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Submission date: 06-Aug-2019 06:49PM (UTC+0800)

Submission ID: 1158058425

File name: tive_Protein_CRP_levels_as_prognostic_markers_for_urosepsis.pdf (1.63M)

Word count: 3426

Character count: 16756

Total Cholesterol and C-reactive Protein (CRP) Levels as Prognostic Markers for Urosepsis

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Abstract

This study was aimed to determine and compared the total cholesterol and C-reactive protein (CRP) levels as a prognosis in urosepsis patients treated at the RSUD. Dr. Soetomo Hospital. There were 30 patients involved in this study and was assigned to the test for total cholesterol and CRP level at the day of admission, three days later, and on the last day (14th days) of sepsis or on the day of the death. The variables were tested using the Spearman's rho test with software SPSS 20. This study found 15 patients who were in septic condition, 14 patients had severe sepsis and one patient had septic shock. There were statistically significant between total cholesterol and CRP levels in determining the outcome of urosepsis patient. The coefficient correlation of total cholesterol was better than CRP. The low total cholesterol levels and high CRP levels can be used as predictors of worsening urosepsis prognosis. Total cholesterol levels showed better performance than CRP as a prognostic marker for urosepsis.

Keywords: Cholesterol level, C-reactive Protein (CRP), Prognostic Marker, Urosepsis

Introduction

Urosepsis was a sepsis that originates from urinary tract infections with symptoms of SIRS¹. Sepsis that was not adequately treated can fall under severe sepsis with MODS and even septic shock^{2,3}. The sepsis can change body hemodynamics, hematology and metabolism body by involving immune system responses and many organ systems^{1,4}. In severe sepsis and septic shock there can be circulatory distress syndrome at the micro and mitochondrial levels. Hemodynamic and severe circulation disorders can cause disruption of oxygen transport and cell respiration which can cause failure of many organs. Mitochondrial dysfunction plays an important role in sepsis where the rate of mitochondrial respiration dysfunction was related to the patient's outcome. Mitochondrial failure associated with sepsis role in respiratory distress, especially in areas of hypoxia and can cause distress networks that can progress to organ dysfunction^{5,6}.

There were several clinical and laboratory variables that can be used as markers to determine and assess the severity of sepsis and determine its prognosis. One of them was total cholesterol. Cholesterol involvement in this sepsis condition allows cholesterol to be used as a biomarker for urosepsis. Decrease in total cholesterol in sepsis occurs from the first time bacterial toxins enter the patient's blood (host) and will further reduce the decrease in patients with severe sepsis accompanied by MODS^{7,8}.

The reduction in total cholesterol was basically a decrease in HDL cholesterol, LDL cholesterol and VLDL cholesterol. The total cholesterol was decrease due to multi factorial factors including increased cholesterol usage in the sepsis process, decreased synthesis and changes in metabolism^{9,10,11}. The use of cholesterol in sepsis occurs since bacterial toxins enter the patient's body. Both endotoxins (lipopolysaccharides) from gram-negative bacteria and lipoteichoic acid (LTA) from gram-positive bacteria will bond between lipopolysaccharide (LPS) and cholesterol (lipoprotein) known as lipopolysaccharide binding protein (LBP)^{12,13}. This cholesterol bond with lipopolysaccharide (LBP) aims to neutralize germ toxins and reduce cellular response caused by gram-negative and gram-positive

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bacteria^{10, 14}. In addition to reduce the cellular response of the host to endotoxin, LBP also aims to present endotoxin monomers (LPS) in membrane bound CD 14 in monocytes, neutrophils and macrophages^{15, 16}. Thus, the invasion of germs can be prevented and overcome^{4, 17}. Decreased cholesterol synthesis in liver also occurs in sepsis, this was related to an increase in cytokine mediators in the form of TNF α , IL-1 and interleukin 6¹⁰. Decreased lipoprotein (cholesterol) was seen after liver cells were exposed to TNF α , IL-1 and IL-6. This study was aimed to determine and compared the total cholesterol and C-reactive protein (CRP) levels as a prognosis in urosepsis patients treated at the RSUD. Dr. Soetomo Hospital.

