IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 11 Ser.9 (November. 2020), PP 12-17
www.iosrjournals.org

Relationship of Interleukin-6 and TNF α With the Occurance of Mods IN Trauma Thoracoabdominal Patients with ISS>16 IN DR. Saiful Anwar Hospital

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Abstractα
***Introduction** : Multitrauma management evaluates clinically and anatomically based on an Injury severity score, the placement of a cytokine as a predictor has not been widely found or used. this study was designed to determine the relationship of levels of Interleukin-6 (IL-6) and TNF α as a marker of survival biology in cases of thoracoabdominal trauma.*
***Material and Methods:** This study is an observational cohort study. The research subjects were thoracoabdominal trauma patients that matched the criteria. Interleukin-6, TNF α and ISS levels will be measured when the subject is in the Emergency Installation. Furthermore, the subject will be followed until the 5th day to determine survival status. To test the research hypothesis the Spearman Correlation correlation test will be carried out, and the independent sample t-test. Inclusion criteria included Thoracoabdominal patients, Subject age between 16 years – 60 years. Injury Severity Score ≥ 16, Subjects coming less than 24 hours after trauma, Subjects having never undergone a major surgical procedure. Exclusion criteria include patients who have metabolic, autoimmune, or other chronic diseases*
***Result:** On the test results it can be seen that the Spearman rank correlation coefficient value is positive between IL-6 and APACHE II score, which is 0.984. Positive direction means that when the Interleukin 6 (IL-6) variable increases, the APACHE II score variable will increase. The correlation of TNF α and APACHE II score also positive, which is 0.320. Positive direction means that when the TNF α variable increases, the APACHE II score variable will increase. Based on the results of the above test it can be seen that the p-value is smaller than alpha 5% (0.005 <0.05) so that H0 is rejected with the conclusion there is a relationship (correlation) between Interleukin 6 (IL-6), TNF α and the APACHE II Score*
***Conclusion:** Increased levels of Interleukin 6 (IL-6) and TNF α in thoracoabdominal trauma patients with ISS ≥ 16*

Date of Submission: 09-11-2020 Date of Acceptance: 23-11-2020

I. Introduction

Trauma is still the leading cause of death in the world, so it is a public health issue. Trauma cases are common in the young age group and the most productive age group in the 15-44 year age group (Polinder et al., 2006; Mackenzie, 2000). Trauma is one of the main causes of death with a death rate of 180,000 people per year in America (Ciriello et al., 2013). Ten percent of deaths worldwide are caused by trauma (Maegel, 2010). Multiple trauma is trauma that simultaneously occurs in 2 or more organs and at least one trauma is life-threatening. To date, many severity scores have been developed to aid in triage, management, and prediction of outcome in trauma or tissue injury patients (Balogh et al., 2003). The Injury Severity Score (ISS) is an anatomical scoring system that provides an overall score for patients with multiple injuries. Another widely used method for early detection of trauma complications is the application of biological markers so as to increase the outcome in severe trauma.

II. Methods

Research Design

This study isanobservationalcohort study. The researchsubjects were multiple trauma patientswho fit thecriteria. Interleukin-6, TNF α and ISS levelswillbemeasuredwhilethesubjectis in theemergencydepartment. Furthermore, subjectswillbefollowed until day 5 todeterminethesurvival status.

Place And Time of Research

ThisresearchwillbecarriedoutatSaiful Anwar Hospital andtheCentralLaboratoryofBiologicalSciences, BrawijayaUniversity Malang. The researchwillbeconducted in February - April 2020.

Population And Sample

The research subjects were trauma patients who came to the emergency room of Saiful Anwar Hospital Malang. The inclusion criteria included thoracoabdominal trauma patients, age ≥ 16 years and ≤ 60 years, Injury Severity Score greater than 16, Subjects came less than 24 hours after trauma, Subjects had never experienced major surgical procedures. Exclusion criteria included patients with metabolic, autoimmune or other chronic diseases. The sampling method used is non-probability sampling (purposive sampling).

Research Procedure

Multi-trauma patients who came to the emergency room at Saiful Anwar Hospital were stabilized according to Advanced Trauma Life Support (ATLS). Patients who attended and signed the study's informed consent were assessed for vital signs, ISS, and performed laboratory examinations. The ISS score is calculated using the TRISS calculator.

