiology clinics. Eligible participants were identified based on ICD-9 diagnoses or myocarditis imaging reports. Inclusion criteria were age 18 or older and a newly diagnosed myocarditis confirmed by a positive troponin test.

Clinical diagnosis of acute myocarditis relied on the combination of clinical symptoms, ECG finding, and cardiac biomarkers typically of myocarditis, excluding acute coronary syndrome. Relevant cases were manually retrieved, collecting baseline demographics, laboratory data (baseline troponin levels), and cardiovascular risk factors (table 1). Positive troponin results were defined as >0.1 mg/L (or 100 ng/L) for "regular" test (REG group) and >14 ng/L (or 0.014 mg/L) for hsTnt test (HS group). ECG recordings were assessed for ST segment deviation and T-wave abnormalities, while echocardiography evaluated for presence of left ventricular dysfunction. Radiological features of myocarditis were determined from cardiac MRI reports. Both groups were followed up for up to six years for heart-failure hospitalizations and all-cause mortality. In this study, patients were followed-up for long-term mortality and the recurrence of myocarditis events until October 31, 2023.

Study Groups and Intervention

The Patients were grouped by date of admission and type of troponin test used upon diagnosis. The first group was composed of patients diagnosed with myocarditis between January 1st, 2000, and January 31st, 2014, in the REG group and the second group was composed of patients diagnosed with myocarditis from February 1st, 2014, to April 30th, 2020, in the HS group. Patients were further followed- up for another 3.5 years period.

Table 1: Baseline characteristics.

	Troponin REG	*Troponin HS*	*P-value*
	N=121	*N=141*	
Age (mean, sd)	37.2±13.06	36.5±14.6	0.685
Gender			
Male	(100)83%	(117)83%	0.916
Female	(41)17%	(24)17%	0.916
N. of Cardiovascular risk factors*			
0	(100)83%	(116)82%	0.687
1	(13)11%	(18)13%	0.503
2	(7)6%	(3)2%	0.138
3	(0)0%	(4)3%	0.045
Smoking	(15)12%	(20)14%	0.672
Normal LVEF (%)	(83)69%	(111)79%	0.048
Peak troponin (ng/L)	1053.49	999.68	0.701
ECG	N=85	N=75	
ST - Changes	(44)51%	(22)29%	0.006
T- Wave Inversion	(29)34%	(34)45%	0.151

*Cardiovascular risk factors: Diabetes, Hypertension, Dyslipidaemia
LVEF= Left Ventricular Ejection Fraction

Outcomes

The primary outcome was long-term mortality and acute myocarditis recurrence rates. Secondary outcomes were composed of diagnosis rate after HS-troponin test application in the emergency-room setting, mild myocarditis cases diagnosed (defined as normal LV function and no cardiac sequela), hospitalization for heart failure and overall mortality.

Statistical Analysis

Data are presented as median (inter-quartile range [IQR]) for continuous variables and frequency (%) for categorical variables. Baseline characteristics between patients were compared using two-sample t-test was used for continuous data and a $\chi 2$ test, for categorical data. The cumulative incidence of the primary outcome over follow-up period and corresponding 95% Confidence Intervals (CI) was calculated for each group with death as competing risk and comparison of the two groups using log rank test. Clinically statistical significance was determined as P<0.005. Statistical analysis was performed using the SPSS software (version 25, SPSS Inc., Chicago IL). The study was approved by the Institutional Ethics Committees in accordance with the Declaration of Helsinki.

Results

The study cohort included 262 consecutive patients newly diagnosed with acute myocarditis. The REG group included 121 patients; HS group included 141 patients. Clinical characteristics, cardiovascular risk factors and demographic features are presented in Table 1. Mean age was 37.2±13.6 years in the REG group and 36.5±14.62 in HS group (p=0.685), most of patients were male (83% in both groups). Mean troponin values were 1053.49±944.78 in REG group and 999.68±1264.23 ng/L in HS group (p=0.701).

Clinical Features

Only 50% of patients in each group had complete ECG data. Higher degree of ST segment changes was observed in REG group, 51% vs. 29% (44/87 patients and 22/75 patients respectively), p=0.006, as presented in figure 1. No significant difference was found in T wave abnormalities between the groups (P=0.151).

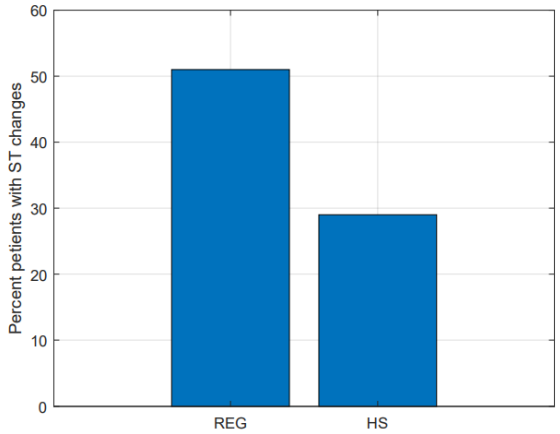

Figure 1: ECG Changes.

