Research Article

New era "soluble triggering receptor expressed on myeloid cells-I" as a marker for early detection of infection in trauma patients

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Abstract *Background:* Previous studies suggested that triggering receptor expressed on myeloid cells-1 is upregulated in the presence of infection.

Objectives: Assess the value of soluble triggering receptor expressed on myeloid cells-I (sTREM-I) in early differentiation of systemic inflammatory response syndrome (SIRS) from infection in trauma patients.

Design: Prospective study in Zagazig University Hospitals between January and September 2010. In Emergency Surgical Departments, Intensive Care of Anesthesia and Microbiology Department.

Participants: Eighty trauma patients divided into 10 patients without evidence of SIRS (control group), then 70 patients with two or more signs of SIRS were classified into low injury severity score group and high injury severity score group.

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Measurements: Plasma concentration of sTREM-I in the three groups was compared. Sensitivity, specificity and predictive values of sTREM-I were compared with the results of procalcitonin. Also, microbiological cultures for infection were examined.

Results: There was a highly significant increase in the level of sTREM-I in patients with sepsis (475.7 ± 97.9 for HISS group and 398.5 ± 103.9 for LISS group) than in the control group (102.7 ± 42.6). Also, there was a highly significant increase in its level in patients with sepsis (475.7 ± 97.9 for HISS group and 398.5 ± 103.9 for LISS group) in comparison to those with SIRS (189.3 ± 26.5 for HISS group and 177.2 ± 40 for LISS group). There was a highly significant increase in procalcitonin in septic patients in comparison to SIRS group (3.9 ± 0.86 for LISS and 7.1 ± 1.4 for HISS). The sensitivity and specificity of sTREM-I were significantly higher than those of procalcitonin (94.7% and 91.8% for sTREM-I and 84.2% and 75.4% for procalcitonin).

Conclusion: The soluble TREM-I was a sensitive and specific marker for early differentiation of infection from SIRS in trauma patients.

1. Introduction

Trauma is one of the main causes of death among people worldwide. Mortality occurs early after trauma (first hits) caused by head injury, severe organ injury or bleeding, followed by a period in which the cause of death may be due to hypoxia, hypovolemia or severe head trauma [1]. Second hits occur in the latter times after trauma causing high incidence of morbidity and mortality caused by infections, ischemia\reperfusion or operations [2].

Massive injury leads to activation of immune system and inflammatory immune response (systemic inflammatory response syndrome, SIRS) with stimulation of many cells in the body including monocytes, macrophages and T-helper-1 lymphocytes [2].

This immune system stimulation leads to systemic release of both pro-inflammatory (TNF, IL_1, IL_6, IL_8 and IL_{12}) and anti-inflammatory cytokines (IL_{10}) or mediators [3].

The function of immune system is to recognize, activate, discriminate, regulate and eradicate the introducing exogenous and pathogenic signals [2]. In injured patients, the neuroendocrine response with production of adrenocorticosteroids and catecholamines leads to an increase in the heart rate, respiratory rate, fever, and leukocytosis [4].

Sepsis is a major cause of morbidity and mortality in trauma patients. There are many risk factors for sepsis in traumatized patients including:

(a) Type of injury (penetrating or non-penetrating).
(b) The host response (age, sex, immune response, diabetes mellitus and trauma severity).
(c) The clinical response to instrumentation, blood transfusion, fluids and splenectomy [4].

Clinical and laboratory signs of systemic inflammation are neither sensitive nor specific for the diagnosis of sepsis especially when microbiological cultures are still negative in cases of antibiotic pretreatment or inadequate sampling [5].

Regular use of broad spectrum antibiotics in patients without infection is harmful, facilitating colonization, superinfection, multidrug-resistant bacteria, toxicity and increases the cost [6].

There is a suggestion that early identification and treatment of severe sepsis and septic shock improve outcomes [7].

