Change in Serum Cystatin C Level as Predictor for Length of Hospital Stay in Patients Undergoing Primary Percutaneous Coronary Intervention

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ABSTRACT

Background. Percutaneous Coronary Intervention (PCI) is one of the most frequently performed medical procedures. Length of stay for patients after undergoing PCI should be standardized to achieve the best quality of health services. The existence of complications is one of the main factors considering the length of stay after PCI. Cystatin C has the ability as a predictor of complications in patients with acute coronary syndrome, especially those undergoing PCI, as well as the increase in length of stay associated with complications after the PCI procedure.
Objectives. To determine the average changes in serum cystatin C levels, the correlation between serum cystatin C levels and length of treatment, and changes in serum cystatin C levels as predictors of length of stay in patients undergoing primary PCI at Dr. Sardjito Hospital.
Methods. Analytical observational study with a prospective cohort method conducted on patients with a STEMI diagnosis who underwent primary PCI procedures in Emergency Room, Cardiovascular Care Unit (CVCU) of Dr. Sardjito Hospital, treated from November 2020 to April 2021. The data was then analyzed for normality, multicollinearity, bivariate, and multivariate tests to see the effect of changes in cystatin C and other variables on the length of stay for patients after primary PCI (p <0.05 is significant).
Results. Of the 111 patients, 92 patients were subjected to further analysis. Patients included in the study had an average age of 59.55 (+10.80) years, majority of men, reduced LVEF, using trans-radial PCI access, Killip I, average eGFR of 64 ml / 1.73m^2, length of stay in hospital is 5 days, delta cystatin C and creatinine 0.10 and 0.04 U / L, respectively. The increase in cystatin C had a moderate positive correlation (0.502) with the length of hospital stay (p<0.001), in multivariate analysis serum cystatin C does not correlate with length of hospital stay (p=0.590). Other variables including LVEF, eGFR, infection, and contrast-induced acute kidney injury had a significant correlation with length of stay (p<0.001). The multivariate test showed that LVEF, eGFR, and infection had the most significant correlation (p = 0.034; 0.001; 0.005 respectively) to the length of hospital stay with a regression coefficient of 0.72; -0.04; and 1.93.
Conclusion. An increase of cystatin C serum does not correlate significantly with the length of hospitalization in STEMI patients undergoing PCI procedure in Dr. Sardjito Hospital.

Keywords. Cystatin C, creatinine, Percutaneous Coronary Intervention (PCI), length of stay

ABSTRAK

Latar Belakang. *Intervensi Koroner Perkutan (IKP) merupakan salah satu prosedur medis yang paling sering dilakukan. Lamanya perawatan pasien pasca menjalani IKP sebaiknya terstandarisasi untuk mencapai kualitas pelayanan kesehatan yang maksimal. Adanya komplikasi merupakan salah satu faktor utama pertimbangan lama perawatan pasien pasca menjalani IKP. Salah satu metode untuk memprediksi lama perawatan pasien adalah stratifikasi risiko terjadinya komplikasi. Cystatin C memiliki kemampuan sebagai prediktor komplikasi pada pasien dengan sindrom koroner akut, khususnya yang menjalani IKP, serta peningkatan lama perawatan berhubungan dengan adanya komplikasi pasca prosedur IKP.*

Tujuan Penelitian. *Mengetahui rerata perubahan kadar cystatin C serum, korelasi kadar cystatin C serum dengan lama perawatan, dan perubahan kadar cystatin C serum sebagai prediktor terhadap lama perawatan pada pasien yang menjalani IKP primer di RSUP Dr. Sardjito.*

Metode Penelitian. *Observasional analitik dengan metode kohort prospektif yang dilakukan pada pasien dengan diagnosis STEMI yang menjalani prosedur IKP primer di unit Instalasi Gawat Darurat (IGD*), Cardiovascular Care Unit *(CVCU) dan bangsal jantung terpadu RSUP Dr. Sardjito Yogyakarta yang dirawat pada bulan November 2020 sampai April 2021. Data kemudian dilakukan uji normalitas, multikolinearitas, bivariat, serta multivariat, untuk melihat pengaruh perubahan cystatin C serta variabel luar terhadap lama perawatan pasien paska IKP primer (dengan* p *< 0.05 dikatakan siginifikan).*

