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Correlation between Complete Blood Count Parameters with Procalcitonin in Immunogenomic Phases of COVID-19 Patients

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Abstract

Coronavirus Disease 2019 (COVID-19), a global pandemic caused by SARS-CoV-2, presents varying degrees of severity influenced by different immunogenomic phase. The immunogenomic phase that occurs in patients with COVID-19 is divided into three phases, namely the initial phase, propagating phase, and complicating phase. Severity disease progression can be monitored from the results of complete blood count (CBC) parameters and several inflammatory parameters such as procalcitonin. The purpose of this study was to investigate, during the immunogenomic phase of COVID-19 patients, the correlation between PCT levels and full blood count parameters. Patients treated at Dr. Soetomo General Hospital for COVID-19 were the subjects of this cross-sectional study. Data analysis used in this study is Kolmogorov-Smirnov Test for normality, followed by Wilcoxon signed-rank test and bivariate Pearson correlation test to determine the correlation between complete blood count (CBC) parameters and PCT. Our findings reveal that most patients are male, predominantly aged between 50 and 60 years. Distinct variation of CBC parameters and PCT levels were observed in each phase. A significant relationship between these hematological markers, the immunogenomic phase and the progression of the disease. The PCT level of COVID-19 patients was associated with parameters of red blood cells, including hemoglobin, hematocrit, and the width-standard deviation of red blood cell distribution, leukocytes and their differential count, including lymphocytes and neutrophils, and platelets. This analysis further understanding regarding the hematological dynamics in COVID-19 patients, providing important information about the pathophysiology of the disease and potential biomarkers for monitoring its progression.

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INTRODUCTION

Wuhan City, Hubei Province, China, was the site of the 2019 Coronavirus Disease (COVID-19) outbreak in December. On March 11, 2020, Global Health Organization (WHO) officials announced the COVID-19 pandemic. This outbreak was initially linked to zoonotic transmission at a market, which subsequently spread rapidly in the community through human activities.[1] To date, COVID-19 is still attacking communities around the world.

The SARS-CoV-2 coronavirus is the one responsible for the COVID-19 pandemic. In mild instances, the illness manifests as a persistent cough and fever; in severe instances, it can progress to pneumonia or acute respiratory distress syndrome, both of which can be fatal. Severe acute infections of COVID-19 involve cytokine storms and hyperinflammation leading to much greater morbidity and death.[2] The disease progresses through three immunogenomic phases: the initial phase (mild or asymptomatic), the propagating phase (moderate to severe pneumonia within 7-14 days of infection), and the complicating phase (multiorgan failure after 14 days).[3]

When assessing the severity of COVID-19 and trying to figure out how afflicted people will fare, a standard full blood count is essential. Factors such as hemoglobin, WBC, and platelets are part of this. The ratio of neutrophils to lymphocytes (NLR) is an important indicator, as increased neutrophils indicate systemic inflammation, while decreased lymphocytes suggest sequestration at inflammation sites and apoptosis.[4] Serious cases of COVID-19 are associated with elevated levels of various other parameters, such as procalcitonin (PCT), C-Reactive Protein (CRP), d-dimer, ferritin, and many more.[4]

An increased risk of severe COVID-19 has been linked to higher levels of procalcitonin (PCT), according to some research.[5] Procalcitonin is crucial in COVID-19. Typically, PCT is elevated in bacterial infections; nevertheless, increased PCT levels in severe cases of COVID-19 may also suggest secondary bacterial infections or significant inflammation. Thus, PCT tend to rise progressively across the immunogenomic phases. Elevated PCT levels may reflect severe disease progression in COVID-19, helping diagnose bacterial co-infection in viral infections, particularly when severe symptoms arise during the complicating phase.[6] The increase in PCT can be explained by looking at its synthesis pathway, that are controlled by different cytokines, like IL-6 and TNF-a. As an abnormal immune response can initiate PCT production, hyperinflammation has been demonstrated to play a role in the progression of COVID-19 infections.[7,8] Nevertheless, there is a lack of research that connects PCT with full blood count parameters in COVID-19 patients, especially when it comes to the immunogenomic stages.