So, there is a need for clinical or laboratory tests to differentiate between sepsis and non-infectious inflammatory disorders. Elevated levels of inflammatory mediators and acute phase reactants are found in sepsis, but none are specific for infection and increased in other inflammatory conditions without infection [5].

There are delays of 24–48 h till definitive quantitative microbial culture results are reached. So, there are many studies on biologic markers in an effort to improve early differentiation of systemic inflammatory response syndrome from infection in trauma patients [8].

The biological marker of sepsis would fulfill some criteria: It must be specific, sensitive and able to be measured early and easily [5].

Procalcitonin is considered a specific marker for severe bacterial infection and differentiate patients who have sepsis from those having SIRS [9].

Procalcitonin is a propeptide of calcitonin produced in the thyroid, normally present in blood at a concentration of < 1 ng/ml and expressed as part of the host's inflammatory response to a variety of insults e.g. trauma, pancreatitis, infection, burn and surgery [10]. It has been shown to be superior to IL_6 and C-reactive protein (CRP) in diagnosis [11].

Also, it is more useful in the follow-up of the cases of sepsis and as a prognostic marker but, there are some limitations for its use e.g. peak plasma concentrations of PCT are reached within 12–24 h of the stimulus [12], PCT half-life in circulation is 24–30 h even in renal failure [13]. So, serial tests can indicate changes in the inflammatory status of the patient, also the test may not be available.

Triggering receptor expressed on myeloid cells (TREM)-1, a recently discovered receptor of immunoglobulin superfamily, activates neutrophils and monocytes/macrophages [14].

Its expression is upregulated on phagocytic cells in the presence of bacteria or fungi. So, its presence in the plasma mediates the acute inflammatory response to microbial products [15].

Conversely, sTREM-1 is not upregulated in samples from patients with non-infectious inflammatory conditions like psoriasis, immune complex-mediated vasculitis and ulcerative colitis. So, this receptor is present only in the cases of infection [16].

The technique used for detection of sTREM-I can be performed within 3–4 h and produce information before blood

culture results. Also, it is inexpensive and applied to small or individual samples [15].

This recent marker has not been evaluated in trauma patients before. So, the purpose of this work was to evaluate whether sTREM-I concentration can differentiate between traumatized patients with SIRS from those with infection.

2. Patients and methods

This study was carried out in the Emergency Surgical Departments, Intensive Care Unit of Anesthesia with the aid of the Microbiology and Immunology Department, Faculty of Medicine, Zagazig University Hospitals between January and September 2010.

The study was conducted on 80 trauma patients, 27 females and 53 males, their ages ranged from 16 to 50 years.

Patients were enrolled in the study if they had two or more of the following signs of systemic inflammatory response syndrome: temperature $> 38\,°C$ or $< 36\,°C$, pulse rate > 90 beats/min, respiratory rate > 20 breaths/min or hyperventilation with partial pressure of arterial carbon dioxide ($PaCO_2$) < 32 mmHg or white blood cell count $> 12.0 \times 10^3 \, cm^{-1}$ or $< 4.0 \times 10^3 \, cm^{-1}$ or $> 10\%$ immature cells [17].

Trauma patients were excluded if their ages were out of the study range, immunocompromized, leukopenic (white blood cells $< 1.0 \times 10^3 \, cm^{-1}$) or neutropenic (polymorphonuclear granulocyte count $< 0.5 \times 10^3 \, cm^{-1}$), burn and diabetic patients. Also, patients discharged early before completion of the study period (14 days) or failed to survive were excluded from the study.

The control group was 10 trauma patients with ISS $\geqslant 25$ but without evidence of SIRS. Then, the study group was 70 patients, classified into two groups according to the injury severity score (ISS) [18] into low injury severity score group (LISS group) in which ISS was between 9 and 25 and the high injury severity score group (HISS group) in which the ISS was > 25. Written informed consent from patients or their relatives was obtained.

The patient age, sex, Glasgow coma scale, ISS, Acute Physiology and Chronic Health Evaluation (APACHE) II score was recorded [19].