Hasil Penelitian. *Dari 111 pasien, terdapat 19 pasien meninggal sehingga 92 pasien yang kemudian dilakukan analisis. Pasien yang diikutkan dalam penelitian rerata berusia 59.55 (+10,80) tahun, mayoritas pria, dengan HFrEF, menggunakan akses IKP transradial, Killip I, rerata memiliki eGFR 64 ml/1,73m², lama perawatan RS 5 hari, serta delta cystatin C dan kreatinin masing-masing 0.10 dan 0.04 U/L. Peningkatan cystatin C memiliki korelasi positif sedang (0.502) dengan lama perawatan RS (*p*<0.001), pada analisis multivariat cystatin C serum tidak berhubungan secara signifikan terhadap lama perawatan (*p*=0.590). Variabel luar meliputi LVEF, eGFR, infeksi selama perawatan, dan gagal ginjal paska IKP primer memiliki korelasi signifikan terhadap lama perawatan (*p*<0.001). Uji multivariat menunjukkan LVEF, eGFR, dan infeksi memiliki korelasi yang paling bermakna (*p *berturut-turut 0.034; 0.001; 0.005) terhadap lama perawatan RS dengan koefisien regresi berturut-turut 0.72; -0.04; dan 1.93.*

Kesimpulan. *Peningkatan kadar cystatin C serum tidak berhubungan secara signifikan dengan peningkatan lama perawatan rawat inap pada pasien STEMI yang menjalani prosedur IKP primer di RSUP Dr. Sardjito.*

Kata Kunci. *Cystatin C, kreatinin, Intervensi Koroner Perkutan (IKP), lama rawat*

INTRODUCTION

Percutaneous Coronary Intervention (PCI) is one of the most frequent performed medical procedures. In 2015-2016 there were 419 primary PCI perform out of a total 1322 PCI cases at Dr. Sardjito Hospital.[1] Length of stay after PCI should be standardized. This is aimed to sustain the health insurance system in a cost-effective manner, where the reducing cost of care is not expected to affect the quality of health services. However, many factors make it difficult to determine the standard length of stay for patients after undergoing PCI.[2]

The presence of complications is one of the main factors in considering the length of stay after PCI. A health economics study showed that patients who experienced complications in a hospital would increase the length of stay compared to patients who did not.[3] Therefore, one of the proposed methods to predict the length of stay is risk stratification of complications.

Cystatin C is widely used as a marker of kidney failure. Cystatin C also plays a role in determining the prognosis of patients with the acute coronary syndrome (ACS), especially patients with ST-elevation myocardial infarction (STEMI). Elevated cystatin C level is associated with increased rate of heart failure, myocardial infarction, stroke, major adverse cardiac events (MACE), and death in STEMI patients undergoing PCI, as well as early diagnosis of contrast-induced acute kidney injury (CI-AKI).[4,5] Given the broad ability of cystatin C as a predictor of complications in patients with ACS especially those undergoing PCI, and the increased length of stay associated with post-PCI complications, we want to analyze the ability of

serum cystatin C as a predictor of length of stay in STEMI patients undergoing primary PCI.

METHODS

This analytic observational study was using a prospective cohort method, carried out in the Emergency Room (ER), Cardiovascular Care Unit (CVCU), and the Cardiac ward of Dr. Sardjito Hospital. Subjects included are all patients with diagnosis of STEMI who underwent primary PCI procedures at Dr. Sardjito Hospital. Patients were then followed during post-procedure care until they were discharged or died during hospitalization. Inclusion criteria included all STEMI patients who underwent primary PCI procedures and signed the consent form. Exclusion criteria included patients with chronic kidney disease who were undergoing regular hemodialysis, patients with previous contrast exposure (within the last 2 days), malignancy, deep vein thrombosis, peripheral vascular disease, cerebrovascular disease, cardiac complications, vascular complications, patients with cardiogenic shock (4th Killip), as well as patients who died 24 hours before examination of serum cystatin C after the primary PCI procedure. In addition to measure serum cystatin C levels and length of stay, the variables thought to affect this study included age, gender, LVEF classification, eGFR value, Killip classification, hypertension, diabetes mellitus, chronic lung disease, PCI access, and complications such as CI-AKI, and infections were also recorded.