A correlation between PCT and full blood count parameters in Indonesian COVID-19 patients, particularly in Surabaya, has received little attention from researchers. In order to better diagnose and treat COVID-19 patients, this study intends to search for a connection between PCT and complete blood count parameters. Elevated PCT levels help guide antibiotic use by identifying bacterial co-infections in COVID-19 cases, supporting a more targeted approach to treatment. Effective antibiotic stewardship is essential to prevent misuse, particularly given that elevated PCT can guide appropriate antibiotic use, especially in bacterial co-

infections, thereby improve patient outcomes in bacterial complications associated with COVID-19. [9]

MATERIALS AND METHODS

Located in Surabaya, East Java, Indonesia from June 2020 through July 2021, participants with COVID-19 were enrolled in this study at Dr. Soetomo General Hospital. Information was culled from COVID-19 patients' medical records. Individuals who met the age requirement of ≥18 years and had a confirmed diagnosis of COVID-19 were considered for participation. The exclusion criteria encompassed patients with no complete medical record of complete blood count (CBC) parameters and procalcitonin. A minimum number of subjects was required for the sample selection, which included consecutive sampling. calculated using Cochran's formula for cross-sectional studies during 2022:

$$n = \frac{Z\alpha^2.p.q}{d^2}$$

Information:
n = number of samples
Z: *alpha risk expressed in z score*
p: *expected prevalence*
q: 1-p
d: *absolute precision* = 5%

An ethical committee at Surabaya's Dr. Soetomo General Hospital gave their stamp of approval to this research (Ref No. 0600/LOE/103.4.2/IX/2021). We gathered information from patients' medical records and routine laboratory complete blood parameters. This study examined variables such as PCT as a dependent variable and complete blood parameters as independent variables in a cohort of COVID-19 patients during the immunogenomic phase, which includes initial, propagating and complicating phase. Immunogenomic phases of patients was determined by an Internist with the criteria as described below. The initial phase of COVID-19 involves asymptomatic or presymptomatic cases and is frequently associated with moderate infections of the upper respiratory tract, including mild fever, dry cough, and sore throat, and malaise, without severe signs like dyspnea, or digestive symptoms, such as diarrhea, nausea and vomiting.

Proinflammatory chemokines and cytokines trigger neutrophil infiltration, worsening lung inflammation. Propagating phase was diagnosed when the infection affects lower airways and organs, with mild to severe pneumonia. Symptoms range from cough and mild breathlessness to severe respiratory distress and hypoxia. Lymphopenia and elevated fibrinogen levels are observed. Complicating phase was diagnosed when organ deteriorates, commonly affecting cardiovascular and kidney, with laboratory findings as severe lymphopenia, high neutrophil and leukocyte counts, and elevated D-dimer levels in non-surviving patients.

Laboratory Testing

Patients who were monitored for procalcitonin and who had their blood counts taken regularly were the ones whose records were used to compile all of the data. Arkan Medical of Indonesia provided the EDTA tubes used to draw blood samples from the veins. Complete blood count parameters and PCT were derived from routine hematology analyzer. Both complete blood count and PCT, samples were processed immediately using the Sysmex XN-1000 analyzer. The Sysmex XN-1000, which integrates impedance, hydrodynamic focusing, and fluorescent flow cytometry, enables comprehensive blood counts and cell differentials,

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facilitating detailed PBMC analysis measurements, providing consistent and high-throughput data necessary. [10]

Centrifugation was used to separate RBCs, and density gradient centrifugation was employed to separate PBMCs, or peripheral blood mononuclear cells. Following isolation, PBMCs were washed and counted for further analysis. Hematology analyzer Sysmex XN-1000 (Sysmex Corporation, Japan) was employed for detailed immune cell profiling for precise quantification of neutrophils, lymphocytes, monocytes, and other leukocyte subsets. PCT were calculated by a chemiluminescent immunoassay (CLIA) in which analyzer introduces antibodies that specifically bind to PCT in the sample. This binding process often involves chemiluminescent or fluorescent markers that emit light. The intensity of the signal is compared to a calibration curve created from samples of known concentration, allowing the system to accurately report the exact level. [10]

Complete blood count parameters included in the analysis were Hemoglobin (Hb), hemocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), MCHC, WBC, RBC, RDW, NEUT, EOS, BASO, MONO, and LYMPH counts, with differential counts in percentage and absolute counts in numbers, PLT, PDV, NLR, and PLR are all components of the hemoglobin concentration mean. Both the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) were calculated by dividing the respective totals of neutrophils and lymphocytes, respectively.

