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Correlation between the level of interleukin-6 serum and blood peripheral leukocyte in patients with severe traumatic brain injury



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ABSTRACT

Background: Increased level of interleukin 6 (IL-6) in patients with severe traumatic brain injury (TBI) has been documented, yet studies of its ability to predict the outcome based on the Leukocyte is limited and lacks clarity. This study aims to evaluate the relationship between serum level of IL 6 and Leukocyte among patients with severe TBI.

Methods: Twenty patients admitted consecutively to the emergency room (ER) with severe TBI were included in this observational, cross-sectional, single-centre study. Venous blood sample for IL 6 and leukocyte was performed less than 24 hours of trauma in the Intensive Care Unit. Age and gender were also recorded. Variable selection was run in stepwise forward fashion. Correlational odds models were

conducted to assess how change in Leukocyte is related to levels of IL 6. Data were analysed using SPSS version 17 for Windows.

Results: The average age of respondents was 32.45±10.71 years old and mostly males (85%). The Glasgow Coma Scale (GCS) was predominant in score 8 (45%). The mean value of IL-6 was 22.00±4.66 pg/ml and 22.53±8.11 x 10³ in leucocyte. The weak insignificant correlation was found between IL-6 and blood peripheral leukocyte using Pearson Correlation test ($r = -0.290$; $p = 0.108$)

Conclusion: The recent findings suggest that there is no correlation between IL 6 levels and Leukocyte in patients with severe TBI.

Keywords: IL 6, Leukocyte, TBI

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INTRODUCTION

Traumatic brain injury (TBI) is an injury that occurs because of the presence of external mechanical pressure that affects the cranium and intracranial components causing temporary or permanent damage to the brain, functional disorders, or psychosocial disorders.¹⁻³ The incidence of TBI increases every year, mainly due to past accidents crossing in developing countries.⁴ The incidence varied from 67 to 317 per 100,000 individuals and mortality was around 4-7% for moderate TBI and 50% for severe TBI. Every year 1.6 million people experience TBI in America, and 270,000 patients need hospital treatment, as well as 52,000 deaths from TBI. In Indonesia, the incidence of TBI is high between 6-12% of all TBIs with a mortality rate of between 25 and 37%.^{3,4}

IL-6 as a proinflammatory mediator of active cells. It can directly interfere with the survival of the cortical and cerebellar neurons and astrocytes, glial cells, and oligodendrocytes from apoptosis by inhibiting apoptotic death in mitochondria.⁵ The level of consciousness is an important component of neurological examination. Systemic assessment in unconscious patients by applying GCS as a numerical scale can provide prognostic information.^{5,6}

The Glasgow Coma Scale (GCS) is a clinical scale that assesses the level of awareness after traumatic

brain injury. Patients are usually divided into minor (14-15), moderate (9-13), and severe (3-8) injury categories. A sharp increase in progressive mortality was noted in patients who came to Emergency Room with GCS scores 3-8.⁶⁻⁸

GCS assessment usually used in the following head trauma or traumatic brain injury (TBI). Head trauma is associated with acute phase response which is characterized by leucocytosis due to increased levels of catecholamines and cortisol. The formation of early oedema after severe head injury also occurs by activating microglia. Therefore, an increase in white blood cells (WBC) calculated after head trauma can be a predictive parameter of the severity of craniocerebral trauma.

METHODS

A cross-sectional correlational analytic study was conducted among respondents who underwent Traumatic Brain Injury (TBI) and met the inclusion criteria at Prof. Dr R.D. Manado Kandou Hospital. A consecutive sampling approach was carried for sampling technique used in this study. The subjects of the study were 24 severe TBI patients who entered the IRDB of Prof. Dr R.D. Manado Kandou Hospital from November to 2018 with less than 24 hours since onset trauma inclusion criteria and TBI with GCS 3-8. The exclusion criteria if refusing

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to examine IL-6 levels and peripheral blood leukocyte levels, people with severe brain injury due to trauma accompanied by other injuries, patients with CT scans have mass effects, people with severe brain injury due to trauma with comorbidities, penetrants, or open TBI. Based on the criteria, only 20 respondents were enrolled in this study.

