Dynamic Changes in Platelet-Lymphocyte Ratio in Diabetic Patients with COVID-19 within First Week of Hospitalization

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Dynamic Changes in Platelet-Lymphocyte Ratio in Diabetic Patients with COVID-19 within First Week of Hospitalization

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Abstract: The platelet-to-lymphocyte ratio (PLR) is an inexpensive, readily available marker of inflammation response that is widely investigated as a prognosis predictor in acute and chronic disease, such as viral pneumonia and diabetes mellitus (DM). Recently, dynamic changes in the PLR during hospitalization have become a concern in novel coronavirus pneumonia cases. The study objective is to determine the PLR trend of diabetic patients with COVID-19 on the basis of some clinical characteristics and outcomes. The records of 35 confirmed COVID-19 patients with DM who were hospitalized in a single center (Dr. Soetomo General Teaching Hospital, Surabaya, Indonesia) for seven days from May 2020 to August 2020 were retrospectively analyzed. We collected data about their clinical characteristics, clinical outcomes, and dynamic changes in the platelet and lymphocyte counts and the PLR. Of the 35 patients, 20 were female, 15 were male, and the median (interquartile range) age was 57. Cough was the most common symptom on admission (71.4%), and most patients were admitted with severe COVID-19 (48.6%). Fifteen patients had new-onset diabetes on admission, and 16 patients had had diabetes for less than five years. Hypertension was the other leading comorbidity (42.8%). There were 22 nonsurvival cases (62.9%). During admission, thrombocytopenia episodes were significantly observed among the elderly ($p = 0.001$), while lymphopenia episodes were significantly found in the nonsurvival cases ($p = 0.037$). The peak PLR commonly occurred on admission (40.0%), while the lowest was typically identified during the last evaluation (42.9%). A declining trend in the average PLR was evident in the severe and nonsurvival cases, and the average ΔPLR showed a statistically significant association with cardiac injury ($p = 0.023$), liver injury ($p = 0.028$), and respiratory failure ($p = 0.045$). The PLR may reflect the inflammatory response caused by COVID-19 infection and might be helpful in the monitoring of COVID-19 patients with DM.

Keywords: COVID-19, diabetes mellitus, platelet-lymphocyte ratio.

新冠肺炎糖尿病患者在住院第一周内血小板-淋巴细胞比率的动态变化

摘要：血小板与淋巴细胞比率(PLR)是一种廉价、易于获得的炎症反应标志物，被广泛研究作为急性和慢性疾病的预后预测因子，例如病毒性肺炎和糖尿病(DM)。近期，住院期间PLR的动态变化成为新型冠状病毒肺炎病例的关注焦点。研究目的是根据一些临床特征和结果确定新冠肺炎糖尿病患者的PLR趋势。回顾性分析了2020年5月至2020年8月在单一中心（印度尼西亚泗水苏友友综合教学医院）住院7天的35名确诊的新冠肺炎DM患者的记录。我们收

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集了有关其临床特征、临床结果以及血小板和淋巴细胞计数以及PLR的动态变化的数据。在这35名患者中，20名女性，15名男性，中位（四分位距）年龄为57岁。咳嗽是入院时最常见的症状（71.4%），大多数患者入院时患有严重的新冠肺炎（48.6%））。15名患者在入院时患有新发糖尿病，16名患者患有糖尿病不到5年。高血压是另一个主要的合并症（42.8%）。有 22 例非存活病例 (62.9%)。入院期间，在老年人中显着观察到血小板减少事件（磷=0.001），而在非存活病例中显着发现淋巴细胞减少事件（磷=0.037）。PLR峰值通常发生在入院时(40.0%)，而最低值通常是在最后一次评估期间确定的(42.9%)。在严重和非存活病例中，平均 PLR 呈明显下降趋势，平均 ΔPLR 显示与心脏损伤 (磷= 0.023)、肝损伤 (磷=0.028)和呼吸衰竭(磷=0.045)具有统计学显着相关性）。PLR可能反映新冠肺炎感染引起的炎症反应，可能有助于监测新冠肺炎合并 DM 患者。