Statistical Analysis

The main variables as well as the characteristic variables of the patients were subjected to statistical analyses. The study participants' descriptive characteristics were analyzed using demographic variables like age and gender, as well as immunogenomic phases such as initial, propagating, and complicating. Data analysis was done to correlate CBC parameters with PCT during the immunogenomic phase of COVID-19 patients. We ran the Shapiro-Wilk normalcy test to see how the data were distributed. In order to look for non-normal data, we used a non-parametric variant of the paired t-test called a Wilcoxon signed-rank test. To further evaluate the relationship between PCT and CBC parameters, the Pearson test was run. The SPSS software, version 25, was used for all statistical analysis. In order for a finding to be deemed statistically significant, the p-value must be less than 0.05.

RESULTS AND DISCUSSION

Patient Characteristics

Information was culled from Dr. Soetomo General Hospital's medical records of COVID-19 patients from June 2020 to July 2021. After collecting 477 samples, they were re-selected based on the criteria for inclusion and exclusion. There were 477 patients surveyed, but only 410 met all inclusion and exclusion criteria.

Sample details and distribution are displayed in Table 1 of the study. The sample consisted of more male COVID-19 patients than female patients in each phase. Males exhibited the highest prevalence of COVID-19 patients, according to other research. [11] These were then categorized into 410 samples in the initial phase, 276 samples in the propagating phase, and 119 samples in the complicating phase. These findings corroborate those of Garna et al. (2021), who found that most COVID-19 patients spend longer than seven days in the hospital, suggesting that most patients

have progressed beyond the acute phase of the disease.[12]

Table 1. Characteristics and distribution of samples in the study

Frequency (%)	Initial Phase (n=410)	Propagating Phase (n=276)	Complicating Phase (n=119)
Gender			
Male	229 (56)	156 (57)	65 (55)
Female	181 (44)	120 (43)	54 (45)
Age		**Mean ± SD**	
18 - 29	23.73 (7.07)	24.53 (5.65)	25.75 (0.7)
30 - 39	34.74 (6.36)	34.67 (6.36)	36.75 (4.24)
40 - 49	44.9 (6.36)	44.76 (6.36)	45.1 (6.36)
50 - 69	54.18 (6.36)	54.15 (6.36)	54.13 (6.36)
≥60	68.07 (19.79)	68.49 (19.79)	69.93 (19.79)

Characteristics of Complete Blood Count Parameters

Red blood cells, white blood cells, platelets, and other CBC parameters, NLR and PLR displayed in Table 2, based on the three immunogenomic phases. Normal ranges were based on the standard normal range provided by Sysmex XN-1000 derived from data analysis of healthy individuals, published guidelines from authoritative bodies like Clinical and Laboratory Standards Institute (CLSI).

As a screening tool for diagnostic evaluations and case monitoring, CBC parameters are assessments.[13] Studies have shown that CBC parameters, such as lymphocyte count, platelet count, NLR, have an important role in the management of COVID-19 patients as it can be used as a prognostic marker.[14]

Average hemoglobin, hematocrit, and RBC of COVID-19 patients in all three immunogenomic phases were below normal range. These findings corroborate those of Henry et al. (2020) and Palladino (2021) who found that patients with COVID-19 had lower hemoglobin levels and hematocrit concentrations, respectively. Studies have indicated that Covid patients are mostly anemic as it is the result of inflammation as a result of the spread of the COVID-19 virus.[14,15]

The red blood cell counts parameters analyzed in this study were MCV, MCH, MCHC, RDW-SD and RDW-SD. During the initial phase of the disease, all red blood cell count parameters were within the normal range. However, in the propagating phase, the average MCV and MCH values results were marginally lower than expected, whereas MCHC and RDW-CV were marginally higher than expected due to the invasion of the COVID-19 virus. Meanwhile, during the complicating phase, the average MCV and MCH values remained slightly lower than in the propagating phase, indicating a continued decline. Conversely, MCHC and RDW-CV values were slightly higher than the averages observed during the propagating phase, suggesting a trend toward increased variability in red blood cell size and concentration.

