


Original Article



C-Reactive Protein Can Predict Outcomes in Patients With Takotsubo Syndrome

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OPEN ACCESS

Received: Jun 17, 2023

Revised: Sep 10, 2023

Accepted: Sep 26, 2023

Published online: Oct 10, 2023

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ABSTRACT

Background and Objectives: Takotsubo syndrome (TTS) is a form of reversible cardiomyopathy often preceded by mental or physical stressors and predominantly affects elderly women. Several cardiac and inflammatory biomarkers are involved in the pathogenesis of the disease. We aimed to investigate the correlation of C-reactive protein (CRP) level with left ventricular ejection fraction (LVEF) and clinical outcomes in patients with TTS.

Methods: The study included patients with discharge-diagnosis of Takotsubo through 2017–2022 from the cardiology department. Demographic, laboratory, echocardiographic, and clinical outcomes were retrospectively obtained. We investigated the relation between CRP and LVEF, length of stay (LOS), in-hospital complications, and recurrence.

Results: A total of 86 patients (93% female, mean age 68.8±12.3 years) were included in the study. The median CRP level was 17.4 (interquartile range [IQR], 6.1–40.1) mg/L, and the mean LVEF was 41.5%, (IQR, 38–50%). Complications occurred in 24 (27.9%) of the patients, and the median LOS was 3 (IQR, 3–5) days. The level of CRP was associated with lower LVEF ($r=-0.39$, $p<0.001$), longer hospital stay ($r=0.25$, $p=0.021$), and recurrence. There was no correlation between CRP and in-hospital complications. In multivariate logistic regression, poor LVEF was associated with TTS recurrence (odds ratio, 1.22; 95% confidence interval, 1.08–1.37; $p=0.001$). Using linear regression, only CRP was correlated with longer LOS and lower LVEF ($p<0.001$).

Conclusions: Among patients hospitalized with TTS, CRP level was associated with poor LVEF and prolonged hospital stay but not with in-hospital complications. Poor LVEF was also associated with TTS recurrence.

Keywords: Takotsubo cardiomyopathy; Inflammation; Cardiovascular outcome

INTRODUCTION

Takotsubo syndrome (TTS) is a form of transient cardiomyopathy that predominantly affects elderly women and often preceded by physical or mental stressor.^{1,2} Several patterns of TTS have been reported with apical type (in which, the basal segments of the heart exhibit hypercontractility while the apical segment becomes hypokinetic/akinetic) being the most common.³ Based on the echocardiographic appearance, less common types have been reported, including the mid ventricular, reverse, focal, and global types.³⁻⁵ The diagnosis at presentation may

be challenging since the clinical features mimic acute coronary syndrome (ACS) in that both conditions present with chest pain, electrocardiogram changes and elevated troponin.⁶⁾ Once the diagnosis is suspected, the probability may be assessed using the InterTAK score.⁷⁾ For definitive diagnosis, the InterTAK diagnostic criteria were recently proposed by the Takotsubo International Registry.⁸⁾ Although mistakenly considered a benign condition, the overall outcome of TTS is comparable to that of ACS.^{9,10)} Several biomarkers have been implicated in the pathophysiology of the disease including catecholamines, natriuretic peptide (NP), and inflammatory markers. For example, TTS-like disease was induced following the administration of catecholamine in animal models.¹¹⁾ Moreover, several biomarkers were suggested for diagnostic purpose and risk stratification of patients with TTS. Patients with TTS usually present with modest increase in troponin level compared to high levels of NP, and therefore NP/troponin has adequate specificity and sensitivity to distinguish TTS from ACS.¹²⁻¹⁴⁾ C-reactive protein (CRP) is a marker of inflammation that usually indicates the severity of infectious and inflammatory conditions. Since inflammation plays a central role in TTS, we thought to investigate its role in the disease based on a retrospective cohort study. We aimed to evaluate the association between CRP and left ventricular ejection fraction (LVEF), and its impact on the clinical course of patients with TTS.

METHODS

Study population

This retrospective study is based on clinical data of patients hospitalized in the cardiology unit, Galilee Medical Center, Nahariya, Israel. The study included patients through 2017–2022 with discharge diagnosis of “Takotsubo syndrome.” To exclude obstructive coronary artery disease, coronary angiography was performed in most cases. In few cases, when the patient refused angiography, TTS was highly suggested by typical echocardiographic appearance and clinical scenario. We excluded patients with sepsis (patients with fever, bacteremia, or evidence for any infectious disease). We also excluded unstable patients requiring inotropic agents or mechanical support. In all cases of suspected TTS, a thorough interview was performed with the patient in order to identify possible stressors before symptom onset. The baseline characteristics, laboratory, and echocardiographic data were obtained based on the computerized files.

