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PLATELET-TO-LYMPHOCYTE RATIO AFFECTS THE INCIDENCE OF CONTRAST-INDUCED NEPHROPATHY IN PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION UNDERGOING PRIMARY PERCUTANEOUS CORONARY INTERVENTION

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Abstract
Background : Contrast-induced nephropathy (CIN) is a condition of acute renal failure that is found after the administration of iodinated contrast media during angiography or other medical procedures. CIN is the third most common cause of acute kidney injury in hospitalized patients. CIN increased mortality, cardiovascular events, and hospital stay. Platelet-lymphocyte ratio (PLR) describes the degree of inflammation involved in the process of the CIN mechanism. Recent research stated PLR was an independent predictor of CIN. The purpose of this study was to explore the impact of PLR on the incidence of CIN in STEMI patients undergoing a primary PCI procedure.
Methods: This prospective observational study involved 61 STEMI patients who underwent primary percutaneous coronary intervention (PCI) procedures at the Haji Adam Malik General Hospital, Murni Teguh Memorial Hospital, and Grandmed Lubuk Pakam Hospital. PLR and baseline creatinine were assessed at the beginning of hospital admission, then creatinine evaluation was examined 48-72 hours after the primary PCI procedure. CIN was defined as an increase of creatinine ≥ 0.5 mg / dL or an increase of ≥ 25% from the initial creatinine 48-72 hours after the Primary PCI procedure.
Results: This study found that 11 (18.03%) subjects were experienced CIN. PLR value was significantly higher in patients experiencing CIN than not CIN (216.38 ± 69.46 and 146.29 ± 61.62, p = 0.001). PLR was positively correlated to the incidence of CIN (r = 0.394, p = 0.002). The PLR cut off value for CIN was 162.47, with a sensitivity of 81.8% and a specificity of 64%, and AUC value of 0.795. In bivariate analysis, PLR was found to be associated with CIN (p=0.008, with OR: 8.0, CI95% 1.556-41.134).
Conclusion: Platelet-to-lymphocyte ratio affects the incidence of CIN, and also has a positive correlation with CIN. It is found that the probability of CIN is in accordance with the PLR value significantly with cutoff 162.47.

Introduction
Contrast-induced nephropathy (CIN) after a percutaneous coronary intervention (PCI) is a serious complication that can increase morbidity and mortality in patients with acute myocardial infarction. CIN is associated with poor prognosis, longer hospital stays, increased costs, increased incidence of end-stage renal failure, revascularization, and increased short-term and long-term mortality[1]. Cho et al found that the incidence rate of CIN was 14.5%. Hospital mortality in patients with CIN was 8.1% and the 1-year mortality rate in patients with CIN was 15.9%[1].

The pathophysiological mechanisms of CIN are complex, complicated, and influenced by many factors. Some of the mechanisms that may be involved are intra-renal vasoconstriction, medulla hypoxia, oxidative stress, endothelial dysfunction, direct tubular epithelial injury that caused by contrast agent and the inflammatory processes[2]. One of simple inflammatory blood marker was The Platelet-to lymphocytes ratio (PLR). The latest study found that high PLR was associated with poor prognosis of coronary heart disease and PLR also was associated with CRP and fibrinogen levels[2]. Currently, PLR is widely studied as a marker of several inflammatory conditions, not only in the area of malignancy but other pathological conditions such as essential hypertension

patients and heart disease patients. PLR values are associated with the incidence of CIN in patient with acute myocardial infarction.[3-7]. Because of the potential role of inflammation in the development of CIN, we investigate the impact of PLR on incidence of CIN in patients with ST-segment elevation myocardial infarction undergoing primary PCI.

Methods

Population and Research Design

This prospective observational study was performed at the Haji Adam Malik General Hospital, Murni Teguh Memorial Hospital, and Grand Medistra Lubuk Pakam Hospital with permission from the Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara. Patients admitted with a diagnosis of STEMI, within 12 h from symptom onset were primarily enrolled in the study consecutively from January 2019 to November 2019. The exclusion criteria were patients with incomplete data, received contrast> 300ml or> 4ml / kgBB during PCI, and patients with cardiac resuscitation.

Study Procedure

The clinical and demographic characteristics of subjects who admitted to the ER with a diagnosis of STEMI within 12 hours from symptom onset were recorded. The complete blood count, cardiac enzymes, blood glucose, urea, creatinine, and lipid levels were recorded in all patients. The serum creatinine level measurement was repeated 48-72 hours after the primary PCI procedure. The PLR was calculated as the ratio of the platelet count (/µL) to the lymphocyte count (/µL).