Previous studies have shown that MCV and MCH values tend individuals in the COVID-19 weight group to have substantially lower.[16] Another study reported higher MCHC levels in the propagating and complicating phases of the disease.[17] These changes in MCHC levels have been linked to lung function, oxygen demand, and COVID-19's total activity. Anemia is a known independent predictor of worsening disease outcomes in COVID-19 patients, and low MCHC levels are a common symptom of this condition. [17]

The study found that average leukocyte (WBC) counts were elevated above normal in both the initial and propagating phases of COVID-19, consistent with previous research that

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Table 2. Characteristics of complete blood parameters

Parameters	Initial Phase (n=410)	Propagating Phase (n=276)	Complicating Phase (n=119)	Normal range
Hb	10.5 ± 1.7	9.45 ± 3	10.1 ± 2.4	11.0 – 16.6 g/dL
HCT	32.1 ± 5.4	28 ± 9.15	29.2 ± 5.5	35.2 – 52.1 %
MCV	92.5 ± 5.2	78.3 ± 3.85	82.75 ± 5.5	86.7 – 102.3 fL
MCH	30.3 ± 1.5	26.45 ± 1.35	28.45 ± 3.35	27.1 – 32.4 pg
MCHC	32.75 ± 0.25	33.8 ± 0.1	34.25 ± 1.75	29.7 – 33.1 g/dL
RBC	3.45 ± 0.39	3.575 ± 0.855	3.5 ± 0.43	3.69–5.46 $x10^6$ /µL
RDW-SD	45.3 ± 2.5	43.2 ± 4.25	45.3 ± 1.6	41.2 – 53.6 fL
RDW-CV	13.5 ± 1.6	15.1 ± 1.95	15.35 ± 1.35	12.2 – 14.8 %
WBC	11.29 ± 0.02	11.215 ± 3.57	9.48 ± 1.76	3.37 –10.0$x10^3$/ µL
NEUT%	85.9 ± 5.3	74.6 ± 5.15	61.75 ± 7.65	39.8 – 70.5 %
NEUT#	9.7 ± 0.62	8.255 ± 2.745	5.99 ± 1.81	0.00– 0.00$x10^3$/ µL
BASO%	0.25 ± 0.15	0.45 ± 0.05	0.9 ± 0.5	0.3 – 1.4 %
BASO#	0.025 ± 0.015	0.055 ± 0.02	0.075 ± 0.035	10^3 / µL
EOS%	0.75 ± 0.75	5 ± 2.75	5.25 ± 2.95	0.6 – 5.4 %
EOS#	0.085± 0.085	0.63 ± 0.48	0.445 ± 0.185	0.00–0.00$x10^3$/ µL
MONO%	6.95 ± 0.75	6.6 ± 2.4	8.05 ± 0.25	4.3 – 10.0 %
MONO#	0.785± 0.085	0.725 ± 0.065	0.76 ± 0.12	0.00–0.00$x10^3$/ µL
LYMPH%	6.15 ± 3.65	13.35 ± 5.45	24.05 ± 3.95	23.1 – 49.9 %
LYMPH#	0.695± 0.415	1.565 ± 0.275	2.21 ± 0.05	0.00–0.00 $x10^3$/ µL
IG%	2.85 ± 1.85	4.2 ± 1.2	0.7 ± 0.3	0.6 – 5.4 %
IG #	0.32 ± 0.21	0.46 ± 0.2	0.065 ± 0.015	10^3/ µL
PLT	198 ± 117	536.5 ± 87	305 ± 109	150 – 450x 10^6 /µL
PDW	11.05 ± 0.55	10.95 ± 0.35	12.15 ± 0.15	9.6 – 15.2 fL
MPV	10.6 ± 0.5	9.4 ± 0.25	11 ± 0.2	9.2 – 12.0 fL
NLR	1.079± 0.107	1.804 ± 0.004	1.104 ± 0.009	<5
PLR	9.574± 0.711	9.316 ± 0.22	9.959 ± 0.338	-

