Original Article

High Levels of Leucocyte and Thrombocyte Increasing COVID-19 Mortality Rate in RSUP Dr. M. Djamil Padang

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Abstract

Background: Different leukocytosis, leucopenia, thrombocytosis, thrombocytopenia, and clinical severity appear in COVID-19's cases. This study is aimed to identify the association between leucocyte, thrombocyte, and clinical severity in COVID-19's outcome.

Methods: A retrospective cohort study involving 121 patients with COVID-19 whom admitted from January to March 2021. Kruskal Wallis test was applied for analysis.

Results: The majority of participants were female (55.4%), aged between 18-49 years old (42.1%), and had comorbidities (81.8%). Most participants had a normal range of leucocyte (57.9%), thrombocyte (62.8%), and moderate clinical severity (67.8%). Subjects with full recovery were 79.3%, with sequelae such as weakness, and/or shortness of breath 3.3%, and deceased 17.4%. Leucocyte and thrombocyte had an association with COVID-19 outcome (P=0.045 and P=0.030 respectively). Clinical severity had no association with COVID-19 outcome (P=0.304).

Conclusion: Leucocyte and thrombocyte have an association with COVID-19 outcome. Clinical severity has no association with COVID-19 outcome.

Keywords: clinical severity, COVID-19, leucocyte, thrombocyte

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INTRODUCTION

Various inflammatory responses may occur in COVID-19 and cause different symptoms, ranging from fever, hypoxia, acute respiratory distress syndrome (ARDS), shock and death.[1] Various studies have shown haematological and immunological changes in COVID-19 patients.[2]

The recovery rate among COVID-19 patient is fairly high, reaching >97%.[3] Patients who have been declared cured may still have symptoms in the form of weakness and shortness of breath. The study of Docherty et al in UK reported that only 12.6% of patients who were declared cured had no symptoms. Complaints of shortness of breath in patients with COVID-19 can be related to inflammation, organ damage, or effects of long treatment, especially in ICU.[4]

Specific parameters are essential for predicting clinical outcome of COVID-19 patients, in addition to providing appropriate treatment, resource efficiency, as well as reducing mortality in patients with COVID-19.[5] Changes in leucocyte, thrombocyte values, and clinical severity may facilitate in classifying and estimating outcomes of patients with COVID-19 in order to provide immediate therapy and improve outcomes.[6] Therefore, this study examined the association between leucocyte, thrombocyte, and clinical severity with COVID-19 outcomes.

METHODS

An analytical study with a retrospective cohort design was conducted from January 2021 to November 2021 at RSUP Dr M Djamil Padang. The population of this study was all COVID-19 patients who were admitted in RSUP Dr M Djamil Padang from January 1 to March 31, 2021 with inclusion criteria of aged 18 years, having medical record data in the form of routine haematology laboratory examination results, clinical degree, and description of clinical condition when leaving the red-zone

isolation room, as well as negative result of Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) examination when the patient was allowed to leave the red-zone treatment room. Patients who had undergone treatment in other hospitals for more than 1 day were not included in this study. This study received approval from the Research Ethics Committee of RSUP Dr. M Djamil Padang on April 23, 2021. The data were analysed using the Kruskal Wallis test to see the association between the variables in this study.

RESULTS

There were originally 192 COVID-19 patients involved in this study from January 1 through March 31, 2021. A total of 71 samples (36.98%) were excluded, among others due to incomplete clinical grade data (6 people), being hospitalized for more than one day before (59 people), and discharged at their own request (6 people), so that only 121 samples (63.02%) were included in this study. Characteristics of participants are defined in Table 1.