Also, the vital signs, respiratory rate, routine blood tests including procalcitonin level, microbiological culture, soluble TREM-I measurement, discharge or death during the follow-up period (14 days) were recorded.

The research team did not interfere with the job of the attending doctors in their order of antimicrobial therapy or microbiological tests.

The diagnosis of infection was depending on the presence of SIRS, laboratory, microbiological tests and the treating doctors.

Different clinical samples were collected according to the suspected site of infection (e.g. wound swab, pus, urine, sputum or tracheobronchial aspirate, intravenous catheter and blood). All specimens were cultured on different microbiological media (nutrient, blood, CLED and MacConkey agar) (Oxoid). The isolated organisms were identified by their colony morphology, microscopic appearance and by different biochemical tests [20].

2.1. Soluble TREM-1 measurements

Five milliliters of venous blood was withdrawn and EDTA was used as anticoagulant. Plasma was collected by centrifugation for 15 min at $1000 \times g$ within 30 min of collection, aliquot and stored at $-20\,°C$ until use in the assay. The sTREM-I concentration in plasma samples was measured with a Quantikine Human TREM-1 immunoassay kit (R&D Systems, Minneapolis, MN) according to the manufacturer's instructions. This assay employs the quantitative enzyme immunoassay technique. Briefly, a monoclonal antibody specific for TREM-1 has been pre-coated onto a microplate. Standards and samples were pipetted into the wells and any TREM-1 was added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells and color develops in proportion to the amount of TREM-1 bound in the initial step. The color development is stopped and the intensity of the color was measured.

3. Statistical analysis

Data were checked, entered and analyzed by using SPSS (version 15). Data were expressed as number and percentage or mean $\pm$ SD as appropriate. Chi-squared (χ^2), t-test and ANOVA test were used when appropriate. Validity of the markers was calculated.

$p < 0.05$ was considered statistically significant. $p < 0.001$ was considered highly significant.

4. Results

From January to September 2010, 80 trauma patients, 27 females and 53 males, were enrolled in this study.

The demographic data and the clinical profile of the study groups and the control group were shown in Table 1.

The mean values $\pm$ SD for the injury severity score were 36.5 ± 8.2, 17.9 ± 2.4, and 34.2 ± 6.9, respectively. The APACHE-II score of the studied groups were 15.9 ± 1.7, 10.8 ± 1.16 and 17.2 ± 1.6, respectively. The mortality rate was 11.25% (all 9 patients) as shown in Table 1.

The other clinical characteristics did not differ significantly between patients with LISS and those with high ISS (Table 1).

Types of injury in patients (head, chest, orthopedic, abdominal or miscellaneous trauma) were expressed as number and percentage (Table 2). There was no significant difference between patients regarding the types of injury.

Microbiological cultures demonstrated sepsis in 19 patients out of 70 patients. Sepsis was caused by Gram-negative bacteria in 10 patients (52.63%), by Gram-positive bacteria in 7 patients (36.84%) and by fungi in 2 patients (10.53%).

Table 3 represented the source of infection in septic trauma patients after the microbiological cultures expressed as number and percentage. Abdominal wounds represented high incidence of infection (31.6%) followed by the chest (26.3%).

As regards the soluble TREM-I and the procalcitonin levels (Table 4), there was a highly significant increase in their levels in patients with sepsis than those of the control group.

Also, there was a highly significant increase in their levels in systemic inflammatory response syndrome groups than those of the control group and there was a highly significant increase

Table 1 Demographic data and clinical profiles.