Methodology

This study was a prospective study of the type of diagnostic test which highlight on the comparison of total cholesterol levels and C-reactive protein (CRP) in assessing urosepsis prognosis through observational analytic research designs. The study sample focused on the patients who were diagnosed with urosepsis (sepsis caused by urinary tract infection) and treated at the RSUD. Dr. Soetomo Hospital. The sample was calculated based on the formula of the sample size for correlative analytic test research. All respondents were required to sign an approval sheet following the research. On the first day, the respondents were classified based on the results of assessment for clinical severity, total cholesterol, CRP, MAP, blood leukocytes, urinalysis, urine culture and blood culture, BGA (blood gas analysis), SGOT, SGPT, BUN, and serum creatinine level. On the third day the patients were reassessed for their clinical severity, total cholesterol, and CRP. Patients were continuing follow this study until the last day of the patient's death, recovery or a maximum of 14 days of treatment. The correlation test was performed between total cholesterol and CRP results on the outcome / prognosis of the urosepsis patient.

The results of the study were collected and processed with the SPSS program. The statistical test used was a bivariate correlation test between total cholesterol and

CRP against the prognosis (outcome) of patients with the Spearman's rho test. The correlation coefficients of each variable was determined to compare the correlation strength between CRP and blood cholesterol against the prognosis (outcome) of patients with urosepsis.

Result and Discussion

Table 1 showed the CRP score and total cholesterol based on outcome. The average results of the first day CRP examination in patients was 177.18 ± 107.37 mg/L, worsening 146.74 ± 62.82 mg/L, whereas in patients with improved outcome showed low average CRP score which was 88.10 ± 74.41 mg/L. The mean CRP values on the third and last day of patients with clinically improved decreased from 56.28 ± 50.15 mg/L to 31.58 ± 37.37 mg/L. The mean CRP of patients died on the third day was 127.10 ± 106.28 mg/L and on the last day was 141.88 ± 105.61 mg/L. The difference (Δ) of CRP between last day and first day showed positive value in the patient with outcome deteriorated which was 38.76 ± 59.02 mg/L, while the negative value in the patient improved and died were -56.52 ± 70.20 mg/L and -35.3 ± 97.53 mg/L respectively.

Examination of total cholesterol based on outcome at the end of the study showed lowest average total cholesterol examination results on the first day in patients with death outcomes that was equal to 63.25 ± 14.15 mg/dL and then increased follow by worsening patients which was 101.38 ± 20.51 mg/dL and improved patients which was 119.5 ± 17.81 mg/dL. Meanwhile, patients with outcome worsening and dying clearly seen total cholesterol values continued to decline. In patients worsening the total cholesterol value for the third day was 93.62 ± 10.68 mg/dL and the last day was 82.25 ± 10.9 mg/dL. In patients who died in third day, total cholesterol value was 56.0 ± 6.98 mg/dL and the last day was 51.0 ± 6.16 mg/dL. The difference (Δ) of cholesterol between the last day and first day showed positive mean value which was 35.3 ± 21.46 mg/dL for patients improved. While, negative mean values in patients who worsened and died were -19.13 ± 18.45 mg/dL and -12.25 ± 11.59 mg/dL.

