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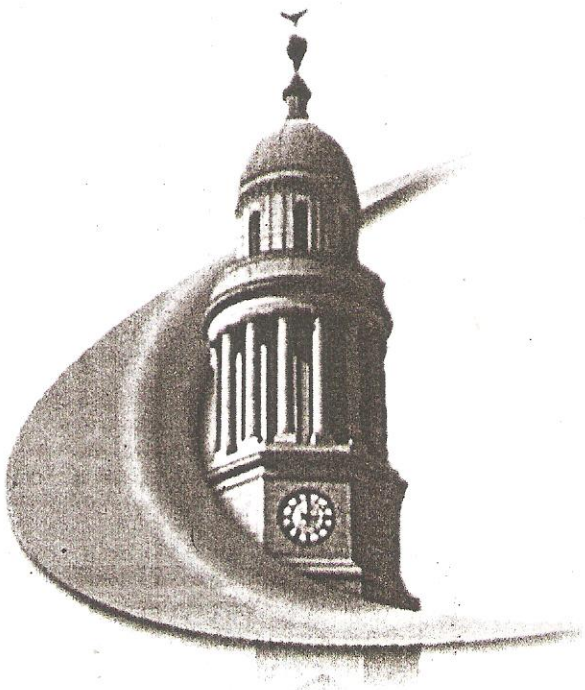

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MACROPHAGE MIGRATION INHIBITORY FACTOR AND INTERLEUKIN-8 COULD AID IN SURGICAL DECISION-MAKING IN PATIENTS WITH MULTIPLE BLUNT TRAUMA

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ABSTRACT

This study was designed to determine serum concentrations of macrophage migration inhibitory factor (MIF) and interleukin-8 (IL-8) in blunt trauma patients and to evaluate their association with surgical decision-making and patient outcome. The study included 45 trauma patients. All patients underwent clinical evaluation using Injury Severity Score (ISS) and gave blood samples, within the first 4 hours after trauma for estimation of serum levels of MIF and IL-8 using ELISA technique. Patients were followed up for either discharge from ICU or the development of adult respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), or multiple organ dysfunction syndrome (MOD). There were 29 patients with ISS<25, 14 with ISS=25-<50 and only 2 patients with ISS>50; 27 patients underwent surgical exploration (12 admitted to ICU and 15 were admitted to surgical wards); the other 18 patients were managed conservatively at either surgical ward or ICU according to their general condition. Thirty-three patients passed smooth follow-up free of morbidity and were discharged; whereas 7 patients developed ARDS, 3 developed SIRS and 2 had MOD. Patients who developed complications had significantly higher ($p<0.05$) ISS score compared to those passed free follow-up. Ten patients (22.2%) had died during follow-up, 4 patients died postoperatively at ICU, while the other 6 patients were managed conservatively at ICU with survival rate after conservative treatment of 66.7% and 85.2% after surgical treatment with a non-significant difference. Five patients had ARDS, 3 had SIRS and 2 had MOD, all had significantly higher ($p<0.05$) ISS score compared to survivors. Mean serum level of MIF was significantly increased ($p<0.05$) in complicated patients and in patients who developed SIRS or MOD compared to those who developed ARDS. Furthermore, mean serum level of MIF was significantly increased ($p<0.05$) in non-survivors compared to survivors. Similarly, mean serum level of IL-8 was significantly increased ($p<0.05$) in patients who developed complications and was significantly higher ($p<0.05$) in patients who developed ARDS and MOD in compared to those developed SIRS, however, serum levels of IL-8 were non-significantly higher ($p>0.05$) in non-survivors compared to survivors. There was a negative significant correlation between survival and ISS ($r=-0.611$, $P<0.001$), and serum levels of MIF, ($r=-0.509$, $P<0.001$) and IL-8 ($r=-0.302$, $P=0.041$). Using ROC curve analysis revealed that estimation of serum MIF at 4-hours after trauma, ($AUC=0.249$) showed the highest specificity and ISS score determination at admission was the best screening test with highest sensitivity. It could be concluded that elevated serum levels of MIF and IL-8 occur early after blunt trauma and could predict the outcome as regards mortality and morbidity and thus could aid surgical decision making regarding the timing of surgical interference.

INTRODUCTION

Severe trauma is the third cause of death, in general, and the first one in the most vital and young population. Blunt abdominal trauma takes 56% cases of multiple traumas of all etiologies. Among multiple injured patients, near to 50% have some system-complications and more than, more of 60% in the group of critically injured, [1].

Blunt abdominal trauma occurs generally together with multiple organ injuries, thus physical examination might yield misguiding information. Diagnostic peritoneal lavage is a sensitive diagnostic tool for intra-abdominal injuries resulting in hemoperitoneum. However, it is not of value in isolated organ injuries or

retroperitoneal injuries. Furthermore, it is an invasive technique and the positive results in intra-abdominal injuries that do not require surgery are its disadvantages, [2].

Ultrasonography has high diagnostic performance in the screening of patients with blunt abdominal trauma due to its being a non-invasive, easily accessible, and less costly tool, however, owing to its high negative predictive value, follow up is mandatory for patients whose results are negative for intraabdomial organ injury, [3]. Computed tomography has high levels of sensitivity in diagnosing intraabdominal injuries, however, it is not usually the first option, because it requires exposure to X-rays, administration of contrast material and has high costs, [4].