The patient will be taken a blood sample of 5 cc and stored in an EDTA tube. The sample will be taken to the Central Laboratory of Biological Sciences, Universitas Brawijaya for examination of levels of interleukin-6 and TNF α. Patients will undergo medical procedures and will be followed during their treatment in the hospital. Patients will be assessed a MOD score and assessed for their survival on day 5 post trauma. The data will be analyzed using statistical analysis

Statistical Analysis

To test the research hypothesis, the Pearson correlation test, Spearman correlation, and independent sample t-test and chi square test will be carried out.

III. Results

Univariate Analysis

Based on Table 1.1, it is found that there are 28 male patients (70%) and 12 female patients (30%).

Tabel 1.1 Respondent Gender

Gender	Frequency	Percentage
Male	28	70%
Female	12	30%
Total	**40**	**100%**

Based on Table 1.2, it is found that patients who have less than 21 years of age are 4 people (10%), 15 people aged 21-30 years (37.5%), 16 people aged 31-40 years (40%) and 5 people aged 41 - 50 years (12.5%).

Tabel1.2 Respondent Age

Age	Frequency	Percentage
<21 years	4	10
21 - 30 year	15	37.5
31 - 40 year	16	40
41-50 year	5	12.5
Total	**40**	**100**

Based on table 5.1, it can be seen that the highest IL-6 level is 51.08 and the lowest value is 9.84. IL-6 levels have an average value of 13.63 with a standard deviation of 10.94. The TNFα level has the highest value of 450.86 and the smallest value is 65.86. The TNFα level has an average of 295.86 with a standard deviation of 94.50. TheAPACHE II score has the highest value of 24 and the smallest value of 6. The APACHE II score has an average of 11.90 with a standard deviation of 4.98.

Tabel 1.3 Variable Distribution

	N	Minimum	Maximum	Mean	Std. Deviation
TNFα	40	65.86	450.86	195.86	94.50
Interleukin (IL)-6	40	3.84	51.08	13.63	10.94
APACHE II Score	40	6	24	11.9	4.98

The p value in the gender group is 0.338, because the p value (0.388)> 0.05 (α = 5%), then H0 is accepted. So that it can be concluded that there is an insignificant difference in TNFα levels in the Gender group. The p value in the Age group is 0.217, because the p value (0.217)> 0.05 (α = 5%), then H0 is accepted. so that it can be concluded that there is no significant difference in TNFα levels in the age group

Tabel 1.4 Differences in TNFα levels based on Gender and Age Group

Group	N	Average TNFα	p	Information
Male	28	196.46±100.38	0.338	Not Significant
Female	12	194.50±83.21		
< 21 year	4	186.77±47.84	0.217	Not Significant
21 – 30 year	15	250.44±106.36		
31 – 40 year	16	183.48±66.75		
41 – 50 year	5	79.14±12.31		

The p value in the sex group is 0.426, because the p value (0.426)> 0.05 (α = 5%), then H0 is accepted. so that it can be concluded that there is an insignificant difference in Il-6 levels in the gender group. The p value in the Age group is 0.282, because the p value (0.282)> 0.05 (α = 5%), then H0 is accepted. So it can be concluded that there is an insignificant difference in Il-6 levels in the group.

Tabel 1.5 Differences in IL-6 levels based on gender and age group

Group	N	Mean IL-6 levels	p	Information
Male	28	15.05±12.26	0.426	Not Significant
Female	12	10.32±6.18		
< 21 year	4	10.34±6.96	0.282	Not Significant
21 – 30 year	15	16.90±14.72		
31 – 40 year	16	14.01±7.86		
41 – 50 year	5	5.24±0.63		

The p value in the sex group is 0.343, because the p value (0.343)> 0.05 (α = 5%), then H0 is accepted. so that it can be concluded that there is no significant difference in the APACHE II score in the gender group. The p value in the Age group is 0.022, because the p value (0.022) <0.05 (α = 5%), then H0 is not accepted. so it can be concluded that there is a significant difference in the APACHE II score in the age group

Tabel 1.6 Difference in APACHE II Score based on Gender and Age Group

Group	N	APACHE II mean score	p	Information
Male	28	11.89±5.33	0.343	Not Significant
Female	12	11.92±4.25		
< 21 year	4	10.75±2.50	0.022	Significant
21 – 30 year	15	15±5.46		
31 – 40 year	16	11.13±3.61		
41 – 50 year	5	6		

IV. Discussion

This study was conducted to assess whether TNFα and IL-6 could be biological markers as predictors of trauma, where the outcome was done by comparing TNFα and IL-6 with APACHE II scores.