Table 1. CRP levels and total cholesterol based on outcome

Criteria	Improved			Worsening			Died		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
1 st CRP (mg/L)	18	88.10	74.41	8	146.74	62.82	4	177.18	107.37
3 rd CRP (mg/L)	18	56.28	50.15	8	148.88	63.15	4	127.10	106.28
14 th CRP (mg/L)	18	31.58	37.37	8	185.50	88.71	4	141.88	105.61
Δ(14 th CRP - 1 st CRP) (mg/L)	18	-56.52	70.20	8	38.76	59.02	4	-35.3	97.53
1 st Chol (mg/dL)	18	119.50	17.81	8	101.38	20.51	4	63.25	14.15
3 rd Chol (mg/dL)	18	128.61	23.61	8	93.62	10.68	4	56.00	6.98
14 th Chol (mg/dL)	18	154.83	25.71	8	82.25	10.9	4	51	6.16
Δ(14 th Chol - 1 st Chol) (mg/dL)	18	35.3	21.46	8	-19.13	18.45	4	-12.25	11.59

The correlation test was performed using Spearman's rho method in order to determine the significance and strength of correlation (correlation coefficient). Correlation test was performed between first day CRP, third day CRP, last day CRP, delta (Δ) CRP (14th CRP – 1st CRP), total cholesterol of first day, third day, last day, and delta (Δ) total cholesterol (Δ 14th Chol -1st Chol) against the outcome of patients with urosepsis. CRP and total cholesterol statistical tests were conducted in all study samples. All study samples were observed and assessed on the outcome or the condition of the patient until the last day the patient was declared cured or died.

Table 2. Results of the Correlation Test of CRP levels with the outcome using the Spearman's rho formula (n = all samples)

		1 st day CRP	3 rd days CRP	14 th days CRP	Δ CRP	Outcome
1 st day CRP	Correlation coefficient	1.000	0.795**	0.694**	-0.171	.459*
	Sig. (2-tailed)	.	0.000	0.000	0.366	.011
	N	30	30	30	30	30
3 rd days CRP	Correlation coefficient	0.795**	1.000	0.849**	0.202	0.543**
	Sig. (2-tailed)	0.000	.	0.000	0.283	0.002
	N	30	30	30	30	30
14 th days CRP	Correlation coefficient	0.694**	0.849**	1.000	.443*	0.686**
	Sig. (2-tailed)	0.000	0.000	.	0.014	0.000
	N	30	30	30	30	30
Δ CRP	Correlation coefficient	-0.171	0.202	0.443*	1.000	0.365*
	Sig. (2-tailed)	0.366	0.283	.014	.	0.047
	N	30	30	30	30	30

* Correlation was significant at the 0.05 level (2-tailed)

** Correlation was significant at the 0.01 level (2-tailed)

Based on Table 3, the value of the correlation test of CRP levels on outcome in patients with urosepsis using the Spearman's rho formula was shown in Table 3. Based on statistical tests it was found that CRP levels on the first, third, fourteen days, and delta CRP (day 14 minus the first day) in patients with urosepsis showed a significant correlation ($p < 0.05$) to the outcome with a significance value of 0.011, 0.002, 0.000 and 0.047 respectively and the correlation coefficients (r) were 0.459, 0.543, 0.686, and 0.365 respectively.

Table 3. Results of Correlation Test of Total Cholesterol Level with outcome using Spearman's rho formula (n = all samples)

		1 st day Chol	3 rd days Chol	14 th days Chol	Δ Chol	Outcome
1 st day Chol	Correlation coefficient	1.000	0.786**	0.769**	0.359	-0.633**
	Sig. (2-tailed)	1	0.000	0.000	0.051	0.000
	N	30	30	30	30	30
3 rd days Chol	Correlation coefficient	0.786**	1.000	0.928**	0.716**	-0.755**
	Sig. (2-tailed)	0.000	.	0.000	0.000	0.000
	N	30	30	30	30	30
14 th days Chol	Correlation coefficient	0.769**	0.928**	1.000	.826**	-0.874**
	Sig. (2-tailed)	0.000	0.000	1	0.000	0.000
	N	30	30	30	30	30
Δ Chol	Correlation coefficient	0.359	0.716**	0.826**	1.000	-0.754**
	Sig. (2-tailed)	0.051	0.000	0.000	-	0.000
	N	30	30	30	30	30

* Correlation was significant at the 0.05 level (2-tailed)

** Correlation was significant at the 0.01 level (2-tailed)

Table 4 illustrated the strength of the correlation which assessed through the magnitude of the correlation coefficient (r). The correlation was stronger if the r value approaches 1 or -1. From the results of statistical tests obtained the value of the correlation coefficient (r) of CRP versus cholesterol on the first day was (0.459 VS -0.633), the third day was (0.543 VS -0.755), the last day was (0.686 VS -0.874) and Δ CRP compared to cholesterol was (0.365 vs -0.754).