Severe injury compromises functions of the antigen-presenting immune cells, resulting in an increased vulnerability toward bacterial sepsis, [5]. Among innate immune cells, macrophages play an essential role in the sensing and elimination of invasive microorganisms. Binding of microbial products to pathogen-recognition receptors stimulates macrophages to release cytokines and other effector molecules that orchestrate the host innate and adaptive immune responses, [6].

Cytokines play the main role in the inflammatory reaction during the early phase response on trauma, [7]. Their secretion predicts system-complications as ARDS, SIRS or even MOD syndromes, [8]. Neutrophil infiltration of the lung is characteristic of early post-traumatic ARDS. Interleukin-8 is elevated in the lung within 2 hrs of major trauma in patients who later develop ARDS, and thus it plays a central role in the recruitment of neutrophils to the lung and their subsequent activation, [9].

Macrophage migration inhibitory factor is a pivotal mediator of innate immunity; first identified as a T-cell cytokine, MIF was rediscovered as a protein released by pituitary cells after exposure to endotoxin or bacteria and in response to stress, [10]. MIF induces powerful proinflammatory biological responses and has been shown to be an important effector molecule of septic shock. High levels of MIF have been detected in the circulation of patients with severe sepsis and septic shock, [11].

Biomarkers in patients with blunt trauma and/or sepsis are needed to tackle the challenges of determining prognosis and optimizing selection of high-risk patients for application of therapy, [12]. Thus, this study was designed to determine serum concentrations of macrophage migration inhibitory factor and interleukin-8 in blunt trauma patients in critical settings and to evaluate their association with surgical decision-making and patient outcome.

PATIENTS & METHODS

This prospective study was conducted at Departments of Surgery and Intensive Care Department at Benha and Tanta University Hospitals in conjunction with Medical Biochemistry Department at Faculty of Medicine, Benha University.

The study included 45 blunt trauma patients. All patients underwent clinical evaluation using the Abbreviated Injury Scale (AIS); an anatomical scoring system; injuries are ranked on a scale of 1 to 6, with 1 being minor, 5 severe, and 6 a non-survivable injury. Then, each injury was allocated to one of six body regions (Head, Face, Chest, Abdomen, Extremities & Pelvis, External) and only the highest AIS score in each body region is used. The 3 most severely injured body regions have their score squared and added together to produce the ISS score. The Injury Severity Score (ISS) provides an overall score for patients with multiple injuries taking values from 0 to 75. If an injury is assigned an AIS of 6 (unsurvivable injury), the ISS score is automatically assigned to 75. The ISS score is virtually the only anatomical scoring system in use and correlates linearly with mortality, morbidity, hospital stay and other measures of severity, [13]. Patients with ISS≥75 or single organ or body region trauma with ISS≥25 were excluded off the study.

At arrival to emergency department, within the first 4 hours after trauma, 5 ml blood sample was obtained, centrifuged and then sera were collected and kept frozen at -80°C till estimation of serum levels of macrophage migration inhibitory factor, [14] and interleukin-8, [15] using ELISA technique.

Patients requiring intensive care, emergency surgical intervention, or both were followed up for either discharge from the ICU or the development of additional morbidity; namely,

\RDS, SIRS, or MOD.

Data were analyzed using t-test and Chi-square (X^2) test. The frequency of occurrence of complications was reported and compared in survivors and non-survivors. Possible inter-relationships between ISS score, estimated levels of both MIF and IL-8 and survival rate were correlated using Pearson's correlation coefficient. Sensitivity & specificity of ISS score and estimated levels of both MIF and IL-8 as predictors for patients' outcome (survivors or non-survivors) were evaluated using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC). Statistical analysis was conducted using the SPSS (Version 10, 2002) for Windows statistical package. P value <0.05 was considered statistically significant.

RESULTS

The study comprised 45 trauma patients; 35 males and 10 females with mean age of 44.8±8.9; range 29-65 years. There were 29 patients with ISS<25, 14 with ISS=25-<50 and only 2 patients with ISS>50, (Table 1).

There were 19 patients presenting with clinical picture suggestive of internal hemorrhage, ultrasonographic examination defined 4 cases with retroperitoneal hematoma which were managed conservatively at the surgical wards and 15 patients with intraperitoneal hemorrhage that underwent exploratory laparotomy for rupture spleen in 4 patients who underwent splenectomy and 11 patients with liver tears that were sutured without excision. Seven patients; 2 had splenectomy and 5 had repaired liver tears were managed at ICU and the other 8 patients at the surgical ward.

Another 14 patients had signs of peritonism and no signs of hemorrhagic shock, 9 patients did not have air under diaphragm on erect X-ray examination and no collection could be identified by US, 2 patients had bad general condition and associated pathology and were conserved at ICU, while the other 7 were followed-up at the surgical ward. The other 5 patients had air under diaphragm and were explored; 3 had traumatic perforation of the left colon and underwent defunctioning colostomy and managed as ICU cases, while the other two patients had resection and re-anastomosis of lacerated jejunal loop and admitted to surgical ward for postoperative follow-up.