Table 1. Characteristics of Confirmed COVID-19 Patients Treated at RSUP Dr. M. Djamil Padang

Patient Characteristics	N (%)
Gender	
Female	67 (55.4%)
Male	54 (44.6%)
Age; median (interquartile), years	53 (18–80)
18–49	51 (42.1%)
50–59	34 (28.1%)
0–69	23 (19%)
>70	13 (10.7%)
Comorbidities	
Yes	99 (81.8%)
No	22 (18.2%)
Leucocyte; median (intequartile)	7,640 (940–87,500)
Low	25 (20.7%)
Normal	70 (57.9%)
High	26 (21.5%)
Thrombocyte; Mean ± SD	235,190.08 ± 99,812.016
Low	19 (15.7%)
Normal	76 (62.8%)
High	26 (21.5%)
Clinical Severity	
Mild	21 (17.4%)
Moderate	82 (67.8%)
Severe	2 (1.7%)
Critical	16 (13.2%)
Outcome	
Recovered	96 (79.3%)
Recovered with Sequelae	4 (3.3%)
Died	21 (17.4%)

It was revealed that 55.4% of patients with confirmed COVID-19 and treated at RSUP Dr M Djamil Padang were females. The average age was 53 years, with majority of them was in the 18–49 years age group (42.1%). There were 81.8% patients with comorbidities. The median value of leucocyte in the study was 7.640/mm^3 (940-87500/mm^3), most of them (57.9%) were in the group with normal leucocyte levels. The mean of thrombocyte was 235,190.08±99,812,016/mm^3, most of them (62.8%) were in the group with normal thrombocyte levels.

Majority of participants had moderate clinical severity at 67.8%, with a cure rate of 79.3% for COVID-19 patients. 92% of confirmed COVID-19 patients whom were treated at RSUP Dr M Djamil Padang with low leucocyte levels were recovered. High leucocyte levels indicated a low cure rate in confirmed COVID-19 patients.

This study found that high mortality rate in confirmed COVID-19 patients was associated with high leucocyte levels. Based on the Kruskal-Wallis test, there was a significant correlation between leucocyte levels and the outcome of COVID-19 with *P*=0.045 (Table 2).

Table 2. Association between Leucocyte and Outcome in Confirmed COVID-19 Patients at RSUP Dr. M. Djamil Padang

Leucocyte	Recovered	Recovered with Sequelae	Died	*P*
Low	23 (92.0%)	1 (4.0%)	1 (4.0%)	0.045
Normal	56 (80.0%)	3 (4.3%)	11 (15.7%)	
High	17 (65.4%)	0 (0.0%)	9 (34.6%)	

High thrombocyte levels indicated a low cure rate in confirmed COVID-19 patients, as well as high mortality rate. The Kruskal-Wallis test showed that there was a significant association between thrombocyte levels and the outcome of COVID-19 with *P*=0.030 (Table 3).

Table 3. Association between Thrombocyte and Outcome in Confirmed COVID-19 Patients at RSUP Dr. M. Djamil Padang

Thrombocyte	Recovered	Recovered with Sequelae	Died	*P*
Low	15 (78.9%)	1 (5.3%)	3 (15.8%)	0.030
Normal	65 (85.5%)	2 (2.6%)	9 (11.8%)	
High	16 (61.5%)	1 (3.8%)	9 (34.6%)	

The highest mortality rate was found in the critical clinical severity group at 25%. The cure rate

in severe clinical severity was 100%, with only 2 subjects. The clinical severity of patients with COVID-19 at the time of admission in this study did not have a significant association with the outcome of COVID-19, with p-value = 0.304 (table 4).

Table 4. Association between Clinical Severity and Outcome for Confirmed COVID-19 Patients at RSUP Dr. M. Djamil Padang

Clinical Severity	Recovered	Recovered with Sequelae	Died	*P*
Mild	16 (76.2%)	0 (0.0%)	5 (23.8%)	0.304
Moderate	68 (82.9%)	2 (2.4%)	12 (14.6%)	
Severe	2 (100.0%)	0 (0.0%)	0 (0.0%)	
Critical	10 (62.5%)	2 (12.5%)	4 (25.0%)	

DISCUSSION

There were more women affected by COVID-19 patients whom treated at RSUP Dr. M. Djamil Padang from January 2021 to March 2021 than men (55.4% vs 44.6%). Similar results were reported by Mardewi's study in Bali, there were more women affected by COVID-19 than men (53.9% vs 46.1%).[6] Different result was reported by Priya et al's study in India which had more men with COVID-19 than women, by 60%.[7]

