Combined at-admission estimation of plasma gelsolin and injury severity score could predict the outcome of multiple trauma patients

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Abstract: To estimate plasma gelsolin levels in multiple trauma patients and its predictability for their outcome in relation to clinical data. The study included 70 multiple trauma patients and 20 healthy adult controls for blood donation as control group for the plasma level of gelsolin. All patients underwent history taking, time elapsed since trauma inflection and amount of external bleeding if present. Clinical evaluation included both Acute Physiology and Chronic Health Evaluation II (APACHE II) and Injury Severity Scores (ISS). Patients were evaluated daily throughout their ICU or hospital stay for the development of secondary morbidities and/or mortality. Venous blood samples were obtained at 12 hours after ICU admission for ELISA estimation of plasma gelsolin level. During hospital stay, 20 patients (28.6%) developed secondary morbidities and 8 patients (11.4%) died. Mean plasma gelsolin levels were significantly lower in patients compared to control levels with significantly lower levels in non-survivors compared to controls and survivors. Development of secondary morbidities showed a positive significant correlation with at admission ISS score and a negative significant correlation with plasma gelsolin. Survival rate showed positive significant correlation with plasma gelsolin level and negative significant correlation with both time since trauma inflection and ISS score. ROC curve analysis, defined prolonged time since trauma inflection as the significant sensitive predictor for both morbidity and mortality, while plasma gelsolin level was significant specific predictor for development of secondary morbidity and combined with ISS score were significant specific predictors for mortality. Conclusion: At admission plasma gelsolin level is a specific independent marker for prediction of the development of secondary morbidities that may progress to endanger patients' life and time since trauma inflection was found to be significant sensitive parameter for the patients' survival irrespective of development of these morbidities.
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1. Introduction

Most patients with severe traumatic injury have a prolonged stay in the intensive care unit, the outcome being a long-term disability or death, with a minority of patients achieving a functionally independent outcome and despite the therapeutic advances; certain patients remain at high risk of infection and the attendant morbidity and mortality. Several clinical studies, (Somasundar et al., 2004 and Jeremitsky et al., 2005) tried to identify certain prognostic factors that may influence outcome; however within certain limitations. Moreover, the development of adverse secondary events including development of adult respiratory distress, systemic inflammatory response syndrome, or multiple organ dysfunction syndromes may mislead the clinician during scoring and disturb the primary score and its predictability (Calfee et al., 2007).

This diagnostic dilemma pointed to the need for an early predictor for these secondary events prior to its commencement; Aslar et al., (2006) found APACHE II score and the arterial lactate level are the most important determinants of clinical outcome in critically injured patients and a correlation exits between lactate and APACHE II and between lactate and base deficit. Cunningham et al., (2006) found the admission lipopoly-saccharide-binding protein (LBP) concentration was significantly greater in non-survivors than in survivors, but after controlling for age and ISS, the admission LBP concentration did not predict death. Meisner et al., (2006) found that in patients with multiple trauma, procalcitonin level provides more information than the C-reactive protein level since only moderate amounts of procalcitonin is induced, and higher concentrations correlate with more severe trauma and a higher frequency of

various complications, including sepsis and infection.

Gelsolin is a protein found in both the cytosol and the plasma that has been reported to function primarily as a part of the actin-scavenging system with Gc globulin (vitamin D-binding protein) (Sun et al., 1999). Cellular disruption or necrosis releases cellular actin, both globular and filamentous fractions, into the circulation which results in capillary plug formation with subsequent tissue ischemia. The plasma actin scavenging system functions to cleave the filaments, cap the ends, preventing repolymerization and assist in the plasma clearance of filamentous actin. Additionally, gelsolin is known for its ability to bind lipids such as lipopolysaccharide, lysophosphatidic acid and phosphotidylinositol (Goetzl et al., 2000 and Karliner et al., 2001) and may modulate the inflammatory system. Experimentally, animals subjected to 40% total body-surface area burns demonstrated attenuated acute lung injury with the infusion of recombinant gelsolin to normal plasma levels (Rothenbach et al., 2004). Therefore, the present study aimed to estimate plasma gelsolin levels in multiple trauma patients and its predictability for their outcome in relation to clinical data.