Five patients were comatosed because of head trauma and were admitted to ICU without surgical interference, 7 cases had flail chest injury associated with pneumothorax (3 patients), hemothorax (2 patients) and hemopneumothorax (2 patients), all underwent insertion of intercostals under-water seal drainage tube and 5 cases were admitted to surgical ward and 2 at ICU for follow-up, (Tables 2 & 3, Fig. 1).

Patients underwent surgical intervention and admitted to ICU had the highest ISS, (Table 3, Fig. 2).

Thirty-three (73.3%) patients passed smooth follow-up free of morbidity and were discharged; whereas the other 12 patients (26.7%) got additional morbidity throughout follow-up course, 7 patients (15.6%) developed ARDS, 3 patients (6.7%) developed SIRS and 2 patients had MOD. Patients who developed follow-up complications had significantly higher (P<0.05) ISS score compared to those passed free follow-up, with a non-significant (P>0.05) difference between ISS score of patients with various types of morbidity, (Fig. 3). Non-survivors developed additional morbidity during their ICU follow-up period, 2 patients had MOD, 3 had SIRS and 5 developed ARDS. Only 2 patients developed ARDS and survived. Non-survivors had significantly higher (P<0.05) ISS score compared to survivors, (Table 4, Fig. 4).

Four patients died postoperatively at ICU; 2 with flail chest, 2 underwent defunctioning colostomy, while the other 6 patients were managed conservatively at ICU, 3 patients had head injury, 2 had peritonism and one patient had retroperitoneal hematoma, (Table 5). Thus, the survival rate after conservative treatment was 66.7% and 85.2% after surgical treatment with a non-significant (X^2=0.012, P>0.05) difference between survival rates after either line of management.

The mean serum level of MIF was significantly increased (P<0.05) in patients who developed complications compared to those who passed free follow-up course (4.64±2.67 ng/ml). Moreover, mean serum MIF showed a significant increase (P<0.05) in patients developed SIRS (15.5±2.3 ng/ml) or MOD (16.8±3 ng/ml) compared to those who developed ARDS

(8.16±3.56 ng/ml), with a non-significant increase (P>0.05) in patients developed MOD compared to those developed SIRS, (Fig. 5). Furthermore, mean serum level of MIF was significantly increased (P<0.05) in non-survivors (5.23±3.56 ng/ml) compared to levels estimated in survivors, (10.74±5.23 ng/ml), (Table 6, Fig. 6).

Similarly, mean serum level of IL-8 was significantly increased (P<0.05) in patients developed complications compared to those who passed free follow-up course (27.45±9.3 ng/ml).

Moreover, mean serum level of IL-8 was significantly higher (P<0.05) in patients developed ARDS (73.5±10.3 ng/ml) and MOD (68±4.24 ng/ml) in comparison to those developed SIRS (41.66±9 ng/ml), with a non-significant increase (P>0.05) in those developed ARDS in comparison to those developed MOD, (Fig. 5). However, serum levels of IL-8 were non-significantly (P>0.05) higher in non-survivors (48.1±19.66 ng/ml) compared to survivors, (34.31±19.56 ng/ml), (Table 6, Fig. 6).

There was a positive significant correlation between ISS and serum levels of MIF, (r=0.623, P<0.001) and IL-8 (r=0.347, P=0.019) with a positive significant correlation between serum levels of MIF and IL-8, (r=0.397, P=0.007), (Fig. 7a-c). However, there was a negative significant correlation between survival and ISS (r=-0.611, P<0.001), and serum levels of MIF, (r=-0.509, P<0.001) and IL-8 (r=-0.302, P=0.041), (Table 6, Fig. 8a-c).

Using ROC curve analysis to evaluate each of the three factors as regards the sensitivity and specificity as a predictor of high mortality judged by the AUC revealed that estimation of serum MIF at 4-hours after trauma, (AUC=0.249) showed the highest specificity and ISS score determination at admission was the best screening test with highest sensitivity, (AUC=0.120), while estimation of serum IL-8 at 4-hours after trauma, (AUC=0.164) was less sensitive and specific predictor of survival, (Fig. 9 a-c).

Table (1): Patients characters

Age (years)		**44.8±8.9 (29-65)**
Sex; M:F		35:10
ISS.	<25	29 (64.4%)
	25-<50	14 (31.1%)
	≥50	2 (4.5%)

Table (2): Patients' distribution according to preoperative diagnosis and operative findings

Preoperative diagnosis	Operative findings & management	Number (%)
Retroperitoneal hematoma	Conservative treatment	4 (8.9%)
Intraperitoneal hemorrhage	Splenectomy	4 (8.9%)
	Repair of liver tear	11 (24.4%)
Peritonism, no air under diaphragm	Conservative treatment	9 (20%)
Peritonism with air under diaphragm	Defunctioning colostomy for left colon perforation	3 (6.7%)
	Resection & reanastomosis for jejunal laceration	2 (4.4%)
Flail chest with pneumo &/or hemothorax	Drainage by under-water seal intercostal tube	7 (15.6%)
Head injury	Conservative treatment	5 (11.1%)

Table (3): Admission data according to ISS and maneuver undertaken

Site of admission	Maneuver undertaken	Number (%)	ISS score
Conservative treatment at	Surgical ward	11 (24.4%)	4.3±2.4 (1-6)
	ICU	7 (15.6%)	20.8±8 (6-29)
Surgical interference and follow-up at	Surgical ward	15 (33.3%)	23.1±12 (5-57)
	ICU	12 (26.7%)	35±11 (9-50)

ISS is presented as mean±SD. ranges in parenthesis.

