

## Initial TLC, NLR, LDH, CRP, D-Dimer, and Procalcitonin in Intubated vs Non Intubated COVID-19 Patients

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### Abstract

COVID-19 is an acute respiratory disease caused by the SARS-CoV-2 virus that has caused a pandemic with symptoms of upper respiratory infection, respiratory failure, and even mortality. Several asymptomatic patients, with no shortness of breath, were found to experience impaired oxygenation in examination for objective data (happy hypoxia). Thus, objective data are needed, including data on inflammatory parameters (TLC, NLR, LDH, CRP, D-dimer and PCT) to monitor the severity and prognosis of COVID-19 patients. This study aimed to evaluate the inflammatory parameters in the initial days of treatment for COVID-19 patients between intubated and non-intubated patients during hospitalization. The study was conducted in the COVID isolation ward of Dr. Hasan Sadikin General Hospital Bandung, Indonesia, from July 2020 to July 2021. This was a retrospective cross-sectional comparative analytical observational study that involved patients' first laboratory examination results. The statistical analysis was performed using Mann Whitney test for numerical data and Chi Square test for categorical data. There were significant differences in inflammatory parameters values in both groups ( $p < 0.01$ ). The TLC values of intubated patients were lower than those of non-intubated patients, while the NLR, LDH, CRP, D-dimer and PCT values of intubated COVID-19 patients were higher than those of non-intubated patients.

**Keywords:** COVID-19, inflammatory, intubation, respiratory failure

### Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease that was declared as a pandemic in March 2020.<sup>1,2</sup> Happy hypoxia as one of the COVID-19 symptoms often leads to underdiagnosis and delays treatment, thereby increasing morbidity and mortality. There is no gold standard examination to distinguish COVID-19 patients with mild symptoms who will remain stable or progress to severe symptoms and require mechanical ventilation or intensive care. It is essential to identify high-risk patients for developing critical illnesses to guide risk stratification, monitoring, and early intervention.<sup>1-3</sup>

One of the main clinical manifestations of severe COVID-19 is respiratory failure, so early preparation for intubation is very important. Hypoxemia in hospitalized COVID-19 patients is independently associated with mortality and is

an important predictor of the need for intensive care. In the hospitalized group, 20% of patients with mild symptoms required mechanical ventilation, and an increase of 70% in the high-risk group.<sup>4,5</sup>

Several studies have been carried out on inflammatory markers in COVID-19 patients at initial admission, including total lymphocyte count (TLC), neutrophil lymphocyte ratio (nlr), c-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, and procalcitonin (PCT). There were significant differences in the results of patients with potential respiratory failure compared to the mild groups.

This study aimed to evaluate differences in inflammatory parameters in the initial days of treatment for COVID-19 patients between intubated and non-intubated patients during hospitalization at Dr. Hasan Sadikin in July 2020–July 2021. The results of this study are expected to contribute to clinical decisions in COVID-19 patients.

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### Methods

This study is a retrospective cross-sectional

comparative analytical observational study. The subjects of this study were medical records of COVID-19 inpatients in Dr. Hasan Sadikin General Hospital Bandung from July 2020–July 2021. The inclusion criteria of this study were patients with confirmed COVID-19 at age of 17 years or older. The exclusion criteria of this study were patients who came to the emergency room already intubated, refuse to be intubated, postoperative patients with mechanical ventilation, and incomplete medical record data. The study was conducted in the COVID-19 isolation ward in Dr. Hasan Sadikin General Hospital Bandung from July 2020–July 2021 after obtaining approval from the Health Research Ethics Committee. Data collected from patient medical records included age, sex, body mass index, comorbidities, CT PCR values, and initial laboratory examination values (TLC, NLR, LDH, CRP, and PCT). The sample size calculation was done with a confidence interval of 95% and a power test of 95%. The minimum sample was 118 patients with 59 samples in the non-intubated group and 59 samples in the intubated group.