Table 4. Strength of correlation of CRP compared to total cholesterol against outcome

Variable	Significant (p)		Correlation coefficient (r)	
	CRP	Chol	CRP	Chol
1 st day	0.011	0.000	0.459	-0.633
3 rd day	0.002	0.000	0.543	-0.755
14 th day	0.000	0.000	0.686	-0.874
Delta	0.047	0.000	0.365	-0.754

Discussion

Increased CRP levels require a minimum of 12-18 hours and CRP increased slowly during sepsis and reaches peak levels in 36-50 hours. The concentration will drop rapidly with a half-life of 19 hours if the stimulus was removed. This causes CRP to be independent and only affected by therapy and actions to eliminate the inflammatory process. In this study, 4 patients died with varying initial CRP levels of 53.0 mg /L, 156.0 mg /L, 186 mg /L and 313.7 mg /L. The high level of CRP can be a description of the number of organ systems that have failed their function¹⁸.

In this study, the first day CRP levels in patients with improved outcomes had the lowest average compared to the first day CRP levels in patients with worsening and dying outcomes, which was 88.10 ± 74.41 mg /L compared to 146.74 ± 62.82 mg /L and 177.18 ± 107.37 mg /L. On the third and final day examination, a very clear pattern was seen that in patients with improved outcomes there was a lower CRP level of 56.28 ± 50.15 mg /L and 31.58 ± 37.37 mg /L. Whereas the worsening of patients continued to increase, 148.88 ± 63.15 mg /L on the third day and 185.50 ± 88.71 mg /L on the last day. In patients with death outcomes, the mean on third day CRP level was 127.10 ± 106.28 mg /L and on the last day it increased to 141.88 ± 105.61 mg /L. The results of the correlation test of CRP levels with the outcome obtained significant values ($p < 0.05$) on the examination for the first, third, and last days were 0.459, 0.543, and 0.686 respectively. These results reflect that low CRP levels were associated with a good prognosis, whereas high CRP levels were associated with a poor prognosis even to death both on the first day, third day and last day examination.

This study was determined that total cholesterol and CRP concentration can be used as predictors of outcome and prognosis of urosepsis. Serial total cholesterol and CRP measurement (periodically) will be more helpful in identifying the patient's condition so that it can provide additional information to increase the aggressiveness of the action to be given. From the results of data analysis in this study it can also be determined that the total cholesterol level compared to CRP showed a higher correlation with the outcome of patients with urosepsis. So that the measurement of total cholesterol levels in patients with urosepsis was better in predicting outcome or prognosis when compared with CRP levels.

Conclusion

In conclusions, total cholesterol levels can be used as a marker of prognosis (improved / worsened / died) in urosepsis patients both on the first, third, and last day examination with a significant correlation ($p < 0.05$). The lower the total cholesterol level the worse the prognosis of the patient and vice versa. CRP levels can be used as a marker of prognosis (improved / worsened / died) in urosepsis patients both on the first, third, and last day examination with a significant correlation ($p < 0.05$). The higher the CRP level the worse the prognosis of the patient and vice versa. Plasma total cholesterol levels showed a greater correlation coefficient than CRP levels on patient outcomes with urosepsis both on the first day examination (-0.633 vs. 0.459), third (-0.755 vs. 0.543), and the last day (-0.874 vs. 0.686). So that total plasma cholesterol levels can be used as a better prognosis indicator than CRP levels.

Ethical Clearance: Taken from the committee

Source of Funding: Nil

Conflict of Interest: Nil

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