Table (4): Follow-up outcome data

		Number (%)	ISS score
Morbidity	Free	33 (73.3%)	18.1±13.3 (1-43)
	ARDS	7 (15.6%)	29±12.6 (22-57)†
	SIRS	3 (6.7%)	40±12.5 (26-50)†
	MOD	2 (4.4%)	31.5±13.4 (22-41)†
Mortality	Survivors	35 (77.8%)	17.2±11.4 (1-43)
	Non-survivors	10 (22.2%)	38.1±11.7 (9-50)*

ISS is presented as mean±SD, ranges in parenthesis
*†: significant versus ISS of patients passed free follow-up course. *: significant versus survivors*

Table (5): Follow-up outcome in relation to line of management performed

Preoperative findings	Survivors	Non-survivors
Retroperitoneal hematoma (Conservative treatment)	3 (6.7%)	1 (2.2%)
Splenectomy	4 (8.9%)	0
Repair of liver tear	11 (24.4%)	0
Peritonism (Conservative treatment)	7 (15.6%)	2 (4.4%)
Defunctioning colostomy for left colon perforation	1 (2.2%)	2 (4.4%)
Resection & reanastomosis for jejunal laceration	2 (4.4%)	0
Flail chest	5 (11.2%)	2 (4.4%)
Head injury (Conservative treatment)	2 (4.4%)	3 (6.8%)
Total	35 (77.8%)	10 (22.2%)

Table (5): Mean (±SD) of serum levels of MIF and IL-8 in studied patients

		MIF (ng/ml)	IL-8 (ng/ml)
Morbidity	Free (n=33)	4.64±2.67 (1.15-10.3)	27.45±9.3 (12-55)
	ARDS (n=7)	8.16±3.56 (3.5-12.4)†	73.5±10.3 (60-85)†
	SIRS (n=3)	15.5±2.3 (13.2-17.8)†‡	41.66±9 (33-51)†‡
	MOD (n=2)	16.8±3 (14.7-18.9)†‡	68±4.24 (65-71)†‡
Mortality	Survivors (n=35)	5.23±3.56 (1.15-15.5)	34.31±19.56 (12-85)
	Non-survivors (n=10)	10.74±5.23 (5.15-18.9)*	48.1±19.66 (21-80)

†: significant versus levels estimated in patients passed free follow-up course
‡: significant versus levels estimated in patients developed ARDS

*: significant versus levels estimated in survivors

Table (6): Correlation coefficient between ISS, serum levels of MIF and IL-8 and survival rate of studied patients

	ISS		MIF (ng/ml)		IL-8 (ng/ml)	
	r	P	r	P	r	P
ISS			0.623	<0.001	0.347	0.019
MIF (ng/ml)					0.397	0.007
Survival rate	-0.611	<0.001	-0.509	<0.001	-0.302	0.041

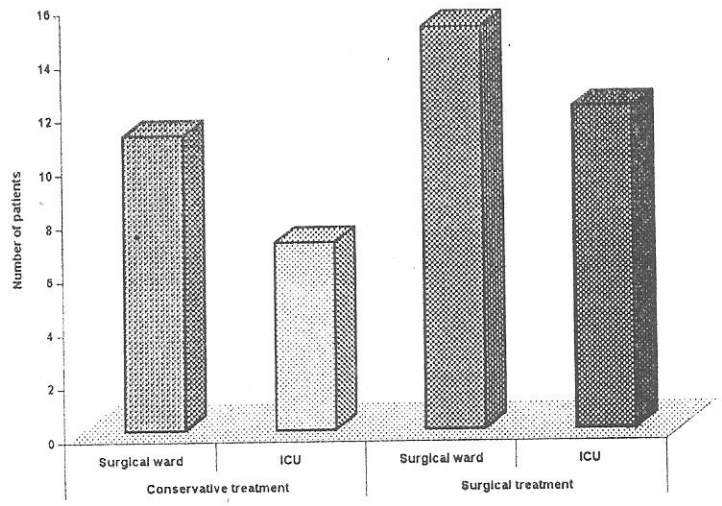

Fig. (1): Patients' distribution according to management and place of admission for follow-up

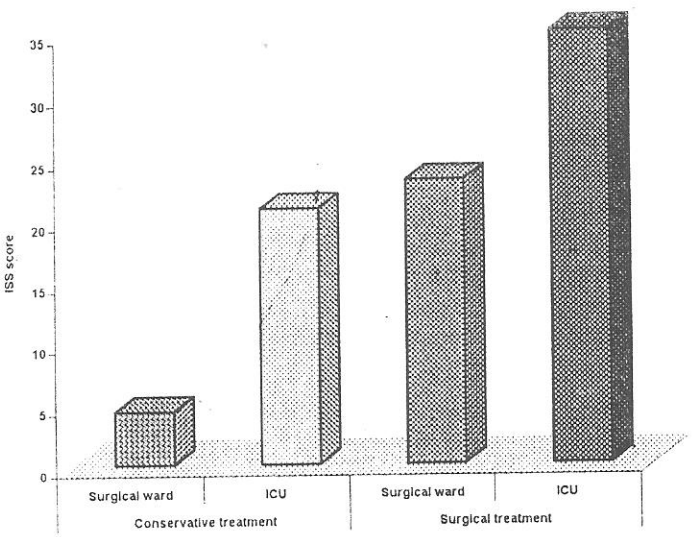

Fig. (2): Patients' distribution according to ISS score and place of admission for follow-up