Basic data were obtained from history taking, medical record data, clinical and supporting examinations (laboratory, echocardiography, imaging) and then recorded into a case report form. Blood specimens were taken to measure cystatin C and creatinine levels before the primary PCI procedure at the clinical laboratory installation of Dr. Sardjito Hospital. Serum creatinine was examined by enzymatic colorimetric methods using a Cobas C501 automatic chemical analyzer. Cystatin C was examined by an enhanced particle immunoturbidimetric assay. Creatinine was used to assess eGFR before and after the procedure.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 23 software, covering univariate, normality, multicollinearity, bivariate, multivariate, and multiple linear regression analysis. This research had received approval from the Medical and Health Research Ethics Commission, Faculty of Public Health and Nursing, University of Gadjah Mada, and approval from the Director of Dr. Sardjito Hospital.

RESULT AND DISCUSSION

Of 111 subjects included in the inclusion criteria, 19 subjects died so that only 92 subjects could be analyzed with the characteristics presented in Table 1.

The mean age of the subjects was 59.6 years with a BMI of 24.58 kg/m^2. A study of patients with ACS at Sanglah Hospital, Denpasar in 2016 who experienced STEMI and performed PCI was mostly 60 years old.[6] Ages 40-60 years increase the risk of ACS by five times.[7] Most of the subjects were male (85.9%). Subjects with comorbid diabetes mellitus were 30.4%, hypertension 60.9%, while chronic lung disease was only 3.3%. Most of the subjects had LVEF Heart failure with reduced ejection fraction (HFrEF) (44.6%). All PCI accesses are radial.

Table 1. Basic characteristics of subjects

		Mean ± SD or Median (min – max)	N	%
Age (years)		59.55 ± 10.80		
BMI (kg/m^2)		24.58 ± 3.69		
Gender	Female		13	14.1%
	Male		79	85.9%
Diabetes mellitus			28	30.4%
Hypertension			56	60.9%
COPD			3	3.3%
LVEF	HFpEF		22	23.9%
	HFmEF		29	31.5%
	HFrEF		41	44.6%
PCI access	Radial		92	100.0%
eGFR	64 (6 - 109)			
Killip	I		80	87.0%
	II		10	10.9%
	III		2	2.2%
Infection			34	37.0%
CI-AKI			10	10.9%
LOS ICCU		3 (1 – 7)		
LOS Hospital		5 (2 – 10)		
Cystatin C Pre		1.10 (0.66 – 4.76)		
Cystatin C Post		1.29 (0.82 – 5.73)		
Delta Cystatin C		0.10 (-0.72 – 2.44)		
Creatinin Pre		1.18 (0.62 – 7.12)		
Creatinin Post		1.22 (0.52 – 7.75)		
Delta creatinin		0.04 (-2.37 – 2.44)		
Contract type	Low osmolar		81	88%
	Iso osmolar		11	12%
Contrast volume	< 300 ml		91	98.9%
	> 300 ml		1	1.1%

Mean ± SD: normally distributed, median (min-max): not normally distributed, n(%): categorical data

The median eGFR value of the subjects was 64 with the lowest value was 6 and the highest was 109. Most of the subjects were in 1st Killip category (87.0%). Subjects with infection during treatment were 37.0% and 10.9% of subjects experienced kidney failure due to contrast during treatment. The median length of stay at the ICCU was 3 days with a range of 1-7 days and the total length of stay in the hospital was 5 days with a range of 1-10 days. Median cystatin C levels pre-PCI was 1.10 and post PCI was 1.29 with a median increase in cystatin C of 0.1 with a range of 0.72 down and up to 2.44. The median pre-PCI creatinine level was 1.18 and post-PCI was 1.2 with a median delta creatinine of 0.04 with a range of -2.37 to 2.44.

