PREDICTOR OF MORTALITY IN COVID 19 PATIENTS

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ABSTRACT

Purpose: The aim of this study to analyse Neutrophil-to-Lymphocyte Ratio (NLR) and Hs-CRP to predicts mortality in COVID-19 patients

Research Methodology: This research was conducted at Moewardi Hospital in July 2020. The inclusion criteria were COVID-19 patients. NLR is neutrophil divided by lymphocytes using a haematology analyser. Examination of HsCRP by ELISA method. Statistical test with an independent T-test and cox proportional hazard analysis with p <0.05.

Results: The results showed that HsCRP and NLR increased in COVID-19 patients who later died and obtained lower levels in survivors (p = 0.001 and p = 0.11). HsCRP increased the risk of death for COVID-19 patients (p = 0.18; HR = 1.036) and NLR also increased the risk of death for COVID-19 patients (p = 0.08; HR = 1.34)

Limitations: this study were not randomized controlled trial, but retrospective study, which is the only studies available during this pandemic. And because of lack of access to individual data, we were unable to perform multivariable regression analyses to adjust for potential confounders in the nonsurvival vs survival group.

Contribution: it will be an input for clinicians when there are high Hs-CRP and NLR to get more intensive care.

Keywords: Mortality, COVID 19

I. INTRODUCTION

An unexplained lower respiratory tract infection has been detected in Wuhan, located in china's Hubei province and was reported to on December 31, 2019. At the beginning of the disease, the cause was unknown and was called an aetiology threat pneumonia on February 11, 2020, WHO (World Health Organization) stated that wa This disease was COVID 19 or coronavirus disease 2019. This disease is spreading very fast and on March 11, 2020, declared that COVID 19 is a global pandemic.¹

Covid-19 cases in Indonesia are increasing. In the Indonesian Ministry of Health data on September 12, 2020, data on the accumulation of cases were 214746 people, while cases under treatment were 53638, cases recovered as many as 152458 people, and cases died were 8650 people. Data in Central Java states that the number of cases of Covid-19 in Central Java is 17460 cases or 8.1% of the national total, active cases still being treated are 5352 people, with a cure rate of 10969 people, and a death rate of 1139 people. The case in Central Java is number 3rd nationally.²

The COVID-19 pandemic is quite worrying because of the widespread and high mortality rates. The death rate from COVID-19 ranges from 0.75% to 3% and may decline in the future. Mortality is the main factor in determining whether infectious diseases are of public concern and the risk of causing a pandemic.³ Chen et al. reported that the COVID-19 mortality rate was 11% based only on patients whose condition was urgent treatment.⁴

This viral infection can produce an overactive immune reaction in humans. This reaction is called a cytokine storm, which results in tissue damage with impaired coagulation. Various kinds of cytokines play a role in the pathogenesis
of this disease, one of which is interleukin 6. Interleukin 6 plays a role in the production of the acute phase, and one of them is hs-CRP. Several markers of inflammation and immune status are potential predictors of prognosis of COVID-19 patients. The NLR has been widely studied as a predictor of prognosis of patients with viral pneumonia. To date, there is no specific anti-viral therapy for COVID-19, and no vaccine is available. Therefore, it is crucial to look for factors that can predict mortality in Covid-19 patients so that it will be input when the patient meets the predictors of death, so he will immediately be treated in an intensive room and get maximum treatment. So, the aim of this study to analyse Neutrophil-to-Lymphocyte Ratio (NLR) and Hs-CRP to predicts mortality in COVID-19 patients.

II. LITERATURE REVIEW AND HYPOTHESIS DEVELOPMENT

COVID 19 or coronavirus disease 2019. This viral infection can produce an overactive immune reaction in humans. This reaction is called a cytokine storm, which results in tissue damage with impaired coagulation. Various kinds of cytokines play a role in the pathogenesis of this disease, one of which is interleukin 6. Interleukin 6 plays a role in the production of the acute phase, and one of them is hs-CRP. Several markers of inflammation and immune status are potential predictors of prognosis of COVID-19 patients. The NLR has been widely studied as a predictor of prognosis of patients with viral pneumonia. To date, there is no specific anti-viral therapy for COVID-19, and no vaccine is available. Therefore, it is crucial to look for factors that can predict mortality in Covid-19 patients so that it will be input when the patient meets the predictors of death, so he will immediately be treated in an intensive room and get maximum treatment. So, the aim of this study to analyse Neutrophil-to-Lymphocyte Ratio (NLR) and Hs-CRP to predicts mortality in COVID-19 patients.

III. RESEARCH METHODOLOGY

This research was conducted at Moewardi Hospital in July 2020. Inclusion criteria were COVID 19 patients who had laboratory examinations of hs-CRP and NLR Neutrophil to lymphocyte ratio is neutrophil divided by lymphocytes using a haematology analyser. Examination of HsCRP by ELISA method. Statistical test with an independent T-test and cox proportional hazard analysis with p <0.05.