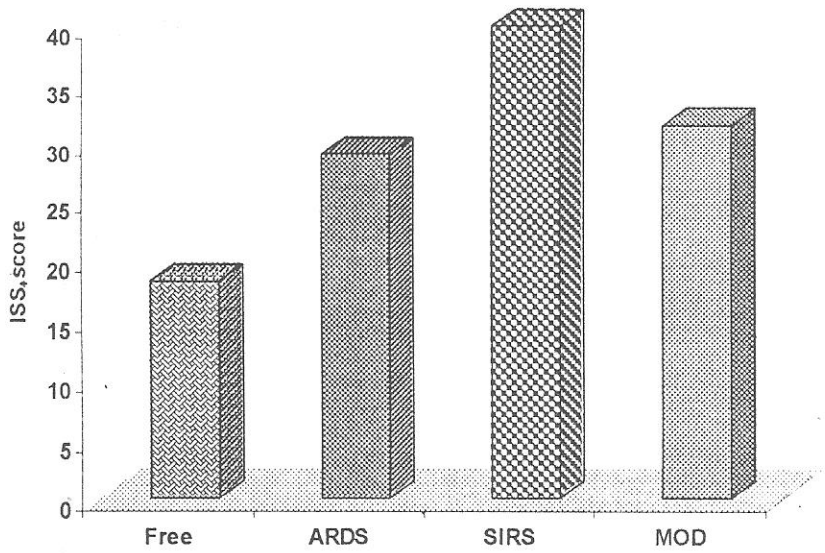

Fig. (3): Mean ISS score of patients according to outcome of follow-up

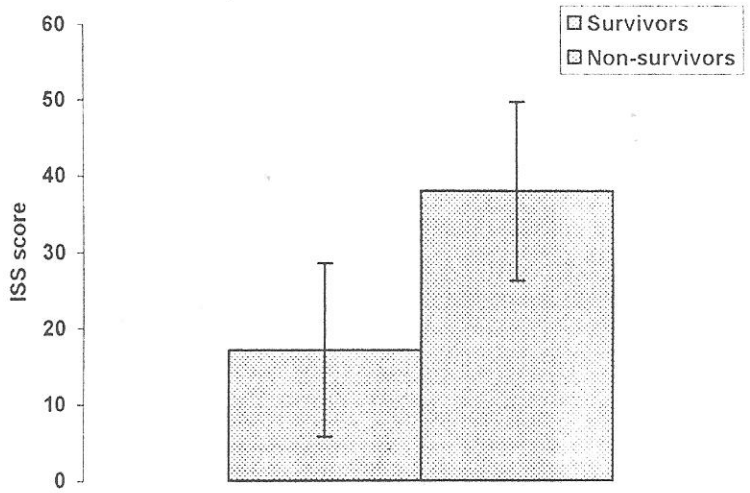

Fig. (4): Mean ISS score of patients according to survival rate

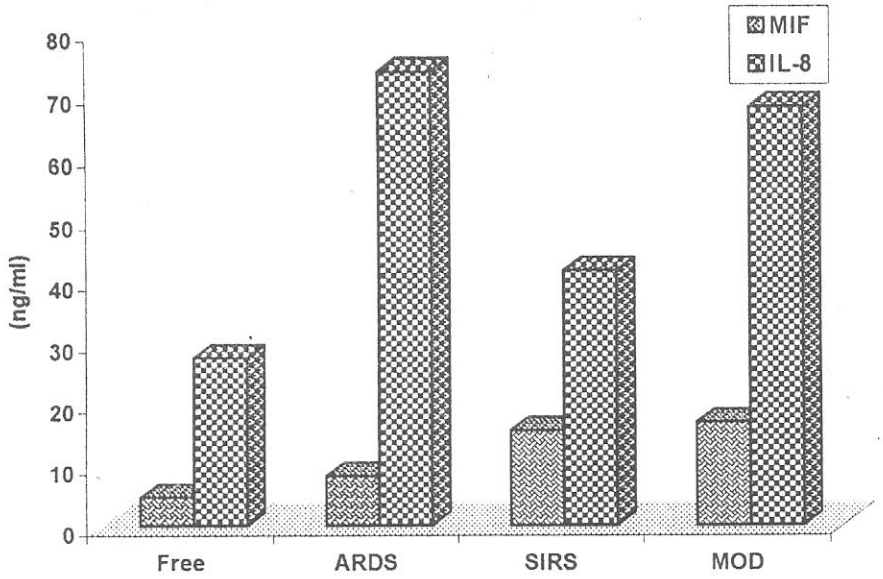

Fig. (5): Mean levels of MIF and IL-8 in studied patients according to follow-up outcome