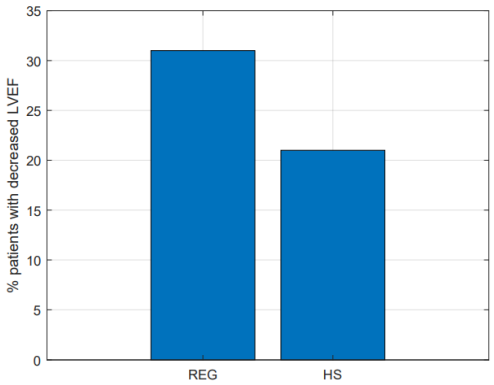

Figure 2: LV Function.

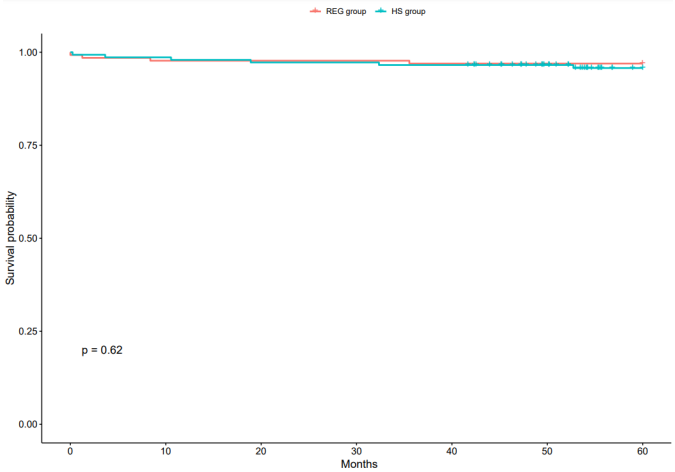

Figure 3: Kaplan-Meier curve for mortality.

Primary Outcomes

Mortality: Overall, fifteen patients have died during follow-up. During the follow up in the preliminary study, five patients have died during the follow-up in both groups. In the extended follow-up, we revealed 2 more mortality cases in the REG group and 3 more cases in the HS group. Death of cardiovascular causes was evident in 4 of 7 cases in the REG group and in 4 of 8 in the HS group. There was no significant difference in all-cause mortality rate between the groups (8/141 patients in the HS group vs. 7/121 patients; p= 0.62), figure 3.

Myocarditis recurrence rate: During the extended follow-up, we identified 22 cases (8.4%) of acute myocarditis recurrence, among them, 3 patients had multiple episodes (3). Recurrence of myocarditis was not associated with increased mortality.

Secondary Outcomes

Myocarditis diagnosis rate: Using hsTnT, there was a nearly two-fold increase in the incidence rate of myocarditis (0.063 patients per day, a patient every 16 days and 0.037 patients per day- a patient every 27 days, respectively), with statistically significance of p<0.001 (95% CI 0·014%-0·038%). Patients in the REG group had higher rates of echocardiography confirmed reduced LV function. Of 141 patients in HS group, 111 patients (79%) had normal LV function compared to 83 of 121 patients (69%) in REG group, p=0.048 (Figure 2).

Recurrent hospitalizations: Only 3 patients were subjected to recurrent hospitalization due to exacerbation of heart failure, of which 1 was in REG group and 2 in HS group, with no statistical significance.

Discussion

In our extended follow-up study of myocarditis patients, the overall survival did not significantly change in either group. however, compared to the general population, there were relatively high cardiovascular mortality rates. The recurrence rate was 8.4% for the entire cohort and did not imply worse prognosis.

Myocarditis is an inflammatory disease of the myocardium caused by different infectious and non-infectious triggers. In 1995, myocarditis was defined by the World Health Organization (WHO)/International Society and Federation of Cardiology (ISFC) as an inflammatory disease of the heart muscle, diagnosed by established histological, immunological, and immunohistochemical criteria [13]. Myocarditis often results from common viral infections and post-viral immune-mediated responses.

Myocarditis may present with a wide range of symptoms, ranging from mild dyspnea or chest pain that resolves without specific therapy to cardiogenic shock and death, due to malignant ventricular arrhythmias and/or fulminant heart failure. The progression of myocarditis exhibits significant heterogeneity in its natural course, ranging from complete recovery to prolonged development of cardiomyopathy or mortality attributed to ventricular arrhythmias and/or severe systolic dysfunction [14]. Dilated cardiomyopathy (DCM) with chronic heart failure is the major long-term sequela of myocarditis. Yet, most individuals with myocarditis presenting as acute dilated cardiomyopathy generally experience a mild form of the disease that resolves spontaneously with no sequels [15,16]. However, it is notable that up to 30% of patients with biopsy-proven myocarditis may experience progression to DCM, and such cases are associated with an unfavourable prognosis [4].

In our cohort there was no noticeable difference in mortality rates between the groups (8/140 vs. 7/121 patients), although th patients diagnosed in the REG group were with more severe manifestations, including heart failure. This could be partially explained by underdiagnosed patients that were not included in the REG group.

