High-sensitivity C-reactive protein as a 6-month predictor of mortality and rehospitalization in patients with heart failure

CrossMark

Memorison Tarigan[1*], Refli Hasan[1], Zainal Safri[1]

ABSTRACT

Background: C-reactive protein (CRP) is an acute phase protein that reacts as a non-specific systemic inflammatory marker. Recent studies indicate that high-sensitivity CRP (hs-CRP) is a strong risk factor for predicting ensuing cardiovascular events.

Objective: To investigate whether hs-CRP could serve as a parameter in predicting 6-month mortality and the likelihood of rehospitalization of patients with HF.

Method: A prospective cohort study observed a total of 44 patients admitted to RSUP Haji Adam Malik Medan diagnosed with primary heart failure (HF) from November 2016 to February 2017. Level of hs-CRP was analyzed at their initial assessment and subjects were followed up for 6 months for mortality and rehospitalization.

Result: Fourteen (31.8%) patients died and nineteen (42.3%) patients were rehospitalized during the 6 months follow up period. The mean value of hs-CRP was higher in the mortality group (4 group (4.386±1.75) than the survivor group (2.227±1.80), P=0.001.

There was no significant difference in the mean value of hs-CRP between rehospitalized patients group (2.858±1.99) compared to the group that was not rehospitalized (2.759±2.15), P=0.880. The analysis using the receiving operating characteristic (ROC) curve obtained area under curve (AUC) of 81% (95% confidence interval [CI]: 0.68-0.94), P=0.001. Based on the ROC curve, an hs-CRP value of 4.25 result in a sensitivity value of 63% and a high specificity value of 90%, P=0.000.

Conclusion: Among HF patients, increasing level of hs-CRP with cut-off value of 4.25 can be used as a 6-month mortality predictor and have a sensitivity of 64% and specificity of 90%. There were no significant differences in hs-CRP level between patients with HF who experienced rehospitalization within 6 months and who did not, hence hs-CRP could not be used as a predictor of rehospitalization within 6 months in patients with HF.

[1]Cardiac Division, Departement of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan-Indonesia

*Corresponding to:
Memorison Tarigan; Cardiac Division, Departement of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan-Indonesia;
memorisont@yahoo.co.id

BACKGROUND

Heart failure (HF) is a complex clinical syndrome caused by disorders of the structure and function of the heart, which alters the ability of the heart to pump blood to comply with the needs of the body. This condition is characterized by hemodynamic disturbances such as decreased cardiac output and increased ventricular filling pressure.[1-3]

Current studies revealed that congestive heart failure should be viewed as a neurohormonal model, where HF results from excessive expression of biologically active molecules that prompt excretion of deleterious substances on the heart and the circulation system.[1] Since the recognition of inflammatory cytokine activation in HF patients, to date, there is rise in the concern of reinforcing comprehension about its contribution to the progression of HF.[4,5]

C-Reactive Protein (CRP) is an acute phase protein that reacts as a non-specific systemic inflammatory marker. The level of CRP increases in response to infection, inflammation or tissue damage. In humans, plasma CRP, which is synthesized by hepatocytes, can surge rapidly more than 1000-fold after acute inflammatory stimuli. CRP is one of the many gene expressions expressed by the liver during an inflammatory process.[6] CRP level can increase within 4-6 hours after a stimulus which will then duplicate every 8 hours and peaks at 36-50 hours. Its plasma half-life of 19 hours is expeditious but in the existence of provocations such as trauma or surgery, may take several days to return to normal values. However, clinicians should note that in critical patients, CRP values can be found low or normal in the first 12 hours of the infection process. In contrast, because of its long half-life, a high CRP value can be seen during the healing phase.[7]

CRP is a strong independent risk factor for predicting ensuing cardiovascular events encompassing myocardial infarction, peripheral vascular disease, ischemic stroke and sudden

cardiac death in previously healthy individuals without antecedent cardiovascular disease.[8]

High-sensitivity CRP (hs-CRP) testing is a method to detect low levels of CRP concentrations, making them more sensitive with a measurement range between 0.1-20 mg/L; this suggests that hs-CRP is an excellent marker to check low degree inflammation. Research conducted by Gottdiener et al. displayed the role of hs-CRP as an independent and substantial predictor in predicting the development of HF.[9] Research by Bursi et al. suggests CRP as an independent predictor of high rates of heart failure and mortality following cardiac infarction.[10] The Valsartan Heart Failure Trial (Val-HeFT) study exhibited that hs-CRP may be used as an independent predictor of morbidity and mortality in patients with heart failure.[11]