The relationship between the increased cystatin C and the increased length of hospital stay was analyzed by Spearman Correlation. The higher the increase in cystatin C, the longer length of hospital stay, with a positive correlation coefficient of 0.50 ($p<0.001$).

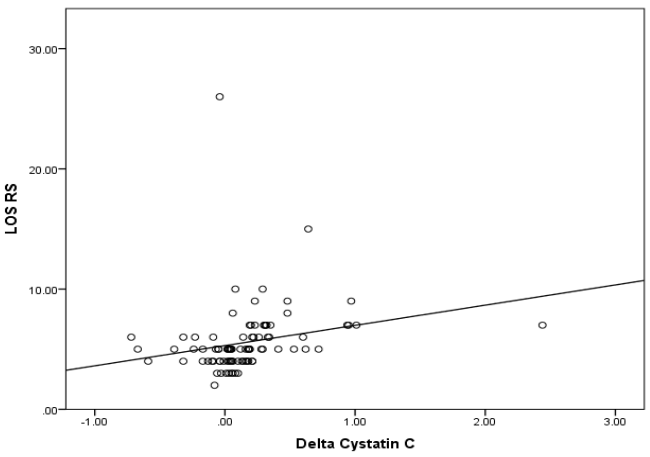

Figure 1. Relationship between Cystatin C increase and length of hospital stay.

In a study conducted by Martuchelli et al. and Abid et al. increased cystatin C correlates with increased mortality and MACE in patients with acute myocardial infarction.[8,9] Cystatin C is produced and secreted by cardiac muscle cells and its synthesis increases when the heart is ischemic so that in STEMI subjects the levels are higher than in subjects without ACS, and it is significantly inverse related to ejection fraction in CHD subjects. Subjects with STEMI and high serum cystatin C (>0.93mg/L) undergoing angioplasty tend to have a higher risk of cardiovascular mortality.[10,11] A decrease in eGFR, especially in subjects over 60 years is a factor that is independently associated with an increase in cystatin C.[12]

Table 2 below shows a significant relationship between LVEF and length of stay, where the median length of stay of subjects with LVEF HFrEF was 6 days, longer than LVEF HFpEF and HFmEF, which were 5 and 4 days ($p<0.001$). A decrease in LVEF is directly proportional to a decrease in kidney function so that a decrease in LVEF is directly proportional to an increase in mortality and worsening clinical outcomes.[13,14] There is a significant correlation between eGFR and length of stay ($p<0.001$) with a correlation coefficient of -0.379 (negative), meaning that the lower the eGFR, the longer the length of stay in the hospital. Length

of stay increased by 0.25 days for every 10 mL/min/1.73 m^2 decrease in eGFR. Estimation of treatment mortality was also higher in the group with low eGFR which occurs progressively with aging.[13,15]

Length of stay for subjects with infection during treatment was 7 days, longer than subjects without infection (5 days, p<0.001). There is an increase in the occurrence of acute infections in subjects with myocardial infarction such as respiratory tract infections such as pneumonia (32%), bronchitis (35%), urinary tract infections (17%), and other infections (16%).[16] Tada et al. stated that subjects with pneumonia caused a higher incidence of death during treatment compared to subjects without pneumonia (12% vs. 1%), similar to a study conducted by Chen et al. in which infection during treatment led to increased length of stay and mortality in NSTEMI patients.[17,18] Infection increases the length of stay in post-myocardial infarction patients with an OR of 3.7 (p=0.008).[19]