2. Patients and Methods

The present study was conducted since Jan 2006 till June 2009 at Departments of Anesthesia & ICU and Clinical Pathology, Benha University Hospital in conjunction with Medical Biochemistry Department, Faculty of Medicine, Benha University. After approval of the study protocol by the Local Ethical Committee, the study was designed to include 70 trauma patients, irrespective of the anatomical site of trauma, required management and admission to surgical ICU. All patients arrived to the emergency unit dying or gasping was excluded of the study. The study was also designed to enroll 20 healthy adult controls for blood donation as control group for the plasma level of gelsolin.

All patients underwent full history taking with special regard time elapsed since trauma infliction, loss of consciousness and time elapsed till its regaining, amount of external bleeding if present. Clinical evaluation included both Acute Physiology and Chronic Health Evaluation II (APACHE II), (Rowan et al., 1993) and Injury Severity Scores (ISS), (Copes et al., 1988) determination.

All patients received first aid management at emergency unit, and when indicated surgical interference was carried upon, patients were admitted to ICU either immediately for conservative treatment or for postoperative follow-up for either discharge from the ICU or the development of additional morbidity or mortality.

Patients were evaluated daily for the development of septic morbidities including systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis or septic shock. The frequency of development and outcome of these complications was recorded either at ICU or at ward after discharge from ICU.

Venous blood samples were obtained at 12 hours after hospital admission and were collected in EDTA containing tube to prevent clotting and plasma was separated by centrifugation and then separated and stored at -80°C till ELISA (Uscn Life Science Inc. Wuhan, USA) estimation of plasma gelsolin level, (Smith et al., 1987).

Obtained data were presented as mean±SD, ranges, numbers and ratios. Results were analyzed using Chi-square test and Wilcoxon Signed Ranks Test. Sensitivity & specificity of evaluated parameters as predictors for patients' outcome were evaluated using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC) and Logestic Regression analysis (Stepwise Method). Statistical analysis was conducted using the SPSS (Version 10, 2002) for Windows statistical package. P value <0.05 was considered statistically significant.

3. Results

The study included 70 patients who had successful resuscitation so as to be fully examined and managed and all were immediately admitted to the surgical ICU. During hospital stay, 11 patients (15.7%) developed adult respiratory distress syndrome (ARDS), 5 patients (7.1%) had sepsis and 4 patients (5.7%) had multiple organ failure (MOF) with a total secondary morbidity rate of 28.6%. At end of one month follow-up, 62 patients (88.6%) were survivors and 8 patients died with a total mortality rate of 11.4%. Three of non-survivors developed septic shock that could not respond to conservative treatment; 4 patients with MOF could not withstand and one patient with ARDS developed acute respiratory failure and died 3-days later. Detailed baseline characteristics and clinical data of the study

population, stratified as survivors or non-survivors, are presented in Table 1 and showed non-significant difference between survivors and non-survivors concerning these data apart from a significantly higher ISS, (Z=2.524, p=0.012) and APACHE II (Z=2.035, p=0.042) scores in non-survivor compared to survivors.

Table (1): Patients' characteristics and clinical data determined at admission

		Survivors	Non-survivors
Number		62 (88.6%)	8 (11.4%)
Age (years)		33.7±9	38±13.4
Gender; M:F		50:12	5:3
Time since trauma (min)		52.5±21.3 (20-100)	77.5±19.3 (45-100)
Scene external bleeding		18 (29%)	5 (62.5%)
Loss of Conscious-ness	Number	10 (16.2%)	3 (27.5%)
	Duration	6±3.5 (4-10)	4.7±2.5 (1-9)
ISS score data		20.3±9.2 (11-59)	45±13.9 (29-66)*
APACHE II score		11.3±4.5 (7-15)	13.9±1.7 (8-19)*

Data are presented as mean±SD, ratios & numbers; ranges & percentages are in parenthesis
ISS score: injury severity score
*: significant versus survivors

Figure 1 shows that mean plasma gelsolin levels were significantly lower (Z=3.576, p<0.001) in patients (127.7±34; range: 45.6-192.4 ng/ml) compared to control levels, (196.4±27.6; range: 134.5-246.5 ng/ml) and were significantly lower in patients categorized according to survival compared to control levels with significantly lower (Z=2.521, p=0.012) levels in non-survivors (84.4±32.2; range: 45.6-145.2 ng/ml) compared to survivors (133.3±30.2; range: 59-192.4 ng/ml).
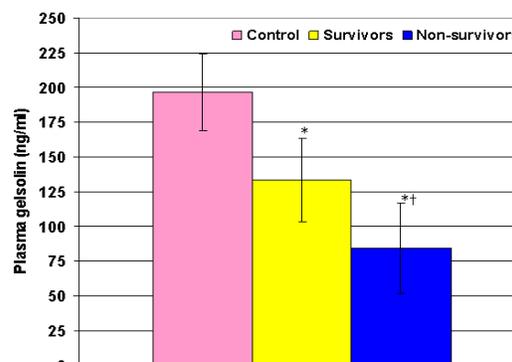

