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THE RELATION BETWEEN ACUTE PHASE REACTANTS AND TRAUMA SEVERITY

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ABSTRACT
Trauma is a leading cause of death in adolescents. The ISS (Injury Severity Score) is an anatomical scoring system that provides an overall score for patients with multiple injuries. No biomarkers have been reported to have demonstrable clinical utility capable of indicating injury severity. This study was designed to compare the relationship of inflammatory reactants with trauma severity score (ISS) , Glascow Coma Score and search correlation. The ISS and GCS (Glascow Coma Scale) of trauma patients were calculated on admission to the ED, and acute phase reactant(CRP, Fibrinogen, Albumin, Ferritin) levels were evaluated. The main outcome measures were admission to hospital; need operation and ISS correlation with inflammatory markers. For statistical analysis, NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software(Utah, USA) programs were used. Study enrollment included 59 patients who met the inclusion criteria. Based on Pearson's correlation analysis, there were negative correlations between mean arterial pressure (MAP) and ISS as well as between fibrinogen levels and ISS. There was no correlation with other acute phase reactants like CRP, ferritin and albumin and ISS. There was a negative correlation between ISS and MAP. Low fibrinogen levels indicate more severe injury, and high ISS. Levels of other inflammatory markers don't correlate with severity of trauma.

INTRODUCTION

Trauma is an important health problem and a leading cause of death particularly in younger adults and adolescents; it may be seen as a neglected disease of modern society. Reported mortality rates for severely injured patients remain substantial, ranging from 7 to 45% [1, 2].

A trauma-scoring system converts the severity of injury into a number, so helping clinicians to speak a common language in quality-assurance and quality-control programmes. The ISS (Injury Severity Score) is an anatomical scoring system that provides an overall score for patients with multiple injuries [1,3].

Although multitrauma is associated with high rates of patient mortality and morbidity, no biomarkers have been reported to have demonstrable clinical utility capable of indicating injury severity nad outcome during early post-traumatic period. Trauma is a leading cause of non-infectious systemic inflammatory response syndromes, the immuno-inflammatory response is initiated in the immediate aftermath following trauma.The normal physiologic responses to trauma and haemorrhage

therefore are manifestations of complex cellular and molecular events. One of these complex events is synthesizing a group of acute phase reactants such as opsonins (CRP), protease inhibitors, haemostatic agents (fibrinogen), and transporters (transferin) by liver [4].

This study was designed to search the relation acute phase reactants during the initial posttraumatic phase in previously healthy adults and to compare the relationship of the early serum peaks of these reactants with ISS.

MATERİAL AND METHODS

Study Design and Setting

This was an observational cohort of consecutive adult emergency department(ED) trauma patients who were between 18 and 75 years old. The prospectively collected database included patients seen from December 2010 to April 2011. The ethics committee of our tertiary-care government teaching hospital approved the study protocol and a written permission was obtained from all participitants or from their relatives.

Selection of Participants

All multiple trauma patients without previosly known chronic disease who were admitted to the trauma unit of our ED within 24 h of trauma and those who were between 18 – 75 years of age were eligible for enrollment. The exclusion criteria were as follows: local trauma, age < 18 years or >75 years, pregnancy, patients with a preexisting or new diagnosis of liver disease, or other metabolic diseases known to independently influence acute phase reactants, admission time >24 hours.

Data Collection and Processing

Patients were managed in the ED according to trauma principles[5,6]. Multitrauma is defined as physical insults or injuries occuring simultaneously in several parts of the body. The ISS is an anatomical scoring system that provides an overall score for patients with multiple injuries [7]. Each injury is assigned an Abbreviated Injury Scale (AIS) score and is allocated to one of six body regions (head, face, chest, abdomen, extremities, and external) [5,7]. Only the highest AIS score in each body region is used. The scores for the three most severely injured body regions are squared and totaled to yield an ISS score [8]. The Glascow Coma Scale (GCS) are used as a measurement of individual physiological disturbance in trauma patients. GCS is determined by three factors (amount of eye opening, verbal disturbances, and motor responsiveness) [9]. Numeric values are given according to the patient response to an external stimulus. The sum of the numeric values for each parameter is used to predict the prognosis of trauma patients, with 3–10 indicative of bad prognosis and 11–15 compatible with good prognosis [5] .

The ISS and GCS were calculated for each patient on admission to the ED, and acute phase reactant (CRP, Fibrinogen, Albumin, Ferritin) levels were evaluated from venous blood samples. For multi-trauma patients, whole blood was collected by venipuncture using a Vacutainer™. Whole blood was immediately centrifuged, and plasma was collected and aliquoted. Plasma samples were stored at -80°C for future use.

The main outcome measures were admision to hospital or not; need operation or not for patient morbidity and ISS for injury severity.