In this study, it was found that there were 28 male patients (70%) and 12 female patients (30%). Based on age, there were 4 (10%) patients aged <21 years, 15 (37.5%) 21-30 years old, and 16 31-40 years old (40%). Patients who will be taken for blood sampling are trauma patients who have experienced trauma with an age of ≥ 16 years, do not have a history of previous metabolic diseases with an ISS score of ≥ 16.

Patients who come to the emergency room at Saiful Anwar Hospital and have met the inclusion criteria will take blood samples and carry out TNFα and IL-6 tests using the ELISA method in the physiological laboratory of Brawijaya University, from the results of the examination, the highest TNFα is 450.86 and the lowest is 65.86 and the average value amounting to 195.86 with a standard deviation of 94.50. While the highest IL-6 level was 51.08 and the lowest value was 3.84, the average value was 13.63 with a standard deviation of 10.94.

In this study, patients will be evaluated clinically parametrically using the APACHE II score, where the components of the assessment consisted of an acute physiological score, a chronic disease score, and a general score with a maximum value of APACHE II of 71 and the lowest of 0. In this study, the APACHE score was obtained, the highest is 24 and the lowest score is 6. APACHE II score has an average of 11.9 with a standard deviation of 4.98.

Testing data normality to determine whether the distribution of data tested has a normal distribution of values or not by using the Kolmogorof-Smirnoff Test. The results of the normality test showed a significance

value (p) for TNFα levels of 0.053, IL-6 levels of 0.001 and for APACHE II scores of 0.004. Because the p value> 0.05 for TNFα, Ho is accepted and it can be concluded that the data used has a normally distributed distribution and a p value <0.05 for IL-6 and the APACHE II score, Ho is rejected and it can be concluded that the data used used to have an abnormally distributed distribution. There is data that is not normally distributed, thus testing is done using the Spearman Correlation and Chi Square test.

The results of the analysis to assess the relationship between TNFα and the APACHE II score using the Pearson rank 5 correlation, it can be seen that the spearman rank correlation coefficient is positive, namely 0.984, meaning that there is a correlation between the TNFα level and the APACHE II score so that the correlation is very strong. This correlation value indicates that the increasing level of TNFα increases the APACHE II score in the patient. Based on the test results above, it can be seen that the p-value is smaller than alpha 5% (0.000 <0.05). The conclusion is that there is a correlation (correlation) between TNFα and the APACHE II score.

The results of the analysis to assess the relationship between IL-6 and APACHE II scores using Pearson rank correlation 5 can be seen that the spearman rank correlation coefficient is positive, namely 0.320, meaning that there is a correlation between IL-6 levels and APACHE II scores with sufficient correlation. This correlation value can indicate that the increasing levels of IL-6 can increase the APACHE II score in patients. Based on the test results above, it can be seen that the p-value is smaller than alpha 5% (0.044 <0.05), so it can be concluded that there is a relationship (correlation) between IL-6 and the APACHE II score.

In post-traumatic patients, there will be dynamic changes in the hemodynamic, metabolic, and immune responses that are influenced by endogenous mediators called cytokines. This inflammatory process is a physiological reflex from the body, causing SIRS followed by compensatory anti-inflammatory response syndrome (CARS). However, if it is excessive, it will enter malignant systemic inflammation (moderate or severe SIRS) which can then lead to ARDS and MODS (Gerard M D, 2006). TNF and IL-1 are the main cytokines in the acute inflammatory response to infection and other stimuli (Decker M, Janet, 2006). At the onset of acute inflammation, IL-6 mediates the acute phase response. When its activity as a pro-inflammatory cytokine continues, acute inflammation turns into chronic inflammation involving an immune response. (Atreyaet al., 2000).