Statistical analysis

Categorical variables are presented by number or frequency (n) and percentage (%). Numerical variables are presented by mean and standard deviation for normally distributed data. If data not normally distributed, the data shown by a median. Association between PLR and CIN was estimated by Spearman's rank correlation coefficient. Comparisons of parametric value between the 2 groups were performed using independent-samples Student t-tests. For bivariate analysis, a Chi-Square test was conducted between PLR value and events outcome. Receiver Operating Characteristic (ROC) analysis was used to determine the optimal cut off value for PLR. All the data were analyzed using SPSS version 24.0, the value of $p < 0.05$ was said to be statistically significant

Results

This study population consisted of 61 patients (mean age 56 ± 8.84 years, 88.5% males) who had measurements of PLR and baseline creatinine, followed by 48-72 hours post primary PCI procedure creatinine measurements. There were 11 (18.03%) subjects who developed CIN. There were no significant differences between the groups regarding CAD risk factors and other clinical features. The CIN group had significantly more 'high-very high' Mehran scores than the no-CIN group. (54.5% vs 10%, $p<0.05$). The baseline characteristics of the study population are presented in table 1.

Table 1. Baseline Characteristics of Study Population

Parameter	CIN		p-value
	CIN (+) (n=11, 18.03%)	**CIN (-) (n=50, 81,97%)**	
Age (years)	54.64 ± 7.42	56.50 ± 9.155	0.531
Sex			
Female (n,%)	3(27.3)	4(11.5)	0.103
Male (n,%)	8(72.7)	46(85.2)	0.103
Hypertension (n,%)	7(63.6)	25(50)	0.627
Diabetes Mellitus (n,%)	4(36.4)	6(12)	0.07
Smoking (n,%)	8(72.7)	44(88)	0.343
Family History (n,%)	7(63.6)	12(24)	0.026

Obesity (n,%)	3(27.3)	25(52.1)	0.249
Hyperlipidemia(n,%)	5(45.5)	16(32)	0.488
CHF (n,%)	5(45.5)	9(18)	0.106
Anemia (n,%)	4(36.4)	8(16)	0.203
Mehran Score	9(0-11)	6(1-17)	0.059
Mehran Score Classification			
High-Very High (n,%)	**6(54.5)**	**5(10)**	**0.003**
Low-Moderate(n,%)	**5(45.5)**	**45(90)**	
Contrast Volume (ml)	100(80-300)	100(75-150)	0.229
LV EF(%)	45(38-49)	45(25-48)	0.665
LV EF<40(n,%)	4(36.4)	9(18)	0.226
Time Onset (hours , min-max)	8(1-10)	5(1-12)	0.09
Admission SBP (mmHg)	130(80-180)	125(80-120)	0.932
Admission DBP (mmHg)	80(60-110)	80(60-130)	0.651
Heart Rate (bpm)	88(48-98)	78(44-98)	0.375
CAD (n,%)			
Singelvessel CAD	8(72.7)	21(42)	0.13
Multivessel CAD	3(27.3)	29(58)	
Medical Therapy (n,%)			
ACE-I/ARB	7(63.6)	27(54)	0.74
Betablocker	5(45.5)	28(56)	0.763
Diuretic	4(36.4)	21(42)	0.503
MRA	2(18.2)	6(12)	0.627
Statin	11(100)	49(98)	>0.999

The baseline laboratory measurements of the study patients are shown in table 2. PLR was significantly higher in patients who developed CIN compared to those who did not (216.38±69.46 and 146.29±61.62 respectively; $p < 0.001$). In addition to having elevated PLR, patients who developed CIN had significantly higher baseline neutrophil, admission blood glucose, post procedure urea, creatinine, but significantly lower lymphocytes and post procedure creatinine clearance.