	Control group ($n = 10$)	LISS group ($\leqslant 25$) ($n = 33$)	HISS group (> 25) ($n = 37$)	p
Age	33.6 ± 9.6 (18–50)	30.9 ± 9.3 (16–50)	29.3 ± 9.4 (16–50)	0.4
Sex (male/female)	7/3	20/13	26/11	
Temperature	37.2 ± 0.5* (36.5–37.5)	38.5 ± 0.4 (38–39)	38.6 ± 0.37 (38–39)	<0.001
Leukocytic count ($\times 10^3$ cm^{-1})	9.9 ± 1.6* (7–12)	12.7 ± 0.8 (12–14.6)	13.2 ± 0.8 (12–14.6)	<0.001
GCS (points)	12.7 ± 1.16 (11–14)	12.3 ± 0.9 (12–14)	11.1 ± 1.2* (10–13)	<0.001
ISS (points)	36.5 ± 8.2 (25–50)	17.9 ± 2.11* (15–22)	34.2 ± 6.9 (27–50)	<0.001
APACHE II (points)	15.9 ± 1.7 (13–18)	10.8 ± 1.16* (9–12)	17.2 ± 1.6 (15–20)	<0.001
Mortality rate (No., %)	1 (10%)	3 (8.6%)	5 (11.1%)	0.9

Data were expressed as mean ± SD or number and percentage as appropriate. $p > 0.05$ is non-significant and $p < 0.001$ is highly significant.
LISS, low injury severity score group; HISS, high injury severity score group; GCS, Glasgow coma scale; ISS, injury severity score.
* Highly significant difference with the other two groups.

Table 2 Types of injury of different studied groups.

	Control group ($n = 10$)		LISS group ($n = 33$)		HISS group ($n = 37$)		p
	No.	%	No.	%	No.	%	
Head injury	3	30	9	27.3	13	35.1	0.77
Chest trauma	1	10	4	12.1	5	13.5	0.95
Orthopedic trauma	2	20	10	30.3	6	16.2	0.36
Abdominal trauma	4	40	8	24.2	11	29.7	0.61
Miscellaneous	–	–	2	6.1	2	5.4	0.73

Data were expressed as number and percentage. $p > 0.05$ is non-significant.
LISS, low injury severity score group; HISS, high injury severity score group.

Table 3 Sources of infection according to the microbial cultures.

Source	No.	%
Abdomen	6	31.6
Chest	5	26.3
Urine	3	15.8
Wound	2	10.5
IV catheter	2	10.5
Blood	1	5.3

Data were expressed as number and percentage.

in their levels in septic patients in comparison to those with systemic inflammatory response syndrome.

It was observed that their levels were higher in patients with high ISS than the low ISS patients (Table 4).

Also, it was observed that the rate of systemic inflammatory response syndrome in trauma patients (51 patients) was higher than the rate of sepsis in them (19 patients only) and there were precipitating factors for the infection e.g. penetrating wounds, exposure to operations, artificial ventilation, urinary catheter, etc.).

Table 5 showed the validity of sTREM-I and procalcitonin in the detection of infection, there was a significant increase in

Table 4 sTREM-I and procalcitonin levels.

	Control ($n = 10$)	LISS group ($n = 33$)		HISS group ($n = 37$)	
		SIRS ($n = 27$)	Sepsis ($n = 6$)	SIRS ($n = 24$)	Sepsis ($n = 13$)
sTREM-I (pg/ml)	102.7 ± 42.6**	177.2 ± 40[+,a]	398.5 ± 103.9[b]	189.3 ± 26.5[+]	475.7 ± 97.9
Procalcitonin (ng/ml)	0.9 ± 0.5**	1.61 ± 0.6[+,a]	3.9 ± 0.86[b]	2.3 ± 0.7[+]	7.1 ± 1.4

** The control group is highly significant in comparison to the other groups.
[+] SIRS versus sepsis in the same group ($p < 0.001$, highly significant).
[a] SIRS in LISS group versus SIRS in HISS group ($p < 0.05$, significant).
[b] Sepsis in LISS group versus sepsis in HISS group ($p < 0.001$, highly significant).

Table 5 Validity of sTREM-I and procalcitonin in detection of infection.

