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Relationship Between Interleukin-6 And The Occurence Of Mods In Multitrauma Patients With Fracture Oniss ≥ 17

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I. Background

Trauma is the main cause of death in the world, so that this is categorized as a public health issue. Trauma cases are common in the young age and most productive age groups with an age range of 15-44 years (Polinder et al., 2006; Mackenzie, 2000). Trauma is one of the leading causes of death with a mortality rate of 180,000 people per year in the United States (Ciriello et al., 2013). 10% of deaths worldwide are caused by trauma (Maegel, 2010). It is estimated that by 2020, 8.4 million people will die each year due to trauma, and trauma from traffic accidents will beranked third in causing disability worldwide and ranks second in developing countries (Udeani, 2013). In Indonesia, there were 108,696 traffic accidents with 31,195 fatalities in 2011 (BPS, 2011). Based on data from the Emergency Service of Dr. Saiful Anwar General HospitalMalang, 46% of the patients were trauma patients with 40% mortality rate and 35% disability rate compared to Singapore where the mortality rate was below 20% and the disability rate was below 8% (Malang Emergency Service, 2002).

Multiple trauma is when a person experiences simultaneous injury in 2 or more organs and a life-threatening injury. This injury can affect many organ systems and commonly requires intensive management on the trauma. Most cases of multiple trauma are musculoskeletal injuries in the form of fractures, dislocations, and soft tissue injuries. The entire process of injury can cause varying organ dysfunctions and complications depending on the degree of injury (Adams, 2011; Hietbrink, 2006).

Currently, there are many severity scores that have been developed to assist in the triage, management, and prediction of results in patients with trauma or tissue injury (Balogh et al., 2003). These scores are based on either anatomical or physiological parameters, or both. One of the trauma scoring systems widely used throughout the world is Injury Severity Score.Injury Severity Score (ISS) is an anatomical scoring system that provides an overall score for patients with multiple trauma. ISS takes value from 1-75. A person is said to experience multiple trauma, if the ISS value is more than or equal to 16 (Steinsballe, 2009). However, this scoring system has weaknesses, especially in the subjective scoring system so that it can potentially cause differences in the selection of therapies and produced outcomes.

Another method that has been widely used for early detection of complications of trauma is through the application of biological markers, so that it can increase outcomes in severe trauma. Biological markers can be defined as clinical indicators that can be directly measured and evaluated as physiological, pathogenic, or pharmacological responses. Biological markers have clinical relevance, they must be sensitive and specific (Adams, 2011). In multitrauma, there are various biological markers to detect inflammatory reactions such as C-reactive protein (CRP), procalcitonin, cytokines, E-selectin and DNA (Giannoudiset al., 2004).

CRP is the most widely used biological marker of inflammation in clinical practice today, although it has several weaknesses such as its inability to differentiate infections from inflammatory responses in initial injuries. Of all available cytokines, IL-6 (Interleukin-6) appears to be the most reliable biological marker for systemic inflammation, and is the initial biological marker of infection. The use of these biological markers together can offer the ability to detect the onset of SIRS (Systemic Inflammatory Response Syndrome) and allow early intervention to prevent MODS (Multiple Organ Dysfunction Syndrome) (Riche, 2000).

Interleukin-6 (IL-6) is a pro-inflammatory cytokine produced by many cells (activated macrophages, endothelial cells, etc.) and plays a role in both natural and adaptive immunity. IL-6 stimulates acute phase protein synthesis by hepatocytes and stimulates the growth of B. lymphocytes (Abbas and Lichtman, 2004). In contrast to other cytokines with paracrine or autocrinefunction, the main effectof increasing IL-6 in the circulation is that it is far from the original location (Stevinken et al, 2002). IL-6 is a major mediator of acute phase protein synthesis (CRP) by hepatocytes (Abbas and Lichtman, 2004). Stevinken et al. suggested that the acute phase response is a biological response to various types of disorders such as infection, tissue injury, or impaired immunity.

This study supports the current paradigm shift regarding the assessment of injury severity (Sammour, 2009) because previous assessments depend on the parameters of subjective anatomy and physiology.

Interleukin-6 is preferred because it has a long duration of detection in the blood, is not affected by kidney function and is able to be measured by a fast measurement system (Watanabe et al., 2005).