Table 2. Relationship of external variables with length of treatment

		LOS Hospital		r	P
		Mean ± SD	Median (min – max)		
Age (years)				0,155	0,070
Gender	Female	5.46 ± 1.61	5 (3 – 8)		0,646#
	Male	5.58 ± 3.04	5 (2 – 26)		
Diabetes Mellitus	No	5.12 ± 1.69	5 (2 – 10)		0,086
	Yes	6.57 ± 4.43	5 (4 – 10)		
Hypertension	No	4.89 ± 1.24	5 (2 – 7)		0,181#
	Yes	6.00 ± 3.49	5 (3 – 10)		
COPD	No	5.55 ± 2.92	5 (2 – 10)		0,255#
	Yes	6.00 ± 1.00	6 (5 – 7)		
LVEF	HfpEF	4.59 ± 1.30	5 (2 – 7)		<0,001*$
	HfmEF	4.62 ± 1.32	4 (3 – 9)		
	HfrEF	6.76 ± 3.75	6 (4 – 10)		
eGFR				-0,379	<0,001*
Killip	I	5.49 ± 3.01	5 (2 –7)		0,213$
	II	5.90 ± 1.20	6 (4 – 7)		
	III	7.00 ± 4.24	7 (4 – 10)		
	IV	-	-		
Infection	No	4.69 ± 1.29	5 (2 – 9)		<0,001*#
	Yes	7.06 ± 4.03	7 (3 – 10)		
CI-AKI	No	5.25 ± 2.87	5 (2 – 10)		<0,001*#
	Yes	6.94 ± 2.54	6 (3 – 10)		

*) significant p<0,05, r) Spearman Correlation, #) Mann Whitney, $) Kruskal Wallis

Length of stay in subjects with CI-AKI was 6 days, longer than subjects without kidney failure (5 days, p<0.001). Contrast directly constricts the vasa recta in order to reduction of vasodilator nitric oxide, while the vasoconstrictor superoxide is increased.

Another mechanism is that endothelial cells and kidney tubules show severe toxicity and apoptosis when exposed to contrast. Due to apoptosis, iodine which is a marker of cell membrane damage regardless of contrast, although in very small amounts can be cytotoxic and cause kidney tubular cell death.[6,20] Subjects with CI-AKI have an increased risk of kidney failure, mortality, length of stay, and cost of care.[20] Another study stated that subjects with CI-AKI (LOS 13 ± 7) required a longer treatment duration than subjects without CI-AKI (LOS 8 ± 3) $p<0.001$.[21]

An increase in serum creatinine of 0.25 to 0.5 mg/dL and 25–50% after coronary angiography is associated with a 4-fold increase in hospitalization mortality and prolongation of LOS in hospital.[22]

Cystatin C levels were included as one of the predictors of CI-AKI which included pre-procedure cystatin C concentrations > 1.04 mg/L, contrast volume > 150 mL, and emergency PCI. Serum creatinine did not increase at 24 hours post-PCI in subjects without CI-AKI, whereas Cystatin C increased, supporting that serum cystatin C is more sensitive as a marker of kidney function than serum creatinine.[6,10,12,14]

Age, gender, diabetes mellitus, hypertension, chronic lung disease and Killip's degree did not show a significant relationship with length of stay ($p>0.05$). Age is also a predictor for MACE in post PCI subjects.[13] Men have a greater risk of ACS than women because of the presence of estrogen in women which protects blood vessels from damage and the effect of estrogen on HDL and LDL levels before menopause.[7] In obesity and overweight there is a progressive effect of atherosclerosis and cardiovascular disease independently and directly associated with an increased risk of ACS.[23] Transradial (TR) approach used in this study significantly reduced the number of access site complications compared to the transfemoral route and the need for noncoronary interventions (transfusion and surgical repair).[24]

DM is one of the cardiovascular risk factors. ACS patients generally have a combination of high triglycerides and low HDL, causing atherosclerosis in coronary.[25] ACS subjects with DM were significantly associated with increased mortality.[26] The study conducted by Swaminathan et al. stated that ±70% of all subjects had hypertension.[14] The occurrence of coronary artery endothelial dysfunction and arterial vasoconstriction is caused by continuously high and persistent blood pressure.[27] However, previous studies have shown that elevated blood pressure is not an independent prognostic of mortality and length of stay in myocardial infarction subjects.[28]