	Sensitivity (%)	Specificity (%)	+ ve predictive value (%)	− ve predictive value (%)
sTREM-I (pg/ml)	94.7	91.8	78.3	98.2
Procalcitonin (ng/ml)	84.2	75.4	51.6	93.9

both the sensitivity (94.7%) and specificity (91.8%) of soluble TREM-I in comparison to the procalcitonin (84.2% and 45.4%, respectively).

The cut-off value of sTREM-I was 254 pg/ml. The positive predictive value for sTREM-I was 78.3% and its negative predictive value was 98.2%. So, it is more sensitive in the early detection of infection.

5. Discussion

The result of this study showed the value and accuracy of rapid measurement of sTREM-1 level in early differentiation between patients with infection and those with systemic inflammation without infection as in trauma patients.

As shown in the result of this study, there was a highly significant increase in sTREM-I level in septic patients than those with systemic inflammatory response syndrome and the control group. It was noticed that the sTREM-I level was higher in high injury severity score group than the low injury severity score one.

These results were in accordance with the result of Gibot [21] who improved that there is a significant increase in both membrane bound TREM-1 and its soluble form during sepsis.

sTREM-I is highly expressed in inflammatory lesions caused by infectious agents e.g. bacteria and fungi but not in non-infective lesions [16].

The results of Rivera and Minei [17] also go hand in hand with the results of this study because they found that in surgical intensive care unit, patients with infection had significant increase in sTREM-I than patients with SIRS with 96% sensitivity and 91% specificity.

And these results were in agreement with the results of Gibot et al. [8] who found that the presence of sTREM-I by itself in broncho-alveolar-lavage fluid was more efficient than any clinical findings or laboratory values in identifying the presence of bacterial or fungal pneumonia in mechanically ventilated patients.

The accuracy of sTREM-I in the detection of infection has been observed in pneumonia [8], pancreatitis [22] and pleural effusions [23].

So, rapid assessment of sTREM-1 level in plasma is considered an effective tool for the early detection of infection.

Also, this study showed the high sensitivity and specificity of sTREM-I than that of procalcitonin in the detection of infection, because the procalcitonin level already increases in trauma patients without infection depending on the severity of injury [24].

In trauma patients without infection, PCT levels will be decreased with time, but if there is infection, PCT level will show higher initial level with sustained elevation in its level [24].

So, serial measurements of PCT level has an important role as a prognostic marker.

In this study, it was observed that higher PCT level was persistent in septic patients but decreased in patients with systemic inflammatory response syndrome during the follow up period (14 days).

Early detection of infection has a major benefit on the clinical course, management and the outcome of patients. The diagnosis of infection is not done by a single test, but it needs medical history, physical examination, biological indicator and microbiological tests [15].

So, sTREM-1 is considered a reliable marker for the early detection and differentiation of patients with sepsis from those with inflammation of non infectious origin.

The clinical role of sTREM-1 comes when its level is low, allowing the physician to stop using antibiotics till the results of culture are ready and protecting the patient from unnecessary use of antibiotics, so may be helpful in clinical decision during the management course of critically ill patients.

6. Conclusion

The level of soluble triggering receptor expressed on myeloid cell-I showed an early significant increase in the cases of bacterial or fungal infection. So, it was a sensitive and specific marker for differentiating infection from systemic inflammatory response syndrome in trauma patients.

7. Limitations

sTREM-I was measured only once. So, we cannot evaluate sTREM-I as a prognostic marker. So, there is a need for serial measurements of sTREM-I. Also, it is needed to assess the factors that increased the incidence of infection in trauma patients, and sTREM-1 did not detect viral infection.

References

[1] Demetriades D, Murray J, Charalambides K, Alo K, Velmahos G, Rhee P, et al. Trauma fatalities: time and location of hospital deaths. J Am Coll Surg 2004;198:20–6.

[2] Lenz A, Glen AF, William G. Systemic inflammation after trauma. J Care Injured 2007;38:1336–45.

[3] Hildebrand F, Pape HC, Krette KC. The importance of cytokines in the posttraumatic inflammatory reaction. Unfallchirurg 2005;108:793–803.