To date, in Indonesia, particularly in RS H. Adam Malik Medan, there was no research about hs-CRP in HF patients. In this study, we will use hs-CRP as a parameter predicting mortality and rehospitalization rate within the first 6 months in patients with HF. Our goal was to find out whether hs-CRP could serve as a parameter in predicting 6-month mortality and the likelihood of rehospitalization in patients with HF. In addition, we wanted to determine the accuracy of hs-CRP in predicting 6-month mortality and probability of rehospitalization in HF patients. We also sought to explore the prognosis of medium-term mortality and morbidity in patients with HF.

METHODS

Study Population
We prospectively observed patients admitted to RSUP Haji Adam Malik Medan diagnosed with primary HF from November 2016 to February 2017. The diagnosis of HF was made on the basis of adept anamneses and physical examinations, electrocardiography, chest x-ray, doppler-echocardiography, cardiac catheterization, and training test. The investigation of HF should fulfill the concurrent presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria listed in the Framingham criteria of HF, and should not conform to the criteria of cardiogenic shock or hypertensive crisis.[3]

To determinte the sample size, we used the sample size formula of:

$$n = \left\{ \frac{(Z\alpha^2 Sen\ p\ .\ (1-p))}{d^2} \right\}$$

where n is the subject size, Sen is the expected sensitivity, p is the prevalence of mortality and rehospitalization of HF paitents, and d is the precision. The expected sensitivity of this study is 90%, therefore the $Z\alpha$ 5% equals to 1.96. The prevalence of mortality and rehospitalization of HF patients in 6 months were 14% and 22%, respectively. The precision value used in this study was 15%. From the sample size formula, we obtained a minimal sample size of mortality and rehospitalization of 21 and 30 samples, respectively.

To avoid bias, we included only patients aged 18 years old and above who were informed of and gave written consent to participate in the research voluntarily to underwent further examinations. For the purpose of this analysis we excluded patients with hs-CRP level more than 10mg/L; patients with acute coronary syndrome; patients with chronic liver disease, chronic renal failure, malignant disease, stroke, or systemic collagen disease; having history of trauma, surgery, burns; and patients who were taking medications that reduce hs-CRP levels such as statins and steroids over the last 1 month prior to the study.

Data Collection
Participants were asked to complete a standardized questionnaire to gather data. Data included name, age, sex, medical record number, address, telephone number, anamnesis, physical examination, and investigation including laboratory examination and imaging examination to diagnose heart failure. Nonfasting blood samples were taken from all subjects who met the inclusion criteria. Serum was then examined using latex particle-enhanced immunoturbidimetric method using Architect (Abbot) Automatic Analyzer and CRP Vario reagent kit. The patients were then followed up for 6 months from the initial examination for their mortality and the occurrence of rehospitalization. The occurrence of rehospitalization was designated by a worsening of the patient's condition and rehospitalized for more than 24 hours after discharged from the hospital subsequent to the initial admission. The information regarding patient's condition was obtained during direct encounters with the patient, data from the patient registry at the hospital, or via telephone with the patient or their family.

Statistical Analysis
The Shapiro-Wilk test was used to assess the normality of the study samples. To see the difference of the means of the variables between mortality and survivor groups, we use independent T-test if the samples were normally distributed, otherwise, Mann-Whitney test was used. To establish the comparative relationship between categorical variables we use Chi-square and Fisher's exact test. The Receiving Operating Characteristic (ROC) curve was generated to get the Area Under

Tabel 1. Characteristic of the study samples based on observation of mortality rate

Characteristic	Total (n = 44)	Mortality within 6 months	Survival within 6 months	P-value
Demography				
Sex				0,738[a]
Male, n (%)	28 (63.6)	8 (57,1)	20 (66,7)	
Female, n (%)	16 (36.4)	6 (42,9)	10 (33,3)	
Total n (%)		14 (31,8)	34 (68,2)	
Age (year), mean (SD)	53.23 (14.11)	57,29 (15,94)	51,33 (13,02)	0,196[b]
NYHA functional class				0,204[c]
Class II	1		1	
Class III	34	9	25	
Class IV	9	5	4	
Total n		14	30	
hs-CRP				
hs-CRP value, mean (SD)	2.914 (2.03)	4.386 (1.75)	2,227 (1,80)	0,001[b]
Echocardiography				
Ejection fraction(%), mean (SD)	46.55 (13.70)	41.64 (9.00)	48,83 (15,00)	0,052[d]