关键词：新冠肺炎、糖尿病、血小板淋巴细胞比。

1. Introduction

Since novel coronavirus–infected pneumonia, known as COVID-19, was declared a pandemic by the World Health Organization (WHO) in March 2020, many studies have been published to investigate this infection. Diabetes mellitus (DM) is a leading comorbidity in patients with COVID-19 [1]. The outcomes of COVID-19 patients depend on their inflammation responses to the viral infection. Many studies report that the peripheral white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are circulating biomarkers that represent the inflammation and immune status related to the prognosis of COVID-19 [2]. The PLR is a relatively new subclinical inflammation marker that has been used as a predictive marker of vascular diseases, oncological disorders, and prediabetes and DM [3], [4]. Some studies show a correlation between the PLR value and the disease progression of COVID-19 in the general population. Since the PLR is related to chronic inflammation in diabetes, we investigated the association of dynamic changes in the PLR with the clinical characteristics and outcomes of COVID-19 patients with DM.

2. Methods

This study protocol was approved by the ethics committee of Dr. Soetomo Public Hospital (Surabaya, Indonesia).

2.1. Data Collection

Thirty-five patients with confirmed COVID-19 and DM who were admitted in Dr. Soetomo Public Hospital (Surabaya, Indonesia) from May 2020 to August 2020 were enrolled. Diagnosis of COVID-19 followed the guidelines of the Ministry of Health of Indonesia and was entered in medical records with the International Classification of Disease (ICD)-10 code U07.1. Record of DM (ICD-10 code E10-11) was collected from the patients' medical history. New-onset diabetes was confirmed via random blood glucose testing on admission, followed by a fasting or 2-hour postprandial blood glucose test or an HbA1c test. All patients were at least 18 years of age. We excluded pregnant women, patients with incomplete medical records, and patients who were discharged before seroconversion. According to interim guidance by the WHO [5], the severity of COVID-19 was classified into two groups: nonsevere (mild and moderate) and severe (severe and critical). In this classification, mild cases involve fever, cough, fatigue, anorexia, shortness of breath, and myalgia without pneumonia or hypoxia; moderate cases involve clinical signs of pneumonia with $SpO2 \geq 93\%$ in free air; severe cases are those with clinical signs of pneumonia with $SpO2 < 93\%$; critical cases involve acute respiratory distress syndrome, sepsis, and septic shock. The onset of diabetes was divided into four groups (less than five years, 5–10 years, more than 10 years, and new-onset diabetes [no prior history of diabetes]). Other comorbidities were also noted from the medical history records of the patients. The hospital units were categorized as low care, high care, and intensive care, and the clinical outcomes were classified as survival and nonsurvival. We also collected data about complication events during hospitalization. The complete blood counts at the time of admission and every three days during hospitalization were noted, including the platelet and lymphocyte counts. Patients who had less than three complete blood counts were excluded. The PLR and ΔPLR were calculated as follows: PLR = platelet count/lymphocyte count; ΔPLR = PLR1 – PLR3.

2.2. Statistical Analysis

The statistical analysis was performed using SPSS version 25.0. The summary statistics of this study population are presented as the mean ± standard deviation (mean ± SD) or the median value with the interquartile range (IQR), as appropriate. The nonparametric (two independent samples) Mann-Whitney U test was used to analyze the variables. All *p* values less than 0.05 based on a two-tailed test were considered statistically significant.

3. Result

3.1. Clinical Characteristics

The 35 studied patients had a median (IQR) age of 57 [11], and their ages ranged from 35 to 81 years; 20 were females, and 15 were males. Cough was the most common symptom (71.5%), followed by dyspnea (65.7%), fever (57.1%), anorexia (48,6%), pharyngalgia (20%), and fatigue (20%). There were 13 nonsevere cases and 22 severe cases. Seventeen patients were admitted in the low care unit, 12 in the high care unit, and 5 in the intensive care unit. Based on the onset of diabetes, 16 patients had diabetes for less than five years, and 15 patients were confirmed with new-onset diabetes. According to other comorbidities, 15 patients reported hypertension, five patients reported coronary heart diseases, two patients were on hemodialysis, one patient reported chronic renal disease, one patient had obesity, and 12 patients were aged > 65 years. During hospitalization, some complications were reported. Respiratory failure was found in 21 patients; sepsis was found in 17 patients; acute kidney injury was found in 10 patients; the liver injury was found in 5 patients. At the end of treatment, there were 22 non-survival cases.