[4] Thornhill R, Strong D, Vansanth S, Mackenzie L. Trauma sepsis. Trauma 2010:12–31.

[5] Gibot S, Cravoisy A. Soluble form of the triggering receptor expressed on myeloid cells-1 as a marker of microbial infection. Clin Med Res 2004;2(3):181–7.

[6] Amyes SG. Strategies and options for minimizing resistance emergence in pulmonary infections. Chest 1998;113:228s–32s.

[7] Otero RM, Nguyen HB, Huang DT, Gaieski DF, Goyal M, Gunnerson KJ, et al. Early goal-directed therapy in severe sepsis and septic shock revisited: concepts, controversies, and contemporary findings. Chest 2006;130:1579–95.

[8] Gibot S, Cravoisy A, Levy B, Bene MC, Faure G, Bollaert PE. Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. N Engl J Med 2004;350:451–8.

[9] Ventetuolo CE, Levy M. Biomarkers: diagnosis and risk assessment in sepsis. Clin Chest Med 2008:591–603.

[10] Becker KL, Nyten ES, White JC, Muller B, Snider RH. Procalcitonin and the calcitonin gene family of peptides in inflammation, infection and sepsis: a journey from calcitonin back to its precursors. J Clin Endocrinol Metab 2004;89: 1512–25.

[11] Muller B, Becker KL, Schachinger H, Rickenbacher PR, Huber PR, Zimmerli W, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. Crit Care Med 2000;28:977–83.

[12] Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. Crit Care Med 2006;34:1996–2003.

[13] Meisner M, Lohs T, Huettemann E, Schmidt J, Hueller M, Reinhar TK. The plasma elimination rate and urinary secretion of procalcitonin in patients with normal and impaired renal function. Eur J Anaesthesiol 2001;18:79–87.

[14] Colonna M, Facchetti F. TREM-I (triggering receptor expressed on myeloid cells): a new player in acute inflammatory responses. JID 2003;187(2):s397–401.

[15] Gibot S, Kolopp MN, Bene MC, Gravoisy A, Levy B, Faure GC, et al. Plasma level of triggering receptor expressed on myeloid cells-I: its diagnostic accuracy in patients with suspected sepsis. Ann Intern Med 2004;141:9–15.

[16] Bouchon A, Facchetti F, Weigand MA, Colonna M. TREM-I amplifies inflammation and is a crucial mediator of septic shock. Nature 2001;410:1103–7.

[17] Rivera CF, Minei JP. Soluble triggering receptor expressed on myeloid cells-I is an early marker of infection in the surgical intensive care unit. Surg Infect (Larchmt) 2009;10(5):435–9.

[18] Baker SP, O'Neill B, Haddon WJR, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 1974;14:187–96.

[19] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–29.

[20] Collee JD, Miles RS, Watt P. Tests for identification of bacteria. Practical medical microbiology, 4th ed., vol. 1. New York: Churchill Livingstone; 1996, p. 131–49.

[21] Gibot S. Clinical review: role of triggering receptor expressed on myeloid cells-I during sepsis. Crit Care 2005;9(5):485–9.

[22] Yasuda T, Takeyama Y, Ueda T, Shinzeki M, Sawa H, Takahiro N, et al. Increased levels of soluble triggering receptor expressed on myeloid cells-1 in patients with acute pancreatitis. Crit Care Med 2008;36:2048–53.

[23] Chan MC, Chang KM, Chao WC, Lin LY, Kuo BI, Hsu JY, et al. Evaluation of a new inflammatory molecule (triggering receptor expressed on myeloid cells-I) in the diagnosis of pleural effusion. Respirology 2007;12:333–8.

[24] Guido WA, Marius K, Ursula S, Wilfried B, Reto S, Wolfgang E. Relationship between procalcitonin plasma levels and severity of injury, sepsis, organ failure, and mortality in injured patients. Crit Care Med 2000;28(4):950–7.