[a] *Fisher's Exact,* [b] *Independent T,* [c] *Kruskal-Wallis,* [d] *Mann Whitney. NYHA, New York Hear Association*

Table 2. Characteristic of the study samples based on rehospitalization rate

Characteristic	Total (n = 41)	Rehospitalization (+)	Rehospitalization (-)	P-value
Demography				
Sex				1.000[a]
Male, n (%)	28 (63.6)	12 (63.2)	16 (64)	
Female, n (%)	16 (36.4)	7 (36.8)	9 (36)	
Total n (%)		19 (43.2)	22 (56.8)	
Age (year), mean (SD)	53.23 (14.11)	49.47 (15.74)	56.08 (12.29)	0.125[b]
NYHA functional class				0.760[c]
Class II	1		1	
Class III	34	15	19	
Class IV	9	4	5	
Total n		19	25	
hs-CRP				
hs-CRP value, mean (SD)	2.914 (2.03)	2.858 (1,99)	2.956 (2.10)	0.876[b]
Echocardiography				
Ejection fraction (%), mean (SD)	46.55 (13,70)	46.74 (14.03)	46.40 (13.73)	0.953[d]

[a] *Fisher's Exact,* [b] *Independent T,* [c] *Kruskal-Wallis,* [d] *Mann Whitney. NYHA, New York Heart Association*

Curve (AUC) on the diagnostic test. The result was considered significant if the p value<0.05. Then, the predictive values were used to determine the cut off value of hs-CRP. Data were processed and analyzed using a computer program with the significance limit of <0.05.

RESULT

This research was conducted in the inpatient ward of Internal Medicine of RSUP Haji Adam Malik Medan starting from November 2016 until February 2017 with a total of 44 samples who conformed to the inclusion criteria. All subjects were then followed up for 6 months after discharged from the hospital.

In the mortality observation, the majority of the study subjects were male (n[%], 28 people, [63.6%]), with the mean age of 53.23 years. The 6-month mortality rate is 31.8%. In the group of male subjects, the mortalities were as many as 8 people (57.1%), and in the group of female subjects as many as 6 people (42.9%).

At the rehospitalization observation, the majority of subjects were male 28 people (63.6%), mean age 53.23 years. Rehospitalization rate within the first 6 months was 43.2% (19 persons). In the male subject group there were 12 people (63.2%) who were rehospitalized, and in the female group, there were 7 subjects who were rehospitalized (36.8%).

There were no significant differences of sex on patients stratified by the observation of mortality and rehospitalization rate within the first 6 months. No significant difference in mean age in both mortality and survivor groups was observed in the mortality observation. There were also no significant differences in the mean age in the group of patients who were rehospitalized and who were not.

The majority of the HF patients were classified in New York Heart Association (NYHA) functional class III. There was a 26.5% mortality rate in patients with NYHA functional class III and 55.6% in patients with NYHA functional class IV. The rehospitalization rate was 44.1% in patients with NYHA functional class III and 44.4% in patients with NYHA functional class IV. Based on the analysis, there was no significant difference in functional class either on mortality or rehospitalization observation.

The mean value of hs-CRP was higher in the mortality group (4.386 ± 1.75) than the survivor group (2.227 ± 1.80). Statistical analysis showed a significant difference in the mean hs-CRP value between the two groups (P = 0.001). There was no significant difference in the mean value of hs-CRP between rehospitalized patients group (2.858 ± 1.99)
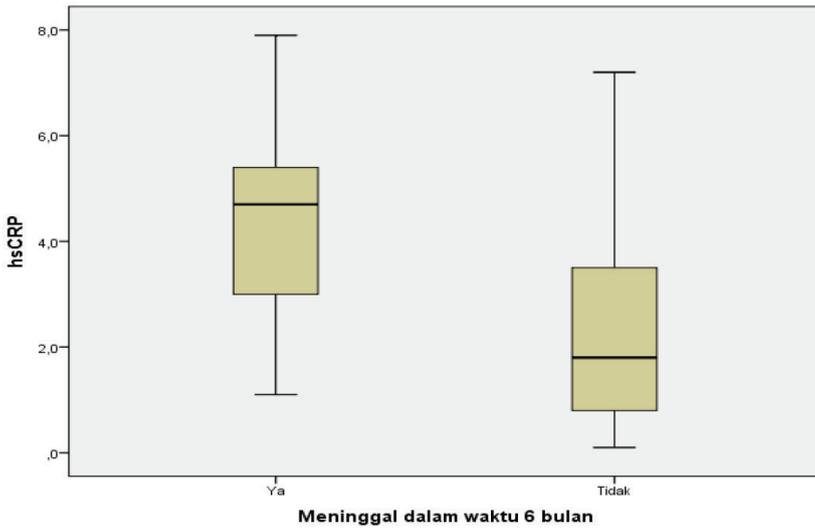
Figure 1. Boxplot graph depicting distribution of hs-CRP value based on mortality rate within the first 6 months