Statistical Analysis

For statistical analysis, NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) programs were used. Other than descriptive analysis (mean, standart deviation, median, rate) also Kruskal Wallis test is used for the parameters those had no normal distribution. Mann Whitney U test is used for comparison of two groups, and detection of the group which caused the difference. For analysis of correlation between ISS and other parameters Spearman's correlation analysis. For the comparison of qualitative data Fisher –Freeman Halton test was used. $p<0.05$ accepted as statistically significant.

RESULTS

Study enrollment included 59 patients who met the entrance criteria for this study—43 males (72,9%) and16 females (27,1%). Patient age ranged from 19 years to 75 years, with a mean age of 42,93 ±15,50 years. All patients or their families agreed to participate in the study. There was a statistical significance with ages and mechanism of injury. Motorcycle accident patients were younger than the other groups ($p<0,05$). But there were no statistical correlation beween GCS, sex parameters between groups of trauma (Table 1).

The patients' mean arterial pressure (MAP), pulse rate(PR), CRP, ferritin, albumin, fibrinogen, GCS, ISS scores are shown in Table 2. None of these patients died in the ED, and 3 patients died within 10 days of hospitalization.

Total 54,2% (n=32) of the patients were sent home, 45,8% (n=27) were taken to the wards from emergency department. Hospitalization time was ranging from 1 to 21 days, mean of 6,11±4,81 days. Table 3 shows hospitalizations to the wards and exitus numbers. The comparison between survivors and non-survivors within 10 days after admission by univariate analysis ISS showed that nonsurvivors had higher ISS.

The correlation analysis between ISS and MAP, PR, CRP, ferritin, albumin, fibrinogen are shown in Table 4. Based on Pearson's correlation analysis, there were negative correlations between MAP and ISS($r=-0,277$; $p<0,05$) as well as between fibrinogen levels and ISS ($r=-0,283$; $p<0,05$). There was no correlation with other acute phase reactants like CRP, ferritin and albumin.

When the relation between ISS and hospitalization, exitus and need to an operation were evaluated, it was found that hospitalization and exitus parameters were significantly associated with ISS. But there was no relation between operation need and ISS (Table 5).

Table 1. Demographics of patients according to mechanism of trauma*

		Car crush(in-car) (n=11)	Car crush (pedestrians) (n=24)	Motorcycle accident (n=9)	Falls (n=13)	*p*
		Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Age *(median)*		47,27±17,38 (51,0)	45,46±15,39 (45,5)	27,44±8,88 (24,0)	44,70±13,66 (39,0)	^{a}*0,013***
GCS *(median)*		14,82±0,41 (15,0)	14,04±2,72 (15,0)	15,00±0,00 (15,00)	14,23±2,49 (15,0)	^{a}*0,515*
Hospitalization days *(median)*		5,67±3,06 (5,0)	7,36±6,33 (7,0)	4,00±3,46 (2,0)	5,50±4,18 (5,5)	^{a}*0,911*
		n (%)	n (%)	n (%)	n (%)	
Sex	Male	9 (81,8)	14 (58,3)	9 (100,0)	9 (69,2)	^{b}*0,095*
	Female	2 (18,2)	10 (41,7)	0 (0,0)	4 (30,8)	
Hospitalization	No	8 (72,7)	13 (54,2)	6 (66,7)	5 (38,5)	^{b} *0,366*
	Yes	3 (27,3)	11 (45,8)	3 (33,3)	8 (61,5)	
Exitus	No	3 (100,0)	9 (81,8)	3 (100,0)	7 (87,5)	^{b}*1,000*
	Yes	0 (0,0)	2 (18,2)	0 (0,0)	1 (12,5)	

^{a}*Kruskal-Wallis Test* ^{b}*Fisher-Freeman-Halton Test* ***p<0,05*

**There were 2 patients in crush injury those were not in consideration for statistical purposes.*

Table 2. Mean medical parameters of the patients (*MAP: mean arterial pressure, PR: pulse rate, CRP: C reactive protein, ISS: Injury Severity Score, GCS: Glascow Coma Scale, Min: Minimum, Max: Maximum, SD: Standart deviation)

	Min-Max	Mean±SD
MAP	80-143	106,50±13,77
PR (Minute/number)	50-120	80,05±14,25
CRP (mg/dL)	0,10-10,20	0,66±1,33
Ferritin	3,6-385,9	81,78±73,28
Albumin (g/dL)	3,2-5,0	4,06±0,35
Fibrinogen	93,6-396,0	260,06±50,31
ISS	1,0-75,0	17,32±16,65
GCS	5-15	14,41±2,09