Until now, in multitrauma management, the clinical and anatomical assessment is based on the ISS, whereas biochemically and immunologically due to a syndrome response, the placement of a cytokine as a predictor has not yet been found or used. Therefore, this study was designed to determine the relationship of levels of Interleukin-6 (IL-6) as a biological marker of survival in cases of musculoskeletal trauma.

II. Material And Method

This study is an observational cohort study. The study subjects were patients with multiple fracture that fit the criteria. Interleukin-6 levels and ISS were measured when the subjectswere in the Emergency Room. Furthermore, the subjectswere observed until the 7th day to determine their survival status. To test the research hypothesis, the Spearman Correlation test the independent sample t-test were performed.

Place and Time

This study was conducted in theEmergency Room of Saiful Anwar General Hospital and Central Laboratory of Biological Sciences, University of Brawijaya Malang. The study was conducted from April, 2018.

Population and Sample

The population was patients with trauma who came to the emergency room of Saiful Anwar Hospital Malang and the sampling method usednon probability sampling (purposive sampling). Patients included in the population sample were according to:

- Inclusion criteria, including:
  1) Multiple trauma patients with fracture
  2) The age of subject greater than 18 years
  3) Injury Severity Score ≥ 17
  4) Subjects who go to emergency room in less than 24 hours after trauma
  5) Subjects who have never experienced a major surgical procedure.
- Exclusion criteria, including:
  1) Patients who have metabolic, autoimmune or other chronic diseases.

Calculation of Sample Size

Sampling in this study used proportion estimation sampling technique using the Lameshows's formula:

$$n = \frac{Z^2_{\alpha}\, p\, q}{d^2} = \frac{Z^2\, p\,(1-p)}{d^2}$$

n = minimum number of samples needed
Z_{α} = standard normal distribution value (table Z) at certainα (1.96)
p = proportion of single trauma patients (92.4%)
q = 1-p = proportion of multitrauma patients (7.6%)
d = limit of error or absolute precision (0.05)

From the fomula, it was found a sample size of 40 people.

Operational Definition

Multiple trauma : Injury to 2 or more organ systems that cause life-threatening conditions accompanied by a systemic reaction due to trauma which then leads to organ dysfunction or failure located far from the vital organ system with no direct trauma injuries.

Musculoskeletal trauma : Trauma of the musculoskeletal system found in 85% of patients with blunt trauma, but rarely causes life-threatening or limb threatening conditions. Fracture is the breakdown of continuity of bone and/or cartilage tissues commonly caused by trauma. Open fracture is a fracture with direct communication to the external environment, either the bone fragment penetrate the skin or the sharp object penetrates the skin (Solomon, 2010).

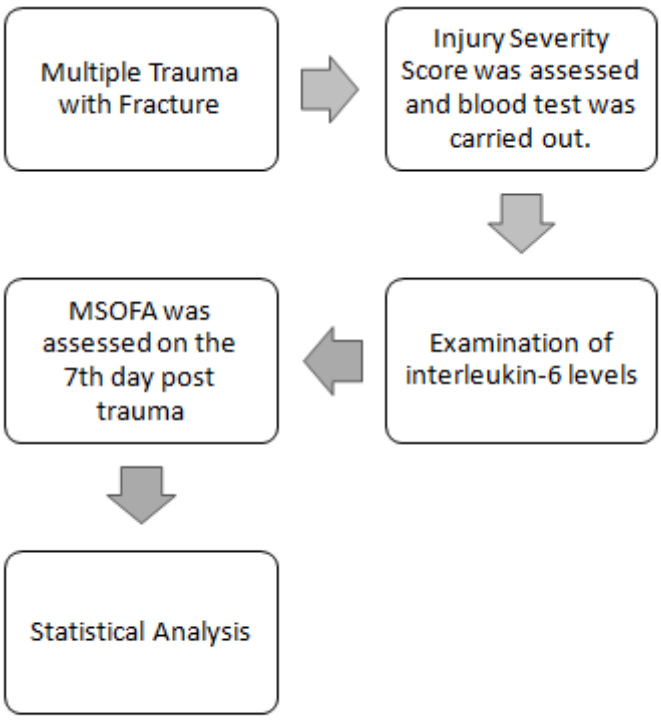
Injury severity score : Injury Severity Score (ISS) is an anatomical score that describes scores for multitrauma patients. Each trauma is characterized by AIS (Abbreviated Injury Scale) representing 6 body parts namely; head,