Descriptive analysis was used to determine the characteristics of the research subjects who became the research sample and the description of the proportions in each variable. Data analysis to see the description of the proportion of each variable that will be presented descriptively can be broken down into descriptive analysis and hypothesis testing. Numerical data is presented with the mean, and standard deviation if the data is normally distributed, whereas if it is not normally distributed, it is presented in the median and range. Categorical data are presented as frequency distribution and percentage.

The numerical data obtained were analyzed using the Shapiro-Wilk ( $N < 50$ ) or Kolmogorov Smirnov ( $N > 50$ ) normality test to assess whether the data were normally distributed or not.

A comparison of characteristics of the study groups for numerical data was done using an unpaired t-test if the data is normally distributed and using Mann Whitney test as an alternative. Statistical analysis for categorical data was done using the chi-square test, and using Exact Fisher for 2x2 tables and Kolmogorov Smirnov for tables other than 2x2 as alternatives. The significance criterion used is the p-value, in which a p-value  $\leq 0.05$  means that the result is statistically significant. Data processing and analysis were done using Statistical Product Service Solution (SPSS) version 25.0 for Windows.

## Results

Overall, the mean age value was 53 years with the percentage of patients being male (50.8%) more than female (49.2%). Based on the statistical analysis, and the comparison of subjects' characteristics between the non-intubated and intubated groups, it was found that the variables of age, gender, and the degree of COVID-19 had very significant differences ( $p < 0.01$ ).

Vital signs comparison between the two groups showed that the respiration rate, saturation, ROX index, and oxygen fraction variables had very significant differences ( $p < 0.01$ ), while the pulse rate variable was quite significant ( $p < 0.05$ ).

The results of statistical analysis comparing the leukocytes, TLC, NLR, LDH, D-dimer, CRP, procalcitonin, and AGD in the two study groups using the Mann-Whitney test showed a very significant difference ( $p < 0.01$ ) between all variables. The intubated group had higher leukocyte, NLR, LDH, D-dimer, CRP, and PCT values compared to the non-intubated group. However, TLC values were found to be lower in the intubated group than in the non-intubated group.

## Discussion

Subjects' characteristics between the intubated and non-intubated groups based on age, sex, and COVID-19 severity have very significant differences ( $p < 0.01$ ). In the non-intubated group, the median age was 46 years, with a higher percentage of females than males, while in the intubated group, the mean age was 61 years, with more males than females. The incidence of severe COVID-19 in this study mostly occurred in the group of patients who were intubated more often in the male group (64%). In previous studies, it was found that plasma ACE-2 concentrations in men were higher than in women, this reflects the higher tissue expression of this receptor leading to susceptibility to COVID-19 infection. The following research was conducted at the Cipto Mangunkusumo National Hospital, Jakarta in 2020, which revealed that the male sex dominated confirmed cases of severe COVID-19. From the statistical test results between the two groups, it was found that there was a very significant difference ( $p < 0,01$ ) in the severity of COVID-19.<sup>6,7</sup>

In this study, the group of patients who were intubated was more common in the elderly

