

Research Article

Cystatin C Serum Level and the Severity of Preeclampsia

Kadar Cystatin C dan Keparahan Preeklamsia

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Abstract

Objective: Determining the cystatin C serum level among normotensive, mild preeclamptic, severe preeclamptic pregnant women and their relationship with the severity of preeclampsia.

Method: The study was held using cross sectional design in Prof. Dr. RD Kandou Hospital in Manado and its network hospitals. We did on 51 samples at term pregnant women, consisting of 17 samples for each group in normotensive, mild preeclampsia, and severe preeclampsia. The data were analyzed using SPSS version 22.0 software through ANOVA and Kruskal Wallis statistical test.

Result: The mean cystatin C serum concentration in normotensive pregnant women, mild preeclampsia, and severe preeclampsia were 0.82 mg/l, 1.03 mg/l, and 1.32 mg/l; respectively. The ANOVA statistical test showed the significant association between cystatin C level and severity of preeclampsia ($p < 0.01$). The ROC curve analysis for cystatin C explained the 88.2% sensitivity and 85.3% specificity for the 1.12 mg/l as the cut off level.

Conclusion: There is a significant association between serum cystatin C level and severity of preeclampsia.

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Keywords: cystatin C, preeclampsia

Abstrak

Tujuan: Mengetahui kadar cystatin C pada ibu hamil dengan tekanan darah normal, preeklamsia ringan dan preeklamsia berat, serta hubungannya dengan keparahan preeklamsia.

Metode: Penelitian dengan desain potong lintang ini dilakukan di RS Prof. Dr. R.D. Kandou Manado dan jejaring. Pemeriksaan kadar cystatin C dilakukan pada 51 sampel ibu hamil aterm yang terdiri dari 17 sampel dari kelompok normotensi, preeklamsia ringan dan preeklamsia berat. Data yang diperoleh diolah dengan statistik ANOVA dan Kruskal Wallis menggunakan perangkat lunak SPSS versi 22.0.

Hasil: Kadar rerata cystatin C pada kehamilan normotensi 0,82 mg/l, pada preeklamsia ringan 1,03 mg/l dan pada preeklamsia berat 1,32 mg/l. Setelah dilakukan uji statistik ANOVA didapatkan nilai $p < 0,001$. Dari analisa kurva ROC untuk cystatin C didapatkan nilai sensitivitas 88,2% dan spesifisitas 85,3% pada 1.12 mg/l sebagai titik potong.

Kesimpulan: Terdapat hubungan yang bermakna antara kadar cystatin C serum dengan keparahan dari preeklamsia.

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Kata kunci: cystatin C, preeklamsia

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INTRODUCTION

Preeclampsia is multiple organ disorders characterized by hypertension (blood pressure $\geq 140/90$ mmHg) and proteinuria after 20 weeks of pregnancy. The clinical features of preeclampsia occur because kidney as the main target become glomerular endotheliosis causing the decrease in glomerular filtration rate.¹⁻³ Preeclampsia is a major cause of morbidity and mortality, both maternal and perinatal in the world. The incidence of preeclampsia is approximately 3.9% of all pregnancies and it causes 50,000 maternal deaths worldwide every year. Preeclampsia and eclampsia impact to 75% of acute renal failure in pregnancy. Altered renal function is an essential component of the pathophysiological process in preeclampsia; thus,

close monitoring of renal function become important for the delivery time before occurring the serious renal damage.²⁻⁵

There are several markers of renal function, such as creatinine, uric acid, and cystatin C. The exchange of mostly low molecular weight substances, such as creatinine, uric acid and cystatin C is occurred in the kidney. Cystatin C is a low molecular weight non glycosylated basic protein of 12.8 kDa composed of 120 amino acid residues which are expressed in all nucleated cells. It is produced at a constant rate and exclusively eliminated from the circulation by glomerular filtration.^{1,2,6}

The use of serum creatinine to assess the glomerular filtration rate is limited due to the decrease in glomerular filtration rate up to 50% with-

out increasing the serum creatinine concentration. The serum level concentration of uric acid and creatinine in preeclampsia does not always raise above normal level so that it diminishes the use of these parameters in monitoring renal function of preeclamptic women. Apart from that, creatinine cannot detect the glomerular filtration rate reduction in the early stage of renal dysfunction. Therefore, the cystatin C serum is considered having superior diagnostic accuracy compared with creatinine and uric acid in preeclamptic women as a marker for glomerular endoteliosis, which signs the renal involvement in preeclampsia.^{1,7,8}

This study aims to determine the average level of cystatin C in normotensive, mild preeclamptic, and severe preeclamptic pregnant women. Besides, we would like to know the association between cystatin C level and severity of preeclampsia.

METHODS

This cross sectional study design with analytic approach was conducted to assess the relationship between cystatin C level and severity of preeclampsia. The population in this study were pregnant women at term in the delivery room Prof. Dr. RD Kandou hospital, Manado and its network

hospitals from August to November 2015. We used consecutive sampling consisting of three groups: 17 normotensive, 17 mild preeclamptic, and 17 severe preeclamptic pregnant women who met the inclusion and exclusion criteria.