Table 2. Comparison of Laboratory Measurements of the Study Population

Parameter	CIN		p-value
	CIN (+) (n=11, 18.03%)	**CIN (-) (n=50, 81,97%)**	
Hb (g/dL)	14(9.4-17)	13.9(8.9-17.7)	0.940
Hematocrit (%)	40.17±5.94	42.26±5.10	0.237
WBC(/µL)	13560(5410-21000)	13105(7310-22830)	0.505
Platelet (10^3/µL)	284.27±69.96	275.32±78.13	0.728
Neutrophil (10^3/µL)	**13.93(3.7-89.40)**	**10.93(4.9-89.40)**	**0.042**
Lymphocytes (10^3/µL)	**1.5(0.73-2.44)**	**1.88(74-10.20)**	**0.013**
Monocytes (10^3/µL)	0.88(0.30-11.50)	0.59(0.25-7.70)	0.91
Eosinophil (10^3/µL)	0.02(0.00-0.15)	0.07(0.00-0.64)	0.061
Basophil (10^3/µL)	0.04(0.01-0.10)	0.05(0.01-0.2)	0.449
Admission Blood Glucose (mg/dL)	**140(109-386)**	**127.50(94-400)**	**0.026**
Pre PCIureum(mg/dL)	24(15-37.5)	28(15-56)	0.208
Pre PCI creatinine (mg/dL)	1.1(0.89-1.25)	1.15(0.26-1.7	0.680
Pre PCI CrCL(ml/i)	73.86(42.08-116.34)	75.66(36.83-326.39)	0.499
Post PCI urea(mg/dL)	**43(34-47)**	**26(15-55)**	**<0.001**
Post PCI creatinine(mg/dL)	**1.4±0.14**	**0.99±0.27**	**<0.001**
Post PCI CrCL(mg/dL)	**58.04(32.87-91.28)**	**83.84(37.49-273.75)**	**0.001**
Total Cholesterol(mg/dL)	188.54±54.50	179.76±50.66	0.609

Triglyceride (mg/dL)	122(35-348)	119(58-348)	0.75
HDL (mg/dL)	**44(30-55)**	**37.5(26-55)**	**0.027**
LDL (mg/dL)	116(77-224)	122(56-227)	0.858
PLR	**216.38±69.46**	**146.29±61.62**	**0.001**

From correlation analysis with Spearman Rank Correlation between PLR and CIN, this study found that PLR had significant positive correlation with CIN, with rho= 0.394, p= 0.002.The result was presented in table 3.

Table 3. Spearman Rank Correlation between PLR and CIN

	CIN
Platelet to Lymphocytes Ratio (PLR)	r=0.394 p= 0.002 n=61

The PLR cutoff value was obtained using the ROC curve as shown in Figure 1, then AUC value to predict CIN is 79.5% with a p value <0.001. The cutoff value was 162.47 with a sensitivity of 81.8% and a specificity of 64%.We performed bivariate analysis between PLR> 162.47 and CIN. There was a significant association between PLR and the incidence of CIN (OR : 8.0, CI 95% : 1.556-41.134, p= 0.008)

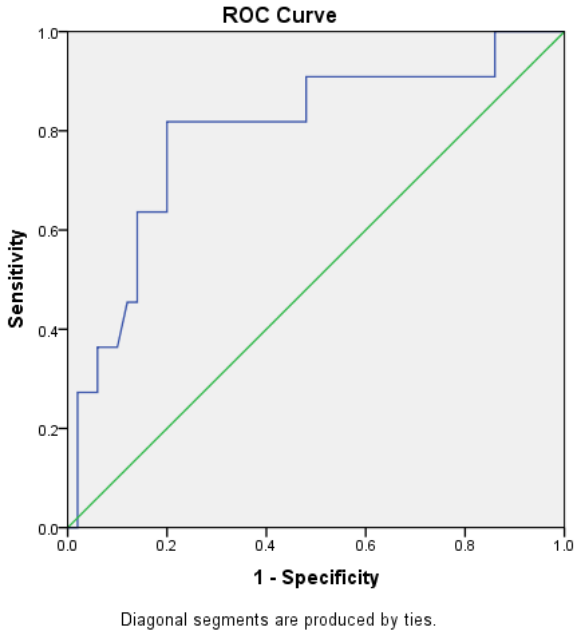

Figure 1 ROC Curve of PLR

Table 4. Bivariate Analysis of PLR-CIN

Parameters	CIN		p	OR	CI 95%	
	CIN (+) n(%)	CIN(-) n(%)			Min	Max
PLR≥162.47	9 (81.8%)	18(36%)	0.008	8.0	1.556	41.134
PLR<162.47	2(18.2%)	32(64%)				