**Table 1 Subject Characteristics**

Variables	Total N=118	COVID-19 Patients Group		P value
		Non intubated N=59	Intubated N=59	
Age (years)				
Median	53	46	61	0.00**
Range (min-max)	18–85	18–67	20–85	
Gender				
Male	60 (51%)	22 (37%)	38 (64%)	0.00**
Female	58 (49%)	37 (63%)	21 (36%)	
BMI (Kg/m <sup>2</sup> )				
Median	25.2	25.4	25	0.21
Range (min-max)	16.4–37.1	16.4–33.8	16.6–37.1	
Comorbidity				
Hypertension	44 (37%)	19 (32%)	25 (42%)	0.56
Diabetes melitus	28 (23%)	12 (20%)	16 (27%)	0.39
Diabetes Melitus & hypertension	13 (11%)	6 (10%)	7 (12%)	0.76
Others	13 (11%)	6 (10%)	7 (12%)	0.79
No comorbid	20 (17%)	16 (36%)	4 (7%)	0.01*
Severity				
Asymptomatic	4 (3%)	4 (7%)	0 (0%)	0.12
Mild	44 (37%)	43 (73%)	1 (2%)	0.00**
Moderate	15(13%)	12 (20%)	3 (7%)	0.27
Severe	55(47%)	0 (0%)	55 (93%)	0.00**
Critical	0 (0%)	0 (0%)	0 (0%)	1
Days				
Median	7	7	7	0.82
Range (min-max)	7–10	7–10	7–10	
CT PCR value				
≤ 30	83 (70%)	43 (73%)	40 (58%)	0.058
>30	35 (30%)	16 (27%)	19 (32%)	
Mean	26.32	25.41	27.15	
Standard deviation	12–39.8	7.24	5.2	

BMI=Body mass index; CT=cycle threshold; PCR=polymerase chain reaction

with a median value of 61 years. Aging is also associated with immunosenescent or immune dysfunction in which elderly people generally have low-level chronic inflammation as a result of continuous exposure to antigens. The results of this study are the following descriptive study conducted at Dr. Cipto Mangunkusumo National Hospital Jakarta in 2020 patients who were

hospitalized from April to August 2020 where the majority were aged between 60–69 years (68%).<sup>8,9</sup>

In the non-intubated group, the median BMI was 25.39 kg/m<sup>2</sup>, while in the intubated group, the median BMI was 24.39 kg/m<sup>2</sup>. The test results showed no significant difference ( $p>0.05$ ) between the two groups. Several studies have

**Table 2 Vital Sign and Oxygen Fraction Comparison between Intubated and Non Intubated COVID-19 Patients**

Variables Median (Min-max)	Non intubated	Intubated	P Value
	Median (Min-max)	Median (Min-max)	
Vital Signs			
GCS	15 (14-15)	15 (7-15)	0.49
TDS (mmHg)	120 (90-179)	130 (80-176)	0.52
TDD (mmHg)	80 (60-120)	76 (52-92)	0.06
Pulse rate (x/menit)	88 (60-120)	90 (65-155)	0.02*
Respiratory rate (x/menit)	20 (18-26)	26 (18-50)	0.00**
Saturation (%)	97 (88-99)	94 (64-199)	0.00**
temperature (°C)	36.7 (35.8-38.3)	36.8 (35.8-38.3)	0.52
ROX-Index	23.095 (9.1-26.2)	3.75 (1.4-14.9)	0.00**
SpO <sub>2</sub> /FiO <sub>2</sub>	461.905 (209.5-471.4)	96 (69-438.1)	0.00**
Support O <sub>2</sub>			
Fio <sub>2</sub> (%)	21 (21-45)	100 (21-100)	0.00**

\* significance&lt;0.05 and \*\* significance &lt;0.01

found that obesity increases the risk of the severity of COVID-19. In obese patients, there are changes in respiratory physiology such

as a decrease in functional residual capacity and expiratory reserve volume. In addition, adipose cells are responsible for the secretion of

**Table 3 Comparison of Leukocyte, TLC, NLR, LDH, D-dimer, CRP, Procalcitonin, and BGA in Intubated and Non Intubated COVID-19 Patients**