All of the patients were examined for serum levels of interleukin-6 (IL-6), and leukocytes count taken from venous blood samples in less than 24 hours post-trauma. The IL-6 was assessed in pg/ml. Data regarding mean, standard deviation, significant value, as well as the correlation between level of interleukin-6 serum and blood peripheral leukocyte in patients with severe TBI were analysed using SPSS version 17 for Windows.

RESULTS

All research subjects were examined and treated at Prof. R. D. Kandou Hospital according to ATLS guidelines. Table 1 shows that the age of sufferers is between the ages of 16 to 45 years with an average age was 32.45 ± 10.71 years, according to the character of the productive age. Based on gender, male sufferers are predominant compared with women (85.0% vs 15.0%) (Table 1). According to the Table 1, the GCS score was predominantly 8 (45%), and the mean value of IL-6 levels was 22.00 ± 4.64 pg/ml. In addition, the average leucocytes count also showed 22.53 ± 8.11 (Table 1)

The normal test results of the data with the Shapiro-Wilk test stated that Leukocytes and IL-6 data normally spread because the p-value was more than 0.05. Therefore, the relationship of leukocytes with IL-6 was tested by the Pearson Correlation

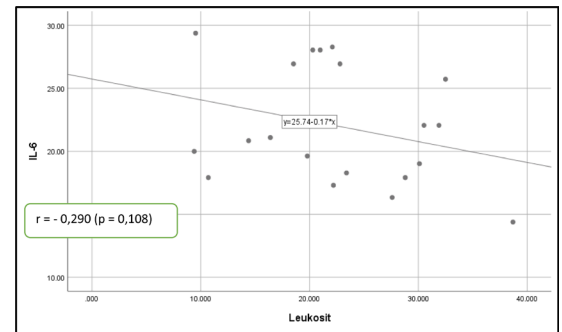


Figure 1 Scatterplot of the correlation between Leukocyte and IL-6 level

Test. The test results were obtained $r = -0.290$ with a p-value = 0.108 (Figure 1). This result states that there is a negative relationship between leukocytes and IL-6, but it is not significant because the value of $p = 0.108 > 0.05$. The relationship between the two variables graphically can be seen in the figure below. The recent finding suggests that there is no statistically significant correlation between IL-6 and blood peripheral leukocyte counts ($P > 0.05$).

DISCUSSION

This study found 20 subjects who met the inclusion criteria and were included in the study. The results of the study show that there are more males than females, aged between 16 and 45 years and the time of arrival at the hospital is below 24 hours after the event. Measurements of IL-6 statistically showed a significant correlation in severe brain injury as determined by the Glasgow Coma Scale (GCS). These results are in accordance with previous findings showing that IL-6 is produced quickly after brain injury. The evidence shows the severity of brain injury in which there is damage to the blood-brain barrier and/or components therein which correlate with anti-inflammatory cytokines after brain injury.⁵ Patients with serum IL-6 levels < 20 pg/ml, significantly show greater survival compared with patients. Sufferers with higher serum levels ($p < 0.01$). Serum IL-6 levels > 20 pg/ml after 30 hours in severe brain injury, two times more often associated with death than lower serum levels.⁸

Hergenroeder et al. Argued that an increase in serum IL-6 levels showed a poor prognosis in patients.⁹ In patients with multi-trauma, IL-6 can be released into the circulation as a result of injury to various organs. Many cell types including monocytes, macrophages, fibroblasts, keratinocytes, T and B cells have shown increased production of IL-6 in response to trauma.⁹

The prognostic potential of IL-6 has the most use in predicting mortality after brain injury due

Table 1 Baseline characteristic of respondents based on age, gender, GCS score, leucocyte counts, and IL-6 levels

Variables	Assessment (N=20)	
	N (%)	Mean±SD
Age (Years)		32.45±10.71
Gender		
Male	17 (85.0)	
Female	3 (15.0)	
GCS Scale		
3	4 (20.0)	
5	2 (10.0)	
6	3 (15.0)	
7	2 (10.0)	
8	9 (45.0)	
IL-6 (pg/ml)		22.00±4.64
Leucocytes (1x10 ³)		22.53±8.11

to trauma, despite the controversy in the literature. Therefore, future assignments are needed to determine the role of IL-6 in predicting other outcomes in the future.¹⁰