Diagonal segments are produced by ties.
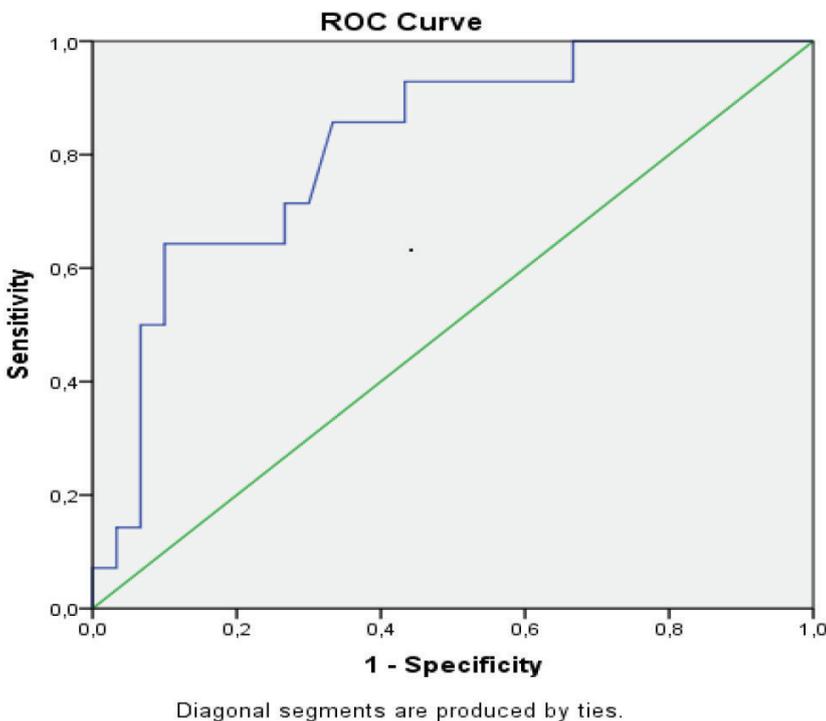
Figure 2. Receiving operating characteristic curve of hs-CRP to predict 6-month mortality

Tabel 3. Sensitivity, specificity, positive and negative predictive value of hs-CRP to assess 6-month mortality

hs-CRP	6-month mortality		Sensitivity	Specificity	PPV	NPV
	Yes	No				
≥4,25	9	3	63%	90%	75	84
<4,25	5	27				

compared to the group that was not rehospitalized (2.759 ± 2.15), with the P value of 0.880.

The mean value of echocardiography was found to be lower in the mortality group (41.64 ± 9.00) when compared with the survivor group (48.83 ± 15.00) but no statistically significant differences were found between the two groups (P=0.052). There was no significant difference in mean echocardiographic values between the rehospitalized and not rehospitalized groups.

Diagnostic value of hs-CRP to predict 6-months mortality

The analysis using the ROC curve obtained AUC of 81% (95% CI: 0.68 to 0.94). In this study, hs-CRP had a satisfactory potential to predict 6-month mortality in patients with HF (p=0.001).

Sensitivity, specificity, and the relation between hs-CRP to the assessment of 6-month mortality

A diagnostic test was performed to assess the sensitivity and specificity of hs-CRP to assess 6-month mortality using the hs-CRP cut off value on the ROC curve; an hs-CRP value of 4.25 result in a sensitivity value of 63% and a high specificity value of 90%. The diagnostic predictive values of hs-CRP of 4.25 were shown in Table 3.

Statistical analysis using chi-square test showed a significant difference of 6 months mortality in patients with HF (Table 4).