Table 1 Clinical characteristic of diabetic patients with COVID-19

Variable	N = 35
Age, years (median/IQR)	57(11)
31-50 years old (n/%)	3/6.7
51-70 years old (n/%)	27/77.1
>70 years old (n/%)	5/14.5
Sex (n/%)	Male 15/42.9; Female 20/57.1
Symptoms and signs (n/%)	
Fever	20/57.1
Cough	25/71.4
Fatigue	7/20
Myalgia	1/ 2.9
Dyspnea	23/65.7
Anosmia	2/5.7
Pharyngalgia	7/20
Anorexia	17/48.5
Diarrhea	4/11.4
The onset of symptoms (median/IQR) days	5/4
Severity on admission (n/%)	
Non-Severe	Mild 0 Moderate 13/37.1
Severe	Severe 17/48.6 Critical 5/14.3
Hospital care unit (n/%)	
Low care	Non-severe 7/20.0 Severe 10/28.6
High care	Non-severe 4/11.4 Severe 8/22.9
Intensive care	Non-severe 2/5.7 Severe 4/11.4
Outcomes	
- Survival	13/37.1
- Non-survival	22/62.9

3.2. Platelet, Lymphocyte, and PLR Features According to Clinical Characteristics and Outcomes

During the disease course, a decreased average of serial platelet counts was found in non-survival patients. The fluctuating values were found in non-severe cases, cardiac injury, and sepsis cases. The rest conditions showed an increased average of serial platelet counts. Increased average of serial lymphocyte counts was found in severe patients, patients who had coronary heart disease, hemodialysis, obesity, patients who experienced liver injury complications, and patients who survived. Decreased average of serial lymphocyte counts was found in age > 65 years, cardiac injury, kidney injury, and sepsis. Thrombocytopenia, a platelet count less than 150 x $10^3/\mu L$, was much more common in severe than non-severe cases (40.9% vs. 15.4%) and non-survival than survival cases (36.4% vs. 23.1%). Lymphopenia was found in new-onset diabetes (50%), severe cases (67.9%), respiratory failure complication (64.3%), sepsis complication (57.1%), and non-survival cases (71.4%). Compared to the survival cases, lymphopenia was much more common in non-survival cases (*p = 0.037*).

Table 2 Platelet counts, lymphocyte counts, thrombocytopenia, and lymphopenia features according to clinical characteristics and outcomes

Variable	n/%	PLT 1 mean ± SD (x10^3/µL)	PLT 2 mean ± SD (x10^3/µL)	PLT 3 mean ± SD (x10^3/µL)	Lymp 1 mean ± SD (x10^3/µL)	Lymp 2 mean ± SD (x10^3/µL)	Lymp 3 mean ± SD (x10^3/µL)	Thrombocytopenia (n/%) [P-value, 95% CI]	Lymphopenia (n/%) [P-value, 95% CI]
Onset of diabetes									
- New-onset	15/42.9	288.5 ± 153.8	297.5 ± 150.1	297.9 ± 162.8	1.32 ± 1.02	1.16 ± 0.64	1.31 ± 0.72	5/33.3 [0.836]	14/93.3 [0.092]
- < 5 years	16/45.7	307.6 ± 102.7	298.1 ± 124	302.1 ± 139.6	1.31 ± 0.54	1.36 ± 0.59	1.47 ± 0.70	5/31.3 [0.984]	12/75 [0.504]
- 5-10 years	1/2.9	-	-	-	-	-	-	-	-
- > 10 years	3/8.6	253 ± 52.8	256 ± 4.4	306 ± 35.3	1.40 ± 0.70	1.45 ± 0.82	1.71 ± 1.13	0	1/33.3 [0.035]
Severity								[0.121]	[0.228]