In this study, the lowest serum IL-6 level was 14.38 pg/ml, and the highest was 29.38 pg/ml with an average of 22.0060 pg/ml. IL-6 levels increase in the first 24 hours after severe brain injury. This is consistent with Hergenroeder et al. whereas IL-6 expression increases in the first 24 hours after severe head trauma, and is consistent with pro-inflammatory properties.⁹

A study conducted by Härtl R et al. found that white blood cell count increases and can be used as a predictive value of neurological damage.¹¹ These data show increased inflammation after intracerebral haemorrhage and are associated with early neurological damage.¹¹

The inflammatory response, activation of endothelial cells, and the release of inflammatory mediators in head injury can increase the number of leukocytes. Head injuries are associated with acute phase responses characterized by leucocytosis due to increased epinephrine and cortisol.¹²

Subramanian PS et al. explained that in brain injury, traumatic microvascular ruptures occur which will be followed by physical occlusion.¹³ The nature of leukocytes is difficult to change shape when compared with erythrocytes so that more pressure is needed so that the leukocytes can pass through small diameter capillary vessels. In situations where tissue perfusion falls, capillary functions as a filter that filters the leukocytes so that there is an increase in leukocytes in peripheral blood. After being trapped in the capillary, leukocytes and endothelial adhesion occur so that the leukocytes will not be released even though the perfusion pressure returns to normal.¹⁹ In this study the mean peripheral blood leukocyte examination was $22.5 \times 10^3/\mu\text{L}$. A WBC number exceeding $17.5 \times 10^6/\text{L}$ had a predictive value for a poor GCS score and length of stay at the hospital.⁷

According to the previous study, an increase of total peripheral blood leukocytes in high risk brain injury on the initial peripheral leukocyte examination was $20.6 \times 10^3/\mu\text{L}$, followed by the mean leukocyte examination 24 hours posttraumatic $22.4 \times 10^3/\mu\text{L}$, and mean leukocyte examination 48 hours posttraumatic $24.8 \times 10^3/\mu\text{L}$.¹⁴ Significant increase in leukocytes early 3 hours after brain injury.¹⁵ Polymorphonuclear leukocytes will accumulate up to 48 hours posttraumatic.¹¹

In this study, the relationship between IL-6 and leukocyte levels was tested with statistics after normal data distribution was seen or not. The normal test results of the data with the Shapiro-Wilk test stated that Leukocytes and IL-6 data

normally spread because the P-value was more 0.05. Therefore, the relationship of leukocytes with IL-6 was tested by the Pearson Correlation Test. The test results were obtained $r = -0.290$ with a value of $p = 0.108$. This result states that there is a negative relationship between leukocytes and IL-6, but it is not significant because the value of $p = 0.108 > 0.05$.

From this study, it can be seen that: (1) IL-6 is produced by microglia and astrocytes and can work as an immunomodulator and immunosuppressive agent. (2) High IL-6 levels tend to lead to worse outcomes after TBI so that IL-6 can be used as a prognostic value. (3) At the beginning of the injury there is accumulation of leukocytes in cerebral microcirculation, adhesion to the microvascular surface, production of the metalloproteinase matrix "MPMP" resulting in damage to the blood-brain barrier, extravasation of leukocytes to brain tissue and finally cytokines released to brain tissue in response to inflammation.

The negative relationship between leukocytes and IL-6 is not in harmony with the existing theory can be caused by several intrinsic and extrinsic factors found in this study. From the bias factor of sample storage, the results of biases from laboratory tests can also influence the results of the study. Nevertheless, this study has a significant and better prognostic value for high IL-6 levels in TBI patients in trauma compared to leukocyte levels, so that it can be used as a reference for future research and standard operating procedures in health facilities.

CONCLUSION

IL-6 increases consistently after traumatic brain injury and as a biomarker of traumatic brain injury that is better than peripheral leukocytes even though there is no statistically significant correlation between them.

CONFLICT OF INTEREST

There is no conflict of interest in this research.

ETHICAL CLEARANCE

Ethics approval has been obtained prior to the study being conducted by the Ethics Committee of Universitas Sam Ratulangi/Prof. Dr R.D. Kandou General Hospital Manado.

AUTHOR CONTRIBUTION

All of the authors are equally contributed to the study from conceptual framework, data gathering, data analysis, until reporting the results of study.

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