The gold standard for the diagnosis of myocarditis is the EMB. According to the Dallas criteria, acute myocarditis is defined as the histologic evidence of lymphocytic infiltrates in association with myocyte necrosis [17]. However, subjected to sampling error, variation in expert interpretation, alteration with other markers of viral infection and immune activation in the heart, EBM seldom is used in clinical routine, and is usually reserved for selected cases with severe or rapidly progressive symptoms, and in specific clinical scenarios, such as myocarditis in the setting of immune checkpoint inhibitor therapy, acute myocarditis or chronic inflammatory cardiomyopathy with persistent or relapsing release of biomarkers of myocardial necrosis, particularly if associated to an autoimmune disorder or ventricular arrhythmias or high-degree atrioventricular block or suspected chronic inflammatory cardiomyopathy associated with peripheral eosinophilia [1,18].

Thus, the diagnosis is commonly established by clinical presentation, cardiac biomarkers, and noninvasive imaging findings. Cardiac MRI is a beneficial tool for the diagnosis of myocarditis, with high sensitivity and specificity. This modality can detect intracellular and interstitial edema, capillary leakage and hyperemia that support the diagnosis of myocarditis (Lake Louis criteria) and in severe cases cellular necrosis and interstitial fibrosis. Based on the Lake Louis criteria, myocarditis can be predicted with a diagnostic accuracy of 78% [19]. In our study,

however, cardiac MRI was more attainable during later period, thus most patients were diagnosed clinically and based on laboratory results.

Biomarkers (such as troponins or creatine kinase) lack specificity, but may help to confirm the diagnosis of myocarditis [20,21]. In patients with acute myocarditis, serum concentrations of troponin I and T are elevated more frequently than creatine kinase myocardial band fraction [7], and higher levels of troponin T have been shown to be of prognostic value. In patients with a history suggestive of myocarditis, an increased cardiac troponin implies myocardial injury, particularly when measured with an assay with high precision. Experimental and clinical studies suggest that serum hsTnT can be a useful diagnostic tool early in the course of myocarditis [20,22]. Cardiac biomarkers in fulminant myocarditis can reach levels similar to those in patients with transmural myocardial infarctions caused by epicardial coronary occlusions [2]. Multiple mechanisms are causative of cardiac troponin leakage in these situations, not solely restricted to irreversible cardiomyocyte necrosis. Potential pathways also include increased left–ventricular filling pressures with subsequent myocardial wall stress, toxicity from inflammatory cytokines, oxidative stress, catecholamine excess and direct cellular damage. However, an absence in hsTnT rise does not rule out myocarditis [22]. Observational studies had failed to prove a significant correlation between the magnitude of troponin measured and prognosis [23-25].

Our research indicates that employing hsTnT in the emergency room enhances the detection rates of myocarditis. This improved rate of recognition resulted in the identification of cases with relatively milder severity and preserved left ventricular function. The diagnosis of myocarditis did not lead to an increased incidence of cardiac complications in the initial follow-up period.

In our study, the mean troponin-T peak in the REG group was 1053.49 ng/L compared with 999.68 ng/L in the HS group. Like previous reports, we could not find a correlation with maximal troponin levels and mortality. This points towards the significance of troponin as a diagnostic rather than prognostic tool.

The underlying mechanism leading to the recurrence of acute myocarditis remain unclear. In most cases, viral infection is resolved after the acute phase with the resolution of clinically evident illness. Nonetheless, in certain patients, viral infection may trigger autoimmune reaction by the emergence of autoreactive T-cells and cardiac mediated antibodies [26,27]. Reactivation of a persistent viral infection is also recognized as a potential factor contributing to recurrence [28]. Like our findings of 8.4% myocarditis recurrence rate, a large registry demonstrated that myocarditis reoccurs in a significant proportion of patients, for 4.5 year follow up is found to be 10.3%. Prolonged initial admission, ventricular arrhythmias, younger age, inflammatory bowel disease and chronic pulmonary disease are associated with recurrences at different phases after acute myocarditis [11].

Our study had several limitations. First, it is of retrospective nature, which is prone to selection bias. Second, the diagnosis of myocarditis in this study was based on clinical suspicion, evidence of myocardial injury, and the exclusion of an acute coronary event. It could be that events identified as myocarditis were in fact atherosclerotic heart disease without significant coronary stenosis, and vice versa, thus a more accurate diagnosis might have affected study results. Third, the study expands over a period of 20 years, during this time some of the documentation was manually retrieved, which may have led to emitting of undiagnosed cases. Some patient files had only partial data, such as a single troponin test, and that could impact peak troponin calculations. Different follow up periods could have also affected outcomes for recurrent hospitalizations. Fourth, the study was conducted in a single center in Israel, clinical practice may vary from different centers in Israel and other countries.

Conclusion

The utilization of hsTnT testing in suspected myocarditis cases has the potential to enhance diagnostic accuracy and identify milder instances. Extended follow-up results indicate an overall positive prognosis for myocarditis recovery, despite a relatively elevated recurrence rate, which does not impact the long-term outcomes.

Author Statements

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