associates high leukocyte levels with severe cases of the disease.[18] The increase in leukocyte, known as leucocytosis, can be attributed to the severe condition experienced by hospitalized COVID-19 patients during the initial and propagating phase, meanwhile the improvement of leucocytosis was noted during the complicating phase.

Differential leukocyte counts revealed elevated neutrophil counts (neutrophilia) during the initial and propagating phases. Neutrophilia is a known marker of venous thrombosis and has likely contributed to inducing a necro-inflammatory response. Neutrophils also take advantage of neutrophil extracellular trap (NET) formation which promote collateral damage during viral infections. Improper NET production as a result of COVID-19 patients may cytokine storms that can become ARDS, SIRS, and

sepsis.[19] This increase in neutrophils is consistent with findings by Palladino (2021), who noted high neutrophil counts in COVID-19 patients seven to nine days after symptom onset. [20]

Lymphopenia, characterized by lower-than-normal lymphocyte counts, was observed in both the initial and propagating phases. This reduction is a well-documented hematological disorder in COVID-19, potentially caused by viral attachment, immune injury, or lymphocyte exudation into inflamed lung tissue.[20,21] Significant lymphopenia, often appearing 7-14 days after symptom onset, correlates with worsening clinical status as it is linked with increased inflammatory mediators and cytokine storms.[21] Thus, it is considered a biomarker of infection severity.[22]

Additionally, the study observed lower basophil levels during the initial phase, which aligns with findings in immunocompromised patients during early viral infections.[20] This decline in basophils further underscores COVID-19 early on in the course of the immune system's complicated reaction to the virus.

Elevated during the propagating phase, which typically phase occurs 7-14 days after hospitalization. This finding aligns with the study conducted by Lucijanic I., 2021 which noted thrombocytosis in COVID-19 patient, particularly among younger individuals and fewer comorbidity.[23] Patients with COVID-19 with significantly higher than normal platelet levels were found to have a longer average stay Elevated platelet levels during this phase may be linked to cytokine storms and have been associated with longer hospital stays. [21,24]

Presentation of PCT levels Based on the Immunogenomic Phase of COVID-19 Patients

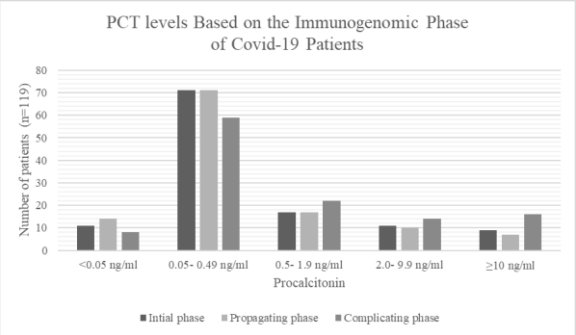

Figure 1. Characteristics of PCT based on immunogenic phase. < 0.5 ng/mL: not a systemic infection; 0.5 – 1.9 ng/mL: suspected sepsis; > 2.0– 9.9 ng/mL: severe sepsis; ≥10 ng/mL: severe bacterial sepsis or septic shock.

