# EVALUATION OF CIRCULATING SOLUBLE TRIGGERING RECEPTOR EXPRESSED ON MYELOID CELLS-1 (sTREM-1) TO PREDICT RISK PROFILE, RESPONSE TO ANTIMICROBIAL THERAPY AND DEVELOPMENT OF COMPLICATIONS IN PATIENTS WITH CHEMOTHERAPY-ASSOCIATED FEBRILE NEUTROPENIA: A PILOT STUDY

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**Running title:** sTREM-1 in febrile neutropenia

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**Abstract**

The soluble Triggering Receptor Expressed on Myeloid cells 1 (sTREM-1) is a useful marker of infection in patients with sepsis, but has not been adequately evaluated in patients with chemotherapy-associated febrile neutropenia (FN). The value of sTREM-1 in this setting has been tested in a retrospective, pilot study using stored serum from 48 cancer patients with documented FN. On presentation, patients were categorized according to the Talcott risk-index clinical score. Circulating soluble sTREM-1 was measured using an ELISA procedure, while procalcitonin (PCT) or interleukins 6 (IL-6) and 8 (IL-8), included for comparison, were measured using an immunoluminescence-based assay and Bio-Plex® suspension bead array system, respectively. Circulating concentrations of both sTREM-1 and PCT were significantly ($P < 0.05$) elevated in patients at high risk for complications or death, as predicted by the Talcott score and were significantly lower in patients who responded to empiric antimicrobial agents. Neither IL-6 nor IL-8 accurately predicted serious complications in patients with FN. These observations, albeit from a pilot study, demonstrate that sTREM-1 is indeed elevated in high-risk patients with FN and is potentially useful to predict their clinical course, either together with, or as an alternative to PCT.

**Keywords**

Febrile neutropenia, soluble TREM-1, Talcott score and procalcitonin

## Introduction

Infections remain the major cause of serious complications in cancer patients with chemotherapy-associated febrile neutropenia (FN), with an overall in-hospital mortality rate of 9.5% in the USA [1]. On presentation with FN, strategies to identify patients at highest risk for progression to severe infection include: i) clinical scoring systems [2,3,4]; ii) measurement of circulating, host-derived markers of inflammation and/or infection, including pro-inflammatory cytokines, acute phase reactants, and procalcitonin (PCT) (reviewed by Sakr *et al*, [5]); and iii) combinations of these strategies [6,7].

Of the circulating biomarkers with predictive potential, those which have attracted the most attention in patients with FN are PCT, interleukin -6 (IL-6), and the acute phase reactant, C-reactive protein [5], with some studies having reported that PCT is superior to IL-6 and/or CRP [7,8,9], while others have reported equivalence [5]. Some studies have suggested that measurement of PCT in FN is best suited to identifying patients who are at low risk for developing severe infection [7,8,10,11], while others have found it to have high positive predictive value for development of severe infection [6,9].

Recently, circulating soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1) has been reported to possess diagnostic value in the detection of bacterial infection [12-14]. Soluble TREM-1, a member of the immunoglobulin superfamily is expressed on a variety of cells of myeloid lineage of the innate

system, especially neutrophils and monocytes, and appears to amplify pathogen-associated, Toll-like receptor-mediated inflammatory responses [13]. Soluble TREM-1 is released from activated neutrophils and monocytes/macrophages and its detection in body fluids is considered to be a potentially useful biomarker of bacterial infection, which may, if used in combination with PCT, improve the recognition of true infection [12]. Soluble TREM-1 concentrations have also been used to predict the prognosis of patients with sepsis [15]. However, to our knowledge, only one previous study [16], has investigated the usefulness of circulating sTREM-1 in FN. Accordingly, we have conducted a retrospective pilot study in which we have measured and compared sTREM-1, PCT, IL-6 and IL-8 in serum specimens from cancer patients with chemotherapy-associated FN and correlated these with the Talcott score and performance status of these patients. In addition, we have evaluated the usefulness of these circulating biomarkers to predict clinical response to empiric antimicrobial therapy, development of complications and outcome of patients with FN.