Figure 1: Mean (±SD) plasma gelsolin levels estimated in patients categorized according to the survival compared to control levels

*: significant versus control   †: significant versus survivors

Patients developed secondary morbidities showed a significantly higher (Z=2.576, p=0.01) ISS score with a significantly (Z=3.246, p=0.001) lower plasma gelsolin levels and were presented after significantly (Z=2.577, p=0.01) longer time since trauma inflection compared to those passed smoothly without development of secondary morbidities. Patients' age and body mass index showed non-significant difference between both patients' groups, (Table 2).

Table (2): Levels of evaluated parameters in studied patients categorized according to the development of secondary morbidities

	Secondary Morbidities	
	No (n=50)	Present (n=20)
Age	33.3±8.8	36.5±11.2
BMI	28.9±3.9	29.7±3.6
ISS score	19.1±7.3	33.2±16.8*
ᵃTime	50.9±20.4	66.5±23.8*
P. Gelsolin	136.4±29.2	106.2±36.3*

Data are presented as mean±SD
Time since trauma affliction (minutes)
P. Gelsolin: plasma gelsolin levels
*: significant versus no secondary morbidities

Regression analysis defined at admission decreased plasma gelsolin as a significant (p<0.001) predictor for the development of secondary morbidities, while long time since trauma inflection and at admission high ISS score were the significant predictors for mortality, (p<0.001 & =0.011, respectively). Using ROC curve analysis, as shown in figures 2 and 3, defined prolonged time since trauma inflection as the significant sensitive predictor for both morbidity, (AUC=0.338, p=0.035) and mortality,

(AUC=0.075, p<0.001), while at admission plasma gelsolin levels were the most significant specific predictor for development of secondary morbidity, (AUC=0.506, p<0.001). On the other hand, at admission, ISS score and plasma gelsolin were the significant specific predictors for mortality, (AUC=0.787 & 0.871, p=0.009 & 0.001, respectively).
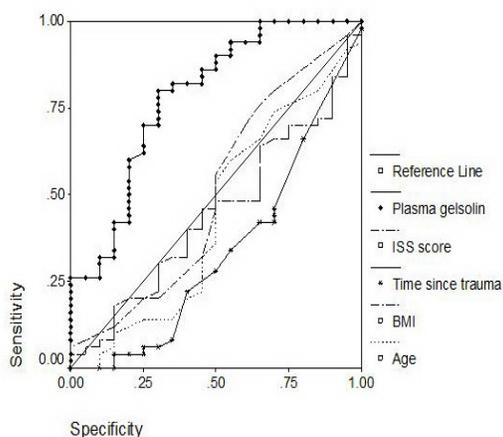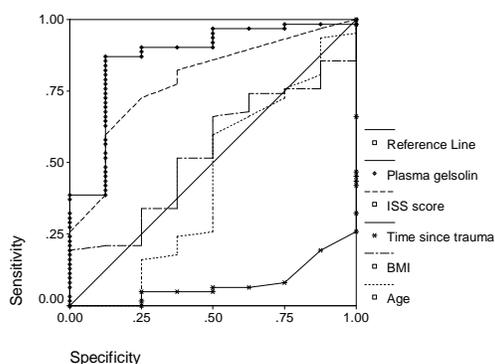

Figure (2): Specificity of evaluated parameters for prediction of secondary morbidities development

4. Discussion

Prediction of outcome, either as regards morbidity or mortality, of multiple trauma patients still a diagnostic dilemma. Twenty of the studied 70 multiple trauma patients developed secondary morbidities with a frequency of 28.6% and 8 patients could not withstand and died with a mortality rate of 11.4%. There was a non-significant difference between survivors and non-survivors as regard the constitutional parameters, and the number had external bleeding. However, non-survivors had

significantly higher APACHE II and ISS scores with significantly longer time since trauma inflection.