Table 3. Hospitalization Times and Ward Types

		Hospitalization Time (days)Min-Max	Mean±SD
Ward	General Surgery	3	11,1
	Thoracic Surgery	3	11,1
	Ortopedics	11	40,8
	Neurosurgery	6	22,2
	Plastic Surgery	1	3,7
	Intensive Care	2	7,4
	Urology	1	3,7
Operation	None	12	44,4
	Yes	15	55,6
Exitus	No	24	88,9
	Yes	3	11,1

Table 4. The correlation analysis between ISS and MAP, PR, CRP, ferritin, albumin, fibrinogen

	ISS	
	r	*p*
MAP	-0,277	*0,034**
PR	0,240	*0,067*

CRP	0,106	***0,423***
Albumin	-0,227	***0,084***
Fibrinogen	-0,283	***0,030****
Ferritin	190	***150***

Spearman's correlation analysis *p<0,05

Table 5. ISS and hospitalization, exitus and need for operation parameters

		ISS		*p*
		Ort±SD	**Ort±SD**	
Hospitalization	**No**	5,47±3,31	3,0	[b] ***0,001****
	Yes	31,37±15,07	27,0	
Exitus	**No**	27,67±10,14	26,50	[b]***0,009****
	Yes	61,00±17,06	66,00	
Need to operation	**No**	29,33±9,68	28,50	***0,941***
	Yes	33,00±18,49	27,00	

[b]*Mann Whitney U test* **p<0,01

DİSCUSSİON

Early estimation of the mortality risk of severely injured patients is mandatory. Estimation of trauma severity currently relies on clinical diagnoses and scoring systems. There is no clinic or laboratory parameter that determines the severity of trauma in acute settings, yet [2, 10]. This prospective study was to detect laboratory or clinic markers that may reflect the extent of trauma in the very early phase after injury.

Inflammation resulting from any form of tissue injury causes an increase in plasma concentration of a number of liver-derived proteins (the acute phase reactant proteins), the measurement of which provides an indication of the magnitude of the inflammatory response. C reactive protein (CRP), ferritin, albumin are examples of an acute phase reactants. Although concentrations increase particularly dramatically in response to inflammation and reflect the degree of ongoing tissue damage, in our study we could not find any relation between ferritin, albumin and CRP levels and ISS. This can be because of early blood draw. Some studies show that increases in the plasma concentration of CRP were not detected until 6–12 h after injury and peaked at 48–72 h [11, 12].

Inflammation causes a decrease in albumin synthesis and an increase in albumin fractional rate, leading to hypoalbuminemia. There were a negative minimal correlation between albumin levels and ISS scores in our study. But this correlation was not statistically significant. In some studies there was a correlation between albumin and intensive care admissions in trauma patients [13, 14]. Statistical insignificance in our study may be due to low patient number.

In our study, fibrinogen levels were found to be affected in patients with trauma.TIC (trauma-induced coagulopathy) reflects disseminated intravascular coagulation (DIC) with a fibrinolytic (hemorrhagic) phenotype based on the observation that trauma DIC patients display prolonged prothrombin time (PT), have low fibrinogen and antithrombin (AT) levels early after injury and have high fibrin/fibrinogen degradation products (FDP) and D-dimer levels indicating massive thrombin generation and activation followed by extensive fibrin(ogen)olysis and consumption coagulopathy [15, 16]. In our results we confirmed that higher ISS was associated with lower fibrinogen levels, and TIC was present in our high ISS group. Our result was same with some newer studies [17, 18]. Low fibrinogen levels indicates more severe injury, and high ISS. Also early calculation of ISS could further increase the ability to predict fibrinogen in these patients.

Trauma scoring systems were developed initially to triage patients in the field and thus, needed to be straightforward and user-friendly. These systems relied heavily on physiologic data, including the level of consciousness. Now, in our study we also found that vital parameters especially mean arterial pressure (MAP) was so important in trauma patient and there was a negative correlation between ISS and MAP. So in the field if MAP is low, the physician would expect higher ISS and a hard patient.

Limitations

Because only 59 patients met inclusion criteria, lack of statistical significance in any of the groupings could result from the small size of the population. Also, the exact time of trauma could not be determined for each patient. The only injury time we could reliably obtain was based on the hospital time of admission. Thus, probable variations in the time between injury and admission to the hospital may have distorted our day-to-day data for metabolic parameters. The results presented here are subject to the limitations inherent to observational studies and, thereby, do not allow independent evaluation of cause-and-effect relationships.

CONCLUSİON

In an emergency setting, numerous studies have shown that laboratory parameters on admission provide

additional value in the clinical prediction of adverse outcome and may directly aid clinical decision-making. We try to find some laboratory parameters to provide important information in the prediction of in-hospital morbidity and mortality. In our research we could not find any correlation between CRP, albumin, ferritin as a marker for trauma severity, but we have seen that low fibrinogen values and low MAP has a correlation with more severe trauma.

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