Laboratory parameters

Maximal levels of CRP, white blood cells (WBC) and troponin were obtained for all patients. For CRP level measurement, the high sensitivity assay is used (normal range, 0.2–1.2 mg/dL).

High-sensitivity troponin I (hs-TnI) level was measured using ARCHITECT assay (Abbott Laboratories, Abbott Park, IL, USA). Cut-off values for abnormal hs-TnI levels were above 20 and 30 ng/L for men and women, respectively. Electrocardiographic changes were reported in case of the following findings: ST-segment elevation or depression, T-wave inversion, and QT segment prolongation.

Echocardiography

Echocardiography was performed using Philips Epiq-7 machine with EPIQ X8-2t transducer (Phillips, Adnover, MA, USA). LVEF was calculated by the Simpson’s biplane method in the apical 4- and 2-chamber views using the formula: LVEF = (Left Ventricular End-Diastolic Volume–Left Ventricular End-Systolic Volume)/Left Ventricular End-Diastolic Volume×100. All echocardiographic studies were performed and interpreted by an expert cardiologist.

Outcomes

For each patient, we obtained the following clinical outcomes: the length of stay (LOS), TTS-related complications (atrial and ventricular arrhythmia, QT segment prolongation, and pulmonary congestion), recurrence, and 1-year mortality rate. Data was derived based on computerized files in a retrospective way.

Statistical analysis

Categorical variables are presented as percentages, while continuous variables by median with interquartile range (IQR). We used Fisher’s exact test and χ^2 test to compare categorical variables between the 2 groups. Independent sample t-test and Mann-Whitney tests were used for continuous variables. To test the influence of CRP on recurrence, in-hospital complications, and LVEF, we used Spearman’s test multivariate regression models and Kaplan-Meier curves. All tests were conducted at a two sided overall 5% significance level ($\alpha=0.05$). Statistical analysis was performed using IBM SPSS statistics, version 27 (IBM Corp., Armonk, NY, USA). The study was approved by the local ethical committee of Galilee Medical Center.

RESULTS

Baseline characteristics and clinical course

As expected, most of the patients (93%) were women, and about 75% of them reported emotional or physical stress before symptom onset. The baseline characteristics are provided in **Table 1**.

Clinical course

All patients survived the index hospitalization without need for

CRP in Takotsubo Syndrome

Table 1. Baseline characteristics of the patients

Characteristics	Values (n=86)
Age (years)	70 (61–78)
Female	80 (93)
Hypertension	55 (64.0)
Diabetes mellitus	24 (27.9)
Hyperlipidemia	49 (57.0)
Tobacco use	18 (20.9)
Chronic kidney disease	8 (9.3)
Trigger	64 (74.4)
LVEF%	41.5 (38–50)
ECG changes	51 (59.3)
Trigger before onset	
Positive stress	3 (3.5)
Negative stress	48 (55.8)
Work related	4 (4.7)
COVID-19 related	3 (3.5)
Post-surgery	6 (6.9)
No obvious trigger	22 (25.6)
Systolic BP (mmHg)	125 (105–139)
Diastolic BP (mmHg)	77 (60–83)
Heart rate (BPM)	79 (67–93)
WBC ($\times 10^3/uL$)	9.1 (7.4–12.3)
Hemoglobin (gr/dL)	12.4 (11.3–13.2)
Creatinine (mg/dL)	0.81 (0.71–0.97)
Troponin (ng/L)	1,922 (852–5,383)
CRP (mg/L)	17.4 (6.1–40.1)

Values are presented as median (interquartile range) or number (%). LVEF = left ventricular ejection fraction; ECG = electrocardiogram; COVID-19 = coronavirus disease 2019; BP = blood pressure; BPM = beats per minutes; CRP = C-reactive protein.

mechanical support. The final diagnosis was confirmed by a senior cardiologist based on the common recommended criteria. Patients were treated depending on symptoms and complications. Inotropic agents and mechanical ventilation were not required in any patient. Beta-blockers and angiotensin-converting enzyme inhibitors were often used when there was evidence of left ventricular dysfunction. Diuretic therapy was used in cases of volume overload (pulmonary congestion). Complications occurred in 24 (27.9%) of patients and included atrial fibrillation, pulmonary congestion, and non-sustained ventricular tachycardia. QT-segment prolongation was documented in more than 50% of the patients, however without Torsades de pointes events. Patients were discharged when they were symptoms free after a median of 3 (IQR, 3–5) days. All patients were alive in 1 year follow-up. Within 5 years, recurrent TTS was reported in 7 (8.1%) of the patients. The flowchart of the study is presented in **Figure 1**.

