Correlation between Angiopoietin-2 and IL-6 as inflammation biomarkers on the severity of coagulopathy and mortality in vasodilated shock patients

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ABSTRACT

Background: Sepsis and vasodilatory shock are serious medical conditions and cause high mortality rates worldwide. It is known that IL-6 and Angiopoietin-2 levels have a role in the etiology of shock in ICU patients. Consequently, this research aims to examine the involvement of Angiopoietin-2 and IL-6 in the severity of coagulation problems in patients with vasodilatory shock.

Methods: The study’s design is observational analytic with a cross-sectional study design, and the data came from those treated in the ICU room and the Emergency Room at RSUD Dr. Soetomo Surabaya from February 2020 to March 2022. Data collected included age, respiratory rate, DIC score, APACHE II score, mortality, IL-6 levels, and Angiopoietin-2 levels. The data was then analyzed using Easy R (EZR).

Result: 27 of the 44 patients (61.4% of the total) belonged to the DIC group. A correlation between IL-6 levels and DIC incidence and mortality at first ICU admission and after 24 hours in the ICU was shown to be significant (p<0.05). There was also a significant correlation between Angiopoietin-2 and both DIC incidence and mortality upon admission to the ICU and after 24 hours in the ICU (p<0.05). It was found that the test specificity and sensitivity of Angiopoietin-2 and IL-6 levels on the severity of coagulopathy disorders and mortality in patients with vasodilatation shock were 85.9% for Angiopoietin-2 and 71.6% for IL-6.

Conclusion: There is a correlation between the severity of coagulation disorders in vasodilated shock and increased IL-6 and Angiopoietin-2. IL-6 and Angiopoietin-2 were to be correlated with mortality and Angiopoietin-2 has higher specificity and sensitivity than IL-6. Multicenter prospective studies are needed to confirm study results.

Keywords: Angiopoietin-2, APACHE, DIC, IL-6, ISTH criteria, Shock.

INTRODUCTION

Sepsis and vasodilatory shock are serious medical conditions and cause high mortality rates worldwide. It is estimated that around 5.3 million people worldwide die from sepsis and organ failure each year, which is equivalent to 30% of sepsis patients who die.¹ In the United States, more than 1.5 million people experience vasodilatory shock each year, most of which is caused by sepsis.³ Vasodilatory shock is the most common cause of shock in the Intensive Care Unit (ICU).⁴ Approximately 25% of patients admitted to the ICU experience a course of disease leading to severe sepsis and vasodilatory shock, which has a mortality rate of more than 50%.⁵ Approximately 6-7% of patients treated in the ICU experience an increased mortality rate of 50% due to this vasodilatory shock.⁶ Vasodilated shock patients also frequently experience disseminated intravascular coagulation. Disseminated intravascular coagulation (DIC) is defined by the International Society on Thrombus and Haemostasis (ISTH) as a variety of syndromes acquired by activation of intravascular coagulation that arise from a variety of infectious and non-infectious disorders.⁷ Therefore, early detection and aggressive therapy are needed to reduce mortality in patients with vasodilatory shock.

Severe systemic inflammation and endothelial damage are one of the mechanisms by which vasodilatory shock occurs.⁷ Including sepsis and non-sepsis, the risk of coagulation disorders increases due to endothelial cell dysfunction.⁸ Previous studies have shown that increased levels of IL-6 are related to the mechanism of hypercoagulation due to endothelial damage.⁹ An increase in Angiopoietin-2 is also associated with conditions with endothelial abnormalities, which shows the potential of Angiopoietin-2 and IL-6 as predictor markers of severity and mortality in patients with vasodilatory shock. Although Angiopoietin-2 has been studied as a predictor of survival or mortality in patients, until now there is no definite predictor marker for the event rate parameter and mortality in...
cases of vasodilatory shock in the ICU.

This study aims to examine the relationship between Angiopetin-2 and IL-6 levels with the severity of coagulation disorders and mortality in patients with vasodilatory shock. This research is expected to make an important contribution to the field of treatment and care for patients with vasodilatation shock in the ICU, as well as open up opportunities for further research in the future.