Variables	Non intubated n=59	Intubated n=59	P Value
	Median (Min-max)	Median (Min-max)	
Laboratorium			
Leukocyte (10x3 mcl)	7,220 (1,510-23,930)	13,760 (1,590-29,500)	0.00**
TLC (U/L)	1,510 (330-3,080)	680 (100-2,320)	0.00**
NLR	3.24 (0.7-47.3)	13.06 (2.4-94.7)	0.00**
LDH (U/L)	232 (110-491)	488 (161-1,337)	0.00**
D-dimer (ng//L)	530 (24-4,060)	2800 (120-49,500)	0.00**
CRP (mg/L)	2.3 (0-48.3)	11.4 (3.1-53)	0.00**
PCT (ng/mL)	0.04 (0.01-5)	0.22 (0.01-23.29)	0.00**
BGA			
pH	7.419 (7.263-7.551)	7.390 (7.063-7.520)	0.01*
pCO <sub>2</sub> (mmHg)	31.4 (22.1-88.4)	35.5 (18.1-142.1)	0.01*
PaO <sub>2</sub> (mmHg)	81.5 (57.0-140.1)	79.3 (42.5-234)	0.07
HCO <sub>3</sub>	28 (20.9-35.7)	28 (20.9-35.7)	1.00
BE	-2 (-9.3-3.9)	-2.2 (-10.6-22)	0.93
SaO <sub>2</sub> (%)	97.4 (89.8-99.8)	96 (68.3-99.9)	0.02*
P/F ratio	382 (127-488)	89 (430-560)	0.00**

\* significance&lt;0,05 and \*\* significance &lt;0,01

proinflammatory adipokines, such as TNF- factor and IL-6. This can impair the innate and adaptive immune responses.<sup>10,11</sup>

The most common comorbidities found in both groups in this study were similar, namely hypertension and diabetes mellitus. A multicenter study in China also revealed that hypertension and diabetes mellitus were the most common comorbidities found in COVID-19 patients, especially in elderly patients.<sup>12</sup> In this study, the comorbid variables did not have a significant difference ( $p > 0.05$ ). This concluded that both the non intubated and intubated groups had the same risk percentage in the need for mechanical ventilation.

Real-time PCR (RT-PCR) is a diagnostic test recommended by WHO to detect SARS-CoV-2. A low cycle threshold (CT) value indicates a high viral load and is thought to be associated with clinical manifestations. Previous studies reported that the CT value of severe COVID-19 cases was significantly lower than that of mild cases. While, other studies suggest that several factors influence CT values such as different specimens, kits, and different techniques used.<sup>13</sup> The CT value in this study had no significant difference ( $p > 0.05$ ) between the two groups.

The TLC median in the non-intubated group (1510/uL) was higher than the intubated group (680/L). Statistic analysis shows a significant difference in TLC between the two groups ( $p < 0.01$ ). The severity of COVID-19 is associated with TLC. Lymphopenia is more common in patients with severe cases. Lymphopenia occurs in 60% of patients with COVID-19 at the initial phase.<sup>14</sup> Four potential mechanisms cause lymphopenia in COVID-19 patients. first, the virus can directly infect lymphocytes, resulting the cell death. Second, the virus can directly damage the lymphatic organs. Third, inflammatory cytokines such as TNF, IL-6, and other pro-inflammatory cytokines cause lymphocyte suppression.<sup>2,14</sup>

NLR median in the non-intubated group (3.24) was lower than the intubated group (13.06) and it shows statistical significance ( $p < 0.01$ ). A study in China reported that NLR  $> 3.3$  was independently associated with severe COVID-19. Elevated NLR describes an increased inflammatory response and is widely used as a predictor of severity in COVID-19 patients.<sup>15,16</sup> The results of the analysis of laboratory values at the PLA Central Theater General Hospital show the average value of the neutrophil-lymphocyte ratio (NLR) of patients with severe symptoms was significantly higher than those with mild symptoms. NLR of COVID-19 patients

was positively correlated with the C-Reactive Protein, Lactate Dehydrogenase, Procalcitonin, fibrinogen, and D-dimer levels.<sup>6</sup>