TNF is a protein group consisting of lymphotoxin a (Lta) and lymphotoxin b (Ltb) which is produced mainly by activated monocytes and macrophages, as well as T cells with a molecular weight of 20 kDa. TNF includes pro-inflammatory cytokine flows and is useful to activate macrophages in the host for defense against microbes, activate cytokine production, increase adhesion molecular expression and activation of neutrophils. is also an additional stimulator for T cell activation and antibody production by B cells (Jimena Cuenca, 2001, Baz et.al., 2008). So that TNFα is one of the biological markers to identify patients with SIRS or MODS (Yousef and Suliman, 2013).

Several studies confirmed studies that there was an increase in TNFα in post-traumatic patients starting 4 hours after trauma and continuing to increase during the observation period. In addition, MODS and the incidence of SIRS also increased with an increase in TNFα levels (Spielmann, 2001). According to a study by Liu and Tang, there was a significant increase in TNFα levels in trauma patients starting 2 hours after trauma. The highest TNFα levels were detected 24 hours after trauma and continued to increase thereafter until day 3 of trauma. According to him, TNFα levels correlate with the injury conditions indicated by the ISS score. The highest TNFα level was found in patients with the highest ISS score, TNFα was examined at 8 hours after the incident, 1, 3 and 5 days thereafter.

Interleukin-6 is a cytokine that is induced by the production of TNFα and based on the results of the study, it can predict the occurrence of complications of MODS in trauma patients. According to Frink et al., Patients with MODS had elevated IL-6 levels compared to trauma patients without MODS. The specificity of the IL-6 level examination was 98.7% while the sensitivity was 16.7%. According to his research> 50% of patients with IL-6 levels> 761.7 pg / mL have a> 50% probability of developing MODS. The limit of IL-6 levels that are at risk of increasing mortality is 2176 pg / mL. Interleukin-6 is said to be the best parameter to assess the likelihood of mortality in trauma patients compared to other parameters.

The sample in this study was not homogeneous, from the age of the respondents <21 years old as many as 4 people (10%), 21-30 years old as many as 15 people (37.5%), and 31-40 years as many as 16 people (40%) . With the results of the T test the p value in the age group is 0.217 because the p value (0.217)> 0.05 (α = 5%) then H0 is accepted, so it is concluded that there is no significant difference between the TNFα level and the age group. In this study, there was no significant difference between TNFα levels and the sex of the patient. The p value in the patient's gender group was 0.338, because the p value (0.338)> 0.05 (α = 5%) then H0 was accepted. With the results of the T test, the p value in the age group is 0.426 because the p value (0.426)> 0.05 (α = 5%) then H0 is accepted, so it can be concluded that there is no significant difference between IL-6 levels and the age group. In this study, there was no significant difference between IL-6 levels and the sex of the patient. The p value in the patient's gender group was 0.282, because the p value (0.282)> 0.05 (α = 5%) then

H0 was accepted. With the results of the T test the p value in the age group is 0.022 because the p value (0.022) <0.05 (α = 5%) then H0 is not accepted, so it is concluded that there is a significant difference between the APACHE II score and the age group. In this study, there was no significant difference between the APACHE II score and the gender of the patient. The p value in the patient's gender group was 0.343, because the p value (0.343)> 0.05 (α = 5%) then H0 was accepted.

The number of samples used in this study was 40 samples which should be based on the calculation using the sampling technique (Lameshows), the number of samples needed was 108. The shortage of this sample caused the results of the study to only apply to the 40 patients studied.The results of this study still cannot be used for similar casesgeneral. The calculation of the ISS score in the sample is still subjective, where there are differences in the assessment of the severity of a multi-trauma patient between different medical personnel.

V. Conclusion

1. There is an increase in IL-6 and TNF α levels in thoracoabdominal trauma patients with ISS ≥ 16
2. There was an increase in IL-6 and TNF α levels accompanied by an increase in APACHE II in thoracoabdominal trauma patients with ISS ≥ 16

Acknowledgements

We thank all staff at Saiful Anwar General Hospital and Department Surgery, Faculty of Medicine Brawijaya University for assisting in completing this research.

Disclosure

All author reports no conflicts of interest in this work.

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Dimas Prasetyo, et. al. "Relationship of Interleukin-6 and TNF α With the Occurance of Mods IN Trauma Thoracoabdominal Patients with ISS>16 IN DR. Saiful Anwar Hospital." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(11), 2020, pp. 12-17.