		face, thorax, abdomen, extremities, external. Only the highest AIS score of each body part is used. AIS assessment is as stated in 88yste 1. The three organs with the most severe scores are squared and summed to generate ISS value (Copes, 2014). The ISS interpretation can be seen in Appendix 1.
SIRS	:	Clinical response to specific and non-specific stimuli (insult), it can be said SIRS if 2 or more than 4 variables are obtained.
Levels of Interleukin-6	:	Pro-inflammatory cytokines measured for its absorption at λ450 nm using ELISA Reader
M-SOFA Score	:	Modified Sequential Organ Failure Assessmentis a score used to assess damage to organs consisting of the lungs, heart, kidney, liver, blood, gastrointestinal tract, and central nervous system. The scores used are in accordance with Goris et al (Frank, 2002).
Survival	:	Patients who survive within 7 days after trauma.

Research Procedure

Multitrauma patients with fractures that came to the Emergency Room of Saiful Anwar Hospital were stabilized according to Advanced Trauma Life Support (ATLS). Patients who came and signed informed consent of this study were assessed using ISS and laboratory tests were conducted. The Injury Severity Score was calculated using the TRISS calculator (www.trauma.org).

5 cc blood samples were taken and stored in EDTA tubes. The sample was taken to the Central Laboratory of Biological Sciences, University of Brawijaya to be examined for interleukin-6 levels. Then, patients underwent medical procedures and were followed up during hospital treatment. The patients were assessed for MSOFA on the 7th day post trauma. The data were analyzed using statistical analysis.



Research Flow

Measurement of Levels of 6 (IL-6) using ELISA (Enzyme-Linked Immunosorbent Assay)Method:

- Antigen-coating step on microtubes plate by mixing serum with 50 µL coating buffer with a ratio of 1:20

- Incubate overnight at 4^0C
- Wash with 0.2% 100 µL PBS-T (PBS+Tween-20) solution in3 x 3 minutes
- Blocking bufferstep(adding 1% BSA in PBS)
- Incubate for 1 hour at room temperature
- Wash with 0.2% 100 µL PBS-T (PBS+Tween-20) solution in3 x 3 minutes
- Step of primary antibody coating with the addition of AntiIL-6+PBS with a ratio of 1:4000
- Incubate for 1 hour at room temperature
- Wash with 0.2% 50 µL PBS-T (PBS+Tween-20) solution in 3 x 3 minutes
- Step of secondary antibody coating with addition of IgG Biotin Anti Rabbit +PBS with a ratio of 1:8000
- Incubate for 1 hour at room temperature
- Wash with 0.2% 100 µL PBS-T (PBS+Tween-20) solution in 3 x 3 minutes
- Add 1:8000 SA-HRP
- Incubate for 1 hour at room temperature
- Wash with 0.2% PBS-T in 3 x 3 minutes
- Add Sureblue TMB (*Toluene Metilene Blue)*
- Incubate for 30 minutes at room temperature
- Stop the reaction with HCl 1 N
- Incubate for 15 minutes at room temperature
- Measure its absorption at λ450 nm with ELISA Reader.

III. Result

The study was conducted at Saiful Anwar General Hospital Malang to calculate MSOFA score, and was conducted at Saiful Anwar General Hospital and the Central Laboratory of Biological Sciences of University of Brawijaya Malang to measure interleukin (IL)-6.

Table 1. Distribution of Variables

	N	Minimum	Maximum	Mean	Std. Deviation
Levels of IL-6 (ng/l)	40	27.31	926.87	294.02	285.67
MSOFA	40	2	11	6.58	3.21

Based on Table 5.1, it can be seen that the highest IL-6 level is 926.87 and the lowest value is 27.31. The average value of IL-6 levels is 294.02 with a standard deviation value of 285.67.

MSOFA score has the highest value of 11 and the lowest value of 2. The average MSOFA score is 6.58 with a standard deviation of 3.21.

Correlation between Interleukin 6 (IL-6) and MSOFA Score

The results of correlation test between Interleukin 6 (IL-6) variable and MSOFA Score using the Spearman's Rank correlation are shown in Table 3.

