Soluble Triggering Receptor Expressed on Myeloid Cells-1 Is an Early Marker of Infection in the Surgical Intensive Care Unit

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Abstract

Background: To determine the value of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) in early differentiation of systemic inflammatory response syndrome (SIRS) from infection in patients in a surgical intensive care unit (ICU).

Methods: Patients were enrolled if there was clinical suspicion of infection and they fulfilled at least two criteria of SIRS at the time of admission to the ICU. The patients were classified as having SIRS (no infection; $n = 37$) or infection ($n = 56$) on the basis of the decision of the treating physician and bacteriological evidence of infection. The plasma concentrations of sTREM-1 in the two groups were compared.

Results: Patients with infection had significantly higher sTREM-1 concentrations than patients with SIRS: Median 398 pg/mL (interquartile range [IQR] 302, 552) vs. 78 pg/mL (IQR 28, 150), respectively ($p < 0.0001$). At a cut-off of 230 pg/mL, sTREM-1 correctly identified patients suffering from infection with 96% sensitivity and 91% specificity.

Conclusions: In the present study, sTREM-1 was an accurate tool for differentiating SIRS from infection in patients in the surgical ICU.

SEVERE INFECTIONS AND SEPSIS are common causes of morbidity and death in surgical intensive care units (ICUs) [1, 2]. Unfortunately, the diagnosis of such infections in acutely injured and surgical patients is not always straightforward. The clinical and laboratory signs of infection, including changes in body temperature and heart rate and leukocytosis, are present in the majority of patients admitted to the ICU after major surgery, trauma, pancreatitis, and burns [3–5]. However, these signs can be manifestations of the systemic inflammatory response syndrome (SIRS) and may be noninfectious in origin [6]. Therefore, they are neither specific nor sensitive for sepsis or infection. It is for that reason at times difficult to differentiate between patients with trauma or shock who have systemic infection and those who do not [7]. In the same way, there is no specific laboratory test for infection, and bacteriological evidence of infection not only may not develop parallel with clinical signs of infection but can take more than 48 h from the time of infection acquisition to become available. Moreover, positive results may be attributable to contamination, and negative results do not exclude the presence of infection or sepsis. Recent evidence suggests that early identification and

treatment of severe sepsis and septic shock improves outcomes [8]. Because the standard clinical and laboratory parameters lack sensitivity and specificity, more specific and sensitive markers are needed to provide an early diagnosis.

The soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) protein can be quantified in biological fluids, and has recently attracted interest as a possible biological marker of bacterial infection [9]. The triggering receptor expressed on myeloid cells (TREM-1) is a 30-kDa cell-surface member of the immunoglobulin superfamily. It is expressed and upregulated on neutrophils and mature monocytes in the presence of bacteria or fungi. At the same time, with upregulation of membrane-bound TREM-1, sTREM-1 is released, and its concentration can be measured in biological fluids [10]. Thus, sTREM-1 may act as a marker of bacterial infection and was a promising diagnostic tool in previous studies performed in medical ICUs [11–12]. However, this marker has not been evaluated in a surgical ICU. The purpose of this study was to evaluate whether biological fluid sTREM-1 concentrations can differentiate between patients with SIRS alone and those with SIRS and infection admitted to the surgical ICU.

Patients and Methods

The Institutional Review Board at The University of Texas Southwestern Medical Center at Dallas approved this study. The study population consisted of patients admitted to the surgical ICU at Parkland Memorial Hospital (Dallas, TX) who presented with two or more of the following signs of SIRS: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$; pulse rate >90 beats/min; ventilatory rate >20 breaths/min or hyperventilation with partial pressure of arterial carbon dioxide (PaCO_2) <32 mm Hg; or white blood cell count $>12,000/\text{mL}$ or $<4000/\text{mL}$ or $>10\%$ immature cells. Patients were excluded if they were immunocompromised, leukopenic (white cell count $<1,000/\text{mL}$), or neutropenic (polymorphonuclear granulocyte count $<500/\text{mL}$). Patients who failed to survive or were discharged early (within 24 h after admission) or who had signed do not resuscitate (DNR) orders also were excluded. As a control group ($n = 15$), we used blood from patients with an Injury Severity Score (ISS) above 25 without SIRS; these patients were matched for age and sex with the study population.

Clinical data collection

Demographics and detailed medical and social history as well as injury characteristics were collected for all patients. Clinical and laboratory data were recorded.

Biological samples were collected within 12–36 h after admission. Samples were centrifuged at 4°C at 3,000 rpm for 10 min, and the supernatant liquids were stored in aliquots at -70°C until analyzed. Protein concentration was determined in bronchoalveolar lavage (BAL) and abdominal fluids.