METHODS

This research is an analytic observational study with a cross-sectional study design. The research was conducted in the ICU and Emergency Room of RSUD Dr. Soetomo Surabaya from February 2022 to March 2022. The sample is all patients with a critical state of vasodilation shock due to sepsis or non-sepsis at the Hospital. The inclusion criteria in this study were patients over 18 years of age and patients with vasodilatory shock in the ICU and Emergency Department. Critical patients are patients with unstable vital signs, hypotension (systolic blood pressure less than 90 mmHg or mean arterial pressure (MAP) less than 65 mmHg) who do not improve with vasopressors and hypoperfusion and are life-threatening and require special patient care. Patients were excluded if their families refused, had congenital heart disease, and patients with end-stage renal disease (ESRD). Data collection was carried out through IL-6 and Angiopoietin-2 laboratory tests. Blood samples were put into a 5 ml venoject tube with EDTA anticoagulant and collected to examine Angiopoietin 2 and Interleukin 6 levels using the ELISA kit method. Subjects are still undergoing hemodynamic monitoring and resuscitation according to the protocol. Samples were taken according to the number of research samples fulfilled. Data were analyzed using the SPSS 24.0 program.

RESULTS

Angiopetin-2 and IL-6 Levels on the Severity of Coagulation Disorders and Mortality in Patients with Vasodilatation Shock

The results of the Spearman correlation test showed that there was a significant correlation between IL-6 levels at the time of admission and the first 24 hours (p <0.05). The results of the Spearman correlation test showed that there was a significant positive correlation between the mean IL-6 and Angiopetin-2 on the level of coagulation disorders with a value of r=0.367 and p=0.014 (p<0.05) for IL-6 and r=0.651 and p =0.0001 (p<0.05) for Angiopetin-2 (Table 1).

Table 1. Correlation between IL-6 and Angiopoetin-2 levels on the severity of coagulation disorders (DIC)

<table>
<thead>
<tr>
<th>Variable</th>
<th>R</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IL-6 (pg/mL)</td>
<td>0.367</td>
<td>0.014</td>
</tr>
<tr>
<td>IL-6-0 (pg/mL)</td>
<td>0.353</td>
<td>0.019</td>
</tr>
<tr>
<td>IL-6-1 (pg/mL)</td>
<td>0.359</td>
<td>0.017</td>
</tr>
<tr>
<td>Rerata Angiopoein-2 (pg/mL)</td>
<td>0.651</td>
<td>0.0001</td>
</tr>
<tr>
<td>Angiopoetin-2-0 (ng/mL)</td>
<td>0.644</td>
<td>0.0001</td>
</tr>
<tr>
<td>Angiopetin-2-1 (ng/mL)</td>
<td>0.645</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

There was a positive correlation between IL-6 at admission and 24 hours on mortality but statistically significant. Angiopetin-2 levels on mortality at admission and 24 hours of stay in the ICU have a positive correlate value and are statistically significant (Table 2).

After analysis, the mean cut-off values for Angiopetin-2 levels for the severity of coagulation disorders and mortality were

Table 2. Correlation of IL-6 and Angiopoetin-2 levels on mortality in patients with vasodilatation shock

<table>
<thead>
<tr>
<th>Variable</th>
<th>R</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6-0 (pg/mL)</td>
<td>0.514</td>
<td>0.0001</td>
</tr>
<tr>
<td>IL-6-1 (pg/mL)</td>
<td>0.482</td>
<td>0.001</td>
</tr>
<tr>
<td>Angiopoetin-2-0 (ng/mL)</td>
<td>0.863</td>
<td>0.0001</td>
</tr>
<tr>
<td>Angiopoetin-2-1 (ng/mL)</td>
<td>0.863</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Figure 1. Specificity and sensitivity test of Angiopoietin-2 and IL6 on the severity of coagulation disorders and mortality in research subjects.
7.75 and 72.79. Meanwhile, the mean cutoff values for IL-6 levels for coagulation disorders and mortality severity were 72.9 and 72.9, respectively. It was found that the test specificity and sensitivity of Angiopoietin-2 and IL-6 levels on the severity of coagulation disorders and mortality in patients with vasodilatory shock were 85.9% for Angiopoietin-2 and 71.6% for IL-6 (Figure 1).