Only 119 COVID-19 patients were followed through the initial, propagating, and complicating phases (Figure 1). Consequently, all subsequent statistical analyses, including comparisons and correlations, will be conducted using this sample size. As the research indicated most COVID-19 patients had procalcitonin (PCT) levels in the range of 0.05-0.49 ng/mL across all immunogenomic phases. This proves that the majority of sufferers experience signs of infection. The results obtained aligns with the study conducted by Tong-Minh et al., 2022 it found that serious cases of COVID-19 and bacteria are frequently accompanied by elevated PCT levels. In a study conducted by Heer et al. (2021), it was found that patients infected with COVID-19 who were ventilator-dependent had elevated PCT levels.[26]

Table 3. Comparison of complete blood parameters with PCT based on immunogenic phase

	Initial Phase (n=119)	**Propagating Phase (n=119)**	**Complicating Phase (n=119)**
PCT	2.15 ± 6.8	2.36 ± 9.76	10.68 ± 35.34

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During the initial phase and propagating phase PCT levels were in the rage of 2.0 – <10 ng/mL (Table 3) which indicate an ongoing severe sepsis. However, during the complicating phase, PCT levels were > 10 ng/mL which indicate critically ill with bacteria-related sepsis or shock. Typically, COVID-19 patients present low PCT levels upon hospital admission. However, these levels often rise within a few days as the disease progresses.

The increase in PCT that occurs in COVID-19 patients indicates that there is a bacterial co-infection.[27] Elevated PCT is particularly concerning as it may indicate the development of COVID-related pneumonitis with a complex pathophysiology involving endothelial dysfunction. Having elevated PCT levels almost quadruples the risk of developing a life-threatening infection.[21] These results emphasize how crucial it is to monitoring PCT levels used to assess the severity of the infection in patients with COVID-19.

Comparison of Complete Blood Count Parameters with Procalcitonin in the Immunogenomic Phase of COVID-19 Patients

In the initial phase, all parameters were not normally distributed except for HCT, MPV and PLR (Table 4). Meanwhile all parameters were not normally distributed except for Hb, HCT and MPV for propagating and complicating phases.

Table 4. Comparison of complete blood parameters with PCT based on immunogenic phase

PCT-CBC Parameters	Initial Phase (n=119)		Propagating Phase (n=119)		Complicating Phase (n=119)	
	Mean±SD	p-value	Mean±SD	p-value	Mean±SD	p-value
Hb (g/dL)	10.8 ± 2.9	<0.001*	11.0 ±2.7	<0.001*	10.6 ±2.5	<0.001*
HCT (%)	32.7 ± 8.8	<0.001*	33.3±8.4	<0.001*	32.0 ±7.6	<0.001*
MCV (fL)	85.4 ± 11.9	<0.001*	86.6 ±6.6	<0.001*	87.3± 6.7	<0.001*
MCH (pg)	28.6 ± 3.0	<0.001*	28.6 ±2.7	<0.001*	28.6± 2.4	<0.001*
MCHC (g/dL)	33.0 ± 1.6	<0.001*	33.1 ±1.6	<0.001*	32.8± 1.3	<0.001*
RBC (10^6 /µL)	4.0 ± 2.6	<0.001*	4.2 ±3.6	<0.001*	3.7± 0.9	<0.001*
RDW-SD (fL)	44.5 ± 6.9	<0.001*	46.1±8.7	<0.001*	48.0 ±8.7	<0.001*
RDW-CV (%)	14.4 ± 2.7	<0.001*	16.0 ±12.6	<0.001*	15.7 ±3.7	<0.001*
WBC (10^3/µL)	11.2 ± 7.3	<0.001*	13.5 ±8.2	<0.001*	12.0± 8.1	<0.001*
NEUT%	79.3 ± 13.8	<0.001*	78.4 ±13.8	<0.001*	73.4± 14.7	<0.001*
NEUT# (10^3/µL)	9.2 ± 6.8	<0.001*	11.3 ±8.0	<0.001*	9.5± 8.1	<0.001*
BASO%	0.280± 0.215	<0.001*	0.380 ±0.310	0.367	0.429± 0.307	0.012
BASO# (10^3/µL)	0.033± 0.036	<0.001*	0.046 ±0.047	<0.001*	0.043± 0.028	<0.001*
EOS%	0.840± 1.219	0.756	1.4 ±2.1	<0.001*	2.4± 2.5	0.038
EOS# (10^3/µL)	0.085± 0.138	<0.001*	0.122 ±0.176	<0.001*	0.213± 0.279	<0.001*
MONO%	7.5 ± 9.9	<0.001*	7.4 ±5.2	<0.001*	8.1± 4.9	<0.001*
MONO# (10^3/µL)	0.780± 1.367	0.357	0.838 ±0.441	<0.001*	0.817± 0.422	0.797
LYMPH%	12.1 ± 8.5	<0.001*	12.3 ±10.1	<0.001*	15.0± 9.7	<0.001*
LYMPH# (10^3/µL)	1.1± 0.6	<0.001*	1.2 ±0.734	<0.001*	1.4± 0.8	0.143
PLT (10^6 /µL)	316 ± 192	<0.001*	339.4 ±180	<0.001*	276.5± 157	<0.001*
PDW (fL)	11.17 ± 1.8	<0.001*	11.2 ±2.0	<0.001*	11.2± 2.4	<0.001*
MPV (fL)	10.6 ± 0.5	<0.001*	10.2 ±0.9	<0.001*	10.2± 1.0	<0.001*
NLR	1.079± 0.107	<0.001*	1.1 ±0.1	<0.001*	1.1± 0.1	0.239
PLR	9.57± 0.711	<0.001*	9.4 ±0.6	<0.001*	9.4± 0.6	<0.001*