-	Non-severe	13/37.1	311.1 ± 96.8	299.8 ± 73.8	308.8 ± 120.5	1.29 ± 0.53	1.52 ± 0.66	1.43 ± 0.87	2/15.4	9/69.2
-	Severe	22/62.9	277.4 ± 138.7	285.4 ± 154.3	299.2 ± 153.8	1.33 ± 088	1.14 ± 0.56	1.42 ± 0.64	9/40.9	19/86.4
Comorbidity										
-	HT	15/42.9	274 ± 122	264.3 ± 132.6	275.7 ± 132.8	1.32 ± 0.74	1.24 ± 0.52	1.45 ± 0.72	6/40.0 [0.351]	12/80.0 [1.00]
-	CHD	5/14.3	256.6 ± 75.6	272.6 ± 95.5	353.8 ± 55.3	1.31 ± 0.48	1.66 ± 0.55	1.67 ± 0.63	1/20.0	3/60.0 [0.234]
-	CKD	1/2.9	-	-	-	-	-	-	-	-
-	HD	1/2.9	247 ± 94.7	292.6 ± 132.9	301 ± 49.5	0.96 ± 0.82	1.39 ± 0.17	2.46 ± 0.62	0	0
-	Age > 65 ys	12/34.3	242.5 ± 109.1	253.2 ± 112	239.9 ± 140.9	1.26 ± 0.80	1.10 ± 0.65	1.16 ± 0.73	8/66.7 [0.001]	11/91.7 [0.219]
-	Obesity	1/2.9	-	-	-	-	-	-	-	-
Complication										
-	AKI	10/28.6	288.2 ± 132.3	272 ± 163.7	287.5 ± 177.8	1.76 ± 1.08	1.25 ± 0.66	1.31 ± 0.82	3/30.0 [0.91]	9/90.0 [0.357]
-	Cardiac injury	4/11.4	272.2 ± 145.9	219.5 ± 173.2	194.5 ± 152.4	1.91 ± 1.03	0.80 ± 0.39	0.89 ± 0.32	2/50.0 [0.402]	0
-	Liver injury	5/14.3	308 ± 161.8	285.8 ± 200.4	315 ± 170.1	1.16 ± 0.73	1.38 ± 0.52	1.18 ± 0.52	0	4/80.0 [1.00]
-	Sepsis	17/48.6	290.9 ± 131.9	255.1 ± 113.6	239.4 ± 138.1	1.43 ± 1.01	1.16 ± 0.71	1.13 ± 0.75	8/47.1 [0.053]	16/94.1 [0.046]
-	Respiratory failure	21/60	286.9 ± 129.8	281.5 ± 127.5	275 ± 144.8	1.18 ± 0.51	1.07 ± 0.61	1.16 ± 0.6	7/33.3 [0.770]	18/85.7 [0.308]
Outcomes									[0.42]	[0.037]
-	Survival	13/37.1	267.6 ± 105	305.8 ± 134.8	361.8 ± 104.6	1.17 ± 0.52	1.42 ± 0.43	1.77 ± 0.57	3/23.1	8/61.5
-	Non-survival	22/62.9	303.1 ± 135.2	281.9 ± 128	267.9 ± 149.3	1.40 ± 0.87	1.19 ± 0.69	1.22 ± 0.73	8/36.4	20/90.9

Notes: PLT - platelet; CI - confidence interval; HT - hypertension; CHD - coronary heart disease; CKD - chronic kidney disease; HD - haemodyalisis; AKI - acute kidney injury

Overall, the peak of average PLR commonly occurred during admission (40.0%), while the lowest commonly occurred during the last evaluation (42.9%). For the onset of diabetes, a declining trend of PLR was found in new-onset and preexisting diabetes less than five years. In preexisting diabetes (5–10 years and more than 10 years), an increased trend of PLR was found, while, when it came to comorbidities, a declined trend was found in people with hypertension and aged more than 65. Coronary heart diseases demonstrated a fluctuating trend (Fig. 1).

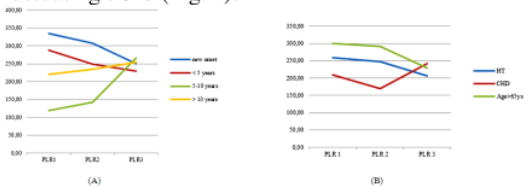

Fig. 1 (A) The trend of PLR at the onset of diabetes; (B) The trend of PLR at patient's comorbidity

Regarding complications, the PLR trend showed a decline in respiratory failure and sepsis and in severe survival and non-survival case, whereas the trend fluctuated for non-severe cases (Fig. 2) and cardiac and liver injuries. An increased PLR trend was found only for acute kidney injuries.