**DISCUSSION**

Critical patients in the ICU can be caused by infection due to sepsis. Systemic inflammation due to sepsis causes the formation of proinflammatory cytokines, including TNF-α, IL-10 and IL-6. Cytokine storms can trigger endothelial damage. Endothelial abnormalities also cause an increase in Angiopoietin-2 and can inhibit anticoagulants, namely thrombomodulin, where the process can directly exacerbate hypercoagulability. Critical patients experience an imbalance between oxygen supply (Delivery oxygen/DO2) and oxygen demand (oxygen consumption/VO2) which can cause hypoxia. Hypoxic conditions can trigger an increase in inflammatory mechanisms in the tissue, thereby triggering endothelial damage. Endothelial damage or dysfunction will also be further exacerbated by an increase in Angiopoietin-2 in the blood. This mechanism will continue until vasodilatation shock can cause MODS and end in mortality (Figure 2).

This study discovered a significant relationship between IL-6 levels and coagulation problems at the time of ICU admission and after 24 hours (p<0.05). At the first ICU admission and after 24 hours in the ICU, patients with coagulation abnormalities had greater IL-6 levels than those without coagulation disorders. A link was also discovered between IL-6 levels and DIC scores. Other researchers have discovered elevated IL6 levels in vasodilatory shock. Furthermore, this study discovered that IL-6 levels in blood serum remained high in DIC patients for the first 24 hours after admission to the ICU (89.80 (65.90-108.30) pg/mL vs. 92.20 (67.60-112) pg/mL). A similar study found that serum IL-6 levels were high in the first 48 hours following ICU admission (70.0 pg/mL on admission; 50.0 pg/mL at 48 hours). These findings may point to an additional anti-inflammatory mechanism involved in vasodilatory shock due to greater endothelial damage in vasodilatory shock patients. The function of IL-6 in diagnosis and prognosis is debatable. According to one recent study, IL-6 levels can be utilized as a predictive marker in individuals with organ dysfunction. Another study discovered that IL-6 had a better diagnostic and prognostic value than PTX3 and PCT in sepsis and vasodilatation shock cases. In another investigation, serum IL-6 levels were found to have a better diagnostic value than PCT, presepsin, and CRP in instances with vasodilation shock. Other research has demonstrated that IL-6 serves mostly as a prognosis signal rather than a diagnostic tool. High IL-6 levels during hospitalization are related to shorter survival than patients with low IL-6 levels. Another study found that IL-6 performed better in evaluating antibiotic efficacy and proposed utilizing IL-6 as a prognostic diagnostic in patients with sepsis and septic shock. As a result, IL-6 monitoring can be valuable clinically in diagnosing disease in the acute phase and evaluating medication success. This is in contrast to watching a decrease in the inflammatory
A significant relationship was found between Angiopoietin-2 and mortality in the ICU. Non-survivors had significantly higher levels of Angiopoietin-2 than survivors. These results align with previous studies that Angiopoietin-2 is associated with mortality in patients in the ICU, namely patients with sepsis and vasodilation shock.46,44,45 Previous research also found an increase in Angiopoietin-2 compared to the control group in patients in the ICU due to sepsis and vasodilatation shock.46,45 Angiopoietin-2 is known to be associated with endothelial dysregulation, tissue hypoxia, and thrombin formation, so patients with sepsis and coagulation disorders can experience an increase in serum Angiopoietin-2 levels as experienced by the sample in this study. Angiopoietin-2 is ultimately useful for patients treated in the ICU, both septic and non-septic, to predict death. The aim is that patients with high levels of Angiopoietin-2 can immediately get aggressive treatment and reduce mortality. Studies have found that high Angiopoietin-2 levels are associated with a worse prognosis in patients with sepsis.46-47 Recent studies have also found that Angiopoietin-2 levels are associated with a worse prognosis in patients with DIC-related sepsis.46 However, the underlying mechanism is still unclear. Studies report that Angiopoietin-2 can increase inflammation and vascular permeability, leading to the development of ARDS.46-55 Moreover, a positive relationship between Angiopoietin-2 and IL-6 has been observed.46 Therefore, an increase in Angiopoietin-2 is associated with the severity of shock.

CONCLUSION
This study demonstrates a correlation between changes in Angiopoietin-2 and IL-6 levels on the severity of coagulation disorders and mortality in patients with vasodilatation shock.
associated with severe trauma. Crit Care, 16(2), R63. doi:10.1186/cc11309