*p-value <0.05; p-value were derived from Asymp. Sig. 2-tailed

During the initial phase, p-value for the variables in this study was <0.001 which indicates that the results were noticeably different. Except, the p-value between procalcitonin and percentage eosinophils and absolute monocytes was 0.756 and 0.357, respectively. Thus, indicating no significant difference between PCT and percentage eosinophils and absolute monocytes.

During the propagating phase, p-value for the variables in this study was <0.001, again indicating a significant difference in outcomes. However, the p-value between procalcitonin and percentage basophils was 0.367. Thus, indicating no significant difference between PCT and percentage basophils.

During the complicating phase, p-value for the variables in this study was <0.001, showing a significant difference in outcomes. However, the p-value between procalcitonin and absolute monocytes was 0.797, between procalcitonin and absolute lymphocytes was 0.143, between procalcitonin and NLR was 0.239, and between procalcitonin, all indicating no significant difference in outcomes.

From this study, complete blood parameters were significantly different when compared to PCT levels in each immunogenomic phase. However, several complete blood parameters were insignificant at different immunogenomic phase, such as percentage eosinophils and absolute monocytes, percentage eosinophils and absolute monocytes, absolute lymphocytes percentage and NLR.

Correlation of Complete Blood Parameters with Procalcitonin in the Immunogenomic Phase of COVID-19 Patients

Table 5. Correlation of complete blood parameters and PCT during the immunogenic phase

PCT-CBC Parameters	Pearson Correlation	Sig. (2-tailed)
Hb	-0.143**	**0.007***
HCT	-0.194**	**0.000****
MCV	-0.029	0.581
MCH	-0.022	0.673
MCHC	0.046	0.385
RBC	-0.079	0.137
RDW-SD	0.049	0.354
RDW-CV	0.007	0.891
WBC	0.154**	**0.004****
NEUT%	0.154**	**0.004****
NEUT#	0.168**	**0.001****
EOS%	-0.101	0.058
EOS#	-0.071	0.179
BASO%	-0.084	0.112
BASO#	-0.006	0.908
MONO%	-0.060	0.255
MONO#	0.005	0.924
LYMPH%	-0.157**	**0.003****
LYMPH#	-0.093	0.078
IG%	0.058	0.280
IG #	0.080	0.134
PLT	-0.118*	**0.026***
PDW	0.061	0.252
MPV	0.098	0.065
NLR	0.025	0.638
PLR	0.091	0.086

* Significant correlation at level 0.05 (2-tailed);
** Significant correlation at level 0.01 (2-tailed).