These data illustrate a fact that trauma itself and its sequalae, and body systems and regions affected impose a high effect on the outcome, in support of this assumption there was a positive significant correlation between the determined ISS score and the survival of trauma patients and the frequency of development of secondary morbidities, however, the correlation was stronger with survival and this was assured using ROC curve analysis that defined ISS score as one of specific predictors of survival not for development of secondary morbidities.

Prolonged time since inflection of trauma till patient arrival to the hospital was found to be a highly sensitive predictor for both mortality and development of secondary morbidities; such parameter indicated bad transport systems for trauma patients, lack of road ambulance first aid facilities and experiences of health care providers, and lack of general knowledge about first aid till arrival of ambulance among population.

Considering survival is a first target for multiple trauma patients, post-traumatic mortalities could not be a secondary to trauma itself but to development of secondary mortalities. Eight patients died among this series all of them had secondary mortalities; 4 had MOF, 3 developed septic complications progressed to septic shock and one had ARDS progressed to acute respiratory failure and patient died. These findings point to the necessity for early prediction of such morbidities; plasma gelsolin, the plasma parameter evaluated through the present study, was found significantly depleted in non-survivors compared to both controls and survivors and in survivors compared to control. These findings illustrate the impact of trauma itself on plasma gelsolin level, irrespective of the outcome and its depletion is a bad finding that predicts the development of secondary morbidities and the possibility of its progression to endanger patients' survival. In support of this assumption, there was a negative significant correlation between plasma gelsolin levels and both morbidities and mortality and regression analysis defined it as a significantly specific predictor for morbidities; a result that assured using ROC curve analysis.

These findings supported that previously documented in literature, Dahl et al., (1999) found gelsolin level on admission was

reduced significantly in the trauma patients compared with normal controls, but they found no correlation between admission levels of gelsolin and ISS or survival. Thereafter, Lee et al., (2006) found low plasma gelsolin levels were associated with increased risk of death occurring in the ICU and could predicted longer ICU stay, prolonged ventilator dependence, and increased overall in-hospital mortality. Also, Wang et al., (2008) found the admission gelsolin levels were significantly decreased in severe sepsis compared with non-septic critically ill patients and healthy control individuals and survivors of severe sepsis exhibited substantial recovery of their depressed plasma gelsolin levels, whereas gelsolin levels in non-survivors remained at or below their depleted admission levels and concluded that plasma gelsolin may be a valuable marker for severe sepsis and recovery of depleted plasma gelsolin levels correlated with clinical improvement.

Gelsolin is one of actin-scavenging proteins that counteract the pathophysiological consequences of actin leaked into the circulation from dying cells, but the capacity of this defense system can be overwhelmed by massive tissue injury. Various studies tried to explore the pathogenesis of gelsolin depletion after trauma Löfberg et al., (1998) measured the serum gelsolin levels in five patients after rhabdomyolysis and observed a tendency of serum gelsolin to increase during the study period of 11 days with no intracellular gelsolin found in the serum, although it is abundant in muscle, and the destruction was severe as judged by other parameters and concluded that serum gelsolin thus behaves differently in rhabdomyolysis than after acute tissue damage in other organs, such as liver necrosis and adult respiratory distress syndrome.

Mounzer et al., (1999) failed to attribute gelsolin depletion to generalized protein loss due to trauma as they reported no correlation between post-traumatic hemoglobin values and plasma gelsolin concentrations but found plasma levels of albumin correlated with plasma gelsolin, however, the extent of plasma gelsolin depletion was much greater than that of albumin and concluded that plasma gelsolin depletion was specific and not a result of generalized plasma protein loss. On contrary, Lee et al., (2006) found plasma albumin depletion of no prognostic value but documented the predictability of depleted gelsolin for development of secondary morbidities, despite the absence of correlation with the development

of ARDS, a contradictory finding to both Mounzer et al., (1999) and the current study.

These data point to a fact that depletion of plasma gelsolin is independent of extent of body protein loss, hemoglobin loss, or sole muscle injury but is dependent on injury severity of other organs and tissues especially in patients liable to secondary morbidities. It could be concluded that at admission estimation of plasma gelsolin is a specific independent marker for prediction of the development of secondary morbidities that may progress to endanger patients' life and time since trauma inflection was found to be significant sensitive parameter for the patients' survival irrespective of development of these morbidities. However, wider scale studies were advocated to correlate the predictability of estimation of plasma gelsolin versus inflammatory markers.

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