**Patients**

Stored (-20°C), unthawed serum specimens from 48/63 patients recruited to an earlier study [7] were analysed in the current study. All patients had a histologically confirmed malignancy and had presented with FN, either with an oral temperature of > 39°C in a single measurement, or > 38°C in two consecutive measurements at least 4 hours apart, together with an absolute neutrophil count of $\leq 0.5 \times 10^9$/L as a result of chemotherapy. Patients were consecutively admitted to a single hospital on

presentation with FN. Approval to conduct the original study had been granted by the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria in November 2000, while approval for performance of the sTREM-1 assays on the stored serum specimens described in the current study (as an extension of the original study), was granted by the same committee in October 2009. Informed consent was obtained from all patients prior to enrolment in the original study.

Patients with both solid tumors and hematological malignancies were included. The anti-cancer agents used in these patients have been described previously [17] and no patients had undergone radiotherapy immediately prior to the FN episode. On presentation, the performance status (PS) of each patient was determined and all patients were categorized using the Talcott system [2] for risk stratification. All patients received broad-spectrum empirical antimicrobial chemotherapy (cefepime/ceftriaxone plus amikacin), except for one patient who received meropenem as a single agent. Patients not responding to empirical therapy received vancomycin, while for patients with persistent fever (> 7 days), amphotericin was added. The patients were closely monitored to determine the following: response to empiric antibiotic therapy, development of serious medical complications including hypotension, respiratory/renal/congestive cardiac failure, intensive care admission, confusion, bleeding requiring transfusion, electrocardiographic changes, arrhythmias requiring treatment, or an allergic reaction, and survival. The presence or absence of any microbiologically-documented infection (MDI) or bloodstream infection, using standard microbiologic cultures of appropriate samples, was recorded.

The patient characteristics with respect to age, gender, circulating leukocyte counts, absolute neutrophil counts, type of malignancy, HIV status, inpatient/outpatient therapy and duration of febrile episodes and antimicrobial therapy are shown in Table 1.

**Laboratory Methods**

*Soluble TREM-1*

Circulating sTREM-1 was measured using a commercial, capture/sandwich ELISA procedure (Quantikine R&D Systems, Inc. Minneapolis, MN, USA). Briefly, 100 μl aliquots of serum (one sample per patient except for 4 patients who had more than one febrile episode), were transferred to the wells of a microplate coated with a murine IgG monoclonal antibody to human TREM-1. Following 2 hours incubation at room temperature, the plates were washed, and bound sTREM-1 was detected and quantified by the serial addition to the wells of a biotin-labeled second antibody, streptavidin-labeled horse radish peroxidase, and enzyme substrate. Following measurement of color intensity using a microplate spectrophotometer at a wavelength setting of 450 nm, concentrations of sTREM-1 in the serum samples were calculated from a standard curve constructed from standards containing known concentrations of sTREM-1 and the results expressed as picograms (pg)/ml. The concentration of sTREM-1 in normal individuals was determined by measuring the serum concentrations of sTREM-1 in 8 healthy control subjects (4 males and 4 females).

*Procalcitonin*

All specimens were re-assayed for procalcitonin (PCT) using an immunoluminescence procedure using a chemiluminometer and compatible reagents according to the manufacturer's protocol (Lumi Test, Brahms Diagnostika, Berlin, Germany), with values of < 0.5 ng/ml considered to be in the normal range.

*IL-6 and IL-8*

Concentrations of the cytokines IL-6 and IL-8 were measured using a Bio-Plex$^{R}$ suspension bead array system (Bio-Rad Laboratories Inc, Hercules, CA, USA) which uilitizes Luminex$^{R}$ xMAP$^{TM}$ technology to enable simultaneous detection and quantitation of multiple different analytes in a single sample. These results are expressed as pg/ml with normal values determined during a preliminary series of experiments using healthy control subjects.

*Study design and statistical analysis*

The objective of the study was to probe the diagnostic and prognostic potential of sTREM-1 in patients with FN. Results are expressed as the mean ± S.E.M. Levels of statistical significance were calculated using the Mann-Whitney U test for comparison of non-parametric data, and a *P* value < 0.05 was considered significant. The sensitivity, specificity, positive predictive value (PPV), positive likelihood ratio and ROC (area under the curve) for procalcitonin and sTREM-1 were calculated using cut-off values of 0.5 ng/ml [18,19] and 100 pg/ml [20], respectively and the Spearman correlation was used to measure the degree of dependency between variables.