IV. RESULTS AND DISCUSSIONS

This study is a retrospective study by looking at the medical records of patients who are hospitalized in the COVID-19 ward. This study was conducted on patients with a proper diagnosis of COVID-19 based on PCR results. the results showed that NLR 4,25 ± 3,27 and hs-CRP 5,46 ± 15,39 mg/L with mortality occurred in 8 patients

Table 1. Baseline characteristic of research subject

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivor</th>
<th>Death</th>
<th>p</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>41</td>
<td>8</td>
<td>0,001</td>
<td>49</td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>6</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>2</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Age</td>
<td>48,5 ± 17,83</td>
<td>55,88 ± 7,06</td>
<td>0,001</td>
<td>49,33 ± 16,76</td>
</tr>
<tr>
<td>NLR</td>
<td>1,89 ± 2,43</td>
<td>4,13 ± 3,75</td>
<td>0,001</td>
<td>2,25 ± 3,27</td>
</tr>
<tr>
<td>Hs-CRP (mg/L)</td>
<td>1,85 ± 2,70</td>
<td>19,9 ± 31,47</td>
<td>0,001</td>
<td>5,46 ± 15,39</td>
</tr>
</tbody>
</table>
HsCRP increased the risk of death for COVID-19 patients \( (p = 0.18; \text{HR} = 1.036) \). This study shows that an increase in hs-CRP correlates with the point death rate, the higher the hs-CRP mortality rate will be higher. Therefore, it could be a predictor of mortality in COVID-19 patients.

NLR also increased the risk of death for COVID-19 patients \( (p = 0.08; \text{HR} = 1.34) \). This study shows that an increase in NLR correlates with the point death rate, the higher the NLR mortality rate will be higher. Therefore, it could be a predictor of mortality in COVID-19 patients.

This study proves that NLR is one of the predictors of the death of Covid-19 patients. This study included 49 COVID-19 patients and the total in-hospital mortality was 8. Most of the patients presented a higher number of neutrophils and a lower number of lymphocytes, that is the increase of NLR, were found in nonsurvivors with COVID-19 compared to survivors. This study is following previous studies that NLR is a marker of the prognostic of COVID-19 patients. Neutrophils are the main component in activated leukocytes and migration from the venous system into organs and neutrophils will release reactive oxygen species (ROS) that can cause DNA damage and damage viruses from within the cell so that cell-mediated cell-dependent antibodies will kill the virus directly through introduction against viral antigens and stimulation of specific and humoral immunity. Besides, neutrophils will interact with cell populations and produce various cytokines and effector molecules such as vascular endothelial growth factors. Also, neutrophils can be stimulated by pro-inflammatory cytokines released by viral response responses such as interleukin 6, interleukin 8, and tumour necrosis Factor Alfa.\(^5\)

The leukocyte immune response stimulated by infectious viruses depends on lymphocytes. The human immune response to physiological stresses such as tissue damage, severe trauma, major surgery and sepsis is characterized by an increase in the number of neutrophils and a decrease in lymphocytes. Inflammation stress is characterized by the ratio of the percentage of neutrophils to the percentage of lymphocytes in the blood and is known as Neutrophil Lymphocyte Stress Factor (NLSF). Physiological conditions, the percentage of neutrophils / lymphocytes is less than 5. In pathological conditions due to severe infection or systemic inflammation, NLR will be increased, therefore some centers use NLR for clinical evaluation of patients with systemic inflammation.\(^6\)
of the increased NLR and NLR causes the progression of COVID 19 so that clinical conditions increase and mortality will also increase.\(^5\) Consistent with the findings from Liu et al, that higher NLR significantly associated with an increased risk of death during hospitalization after adjustment for other confounders, the male had a more significant association with the risk of mortality than the female.\(^7\)

C-reactive protein (CRP) is an acute inflammatory protein produced by liver mainly as a reaction to IL-6 and that inflammatory markers can play a role in predicting severity in Community Acquired Pneumonia.\(^8\) In COVID-19 patients, CRP might expression of lung damage, and the respiratory distress consequent to the abnormal inflammation status. CRP correlates with the diameter of the lung lesion.\(^9\) The result of the meta-analysis, nonsurvivors of COVID-19 infections, displayed significantly higher CRP concentrations compared to the survivors (\(P = 0.000\), the standard difference in means = 1.371). CRP is an acute phase protein that responsible for the clearance of pathogens through the complement system and enhanced phagocytosis.\(^10\)

The pathogenesis of COVID 19 infection is not well known. Cellular immune response and cytokine storms are suspected of playing an essential role in the severity of the disease. In a study by Lu et al., they stated that hs-CRP plays an essential role as a predictor of the severity and mortality of COVID 19. Hs-CRP is a marker of severe inflammation, and hs-CRP will increase rapidly and respond to inflammation by activating complement, which stimulates excessive cytokine production. Lu et al. study showed that Hs-CRP plays an essential role as a predictor of mortality in young adult COVID 19.\(^11\)

V. CONCLUSION

Neutrophil-to-Lymphocyte Ratio (NLR) and Hs-CRP predict mortality in Covid-19 Patients. This study is one of the shreds of evidence that the NLR and Hs-CRP examination at the beginning of the diagnosis of COVID-19 can be a predictor of death in COVID-19 patients. Therefore, it will be an input for clinicians when there are high Hs-CRP and NLR to get more intensive care.

Limitation and Study Forward

This study were not randomized controlled trial, but retrospective study, which is the only studies available during this pandemic. And because of lack of access to individual data, we were unable to perform multivariable regression analyses to adjust for potential confounders in the nonsurvival vs survival group.

Acknowledgement

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4. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study