Discussion

The mechanisms of CIN are complex, multifactorial and have not yet been fully understood. CIN has been known as contrast-induced acute kidney injury and is a major adverse effect caused by exposure to intravascular iodinated contrast medium[7]. Various studies state the mechanisms that may be involved in CIN were intrarenal vasoconstriction, decreased renal blood flow, hypoxia medulla, oxidative stress, endothelial dysfunction, kidney cell injury directly due to contrast agents and inflammation[2]. Emerging risk factors such as arterial stiffness, oxidative stress, elevated homocysteine, hsCRP, NT proBNP, serum uric acid levels, procalcitonin, red cell distribution width, and NLR, have been linked to CIN development[4,8]. There is a potential role of the inflammatory process and aggravated prothrombotic status in the development of CIN, and mediators reflecting inflammation and thrombosis such PLR might be a marker of CIN. Thus we investigated the association of PLR and CIN in patients with STEMI undergoing primary PCI.

In this study, PLR of the CIN group was significantly higher compared to the non-CIN group, (216.38 ± 69.46 vs 146.29 ± 61.62 respectively, p= 0.001). This is in accordance with the research of Sun et al. which found PLR value in CIN group was higher compared to non-CIN group (173.8 ± 62. vs 116.2 ± 51.7 respectively, p=0.001) and Dermicelik et al also found the PLR value was significantly higher in the CIN group compared to the non-CIN group (160.8 ± 29.7 vs 135.1 ± 26.1 respectively, p= 0.001)[2,4]. PLR is a marker in the blood that reflects the severity of inflammation. Although the exact mechanism of CIN development is still uncertain, it is suspected that inflammation plays a major role in the mechanism of CIN. The results of the present study agree with the existing literature and further strengthen the predictive role of the PLR for CIN following catheter interventions.

High PLR predicts the incidence of CIN in patients with acute myocardial infarction who undergo percutaneous intervention procedures. This study performed ROC analysis to find the cut off value to predict the incidence of CIN. The cut off of PLR for CIN was 162.47 with a sensitivity of 81.8% and a specificity of 64%, with an AUC value of 0.795 (p = 0.002). This is not much different from Velibey et al study that found PLR in patients with CIN in IMAEST populations who undergo primary PCI procedures with a cut off of 177.5 which has a sensitivity of 60% and a specificity of 72% with an AUC of 0.660 (p = 0.001)[3].

In this study, the incidence of CIN was 18%. The incidence of CIN varies from 2% in the low risk population to >50% in high-risk groups[3,7]. Individual risk factors that predict CIN have been identified and cumulative risk scores have also developed. Mehran et al made a score to predict the risk development of CIN[9]. Patients at higher risk include those with baseline chronic kidney disease, diabetes mellitus, congestive heart failure, hypovolemia, periprocedural hypotension, anemia, those who are older, and those for whom with a high total contrast volume and periprocedural use of IABP[3,9]. In the present study, patients with CIN have more high-very high Mehran scores compared to patients with no-CIN.

A complete blood count is an easy, readily available, and routine examination that provides information about red blood cells and WBCs, platelets, the count and dimensions of subgroups of cells including red cell distribution width and platelet distribution width, and markers such as the PLR and NLR. White blood cell count and subtypes are recognized as inflammatory markers in cardiovascular diseases[5]. The previous study found the association of NLR in predicting CIN among patients with STEMI and NSTEMI[10,11]. They found that NLR was higher in the CIN group and PLR was an independent predictor of CIN[10,11]. Like the NLR, a high PLR is also associated with an increased risk of death and reinfarction after PCI. One possible cause of the high PLR was increasing in the inflammatory response. The advantage of PLR was both platelet and lymphocyte components reflect hyperactivity from coagulation and inflammation, and both are important mechanisms for causing CIN, so PLR can be a potential marker for CIN[1].

This study has some limitations. The number of study samples is small so the study is could not assess other confounding factors. This study examines laboratory parameters in 3 different centers and using different devices, even though using the same parameter unit. There are variations in the preparation of CIN prevention before the procedure, and the study did not distinguish the degree of osmolarity of contrast media given to the subject. This study did not analyze heterogeneity among the study population.

Future studies are expected to involve a larger number of research samples to provide more study power and involve more centers. It is hoped that further studies can rule out factors that could affect kidney function directly so that the bias factor could be reduced. Hopefully, a future study could also do serial creatinine examination to find the maximum peak creatinine value and can analyze more for independent risk factors that cause CIN.

Conclusions

PLR value affects the incidence of CIN. PLR is positively correlated with CIN. It is found that the probability of CIN is in accordance with the PLR value significantly with cut off 162.47.

Conflict of Interest

The authors declare that there is no conflict of interest.

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