## Results

*Soluble TREM-1, PCT, IL-6 and IL-8*

These are shown in Table 2 for the groups categorized according to performance status (PS), Talcott score, response to initial antimicrobial therapy, presence or absence of serious complications, survivors and non-survivors, as well as the presence or absence of microbiologically-documented infection (MDI), including bloodstream infections.

The concentration of sTREM-1 in healthy control subjects was 63 $\pm$ 3 pg/ml, while the corresponding value for IL-6 and IL-8 was < 6 pg/ml. Circulating sTREM-1 and serum PCT concentrations increased progressively as the PS of the patient deteriorated from PS1 to PS3, and decreased progressively from Talcott class 1 to 4 in keeping with a decline in disease severity predicted by the Talcott system. Patients who responded to initial empiric antimicrobial therapy had significantly lower sTREM-1 and PCT concentrations than those who did not, and these were significantly greater for those patients who subsequently developed serious complications. Both sTREM-1 and PCT predicted the presence of bloodstream infections, but not other types of microbiologically-documented infections. The mean sTREM-1 and PCT concentrations for survivors were significantly lower than those of non-survivors.

The cytokine concentrations showed similar trends to those observed with sTREM-1, but did not reach statistical significance.

The sensitivity, specificity, positive predictive value (PPV), likelihood ratios and area under the ROC curve of circulating sTREM-1and PCT concentrations to predict response to empiric anti-microbial therapy, resolution without complications, development of serious complications and mortality are shown in Table 3. The threshold concentrations of circulating sTREM-1and PCT selected to derive these variables were 100 pg/ml and 0.5 ng/ml respectively, and 100 or 200 pg/ml to predict mortality with sTREM-1. Soluble TREM-1 concentrations predicted each of the above events with reasonable accuracy, particularly with respect to the development of serious complications or death with positive likelihood ratios of 2.5 and 3, respectively. Similar results were obtained for the serum PCT concentrations. The concentrations of sTREM-1 and PCT were closely correlated in patients with FN ($r = 0.63$; $p < 0.0001$).

## Discussion

Febrile neutropenia (FN) commonly occurs in patients with hematological or solid malignancies who receive chemotherapy and is associated with significant morbidity and mortality [1]. Consequently, numerous clinical prediction rules have been developed for stratifying the risk of complications and/or death in this heterogeneous population of patients [2,4] so that early, appropriate, empiric antimicrobial therapy can be instituted. Circulating soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) has been evaluated in the current study as a biomarker to predict the risk profile and onset of complications in patients with FN. The concentrations of sTREM-

1 were significantly elevated in patients presenting with neutropenia and fever and accurately predicted the response to initial empiric antimicrobials as well as the subsequent development of serious complications. This is important as patients who respond rapidly to initial antimicrobial agents are less likely to develop complications and could complete their therapy as outpatients [21] with consequent reductions in hospitalization-associated complications and costs [22]. The elevated concentrations of sTREM-1 in the setting of severe leukopenia suggests that the number of circulating inflammatory cells able to express this receptor remains adequate despite significant reductions in bone marrow-derived neutrophils.

Previous studies have validated the Talcott grading system as a clinical predictor of outcome in patients with FN [23]. Circulating sTREM-1 concentrations correlated closely with the Talcott class increasing progressively as the magnitude of risk escalated. This suggests that sTREM-1 concentrations increase as the patient's clinical status deteriorates, even in the presence of severe leukopenia. Soluble TREM-1 concentrations also increased as the performance status (PS) of the patients on initial evaluation deteriorated, further supporting the potential usefulness of sTREM-1 as a biomarker of underlying disease severity. Although the current study is limited by a relatively small number of patients and requires validation in a prospective study, sTREM-1 concentrations were significantly lower in patients who survived than those who did not with a positive likelihood ratio for mortality of 39 at concentrations exceeding 200 pg/ml.