Diagnosis of infection

The attending physician ordered microbiological tests and antimicrobial therapy according to the usual practice in the surgical ICU, without interference by the research team. The diagnosis was based on the decision of the treating physician, bacteriological evidence of infection, and the presence of SIRS and positive microbial cultures plus:

- Pulmonary infection: New or persistent consolidation on chest radiography; purulent tracheobronchial secretions; and clinical pulmonary infection score >6 as previously defined;
- Blood stream infection: Positive blood culture without evidence of any other underlying infection;
- Urinary tract infection: Positive urine culture;
- Abdominal infection: Positive cultures of peritoneal fluid at the time of surgery, purulent abdominal fluid with positive results on bacterial culture, or secretion of purulent fluid from intra-abdominal drains with positive results on bacterial culture.

The American College of Chest Physicians/Society of Critical Care Medicine consensus classification was used for the diagnosis of SIRS, sepsis, severe sepsis, and septic shock [13]. For this study, complicated sepsis was defined as severe sepsis with septic shock.

Soluble TREM-1 measurements

The sTREM-1 concentration in plasma and fluid samples was measured with a DuoSet enzyme-linked immunosorbent

assay kit (R&D Systems, Minneapolis, MN) according to the manufacturer's instructions. All determinations were performed in triplicate.

Statistical analysis

Descriptive statistics included the number and percentages for categorical variables and median (range) for continuous data. Categorical data were compared using the chi-square or Fisher exact test. Continuous data were analyzed by the Mann-Whitney U test.

Plasma soluble sTREM-1 concentrations were expressed as the median with the interquartile range (IQR). The ability of sTREM-1 to predict infection was evaluated by performing receiver-operator characteristic (ROC) analyses to compare patients SIRS and infection. Furthermore, the areas under the ROC curves (AUCs) were determined, as well as the positive/negative predictive values. Positive and negative predictive values indicate the proportion of patients with a sTREM-1 concentration greater than or below the chosen cut-off point. The SPSS version 16 (SPSS Chicago, IL) and Graphpad (Prizm, San Diego, CA) programs were used for data analysis.

Results

Ninety-three subjects (73 trauma and 20 general surgical) who fulfilled the SIRS inclusion criteria were enrolled prospectively (70 men and 23 women) (Table 1). The median age of the patients was 35 years. Co-morbidities were rare ($\leq 12\%$). The duration of stay in the ICU was 14 ± 12 (standard deviation) days. A total of 65 (70%) had an ISS ≤ 25 . Blunt trauma was the mechanism of injury in 80% of the patients. Severe injury occurred with the following frequency: Chest 66 (71%), head 44 (47%), and abdomen 43 (46%). Eleven patients (12%) died. Sixty percent developed one or more infections, with 34 patients (37%) developing sepsis and 22 (24%) complicated sepsis. Gram-negative bacteria were isolated from 28 patients (30%), gram-positive bacteria from 22 (23%), and fungus from 6 (7%). The main sources of infection were the lungs (33; 60%), followed by the abdomen (8; 13%), blood (7; 12%), wound (4; 7%), intravenous catheter (3; 4%) and urine (2; 3%), and one patient had empyema.

TABLE 1. DEMOGRAPHIC AND CLINICAL DATA OF ENROLLED PATIENTS

	SIRS (n = 37)	Infection (n = 56)
Mean age (years) $\pm$ SD	36 $\pm$ 17	34 $\pm$ 14
Number (%) male	28 (76)	42 (75)
ISS $\pm$ SD	29 $\pm$ 9	32 $\pm$ 10
ISS >25 (%)	21 (57)	42 (75)
Mean total LOS $\pm$ SD	12 $\pm$ 34	36 $\pm$ 27
Surgical ICU LOS $\pm$ SD	7 $\pm$ 8	19 $\pm$ 12
Sepsis	—	34 (37)
Complicated sepsis (%)	—	22 (24)
Died (%)	5 (13)	6 (11)
Median soluble TREM-1 (pg/mL)(IQR)	78 (28, 150)	397 (303, 552)

ICU = intensive care unit; IQR = interquartile range; ISS = Injury Severity Score; LOS = length of stay; SD = standard deviation; TREM = triggering receptor expressed on myeloid cells-1.

FIG. 1. Plasma concentrations of soluble triggering receptor expressed on myeloid cells-1 according to diagnosis (SIRS = systemic inflammatory response syndrome [$n=37$] vs. infection [$n=56$]). Dots represent individual values; bars represent medians. Probability is for comparison of SIRS and infection.