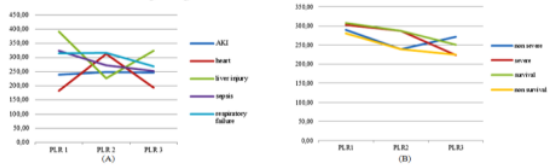

Fig. 2 (A) Trend of PLR at patient's complications; (B) Trend of PLR at patient's severity and outcomes

ΔPLR was calculated from the difference between the first (PLR1) and the last PLR (PLR3). ΔPLR revealed a significant association with some conditions, including cardiac injury (41.2 ± 27.55, $p = 0.023$), liver injury (338.09 ± 207.26, $p = 0.028$), and respiratory failure (159.34 ± 171.19, $p = 0,045$) (Table 3).

Table 3 PLR and ΔPLR features according to clinical characteristics and outcomes

Variable	n/%	PLR 1	PLR 2	PLR 3	ΔPLR (P-value, 95% CI)
The onset of diabetes					
- New-onset	15/42.9	335.31 ± 233.88	307.14 ± 159.98	250,03 ± 117.88	180.39 ± 143.12 (0.286)
- < 5 years	16/45.7	288.42 ± 179.48	249.11 ± 131.36	229,47 ± 130.08	162.89 ± 212.95 (0.260)
- 5-10 years	1/2.9	-	-	-	-
- > 10 years	3/8.6	220.92 ± 121.46	234.94 ± 164.78	254,40 ± 194.91	92.17 ± 33.23 (0.906)
Severity					(0.838)
Non-severe	13/37.1	290.0 ± 176.92	239.64 ± 122.69	271.46 ± 154.71	157.89 ± 202.63
Severe	22/62.9	302.59 ± 215.31	287.50 ± 157.29	223.71 ± 103.04	168.07 ± 153.60
Comorbidity					
HT	15/42.9	259,62 ± 143.09	248,08 ± 149.61	206,88 ± 104,57	111.85 ± 128.79 (0.102)
CHD	5/14.3	209,63 ± 210.6	170,47 ± 57.91	241,44 ± 98,99	73.61 ± 61.19 (0.172)
CKD	1/2.9	-	-	-	-
HD	1/ 2.9	-	-	-	-
Age > 65 ys	12/34.3	300,48 ± 230.93	291,59 ± 172.87	229,86 ± 121,94	165.02 ± 108.87 (0.754)
Obesity	1/2.9	-	-	-	-

Complications					
AKI	10/28.6	238,93 ± 226,74	249,23 ± 151,39	247,60 ± 161,26	159.35 ± 171.19 (0.715)
Cardiac injury	4/11.4	182,25 ± 313,15	313,15 ± 212,84	194,56 ± 96,77	41.2 ± 27.55 (0.026)
Liver injury	5/14.3	391,48 ± 226,86	226,86 ± 166,55	323,99 ± 201,36	338.09 ± 207.27 (0.030)
Sepsis	17/48.6	315,36 ± 316,39	316,39 ± 149,66	269,87 ± 141,14	216.61 ± 207.38 (0.198)
Respiratory failure	21/60	323,21 ± 272,49	272,49 ± 152,27	251,74 ± 151,07	196.81 ± 182.20 (0.047)
Outcomes					(0.473)
Survival	13/37.1	308,37 ± 221,43	287,89 ± 151,17	251,32 ± 137,84	134.76 ± 144.16
Non-survival	22/62.9	280,22 ± 161,83	238,99 ± 145,26	224,73 ± 101,67	181.76 ± 185.38

Notes: PLT - platelet; CI - confidence interval; HT - hypertension; CHD - coronary heart disease; CKD - chronic kidney disease; HD - haemodyalisis; AKI - acute kidney injury