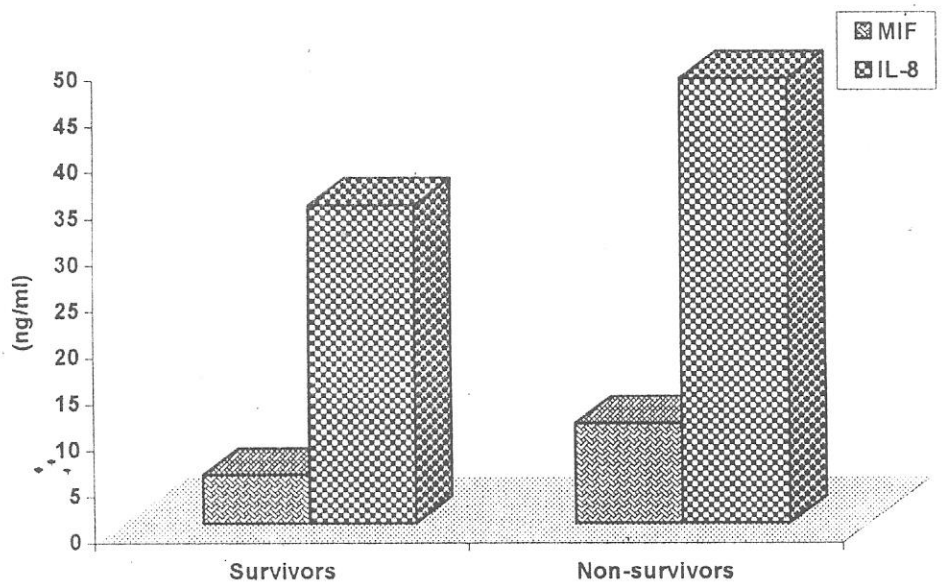

Fig. (6): Mean levels of MIF and IL-8 in survivors and non-survivors

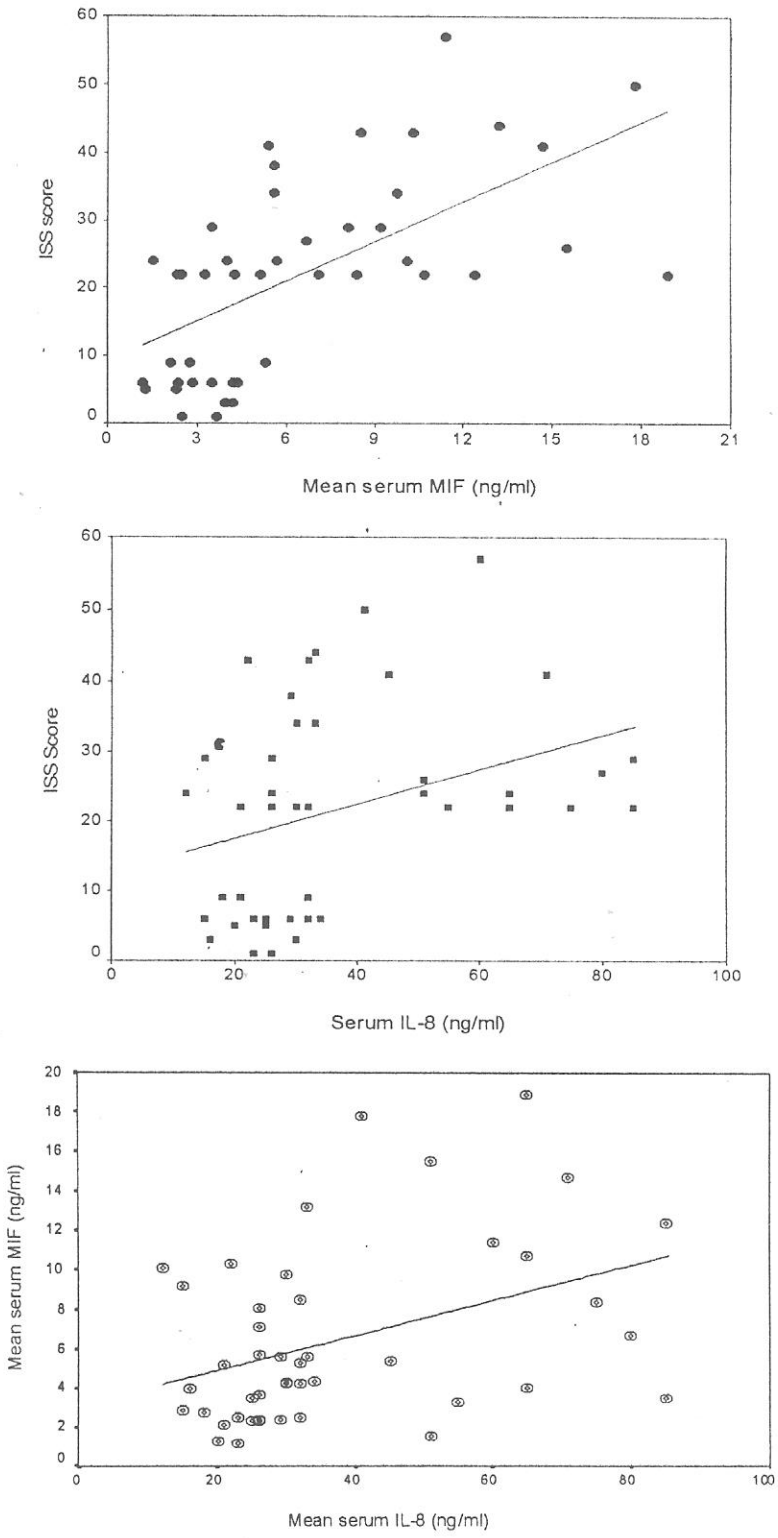

Fig. (7 a-c): Correlation between ISS, serum levels of MIF and IL-8 in the studied patients