Table 4. Correlation between hs-CRP and 6-month mortality

hs-CRP	P-value
≥4,25	0,000
<4,25	

DISCUSSION

HF is still one of the major health burden issues in both developed and developing countries that are associated with high rates of morbidity and mortality. Hospitalization due to worsening in patients with chronic heart failure is associated with high rates of mortality and morbidity both at the time of treatment and post-treatment.[12]

In this study, we can observe the high mortality rate, which was exhibited by the rate of mortality and rehospitalization in the first 6 months were 31.8% and 43.2%, respectively. Although the mortality rate in this study was not as large as that found by Cheraghi et al.[13], which reached 45.8% but was higher than that of Mehta et al.[14], which was 14% (11-18%). The observation of rehospitalization

rate within 6 months was similar to the study of Cotter et al. in which rehospitalization caused by worsening of HF in the study subjects was about 40%.[15]

The left ventricular ejection fraction (LVEF) values were found to be lower in the mortality group than the survivor group but did not differ significantly (41.64±9.00 vs. 48.83±15.00, P-value=0.052). These results were consistent with a study conducted by Kozdag et al. where cardiac function was lower in the mortality group but did not differ significantly from the survivor group.[16]

This study showed a significant difference in the value of hs-CRP between the mortality and survivor groups in mortality observations (4.386±1.75 vs. 2.227±1.80, P-value=0.001). This result was consistent a study conducted by Kozdag et al. which revealed high hs-CRP value provides poor prognosis of mortality in GJ patients with hs-CRP (4.57 ± 5.25 vs. 1.88 ± 2.75, P <0.001) and hazard ratio (HR) 1.1 (1.05 -1.15).[16]

There was no significant difference in hs-CRP values of patients who were rehospitalized compared to those without within 6 months (2.858±1.99 vs. 2.759±2.15, P-value= 0.880). This result was different from that of Kozdag et al. where the hs-CRP values of the patients in the rehospitalized group were significantly higher (2.70 ± 3.67 vs. 2.38 ± 4.34, P = 0.044).[16]

The analysis result using ROC curve obtained AUC equal to 81% (68%-94%). The hs-CRP value higher than 4.25 has a good aptitude to predict 6-month mortality in patients with HF with a specificity of 90% and an NPV of 84%. This result is in accordance with a study by Zhu et al. in predicting 5-year mortality in patients with heart failure with a 71% AUC score, using an hs-CRP value > 3 with 96% NPV to predict cardiovascular mortality.[17] Galal et al. also show that hs-CRP≥3.0 has a prognostic value with 81.5% sensitivity and 87% specificity.[18]

One study showed that individuals with CRP>3mg/dL at initial admission have higher mortality rates.[19] Research by Anand et al. showed the study subjects with hs-CRP>3.23 had mortality risk with HR=1.56 (1.25-1.93).[11]

Research Kalogeropoulos et al. showed different results where the hs-CRP value at initial admission was unrelated to mortality, but higher hs-CRP at 30 days among survivors (hs-CRP = 4.7) was associated with a higher 180-day mortality rate HR = 1.35 (1.06-1.72).[20]

In the recent years, many research data have implicated CRP as inflammation marker in CHD, and CRP can provide a strong predictor of cardiovascular disease in both men and women population. CRP concentrations may increase in both ischemic and non-ischemic HF patients, particularly in patients with severe acute HF.[21] One study showed high CRP sensitivity associated with HF. High CRP values in the elderly patients can predict the advancement of HF.[9]

CRP has many pathophysiological roles in HF either in direct or indirect mechanisms by stimulating changes in function and structure of the arterial wall and cardiac as well as vascular remodeling. These alterations are bound to activate the angiotensin-aldosterone system, angiotensin receptors, and promote proatherogenic properties of angiotensin.[22] Various studies have attempted to assess hs-CRP as a manner of predicting mortality rates as well as the risk of rehospitalization in patients with HF. A study showed that CRP values were elevated in patients with HF.[11]

A study involving more than 4000 subjects from the general population showed CRP as an independent risk factor for HF and was associated with mortality, morbidity and the relative risk of hospitalization due to HF events were doubled in subjects with CRP>3mg/L.[11,23] Another study has also exhibited a correlation between CRP level in forecasting hospitalization owing to a deterioration in the HF functional class.[24]