4. Discussion

COVID-19 is an acute infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients with diabetes are at risk for increased incidence of infection and worse outcomes [6], [7]. In this study, new-onset diabetes was found in almost half of the total patients. It might have been caused by a direct infection of SARS-CoV-2 on the β-cell function, which lead to the severe deterioration of metabolic control and the development of new-onset diabetes [7]. Since most patients were aged between 51 and 70 and diabetes is more prevalent in the elderly [8], we assume that the patients with new-onset diabetes already had diabetes before that was never confirmed with a medical checkup. This study showed the same results as previous studies related to the greater prevalence of hypertension in COVID-19 patients with diabetes because hypertension is one of the impacts of the insulin-resistant state and diabetes mellitus [7], [8]. We found that several complications occurred during hospitalization. A previous study reported sepsis as a common complication, and the current study also found this. However, further investigation is needed to determine whether the cause of sepsis in this study is viral pneumonia only or co-occurring bacterial pneumonia [9]. Since most of the patients were admitted with severe COVID-19 in this study, abnormal hematologic parameters could be found in initial laboratory results, including thrombocytopenia and lymphopenia [10], [11]. Moreover, thrombocytopenia was identified in severe and non-survival cases; this may be the result of a systemic inflammatory response by platelets including hyperactivation and aggregation of platelet and thrombus formation, causing disseminated platelet consumption [12], [13]. Extensive lung damage in severe COVID-19 may lead to decreased platelet release from fully affected megakaryocytes [11]. Lymphopenia has been established as a key feature of severe COVID-19 and contributes to mortality [10], [14]. This study showed that lymphopenia was much more common in non-survival cases compared to survival cases. A possible cause of lymphopenia is that lymphocytes express the ACE2 receptor on their surface; thus, SARS-CoV-2 may directly infect those cells, leading to cell lysis. Additionally, patients with diabetes mellitus already have an imbalance of T lymphocyte subsets related to adaptive immune activation and chronic inflammation [15]. Since platelets and lymphocytes have a role in inflammation response, their ratio may reflect the severity of inflammation from an infection [2]. Previous studies have reported that the difference (ΔPLR) between the PLR at the time of admission and the maximum PLR during treatment was correlated with longer hospitalization and severe pneumonia [12]. In this study, we found that the difference (ΔPLR) between the PLR at the time of admission and the PLR at the end of treatment showed a statistically significant association with some complication events including cardiac injury, liver injury and respiratory failure. It is possible that the serial platelet counts continually decreased while the serial lymphocyte counts stayed at a low level from the beginning of admission. This may indicate that severe inflammation had already occurred prior to admission and led to the decompensation of platelets.

5. Conclusion

This single-center observational study revealed some findings that are consistent with previous studies, such as that thrombocytopenia and lymphopenia during treatment are considered cardinal laboratory findings in severe disease. In terms of the PLR, this study reported different trends in some clinical conditions and outcomes in diabetic patients with COVID-19. The previous study by Qu et al. calculated the difference (ΔPLR) between the PLR at the time of admission and the maximum PLR during treatment [12], while in this study, the ΔPLR is defined by the difference between the PLR at the time of admission and the last PLR so that the new findings could be analyzed with different approaches. The significant association between ΔPLR and complication conditions, such as liver injury, cardiac injury and respiratory failure due to a COVID-19 infection may emphasize that PLR may reflect the inflammatory response caused by a COVID-19 infection. As an inflammation marker, PLR is relatively new, but the calculation of PLR is simple and cheap compared to measuring other inflammatory markers such as C- reactive protein (CRP), cytokines interleukin 6 (IL-6), IL-1β and the tumor necrotizing factor α (TNF-α). Furthermore, it can also be done quickly after the routine blood test on admission.

Therefore, the authors suggest using serial PLR as a marker of inflammation when monitoring COVID-19 patients, especially for those with diabetes mellitus. Since this study was conducted in only one center, it has some limitations. First, our center is the main referral hospital in Surabaya, and most of the patients in this study were with moderate to critical COVID-19 on admission, so it was not possible to analyze the changes to PLR in mild cases. Second, some severe patients in this study could not be admitted to high care or intensive care units because of the limited facilities available at that time. This meant that those patients were not able to receive the standard treatments, which may have affected the course of the disease as well as the changes in PLR during hospitalization. Third, the number of samples in this study is very small, which may limit the statistical power of this research. Further research is needed to confirm the findings in this study.

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