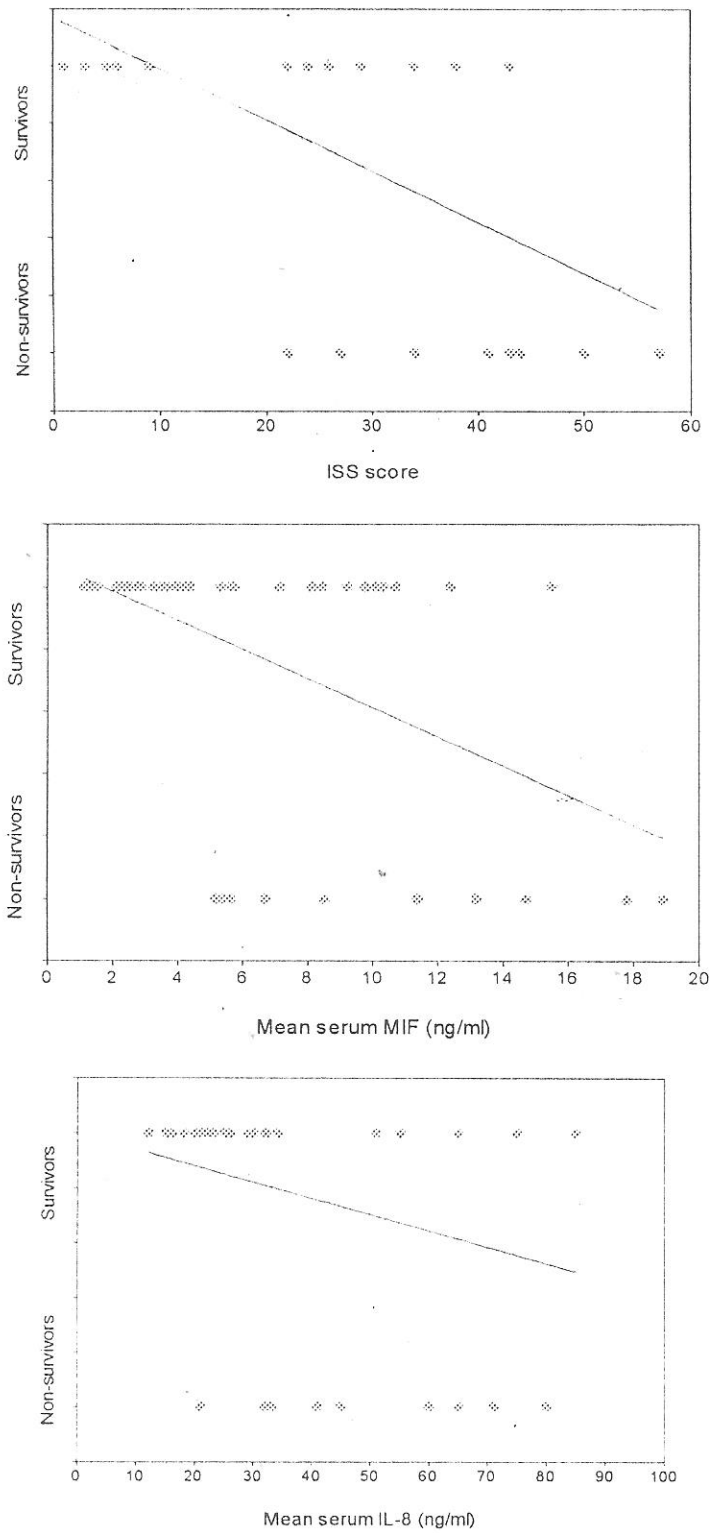

Fig. (8 a-c): Correlation between survival rate and ISS, serum levels of MIF and IL-8 in the studied patients