Serum PCT concentrations accurately predict outcome in patients with sepsis in the absence of neutropenia [24], although conflicting results have been reported in patients with FN [5,25]. Despite these apparent inconsistencies, serum PCT concentrations in the current study correlated closely with those of sTREM-1, suggesting that these biomarkers, either alone or in combination, may be useful for predicting the clinical course of patients with FN. Furthermore, in this setting, both sTREM-1 and serum PCT predicted the presence of bloodstream infections.

In contrast to sTREM-1 and PCT, the concentrations of IL-6 and IL-8 did not accurately reflect response to treatment, complications, or risk profiles in these patients. This may be due to the short half-lives of these molecules in the circulation [26] or individual differences in the magnitudes of systemic inflammatory response to microbial pathogens [27].

The findings of the current study are important considering the reliance on subjective clinical parameters incorporated into recently published prediction rules. Clinical criteria such as a “patient looks ill” [28] may not be consistently applied by clinicians. Notwithstanding the importance of an appropriate clinical evaluation of patients with FN, sTREM-1 could be used as an adjunctive biomarker to facilitate the decision-making process in these high risk patients. Conceivably, a threshold value for sTREM-1 of 100 pg/ml could guide clinicians treating patients who do not fit clearly into low- or high-risk groups. Patients with sTREM-1 concentrations below this threshold appeared to demonstrate a favorable outcome.

Recent evidence suggests that elevated concentrations of sTREM-1 may also predict the absence of metastatic disease in breast cancer [29], although the concentrations are considerably lower than those in patients with acute bacterial infection. Although sTREM-1 and PCT may be valuable biomarkers in neutropenic sepsis, the cost implications of their routine use in clinical practice needs to be evaluated.

In conclusion, circulating sTREM-1 appears to hold promise as an objective biomarker which could be used to complement clinical prediction rules and thereby expedite the clinical decision-making process in patients presenting with FN.

**Table 1:** Patient characteristics at initial presentation

| | | |
|---|---|---|
| **Age** | 51 ± 2 years (63) | |
| **Duration of febrile episode** | | |
| **≤ 24 hours (% total)** | 75 | |
| **> 24 hours (% total)** | 25 | |
| **Duration of antimicrobial therapy** | | |
| **≤ 7 days (% total)** | 60 | |
| **> 7 days (% total)** | 40 | |
| **Sex** | Male: 12 | Female: 36 |
| **Solid Tumor** | 9 | 29 |
| **Hematological Malignancy** | 3 | 7 |
| **Total WCC** | 0.7 ± 0.14 (1.5) | 1.08 ± 0.13 (3.18) |
| **Absolute Neutrophil Count** | 0.13 ± 0.05 (0.5) | 0.17 ± 0.03 (0.5) |
| **HIV Status** | 1 positive | |
| **Hospital Admission** | 10 inpatients<br>2 outpatients | 24 inpatients<br>12 outpatients |

Results are expressed as the mean ± S.E.M. (Range).