Impact of CRP level on outcomes

CRP level was inversely correlated to LVEF ($r=-0.39$, $p<0.001$; **Figure 2**) and to prolonged hospitalization ($r=0.248$, $p=0.021$; **Figure 3**). Patients with higher CRP level experienced more symptomatic disease, though there was no difference in the prevalence of complications during the index hospitalization (**Figure 4**).

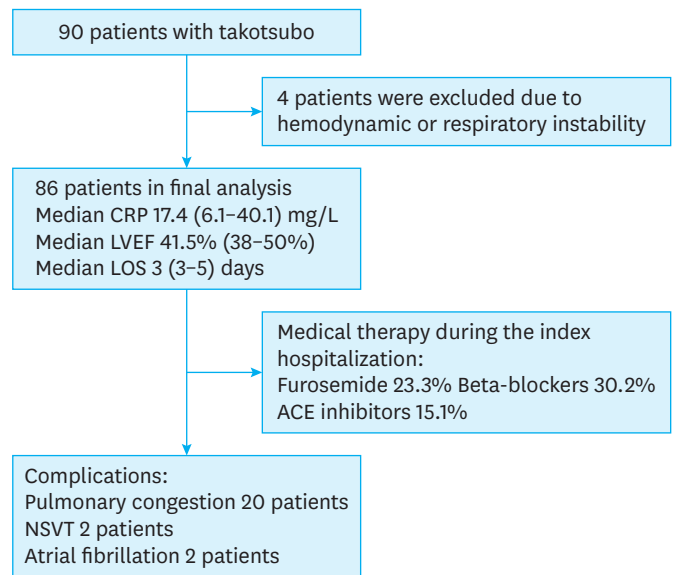


Figure 1. Flowchart of the study. CRP = C-reactive protein; LVEF = left ventricular ejection fraction; LOS = length of stay; ACE = angiotensin-converting enzyme; NSVT = nonsustained ventricular tachycardia.

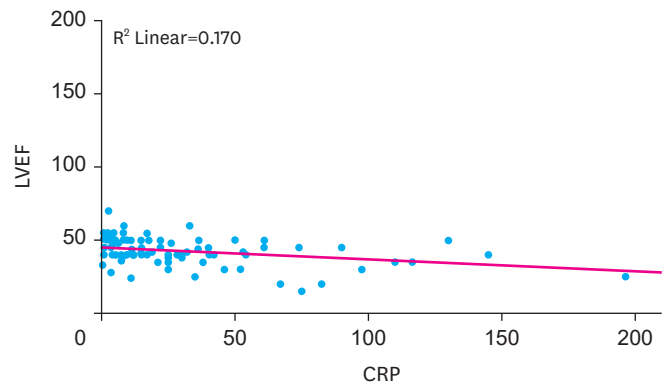


Figure 2. The correlation between CRP and left ventricular function. An inverse correlation was observed between CRP and EF. We hypothesize that severe cases of TTS, characterized by poor EF, are associated with enhanced inflammatory process reflected by high CRP level. CRP = C-reactive protein; EF = ejection fraction; TTS = Takotsubo syndrome; LVEF = left ventricular ejection fraction.

TTS recurrence occurred in 7 patients. We evaluated the correlation between CRP level (divided to 4 quarterlies) and TTS recurrence as shown in **Figure 5**.

However, when implementing multivariate logistic regression (including age, gender, diabetes, hypertension, CRP, and LVEF), only poor LVEF was associated with an increased risk of TTS recurrence, (odds ratio, 1.22; 95% confidence interval, 1.08–1.37; $p=0.001$). Using linear regression with the above mentioned variables, only CRP was correlated with longer LOS ($p<0.001$). In addition, only CRP level was associated with lower LVEF ($p<0.001$).