A bivariate correlation analysis was conducted to examine the relationship between complete blood parameters and procalcitonin levels across the immunogenomic phases of COVID-19, using the Pearson correlation method. The analysis, as detailed in Table 5, revealed a moderate yet significant positive correlation (p-value < 0.05) between procalcitonin and several key blood parameters, including hemoglobin (Hb), hematocrit (HCT), red cell distribution width-standard deviation (RDW-SD), white blood cell count (WBC), neutrophil percentages and counts (neutrophils% and neutrophils#), lymphocyte percentages (lymphocytes%),

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and platelet count (PLT). These findings suggest a meaningful relationship between procalcitonin and these hematological markers, which may reflect the inflammatory and immune responses in COVID-19 patients during different phases of the disease.

These results highlight the complexity of the immune response in COVID-19, where certain blood parameters are closely linked with procalcitonin levels, while others show weaker or non-significant correlations. The significant correlations between PCT and WBC, neutrophil percentage and counts, and platelets align with the understanding that these markers are central to the body's response to infection. Neutrophilia, or elevated neutrophil counts, is a hallmark of severe inflammation and is often observed in COVID-19 patients, particularly during the propagating phase of the disease. IgG levels also usually increase after a long period of infection and the levels will decrease in patients with critical conditions compared to severe and mild conditions.[28] Meanwhile, eosinophils has an insignificant relationship between PCT as eosinophils are considered end-effector cells related to helminth infections, allergic inflammation, and causes of tissue damage.[29]

Meanwhile, moderate correlations between PCT and tests for hemoglobin, hematocrit, and the width-standard deviation of the red blood cell distribution suggest that these parameters are also influenced by the inflammatory milieu in COVID-19. Researchers found a correlation between the number of red blood cells in a patient's blood and the severity of their COVID-19 symptoms.[30,31] This is also supported by data obtained from this study that in all three phases of the immunogenomic, erythrocyte levels are less than normal which indicates the occurrence of anemia. Anemia, often characterized by low Hb and HCT levels, can be a consequence of chronic inflammation, while an increased RDW-SD reflects heterogeneity in red blood cell size, which may be linked to the stress response during infection. The association of these parameters with PCT indicates that they may serve as indirect markers of disease severity, particularly in the context of systemic inflammation.

Elevated PCT levels, along with changes in WBC, neutrophils, and platelets, suggest a robust inflammatory response that could be predictive of disease severity. The findings underscore the importance of a comprehensive approach to understanding the interactions between various hematological markers and procalcitonin during the different stages of COVID-19, which could provide insights into disease progression and severity.

STRENGTH AND LIMITATION

What made this research stand out was observed correlations between PCT, and various blood parameters provide insights into the mechanisms of disease progression in COVID-19. Due to its retrospective character, this study had certain limitations.

Many of the COVID-19 patients did not pass through all the immunogenomic phase. To confirm these results and investigate the possible causal links between these variables, future research should use longitudinal designs and larger samples and disease outcomes. Additionally, investigating the role of other biomarkers and their interactions with PCT could further enhance our understanding of COVID-19 pathophysiology.

CONCLUSIONS

This study provides a comprehensive analysis of COVID-19 patients based on various hematological parameters across different immunogenomic phases of the disease. The findings reveal significant differences in complete blood count parameters with PCT levels in each phase of the immunogenomic progression of the disease. Additionally, distinct variation in PCT levels was observed in each phase, indicating a significant relationship between these hematological markers and the immunogenomic phase or the progression of the disease. Hemoglobin, hematocrit, and the width-standard deviation of the red blood cell dispersal are some features of red blood cells, leukocytes and its differential count, such as neutrophils and lymphocytes as well as platelets were correlated with PCT level of COVID-19 patients. This analysis enhances our understanding of the hematological dynamics in COVID-19 patientsmaking important contributions to our understanding of the pathophysiology of the disease or potential biomarkers for monitoring its progression.

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ETHICAL CLEARANCE

With reference number 0600/LOE/103.4.2/IX/2021, the Ethical Committee of Dr. Soetomo General Hospital in Surabaya gave their approval to the study protocol.

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CONFLICT OF INTEREST

No conflicts of interest have been identified by the writers.

AUTHOR CONTRIBUTION

Every writer has made contributions to this work, we affirm. Every author has contributed to the initial draft and has made significant edits to improve it. With this work, all authors have signed off and taken responsibility.

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