In this study, the LDH level was significantly higher in the intubated group than in the non-intubated group. intubated patients mostly belong to the category of severe symptoms, resulting in a high inflammatory response that causes a high release of LDH in the circulation. Oxygenation levels in the intubated group were also lower compared to the non-intubated group which proved severe tissue hypoxia.<sup>17,18</sup> Northern Italy LDH level correlates with the degree of decrease in lung function which is characterized by a decrease in the value of  $\text{PaO}_2/\text{FiO}_2$ , so that it can be used as a predictor of respiratory failure.<sup>18</sup> In a previous study it was found an increase in median LDH levels in patients with severe conditions was 247 U/L, while in the mild groups was 197. U/L.<sup>19</sup> constitutes a Public Health Emergency of International Concern. It is well known that COVID-19 patients may have increased serum lactate dehydrogenase (LDH)

The Median CRP level in the nongroup (2.3 mg/dL) was significantly lower than in the intubated group (11.4 mg/dL). A previous study reported that the initial CRP level of  $> 10$  mg/dL could be used as an indicator of the severity of the disease while the results of other literature studies reported a CRP level cut-off was  $> 4$  mg/dL.<sup>20</sup> Cytokine storms in COVID-19 patients occur due to an excessive inflammatory response resulting in increased CRP synthesis and causing more damage to target organs, especially the lungs that cause ARDS and death.<sup>15,21</sup> Results of this study found there was a significantly higher CRP level in the intubated group compared to the non-intubated group. This is associated with intubated patients mostly belonging to the category of severe symptoms, resulting in a high inflammatory response that causes a high release of CRP in the circulation reflecting severe lung damage.

The median D-dimer level in the intubated group (530 ng/L) was significantly lower than the intubated group (2,800 ng/L). the previous study reported that an initial D-dimer level  $> 1,000$  ng/L at the time of hospital admission can be used as an indicator of the severity of COVID-19 disease.<sup>22</sup> Elevated D-dimer is a thrombosis marker that is usually found in severe symptoms and associated with disease severity. D-dimer can also be used as an indicator of fibrinolytic system activity. Inflammatory cytokines activate the coagulation cascade and inhibit fibrinolysis in patients with severe COVID-19 symptoms.



D-dimer level has been demonstrated as a predictor to pulmonary embolism, which can affect the prognosis of COVID-19 patients.<sup>22,23</sup>

The median PCT level in the non-intubated group (0.04 ng/mL) was significantly lower than in the intubated group (0.22 ng/mL). In contrast to bacterial infections, in viral infections, PCT synthesis is inhibited by interferon- $\gamma$  (INF- $\gamma$ ) PCT levels were reported to be significantly increased in severe or critically ill COVID-19 patients. This indicates in COVID-19 severe cases or critical cases are more susceptible to bacterial coinfection. The meta-analysis study concluded that an increase in PCT >0.5 ng/mL was associated with an increase in mortality.<sup>14</sup> Other meta-analyses showed that the PCT level was 5-fold higher in severe and critical case infection than in mild cases and 4 times higher than in moderate patients, and 8 times higher in the critically ill case than in the moderate case.<sup>24</sup>

A comparison of blood gas analysis between the two groups showed that pH, SaO<sub>2</sub>, and P/F ratio levels were significantly lower in the intubated group compared to the non-intubated group. Meanwhile, the pCO<sub>2</sub> level in the intubated group was statistically higher than in the non-intubated group. However, the blood gas analysis parameter of the two groups was still within the normal range, only the P/F ratio in the intubated group was lower. Therefore, the blood gas analysis on the initial day of treatment (days 7–10) does not reflect the need for intubation in COVID-19 patients.

The limitations of this study were the absence of an IL-6 assay which is a specific marker for the occurrence of an inflammatory response or cytokine storm in COVID-19 to confirm the correlation with the inflammatory parameters in this study. The possibility of bias is due to the absence of information about the previous disease and the therapy consumed both before and after treatment. The need for further examinations such as imaging study or culture exam.

In conclusion, the parameters of inflammatory markers in COVID-19 patients (TLC, NLR, LDH, CRP, D-dimer, and PCT) on the initial day of treatment reflect the level of lung damage in COVID-19 patients and can be considered as a reference for risk stratification for patients who tend to require intubation.

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