Soluble TREM-1 concentrations

The sTREM-1 protein was not detected in 97% of the 15 patients having an ISS ≤ 25 without SIRS (control group). The median sTREM-1 concentration (IQR) in the test group was 298 pg/mL (108, 423). The median sTREM-1 concentration was significantly higher ($p \leq 0.001$) in the infected group: 398 pg/mL (302, 552) vs. 78 pg/mL (28, 150) for the SIRS group (Fig. 1).

Value of sTREM-1 as a diagnostic and differentiation marker of SIRS and infection

A sTREM-1 cut-off value of ≥ 230 pg/mL yielded a sensitivity of 98% (95% confidence interval [CI] 90, 99), a specificity of 91% (CI 78, 98), a positive likelihood ratio of 12.1, and a negative likelihood ratio of 0.02 for differentiating patients with SIRS from those with infection. According to the ROC analysis, the maximum power of sTREM-1 to discriminate between SIRS and infected patients was 0.97 (CI 0.93, 1.00) (Fig. 2).

Peritoneal fluid and bronchoalveolar lavage fluid sTREM-1

We measured sTREM-1 in peritoneal fluid from 12 patients (seven abdominal abscess and five SIRS) and BAL fluid from 33 (22 pneumonia and 13 SIRS). Significantly higher concentrations of sTREM-1 were associated with the presence of infection (abdominal abscess or pneumonia) (Fig. 3). There were not enough subjects to do further analysis.

Discussion

The diagnosis of infection in acutely injured and surgical patients is not always straightforward. Systemic inflamma-

FIG. 2. Receiver operator characteristic (ROC) curve for soluble triggering receptor expressed on myeloid cells-1 concentration as means of differentiating systemic inflammatory response syndrome from infection.

tion frequently is present without obvious infection after trauma and major surgery. Standard laboratory tests often lack both sensitivity and specificity in differentiating which patients should receive antibiotics, and results from most confirmatory microbiological tests not only are not available immediately but may not rule out infection definitely. These limitations are of concern, as early identification and appropriate treatment of infection has a major effect on the clinical course and outcome of critically ill surgical patients [8].

There is a clear need for a reliable marker that allows early identification of infection. The ideal marker should be present early in the course of the disease, be measurable rapidly and easily, of prognostic significance, sensitive enough to detect infection in patients with minimal host response, and specific enough to discriminate infection from other causes of SIRS [14]. A significant amount of evidence has accumulated regarding the clinical potential of TREM-1 as a marker [11, 12, 15–22]. The protein is upregulated and expressed in response to binding of bacterial agonists by neutrophils and monocytes. Studies in animal models have shown that TREM-1 may be involved in the amplification of the inflammatory response to endotoxins and that its upregulation during infections is accompanied by increased release of its soluble form (sTREM-1), which can be measured in biological fluids. Moreover, TREM-1 is highly expressed in inflammatory lesions caused by infectious agents such as bacteria and fungi, but not in lesions caused by non-infective agents [23]. Such properties make sTREM-1 a perfect biochemical marker of bacterial infection.

Our study demonstrates that measurements of sTREM-1 in plasma from patients in the surgical ICU may be a valuable tool for early distinction between infected and non-infected patients. Our data also suggest that measurements of sTREM-1

FIG. 3. Concentrations of soluble triggering receptor expressed on myeloid cells-1 in abdominal fluid (**A**) and bronchoalveolar lavage fluid (**B**) from patients with systemic inflammatory response syndrome (SIRS) or infection (abdominal abscess in panel A and pneumonia in panel B). Dots represent individual values; bars represent medians. Probability values are from comparisons of SIRS and infection.

in BAL and peritoneal fluid may be useful in revealing the presence of localized infections.

Several studies have reported the potential usefulness of assessing sTREM-1 in biological fluids for the diagnosis of infection. Its accuracy has been demonstrated in sepsis [24], pneumonia [12, 25], pancreatitis [26], and pleural effusions [15]. However, most of these studies have been performed in medical ICUs; to our knowledge, ours is the first study in trauma/surgical patients.

Our study has limitations; one is the relatively small number of subjects, and the second is that sTREM-1 was measured only on admission to the surgical ICU. Thus, we cannot evaluate sTREM-1 as a prognostic marker. Prospective cohort studies including a greater number of patients with suspected infection, preferably collecting samples at multiple time points, are needed to substantiate our findings.

In conclusion, our results demonstrate that early measurement of plasma sTREM-1 may improve our ability to

differentiate patients with infection from those with systemic inflammation of noninfective origin. This may be especially useful among trauma and surgical patients, in whom the diagnosis of infection is not straightforward.

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Author Disclosure Statement

No conflicting financial interests exist.

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