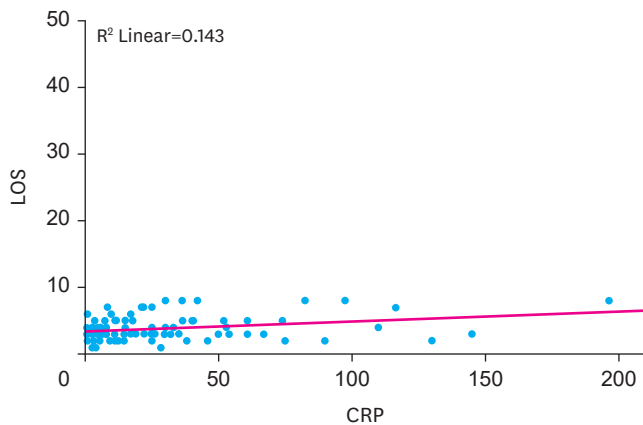


Figure 3. The correlation between CRP level and LOS. We demonstrated a modest correlation between CRP level and LOS. LOS reflects, in part, the severity of the disease and the duration of symptoms. It should be noted that there were no patients with severe sepsis in the study and therefore CRP during the index hospitalization is related to TTS only. CRP = C-reactive protein; LOS = length of stay; TTS = Takotsubo syndrome.

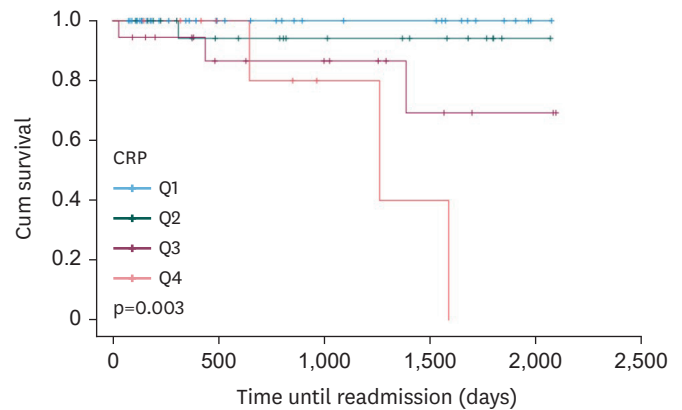


Figure 5. Kaplan-Meier of TTS risk of recurrence stratified by different CRP levels. Seven patients had recurrent TTS, 6 of them have CRP above 80 mg/L. Patients with higher CRP level (3rd and 4th quarterlies) have higher risk for readmissions ($p=0.003$). TTS = Takotsubo syndrome; CRP = C-reactive protein.

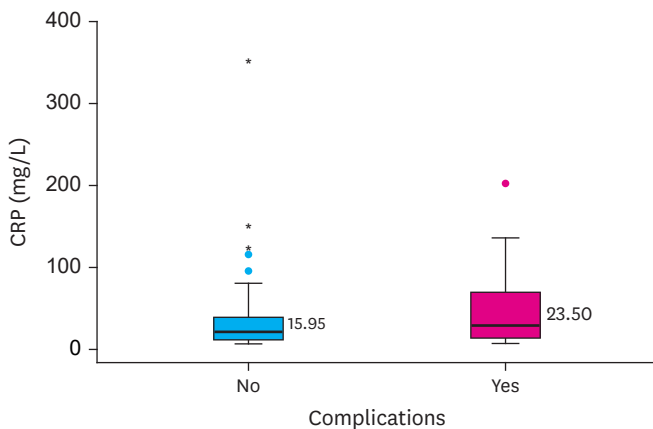


Figure 4. Complications and CRP level. In 24 patients with in-hospital complications (including atrial fibrillation, pulmonary congestion, and non-sustained ventricular tachycardia) the median CRP level was 23.5 (IQR, 7.6–65.5) compared to 15.9 (IQR, 5.3–34.0) mg/L in the group without complications ($p=0.154$). CRP = C-reactive protein; IQR = interquartile range.

The association between troponin level and outcomes has also been assessed. A weak correlation was demonstrated between maximal troponin and LOS ($r=0.194$, $p=0.036$) and a moderate inverse correlation with LVEF ($r=-0.327$, $p=0.002$). Nonetheless, a strong correlation existed between troponin and CRP ($r=0.412$, $p<0.001$). These observations reinforce the findings that symptomatic patients with reduced LVEF have higher CRP level, along with previous known findings that TTS often presents with modest increase in troponin level.