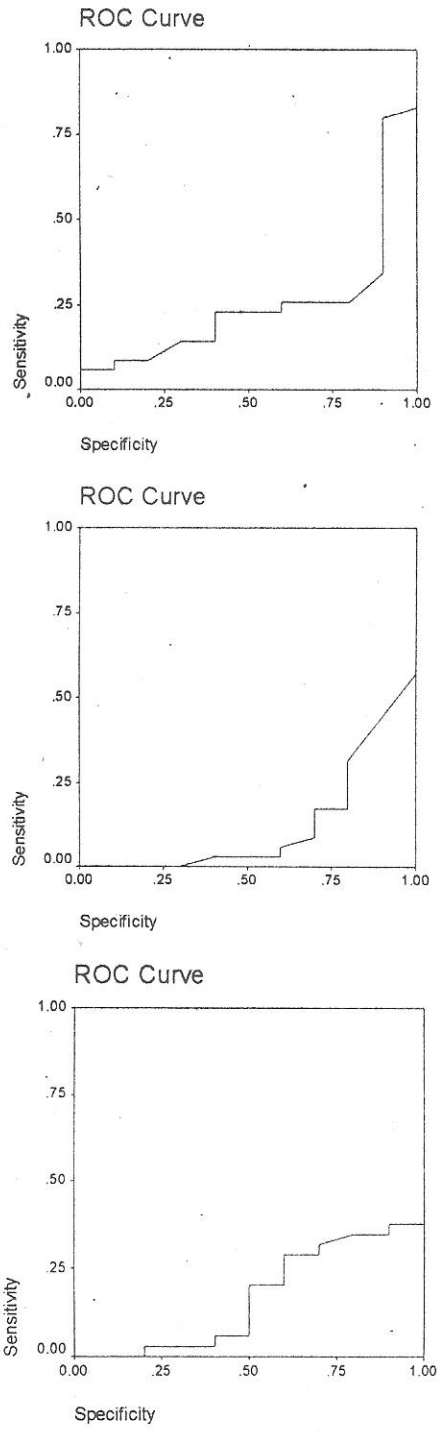

Fig. (9 a-c): ROC curves evaluating the sensitivity and specificity of ISS scoring and serum levels of MIF and IL-8 estimated at 4-hours after occurrence as predictors of ICU survival

DISCUSSION

The results of the current study showed that the survival rate after conservative treatment was 66.7% and 85.2% after surgical treatment with a non-significant (X^2=0.012, P>0.05) difference between survival rates after either line of management. This signified that trial of conservation is not a deleterious decision and could spare unnecessary surgical interferences, morbidity and costs even in patients with multiple trauma but with low ISS.

These findings go in hand with Karkiner et al., [16] who evaluated the efficacy of non-operative management of any grade of hepatic injuries due to blunt abdominal trauma and reported low complication and mortality rates with shorter hospital stays. Moreover, Omoshoro et al., [17], reported that non-operative treatment in centers with suitable facilities is safe and effective in patients presenting with liver gunshot injuries who are hemodynamically stable with no evidence of peritonism. Both studies documented that early diagnosis could aid the decision-making either to conserve or to proceed for surgical exploration and is of utmost importance as the delays result in increased rates of mortality and morbidity.

Mean serum level of MIF was significantly increased while serum levels of IL-8 were non-significantly increased in non-survivors compared to levels estimated in survivors. These results signified that serum levels of both MIF and IL-8 were increased within <4 hours after trauma. These results coincided with Strecker et al., [18], Minambres et al., [19] and Chuang et al., [20], who detected elevated serum levels of proinflammatory cytokines early after trauma.

The obtained results indicated that elevated serum levels of MIF could differentiate patients who are suspected to survive from those who may have fatal outcome. In support of this assumption, there was a positive significant correlation between serum MIF and injury severity scale determined clinically according to the anatomical site of the trauma affliction.

These results agreed with those previously documented in literature regarding the relation between early cytokine changes after trauma affliction and the outcome of trauma afflicted to special sites as documented by Strecker et al., [18], who reported that the amount of fracture and soft-tissue damage can be estimated early by analysis of serum IL-6, IL-8 and creatine kinase and is of great importance with regard to long-term outcome after trauma.

Also, Minambres et al., [19], reported that IL-6 is elevated in patients with acute brain injury, and a significant relationship exits between the severity of acute brain injury and the transcranial IL-6 gradient at admission and concluded that it can be considered to be a prognosis marker at admission but both studies could not consider these changes as markers for fatal outcome.

The obtained results agreed with Chuang et al., [20], who compared serum concentrations of MIF and tumor necrosis factor-œ, IL-10, IL-6 and IL-8 in survivors and non-survivors after severe blunt trauma. They reported that high serum MIF concentration reflects the severity of trauma and might be a valuable predictor for the outcome of severe blunt trauma.

The mean serum level of both MIF and IL-8 significantly increased in patients who developed complications compared to those who passed free follow-up course whether underwent surgery or not or admitted to ward or to ICU. In support of this finding there was a positive significant correlation between serum levels of MIF and IL-8 and between both and the ISS score of injury. These results go in hand with Pape et al., [21], who reported correlation between elevated serum levels of IL-6 and IL-8 and postoperative morbidity in patients with lower limb multiple trauma.

Patients who developed MOD had the highest levels of MIF and IL-8, while those who developed SIRS had high serum MIF levels and those who developed ARDS had high serum levels of IL-8. Thus, it could be suggested that immediately after trauma, patients with higher IL-8 are most liable to develop ARDS, and those with higher MIF are most liable to develop SIRS or MOD. These results agreed with Joshi et al., [22], who reported that average MIF concentration in plasma of trauma patients was 14 fold higher than that of healthy controls and higher MIF levels were associated with positive cultures (blood, urine, sputum, wound) for infection.

Also, our results agreed with Beishuizen et al., [23] and Gando et al., [24] who recorded that in multitrauma cases, patients with septic ARDS or SIRS, respectively, showed higher MIF levels

than those who did not develop these septic complications. Liener et al., [25], reported that trauma is a very strong stimulus to activate MIF and IL-8 production. Recently, Bozza et al., [11], found that elevated MIF level in patients with posttraumatic septic complications appears to be an early indicator of poor outcome.

It could be concluded that elevated serum levels of MIF and IL-8 occur early after blunt trauma and could predict the outcome as regards mortality and morbidity and thus could aid surgical decision making regarding the timing of surgical interference.

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