Table 3 Correlation between Interleukin 6 (IL-6) and MSOFA Score

Correlation of Variables	r Spearman	p-value
Interleukin 6 (IL-6) – MSOFA	0.410	0.009

Based on the test results in Table 3, it can be seen that the Spearman's rank correlation coefficient value is positiveof0.410. Positive direction means that when the Interleukin 6 (IL-6) variable increases, the MSOFA score variable will increase. The resulting correlation coefficient shows the extent of relationship of 0.410. This correlation value indicates that the relationship between the interleukin 6 (IL-6) variableand the MSOFA score variable is in the moderate category. Based on the above results, it can be seen that p-value is smaller than alpha of 5% (0.005 <0.05), so that H0 is rejected. Thus it can be concluded that there is a relationship (correlation) between Interleukin 6 (IL-6) and MSOFA Score.

IV. Discussion

Trauma is the main cause of death in the world, so this is categorized as a public health issue. Trauma cases are common in the young and most productive age groups with an age range of 15-44 years (Polinder et al., 2006; Mackenzie, 2000). Scoring systems are developed to assist in triage, management, and prediction of results in patients with trauma or tissue injury (Balogh et al., 2003). These scoresare based on either anatomical or physiological parameters, or both.

Another method that has been widely used for early detection of complications of trauma is through the application of biological markers, so that it can increase outcomes in severe trauma. Biological markers can be defined as clinical indicators that can be directly measured and evaluated as physiological, pathogenic, or

pharmacological responses. Biological markers have clinical relevance, they must be sensitive and specific (Adams, 2011).

This study was conducted to assess whether IL-6 can be a biological marker as a specific predictor of trauma, where the outcome is carried out by comparing between IL-6 and M-SOFA score.

This studyobtained26 male patients (65%) and 14 female patients (35%). According to age, there were 5 patients (12.5%) in the age range of 18-21 years, 20 patients (50%) in the age range of 21-30 years, and 15 patients (37.5%) in the age range of 31-40 years. The patients undergoing blood sample test were patients with trauma with age of > 18 years, had no past metabolic disease history on ISS score of ≥17.

The blood samples of the patients who came to the emergency room at Saiful Anwar Hospital and had fulfilled the inclusion and exclusion criteria were taken and IL 6 was examined using ELISA at the Faal Laboratory. Based on the results of examination,the highest IL-6 level was 926.87 and the lowest value was 27.31. IL-6 levels had an average value of 294.02 with a standard deviation value of 285.67.

In this study, patients were evaluated clinically and parametrically using M-SOFA, where the components of assessment were respiratory system, cardiovascular system, liver function, GCS, and kidney function. The maximum value obtained from M SOFA score was 20, and the lowest value was 5. In this study,it was obtained that the highest MSOFA score was 11, while the lowest score was 2. The average MSOFA score was 6.58 with a standard deviation of 3.21.

Data normality test was performed to find out whether the data was normally distribution or not by using Kolmogorof-Smirnof test. From the results of the normality test using Kolmogorof-Smirnof test,it can be seen that the significance values for IL-6 and MSOFA score were 0.063 and 0.213, respectively. Because p value > 0.05, then Ho was accepted, and it can be concluded that the data was normally distributed. Thus, the tests using Pearson Correlation and independent t test can be continued because both assumptions had been fulfilled.

Based on the analysis results to assess the relationship between interleukin 6 and M SOFA using a correlation test between Interleukin 6 (IL-6) and MSOFA Score variables using Rank Pearson correlation, it can be seen that the Spearman rank correlation coefficient value was positive of 0.495. Positive direction meant that if the Interleukin 6 (IL-6) variable increases, the MSOFA score variable will increase. The resulting correlation coefficient indicated the extent of the relationship of 0.495. This correlation value indicated that the relationship between the Interleukin 6 (IL-6) and the MSOFA score variables was in the moderate category. Based on the above test results, it can be seen that the p-value was smaller than alpha of 5% (0.001 < 0.05), so that H0 was rejected. Thus, it can be concluded that there was a relationship (correlation) between Interleukin 6 (IL-6) and MSOFA Score.