Research by Long et al in China revealed that number of men and women with COVID-19 was identical, amounting to 49.8%.[8] Majority of men are affected by COVID-19 possibly due to androgen hormonal activity via the Transmembrane Protease Serine 2 (TMPRSS2) pathway, which facilitates binding of SARS-CoV2 to the ACE-2 receptor.[9] Chen et al's study reported that in East Asian women, the expression of ACE2 receptors was higher, so they were more likely to be exposed to COVID-19.[10]

Most participants in this study were 18–49 years old (42.1%) and only a few numbers of patient were >70 years (10.7%). Subkhan et al. revealed that patients with COVID-19 were mostly dominated by people aged 34 to 59 years old, but severe cases were mostly occurred at the age of >60 years with comorbidities.[1] This study is following the study by Huang et al. The COVID-19 which reported that patients were mostly 25–49 years old (49%).[11]

Jie et al meta-analysis study in 11 countries also revealed that majority of COVID-19 patients had an average age of 40 years (95% CI=42.8–50.6).[12] This situation is possible since the age group of 18–49 year is productive age with high mobility. Ghiffari's study in Jakarta affirmed a relationship between population mobility and an increase in the number of confirmed cases of COVID-19.[13] Older people who suffer from COVID-19 are more susceptible to worsening clinical conditions, even death, due to decreased function of T cells and B cells, and excessive cytokine production, which causes a prolonged inflammatory response.[14]

81.8% participants of this study had comorbidities. Several comorbidities were found in participants, including stroke (3 people), hypertension (31 people), cardiovascular disease (19 people), chronic lung disease (6 people), malignancy (8 people), kidney disease (14 people), diabetes (18 people), and pregnancy (15 people). Comorbidities in COVID-19 in the form of chronic diseases may trigger chronic inflammation, increased ACE2 expression, and impaired immunity, making them susceptible to infection including SARS-CoV2.[14]

Patients with age >65 years and comorbidities, especially cardiovascular and diabetes, had better prognosis. Patients with poor well-being, 20.3% of them require ICU care, may experience multi-organ failure and increased mortality.[12,15] Long's study also stated that comorbidities were associated with clinical deterioration of COVID-19.[8]

A total of 57.9% of patients with COVID-19 in this study had normal range of leucocyte levels. High leucocyte levels was found in 21.5% of COVID-19 patients. The mean of leucocyte levels in mild clinical severity was 6470:3195/mm^3, moderate clinical severity was 7220:4998/mm^3, severe clinical severity was 5530/mm^3 and 8680/mm^3, and critical clinical severity was 10570:10368/mm^3. High leucocyte levels accompanied by a decrease in lymphocytes in patients with COVID-19 may lead to clinical deterioration. This is thought to be the result of increased levels of neutrophils in response to cytokines and chemokines due to endothelial damage, which also releases cytokines and chemokines. The repetition of this process increases the release of stored neutrophils from the bone

marrow and increases the levels of cytokines and chemokines in the body. This situation is exacerbated by the binding of the virus to lymphocytes which reduces the production of CD4+ and CD8+, in an effort to avoid the body's immune response.[16]

The high leucocyte levels in COVID-19 patients in this study had a significant relationship with death as an outcome. The study of Li et al revealed an increase in leucocyte levels among patients with severe and critical clinical severity, as well as in patients died from COVID-19.[17] A study by Zhao et al reported that patients with high leucocyte levels 17.3% of them required oxygen supplementation, and 46.2% required ICU care; the mortality rate was also higher than patients without an increase in leucocyte levels (19.2% vs. 5.8%).[18]

A study by Alamin et al in Saudi also reported high levels of leucocyte in patients died from COVID-19.[19] An increase in leucocyte, especially neutrophils, is usually accompanied by an increase in systemic inflammatory responses such as IL-6 serums. The increase in serum IL-6 then increases the differentiation of Th17 cells from T cells. Increase in Th17 cells consequently increases the release of reserves and activation of neutrophils, increasing cytokines, which can trigger a cytokine storm, tissue damage, resulting in severe pneumonia, and even death.[18]