In COPD subjects who are hospitalized, cardiovascular disease is the most common comorbid.[29] Length of stay, long-term MACE, and mortality was higher in subjects with COPD after coronary angioplasty.[30] However, Bundhun

et al., stated that the incidence and prognostic outcomes in COPD subjects with ACS (NSTEMI) showed that COPD was not an independent predictor of the majority of short and moderate-term clinical outcomes in most post-PCI subjects.[30] Killip's classification is a predictor of length of stay, mortality during hospitalization, and mortality at 6 months.[31] In this study, follow-up was not carried out for up to 6 months so that the data could not be rationalized.

The length of ICCU treatment is in accordance with the study conducted by Bae et al. which states that the majority of subjects significantly require ICCU care for 3.5 days.[13] Another study also stated that after primary PCI, the most (46.3%) of all subjects with myocardial infarction required an intermediate LOS (4–5 days), followed by the short LOS group (≤3 days, 26.9%) and long LOS (>5 days). days, 26.8%) p<0.001 (Swaminathan et al., 2015).[14] Shorter LOS has been reported to increase the risk of mortality and rehospitalization, although some studies have also reported no significant change in rehospitalization and mortality at 30 days despite a significant decrease in LOS. Subjects with long LOS had the highest 30-day mortality and MACE because they had more severe comorbidities and complications, so it was estimated that readmission would occur within 30 days. Very early hospital discharge (same-day discharge) is associated with increased 30-day mortality and MACE.[14]

Based on the results of bivariate analysis, independent variables and confounding variables that had a p-value of <0.05 were continued in multivariate analysis. Multivariate analysis was analyzed by Multiple Linear Regression test, namely the length of treatment on a numerical scale. Multivariate analysis is presented in the following table.

Table 3. Multivariate Analysis

	Model I		Model II		Model III	
	B	p	B	P	B	P
Constant	6.082	0.000	6.118	0.000	6.310	0.000
Delta cystatin C	0.26	0.590				
LVEF	0.64	0.067	0.67	0.048	0.72	0.034
eGFR	-0.03	0.002	-0.03	0.001	-0.04	0.001
Infection	1.89	0.006	1.87	0.006	1.93	0.005
CI-AKI	1.01	0.200	1.14	0.086		

The multivariate test table above shows that LVEF, eGFR, and infection had a significant effect on length of stay (p<0.05). Correlation between LVEF and length of stay was obtained by a regression coefficient of 0.72, meaning that any decrease in the degree of

LVEF would extend the length of stay by 0.72 days (p=0.034). Correlation between eGFR and length of stay was found to have a regression coefficient of -0.04, meaning that every 1 unit decrease in eGFR will increase the length of stay by 0.04 days (p=0.001). Correlation between infection and length of stay was obtained by a regression coefficient of 1.93, meaning that subjects with infection would experience a length of stay of 1.93 days longer than subjects without infection (p=0.005). A further explanation has been discussed in the previous section.

In this study, the increment in serum cystatin C levels did not significantly prolong the length of stay, this might because in this study population, increment in cystatin C or creatinine levels of the majority of subjects was not clinically significant so that the evaluation of kidney function can be performed during the outpatient.

Limitations of this study include most of the research subjects are male and elderly subjects, so it cannot be generalized to the population. There was no evaluation of cystatin C level after 24 hours which delayed contrast acute kidney injury might not be detected. In this study, there was also no record of the amount of fluid that was administered after PCI was performed. Number of subjects was not sufficient to allow for the exclusion of confounding variables wherein multivariate analysis it was found that LVEF, eGFR, and infection were confounding variables that significantly affected length of stay, so it was necessary to exclude.

CONCLUSION

The median change in serum cystatin C levels in STEMI patients undergoing primary PCI procedures was 0.10 (-0.72 - 2.44). The increment in serum cystatin C levels was not significantly associated with the increment in the length of hospitalization in STEMI patients undergoing primary PCI procedures at Dr. Sardjito Hospital.

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