The inclusion criteria were single fetus of pregnant women at term and would like to participate in this study. We excluded diabetes mellitus, chronic hypertension, kidney disease pregnant women, maternal infection, twin fetus, and also intrauterine fetal death (IUFD).

The blood sample from subjects were collected and we examined the level of cystatin C in the Prodia laboratory Manado through immunonephelometric assay. This method uses the plasma serum for the examination and it can stabilize for a week in 2-8°C and three months in -20°C. The reference normal range is from 0.50-0.96 mg/l.

Data were analyzed with ANOVA statistical test to find the relationship between cystatin C level and severity of preeclampsia. Kruskal-Wallis statistical test was used to find the relationship between the degree of proteinuria and level of cystatin C serum. The data were processed using the Statistical Product and Service Solutions (SPSS) for Windows version 22.0.

Table 1. Characteristics of Subjects

Characteristics	Normotensive		Mild Preeclampsia		Severe Preeclampsia	
	N	%	N	%	N	%
Age (years old)						
≤ 20	4	23.5	-	-	2	11.8
21-35	10	58.8	12	70.6	9	52.9
≥ 35	3	17.6	5	29.4	6	35.3
Parity						
Primigravida	7	41.2	4	23.5	6	35.3
Multigravida	10	58.8	13	76.5	11	64.7
Occupation						
Housewife	13	76.5	14	82.4	15	88.2
Private employee	3	17.6	2	11.8	-	-
Student	-	-	-	-	1	5.9
Government employee	-	-	1	5.9	1	5.9
Farmer	1	5.9	-	-	-	-
Tribe						
Minahasa	15	88.2	15	88.2	16	94.1
Java	2	11.8	2	11.8	0	-
Gorontalo	-	-	-	-	1	5.9
Marriage						
1	17	100	17	100	15	88.2
> 1	-	-	-	-	2	11.8

RESULTS

We conducted this study on population of pregnant women at term who were admitted in Prof. R.D. Kandou hospital and its network hospitals on the period of August to November 2015. We got 51 women who divided each 17 women into normotensive, mild preeclampsia, and severe preeclampsia. Table 1 depicted the characteristics of the subjects in this study.

The results showed that the highest level of cystatin C serum for normotensive pregnant women was 1.11 mg/l and the lowest level was 0.66 mg/l. Meanwhile, the highest and lowest level of cystatin C serum in mild preeclamptic group were 1.25 mg/l and 0.83 mg/l. In the severe preeclamptic group, the highest cystatin C level was 1.58 mg/l and the lowest level was 0.98 mg/l.

Table 2 explained the increase of cystatin C serum level was in accordance with the severity of preeclampsia. The ANOVA statistical test showed that the cystatin C was different among these group ($p < 0.001$) and it would be higher in line with the severity of preeclampsia.

Table 2. Statistical Analysis Cystatin C Level in Normotensive Pregnant Women, Mild Preeclampsia and Severe Preeclampsia

	Cystatin C Serum Level		
	Mean (mg/l)	Std Deviation	p value
Normotensive	0.82	0.124	<0.001
Mild preeclampsia	1.03	0.121	
Severe preeclampsia	1.32	0.168	

From the ROC curve analysis of cystatin C, we got the sensitivity and specificity value of 88.2% and 85.3% for 1.12 mg/l as the cut off level (Figure 1).

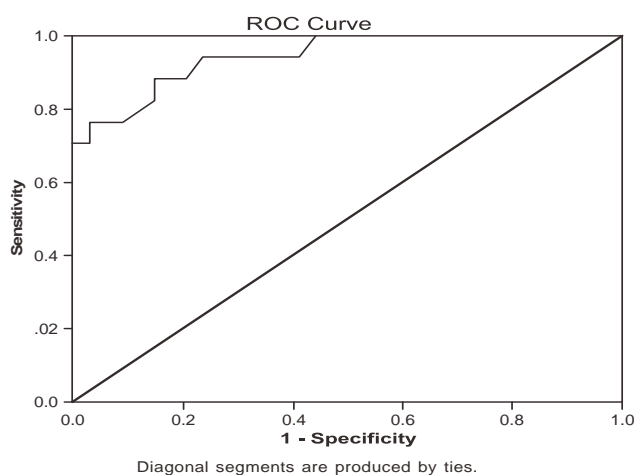


Figure 1. Analysis of the Cystatin C ROC Curve

Meanwhile, the Kruskal-Wallis statistical test was performed to determine the relationship between level of cystatin C and proteinuria. It resulted the degree of proteinuria was associated with the cystatin C serum level ($p < 0.001$) (Figure 2).