Most patients had normal range of thrombocyte levels (62.8%). Patients with mild clinical severity had a mean of thrombocyte count of 279714±110635/mm^3, moderate clinical severity with 231658±94042/mm^3, severe clinical severity with 285000/mm^3 and 293000/mm^3, and critical clinical severity with 188125±100135/mm^3. Low thrombocyte levels were found in 15.7% of patients, while high thrombocyte levels were found in 21.5% of patients. Research by Li et al in China showed that low thrombocyte levels were associated with inflammatory process and death in patients with COVID-19.[20]

Study by Lippi et al through a meta-analysis found that low thrombocyte levels were closely related to severe and critical clinical severity.[21] Research by Lanini et al in Italy found that thrombocyte levels at the beginning of patient's treatment was not related to the clinical severity and outcome of COVID-19, although the decrease in thrombocyte levels found in the treatment indicated a poor prognosis.[22]

Low thrombocyte levels are thought to occur due to the use of thrombocyte in repair of microvascular endothelial damage due to SARS-CoV2 virus infection and subsequent inflammation. The use of thrombocyte is seen as a microthrombus event that triggers ARDS and multiorgan failure, and is associated with clinical deterioration.[23] A study by Yang et al reported that SARS-COV2 infection caused diffuse alveolar damage, which then trapped megakaryocytes, and prevented platelets release from megakaryocytes.[24] Increased thrombocyte levels in COVID-19 are thought to be due to inflammation with an increase in various cytokines, including IL-6 which increases the expression of Thrombopoietin messenger ribonucleic acid (TmRNA) in the liver, thrombopoietin levels, and thrombocyte levels in the blood.[25]

Most of the COVID-19 patients whom treated at RSUP Dr M Djamil Padang were in the moderate clinical severity group (67.8%). The group with severe clinical severity was the group with the least number of treatments (1.7%), while the critical clinical ones were 13.2%. This study did not find a significant association between clinical severity and COVID-19 outcomes. Study by Li et al in China revealed that clinical severity was associated with mortality, although it was not statistically related.[26]

Eastin et al's study found that an increase in mortality was related to clinical severity, in which 52.4% of patients with critical clinical severity were dead, and 38.1% of them still required mechanical ventilation.[27] There were 79.3% patients with COVID-19 who were fully recovered, 3.3% were recovered with sequelae, and 17.4% were deceased. Research by Nalbandian et al reported that respiratory complaints after COVID-19 in Wuhan reached 76%. As many as 42-66% of patients still complained about shortness of breath up to 100 days after being declared cured.[28]

Most deaths were seen in the critical clinical severity (25%), followed by mild clinical severity at 23.8%. The severe clinical severity in this study was 0%. There was no case of death in severe clinical severity group since there were only 2 participants, so it could not provide a severe clinical severity outcome. The number of deaths in mild clinical severity in this study may be related to comorbidities, 15 of the 21 people with mild clinical severity had comorbidities, and 5 deceased patients had comorbidities, including coronary artery disease (CAD) in 3 people, and pregnancy in 2 people. Drew and Adisasmita's research in East Jakarta, as well as Hidayani's literature study, confirmed an increased risk of mortality in COVID-19 with comorbidities.[29,30] Similar results were reported by Priya's study, in which patients with COVID-19 ad comorbidities had 3 times higher mortality rate than COVID-19 patients without comorbidities. This figure could be higher if the patient with COVID-19 has a combination of comorbidities.[7]

LIMITATIONS

This study found a significant association between high levels of leucocyte, thrombocyte, and the outcome of patients with COVID 19. However, there may be other factors affecting the levels of leucocyte and thrombocyte that were not assessed in detail, so there may be bias in this study.

CONCLUSION

Most of COVID-19 patients whom treated at RSUP Dr M Djamil Padang were women with age ranged between 18–49 years, had comorbidities, normal range of leucocyte and thrombocyte levels, and moderate clinical severity. This study found a significant association between high levels of leucocyte and thrombocyte with the outcome of COVID-19. This study did not find a significant association between clinical severity and COVID-19 outcomes. High levels of leucocyte and/or thrombocyte can be considered as components of monitoring in patients with COVID-19. Further study is suggested to develop an assessment of leucocyte and thrombocyte as predictors of COVID-19 outcome.

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CONFLICT OF INTEREST

None.

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