DISCUSSION

Although the mechanism of TTS is not fully clear yet, it is well established that inflammation plays a central role.¹⁵⁻¹⁸ In the current study we investigated the association between CRP level, a marker of inflammation, and the clinical outcomes in stable patients with TTS. We found that higher CRP level is associated with reduced LVEF and longer LOS, a potential indicator of symptomatic disease. Moreover, CRP level in the index hospitalization may also be related to recurrence. Previously, Morel et al.¹⁹ showed that leukocytosis and higher CRP levels are associated with reduced LVEF and enhanced myocardial iodine 123 meta-iodobenzylguanidine uptake in single photon emission computed tomography in the mid-ventricle and apical segments in the acute phase of TTS. Moreover, residual inflammation (reflected by high CRP on discharge) was also associated with increased cardiovascular events and impaired cardiac function recovery in a recent study.²⁰ These results are consistent with the findings of our study reflecting a significant role of CRP and inflammation in TTS. Likewise, in an experimental takotsubo-like cardiomyopathy model in rats (induced by intraperitoneally isoprenaline injection), chronic inflammatory changes were evident by early neutrophile followed by macrophage infiltrates.²¹ A recent histological analysis of endomyocardial biopsies obtained from patients with TTS also showed similar results of inflammatory cells with multiple vacuoles and glycogen as a possible result of protein metabolism disturbance.²² We suggest that CRP, a simple biomarker of inflammation, may be used for risk stratification of patients with TTS along with NP levels. CRP may indicate the severity of the disease, cardiac dysfunction, and possibly the risk of recurrence. Although extremely high CRP level should warrant

other inflammatory etiology such as acute myocarditis, it should be noted that tissue inflammation in TTS has been documented also in such cases.^{19,23)} TTS related to inflammatory diseases or checkpoint inhibitors may also be associated with extremely high CRP level and erythrocyte sedimentation rate.^{24,25)} Cardiac magnetic resonance imaging may be very useful in making the differentiation between TTS and myocarditis. One of the strongest predictors of cardiovascular outcomes in TTS is cardiac function (both systolic and diastolic) during the acute phase and upon discharge.²⁶⁾ Cardiac function evaluated by standard echocardiography or global longitudinal strain was shown to be associated with long-term mortality with incremental prognostic value and can predict complications in TTS such as cardiogenic shock and delayed recovery.²⁷⁾ In their study, Citro et al.²⁸⁾ reported that LVEF below 35% at presentation represents an independent risk factor for major adverse cardiovascular events in the short and long term. In our study, patients with higher CRP level have also longer hospital stay although without increase in complications. Hospital stay during the acute phase of TTS is derived from symptom duration and complications and it is reasonable that patients with marked inflammatory process experience more symptomatic disease. In one nationwide registry, the average LOS for TTS was 4 days with a trend of increase in hospitalization rate without change in the short- or long-term outcomes.²⁹⁾ It is now well established that TTS does not always has a benign course, and that the overall mortality rate is comparable to ST-elevation myocardial infarction due to potentially fatal complications.^{1,30)} The lack of association between CRP and complications in our study may be attributed to the small study population and the relatively low rate of complications as we included stable patients. Since CRP level was correlated to cardiac function in the acute phase and to prolonged hospital stay, it would be reasonable to use it in a routine way for risk stratification and follow-up.

Our study has several limitations. First, we included only patients with stable hemodynamic condition without major complications such as intractable ventricular arrhythmia, cardiogenic shock or left ventricular outflow tract obstruction. The low complications rate in the study population may explain why the difference between the groups did not reach statistical significance. Second, the small study-population and the retrospective design may also limit the conclusions for the whole population. Third, NP level was not available in many patients and was dismissed from the final analysis. NP level has been used for risk stratification in patients with TTS and for differentiation from ACS. It might be interesting to investigate the additive value of CRP on top of NP in risk stratification. Fourth, we evaluated the impact of disease severity by the correlation between CRP and LOS, however, LOS may be affected by other non-medical factors such as

patient preference. A more specific disease score that addresses the symptoms may be more reliable for this purpose. Fifth, other confounders that could not be taken in account may affect the results of the study. Further studies are warranted in order to establish the routine use of CRP for risk stratification in TTS.

In conclusion, the level of CRP in our study population correlated with poor LVEF and longer hospital stay in patients with TTS. We recommend the routine use of CRP for risk stratification in addition to other parameters in the acute phase of patients with TTS.

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Moady G; Data curation: Sweid R; Formal analysis: Moady G, Sweid R; Investigation: Moady G, Yelin B; Methodology: Moady G, Sweid R; Supervision: Atar S; Writing - original draft: Moady G, Yelin B; Writing - review & editing: Moady G, Atar S.

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