Trauma patients induce inflammatory response generally characterized by changes in inflammatory and the immunological system of the body. The consequences of the inflammatory process on trauma patients can cause adverse effects on vital cell systems which ultimately lead to multiple organ dysfunction (arch surgery, 1985). Proinflammatory cytokines are synthesized and released in high amounts by macrophages, as the main pro-inflammatory cytokines, IL-1, IL-2, IL6, IL 8 and TNF∝ have been studied (champion HR, 1989). IL-6 is the main stimulator for the production of most acute phase proteins (Gauldie, 1987), while other involved cytokines affect some acute phase protein groups.

Interleukin 6 is a glycoprotein with a molecular weight of 22-29kd and is produced by several cell types, including T cells, B cells, and endothelial cells. Interleukin 6 production is induced by LPS, interleukin 1, and TNFalpha. Then, Interleukin 6 induces B lymphocyte proliferation to increase immunoglobulin synthesis and induce proliferation of lymphocytes T. In addition, interleukin 6 increases T cell differentiation and natural killer cell activity. Thus, interleukin 6 is one of the best prognosis marker to find out the outcome of patients with SIRS, or MODS (Giannouids p v et al, 2004).

From the results of this study, it was found that there was a positive relationship between increased interleukin 6 (IL-6) and M SOFA, as an initial marker that can be used for clinical parameter and produce prognostic values in trauma patients. The result of this study was in accordance with study conducted by from Y. Yagmur et al, 2008 entitled *The Relation Between Severity of Injury and Early Activation of Interleukin in Multiple Injured Patient*concluding that if IL 6 increases, then MSOFA scorealso increases in trauma patients.

Some studies confirmed the immediate study of posttraumatic interleukin 6 levels, where patients with most severe degree of trauma have the highest levels of interleukin 6. It was stated that there was a relationship between an increase in the initial level of cytokine interleukin 6, a high Injury Severity Score, and late adverse outcome. The study conducted by Gebhard et al in 2000 described post-traumatic interleukin 6 levels. This study found that there was a correlation between the levels of cytokineinterleukin 6 within 6 hours post trauma and the degree of trauma. Patients with the most severe injuries had the highest levels of cytokineinterleukin 6. The study concluded that the levels of cytokine interleukin 6 can be used to evaluate the impact of trauma on the patient's body (Gebhard F et al, 2000).

The study of Giannoudis et alin 2008 found that the levels of cytokine interleukin 6 can predict the occurrence of complications in patients with multiple trauma, one of which is the complication of MODS, at 300pg/mL cut off points with 78% accuracy, 72% sensitivity, and 78% specificity (Giannoudis et al, 2008). In addition, the study of Stensballe et al. in 2009 found that on the first day patients who had cytokine interleukin 6 levels of more than 300pg/mL would experience mortality within 30 days (Stensballe, 2009). Whereas in a study of Frink et al. in 2009 on multiple trauma patients experiencing MODS,it was found an increase in the levels of cytokine interleukin 6 with an accuracy of 84.74%, a specificity of 98.3, a sensitivity of 16.7% with a cut-off point of 761.7 pg/mL. The threshold for the occurrence of MODS was761.7 pg/mL and 2176.0 pg/mL for mortality rate.

The sample in this study was not homogeneous. According to the age of respondents, 5 respondents (12.5%) were in the age of less than 21 years, 20 respondents (50%) in the age range of 21-30 years, and 15 respondents (37.5%) in the age range of 31-40 years. Based on the result of t test, p value for the age group was 0.626, because p value (0.626)> 0.05 (α = 5%), then H0 was accepted. Thus, it can be concluded that there was no significant difference between the levels of IL-6 and the age group. This study found that there was no significant difference between the levels of interleukin-6 (IL-6) and the patient's gender. P value of the gender group was 0.611, because p value (0.611)> 0.05 (α = 5%), then H0 was accepted. Thus,it can be concluded that there was no significant difference between thelevels of IL-6 and the gender group.

V. Conclusion

This study found that there was an increase in IL-6 levels in multiple trauma patients with fractures on ISS ≥ 17. Interleukin 6 examination can predict the occurrence of MODS in multiple trauma patients with fractures and cytokine interlukin 6 can predict mortality and can be used to identify multi-trauma patients who wereat risk of MODS.

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