Based on a community study, plasma CRP levels were able to predict the progression and prognosis of HF.[25] Increases in hs-CRP values were associated with a poor prognosis in patient with HF.[16] A research by Huang et al. paraded an association between increased CRP values and the severity degree of HF and was associated with the clinical outcomes.[24] An investigation conducted by Scirica et al. revealed an increased risk for readmission and mortality due to HF in patients with high CRP concentration.[26] This is consistent with one study that demonstrated that in decompensated HF patients, there was an increase in mortality rate as the mean CRP values increased.[19]

A research conducted by Bogaty et al. showed higher mortality rate within 1-year follow-up period in ACS patients with higher CRP values at the first admission.[27] Similar results were found in a study conducted by Liebetrau et al. which displayed ACS patients with atrial fibrillation who have high hs-CRP values had a high mortality rate within 6-month observation.[28] Research conducted by Kalogeropoulos et al. revealed that patients who had worsening HF experienced an increase in hs-CRP value, and a rise in hs-CRP value within 30 days after hospital admission is associated with mortality in 180 days.[20]

A study conducted by Alonso-Martinez et al. demonstrated an association between an increase

in CRP value with HF functional class, mortality, and rehospitalization rate of patients with HF.[29] Several studies also showed that hs-CRP is a strong independent predictor in determining prognosis and rehospitalization of patients with HF and thus the use of hs-CRP level to establish the risk stratification and treatments of HF should be considered.[16,18,21] The relationship between mortality and CRP values may be linked to the worsening of the cardiac function.[11,16,18,21,29]

Our study has a number of limitations. One of the limitations of this study is that this study did not perform the assessment of the patient's lifestyle and patient's compliance compliance in taking medicine and routine visit to the outpatient clinic. Another plausible limitation is the lack of evaluation of the possibility of other comorbid that may aggravate the condition of the patients following the initial assessment. Also, this study did not include repeated hs-CRP examination to investigate the hs-CRP value after the initial assessment.

CONCLUSION

In conclusion, this study shows a 6-month mortality prevalence of HF patients of 31.8% and 6-month rehospitalization rates of 43.2%. The study revealed that there were different hs-CRP values among HF patients who experienced cardiovascular death compared to those who survived within 6 months after the initial assessment. Hs-CRP with a value of 4.25 can be used as a 6-month mortality predictor in patients with HF and have a sensitivity of 63% along with a specificity of 90%. There were no significant differences in hs-CRP level between patients with HF who experienced rehospitalization within 6 months and who did not, hence hs-CRP could not be used as a predictor of rehospitalization within 6 months in patients with HF.

The number of the study sample was comparatively small; thus further investigation with more research samples and extended observation periods are needed. Despite that, this study strengthens the necessity to look into the hs-CRP level of HF patients as an inflammatory marker, during the initial assessment and also throughout further evaluations. Also, patient management and additional education after diagnosis are required to heighten patient's compliance.

REFERENCE:

1. Mann DL, Chakinala M. Heart failure: Pathophysiology and Diagnosis of Heart Failure. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine 19th ed. New York: McGraw-Hill Education. 2015. p. 1500-6.
2. PERKI. Pedoman Tatalaksana Gagal Jantung 1st ed. Jakarta: Perhimpunan Dokter Spesialis Kardiovaskular Indonesia; 2015.
3. Panggabean M. Gagal Jantung. In: Setiati S, Alwi I, Sudoyo A, K M, Setiyohadi B, Syam A, editors. Buku Ajar Ilmu Penyakit Dalam. 6th ed. Jakarta: Interna Publishing. 2014. p. 1132-5.
4. Levine B, Kalman J, Mayer L, et al. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. New England Journal of Medicine. 1990;323(4):236-41.
5. Gullestad L, Ueland T, Vinge LE, et al. Inflammatory cytokines in heart failure: mediators and markers. Cardiology. 2012;122(1):23-35.
6. Black S, Kushner I, Samols D. C-reactive protein. Journal of Biological Chemistry. 2004;279(47):48487-90.
7. Aguiar FJB, Ferreira-Júnior M, Sales MM, et al. C-reactive protein: clinical applications and proposals for a rational use. Revista da Associação Médica Brasileira (English Edition). 2013;59(1):85-92.
8. Clearfield MB. C-reactive protein: a new risk assessment tool for cardiovascular disease. Journal-american osteopathic association. 2005;105(9):409.
9. Gottdiener JS, Arnold AM, Aurigemma GP, et al. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. Journal of the American College of Cardiology. 2000;35(6):1628-37.
10. Bursi F, Weston SA, Killian JM, et al. C-reactive protein and heart failure after myocardial infarction in the community. The American journal of medicine. 2007;120(7):616-22.
11. Anand IS, Latini R, Florea VG, et al. C-reactive protein in heart failure. Circulation. 2005;112(10):1428-34.
12. Greene SJ, Fonarow GC, Vaduganathan M, et al. The vulnerable phase after hospitalization for heart failure. Nature Reviews Cardiology. 2015;12(4):220-9.
13. Cheraghi M, Sadeghi M, Sarrafzadegan N, et al. Prognostic factors for survival at 6-month follow-up of hospitalized patients with decompensated congestive heart failure. ARYA atherosclerosis. 2010;6(3):112.
14. Mehta PA, Dubrey SW, McIntyre HF, et al. Improving survival in the 6 months after diagnosis of heart failure in the past decade: population-based data from the UK. Heart. 2009;95(22):1851-6.
15. Cotter G, Metra M, Davison BA, et al. Worsening heart failure, a critical event during hospital admission for acute heart failure: results from the VERITAS study. European journal of heart failure. 2014;16(12):1362-71.
16. Kozdag G, Ertas G, Kilic T, et al. Elevated level of high-sensitivity C-reactive protein is important in determining prognosis in chronic heart failure. Medical Science Monitor. 2010;16(3):CR156-CR61.
17. Zhu L, Zou Y, Wang Y, et al. Prognostic Significance of Plasma High-Sensitivity C-Reactive Protein in Patients With Hypertrophic Cardiomyopathy. Journal of the American Heart Association. 2017;6(2):e004529.
18. Galal H, Awad O, Ghareeb M, et al. Prognostic Value of Plasma Levels of High Sensitivity C-Reactive Protein in Chronic Systolic Heart Failure of Ischemic Origin. Heart Mirror Journal. 2013;7(2).
19. Villacorta H, Masetto AC, Mesquita ET. C-reactive protein: an inflammatory marker with prognostic value in patients with decompensated heart failure. Arquivos brasileiros de cardiologia. 2007;88(5):585-9.
20. Kalogeropoulos AP, Tang WHW, Hsu A, et al. High-sensitivity C-reactive protein in acute heart failure: insights from the ASCEND-HF trial. Journal of cardiac failure. 2014;20(5):319-26.
21. Yin W-H, Chen J-W, Jen H-L, et al. Independent prognostic value of elevated high-sensitivity C-reactive protein in chronic heart failure. American heart journal. 2004;147(5):931-8.

22. Adukauskienė D, Čiginskienė A, Adukauskaitė A, et al. Clinical relevance of high sensitivity C-reactive protein in cardiology. Medicina. 2016;52(1):1-10.
23. Engström G, Melander O, Hedblad B. Carotid intima-media thickness, systemic inflammation, and incidence of heart failure hospitalizations. Arteriosclerosis, thrombosis, and vascular biology. 2009;29(10):1691-5.
24. Huang W-P, Yin W-H, Jen H-L, et al. C-reactive protein levels in chronic congestive heart failure. Acta Cardiologica Sinica. 2004;20(1):7-14.
25. Seta Y, Shan K, Bozkurt B, et al. Basic mechanisms in heart failure: the cytokine hypothesis. Journal of cardiac failure. 1996;2(3):243-9.
26. Scirica BM, Cannon CP, Sabatine MS, et al. Concentrations of C-reactive protein and B-type natriuretic peptide 30 days after acute coronary syndromes independently predict hospitalization for heart failure and cardiovascular death. Clinical chemistry. 2009;55(2):265-73.
27. Bogaty P, Boyer L, Simard S, et al. Clinical utility of C-reactive protein measured at admission, hospital discharge, and 1 month later to predict outcome in patients with acute coronary disease: the RISCA (Recurrence and Inflammation in the Acute Coronary Syndromes) study. Journal of the American College of Cardiology. 2008;51(24):2339-46.
28. Liebetrau CL, Gaede L, Szardien S, et al. High Sensitivity CRP Predicts Long-Term Mortality in Patients with Atrial Fibrillation and Evident Acute Coronary Syndrome. International Journal of Clinical Medicine. 2013;4(03):137.
29. Alonso-Martinez JL, Llorente-Diez B, Echegaray-Agara M, et al. C-reactive protein as a predictor of improvement and readmission in heart failure. European journal of heart failure. 2002;4(3):331-6.