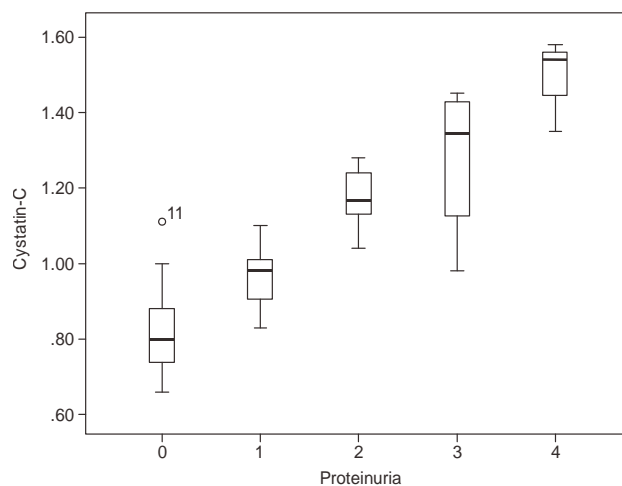


Figure 2. The Association between Proteinuria and Cystatin C Serum Level

DISCUSSION

In this study, the characteristics of subjects were assessed by maternal age, parity, occupation, marriage, and tribe. From the Table 1, we got the age of subjects ranging from 15 to 42 years old. The highest distribution of this study were 21-34 year old women, multiparity, and Minahasa tribe as the origin tribe in Sulawesi.

The result of cystatin C serum level in this study was significantly different among normotensive, mild preeclampsia, and severe preeclampsia with the value of 0.82 mg/l, 1.03 mg/l, 1.32 mg/l; respectively ($p < 0.001$). It concluded that there was significant association between cystatin C level and the severity of preeclampsia. Study conducted by Sharma, et al. in 2014 found the concentration of cystatin C was significantly higher in preeclamptic women (1.31 ± 0.4 mg/l) compared with normotensive pregnant women (0.96 ± 0.2 mg/l) with $p < 0.001$. Apart from that, Kurnia, et al. in 2014 compared 19 severe preeclamptic cases 25 normotensive cases. They concluded there was significant difference in serum cystatin C level in severe preeclampsia compared with normotensive pregnant women. The mean level of cystatin C serum in preeclampsia and normotensive women was

1.16 ± 0.31 mg/l and 0.92 ± 0.16mg/l.^{9,10} The raising level of cystatin C serum in preeclamptic women is caused by the alteration in renal morphology. Endotheliosis will inhibit glomerular filtration which impacts to decrease the glomerular filtration rate. Cystatin C has a small molecular weight which is freely through the glomerular membrane. Cystatin C is not secreted by the tubules; however, it will be fully resorbed and catabolized by the renal tubules; thus, the cystatin C serum level is a better marker in determining the glomerular filtration rate reduction in preeclampsia.^{9,10}

In this study, the analysis of the ROC curve for cystatin C value was 88.2% for sensitivity and 85.3% for specificity. Based on this sensitivity and specificity, it remarks that cystatin C is a better screening test than creatinine for early detection of renal dysfunction in preeclampsia patients with preeclampsia. Cystatin C is very sensitive in assessing the change of glomerular filtration rate in the early stage of renal impairment. Creatinine is a biomarker that has been widely used as renal function biomarker; nevertheless, it shows less sensitive in the early stage of impaired renal function. Furthermore, unlike creatinine, cystatin C is not significantly affected by diet, infection, liver function, malignancy, and muscle mass so that it displays good prediction in evaluating the glomerular filtration rate.^{1,5,8} This result was similar to other studies. Sumithra, et al in 2013 showed cystatin C had 76.7% sensitivity and 86.7% specificity. The ROC curve analysis study by Helena Strevens, et al. depicted the 91.1% sensitivity and 86.6% specificity for cystatin C; 76.7% sensitivity and 63.9% specificity for creatinine; 69.8% sensitivity and 87.6% specificity for uric acid. The ROC analysis of the study showed that cystatin C had more superior diagnostic accuracy than uric acid and creatinine.^{1,7}

In this study, there was a significant association between serum cystatin C level and proteinuria, whereas the higher cystatin C level was correlated with the higher degree of proteinuria. Study held by Roberto Costa, et al. in 2015 suggested the correlation between serum cystatin C level and proteinuria level. Patients with severe proteinuria had cystatin C level higher than mild proteinuria. Glomerular cell damage increased the permeability of the glomerular basement membrane which caused the leakage of protein.² A study of renal biopsy conducted by Stevens, et al. in 2003 found

that cystatin C level was correlated with the severity of renal structural changes (glomerular endotheliosis) which is typical in preeclamptic patients. Cystatin C is a reliable marker of renal function in assessing the severity of preeclampsia. Therefore, cystatin C level should be evaluated in determining the delivery time.^{1,9,11,12}

Study by Saleh, et al. showed that cystatin C level was significantly higher in women who would develop into preeclampsia than in normotensive women (0.76 mg/l vs. 0.53 mg/l, p = 0.008). Cystatin C level start rising in early second trimester in women who subsequently develops preeclampsia in the third trimester. The cystatin C level increase in the second trimester reflects early change in the glomerular filtration rate to predict the onset of preeclampsia.¹³

CONCLUSION

There is a significant association between serum cystatin C level and severity of preeclampsia. The level of serum cystatin C may be considered as an additional laboratory examination in patients with preeclampsia. Future study should be held in larger subjects including complication of preeclampsia (eclampsia and HELLP syndrome). Therefore, cystatin C level can be used as a predictor for the occurrence of preeclampsia.

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