**Table 2:** Relationship between markers of inflammation and outcome in patients with febrile neutropenia.

| | **sTREM-1 (pg/ml)** | **PCT (ng/ml)** | **IL-6 (pg/ml)** | **IL-8 (pg/ml)** |
|---|---|---|---|---|
| All patients combined (n = 48) [Range] | 116 ± 15 [548] | 3.8 ± 2 [75] | 4398 ± 2577 [114329] | 5000 ± 2762 [108931] |
| Performance status 1 (n = 17) | 77 ± 11 | 0.5 ± 0.3 | 332 ± 126 | 642 ± 211 |
| Performance status 2 (n = 20) | 93 ± 10* (p = 0.0007) | 0.5 ± 0.2* (p = 0.011) | 317 ± 86 | 483 ± 140 |
| Performance status 3 (n = 11) | 220 ± 49* (p = 0.009) | 15 ± 8.5* (p = 0.0111) | 18501 ± 10786 | 20402 ± 11505 |
| Talcott 1 (n = 13) | 163 ± 43 | 7.7 ± 5.7 | 12428 ± 9080 | 11037 ± 8410 |
| Talcott 2 (n = 4) | 139 ± 29 | 1.15 ± 0.8 | 1053 ± 600 | 1299 ± 512 |
| Talcott 3 (n = 15) | 116 ± 23 | 4.7 ± 4.5 | 2968 ± 2721 | 6061 ± 5339 |
| Talcott 4 (n = 16) | 73 ± 9* (p = 0.013) | 0.6 ± 0.3* (p = 0.023) | 325 ± 137 | 337 ± 100 |
| Response to empiric therapy (n = 29) | 85 ± 8 | 0.43 ± 0.2 | 348 ± 90 | 597 ± 148 |
| No response to empiric therapy (n = 19) | 165 ± 32* (p = 0.015) | 9 ± 5 | 10810 ± 6476 | 11984 ± 6928 |
| Absence of serious complications (n = 36) | 85 ± 8 | 0.4 ± 0.1 | 304 ± 72 | 550 ± 119 |
| Serious complications developed (n = 12) | 209 ± 45* (p = 0.0004) | 14.2 ± 7.8* (p = 0.009) | 17022 ± 9957 | 18723 ± 10636 |
| Survivors (n = 43) | 89 ± 7 | 0.5 ± 0.2 | 337 ± 66 | 588 ± 114 |
| Non-survivors (n = 5) | 344 ± 73* (p = 0.0001) | 32 ± 16.3* (p = 0.0003) | 40140 ± 20620 | 43838 ± 21818 |
| No documented infection | 89 ± 7 | 0.52 ± 0.18 | 347 ± 79 | 647 ± 142 |
| Microbiologically-documented infection (MDI) | 94 ± 18 | 0.62 ± 0.5 | 302 ± 116 | 402 ± 148 |
| No bloodstream infection | 90 ± 7 | 0.5 ± 0.2 | 337 ± 66 | 588 ± 114 |
| Bloodstream infection present | 344 ± 73* (p = 0.0001) | 32 ± 16.3* (p = 0.0003) | 40140 ± 20620 | 43838 ± 21818 |

Soluble triggering receptor expressed on myeloid cells (sTREM-1), procalcitonin (PCT), interleukin-6 (IL-6) and interleukin-8 (IL-8) for all patients combined, as well as the values for performance status (PS), Talcott class, response or lack of response to empiric therapy, absence or presence of serious complications, survivors and non-survivors, absence or presence of microbiologically-documented infection and absence or presence of bloodstream infections. Results are expressed as the mean ± S.E.M. **P* values for comparison of the groups within each category.

**Table 3:** The sensitivity, specificity, positive predictive value (PPV), positive likelihood ratio (LR) and ROC (area under curve) of soluble triggering receptor expressed on myeloid cells (sTREM-1) and procalcitonin (PCT) to predict response to empiric therapy, development of serious complications and death in patients with febrile neutropenia.

| | | **Response to empiric therapy** | **Development of serious complications** | **Death** |
|---|---|---|---|---|
| **Sensitivity** | **sTREM-1** | 0.66 (0.46 – 0.82) | 0.75 (0.43 – 0.95) | 0.99 (0.48 – 1.0) |
| | **PCT** | 0.86 (0.68 – 0.96) | 0.58 (0.28 – 0.85) | 0.8 (0.28 – 0.99) |
| **Specificity** | **sTREM-1** | 0.47 (0.25 – 0.71) | 0.7 (0.53 – 0.84) | 0.66 (0.5 – 0.8) |
| | **PCT** | 0.47 (0.25 – 0.71) | 0.81 (0.65 – 0.92) | 0.82 (0.67 – 0.92) |
| **PPV** | **sTREM-1** | 66% (46 – 82%) | 45% (23 – 69%) | 25% (10 – 49%) |
| | **PCT** | 71% (54 – 85%) | 50% (23 – 77%) | 33% (10 – 65%) |
| **Positive LR** | **sTREM-1** | 1.25 | 2.5 | 3 |
| | **PCT** | 1.64 | 3 | 4.4 |
| **ROC (Area under curve)** | **sTREM-1** | 0.7 (0.55 – 0.87) | 0.84 (0.73 – 0.96) | 0.99 (0.97 – 1.013) |
| | **PCT** | 0.65 (0.47 – 0.82) | 0.77 (0.59 – 0.95) | 0.94 (0.85 – 1.03) |

The 95% confidence intervals are indicated in brackets.

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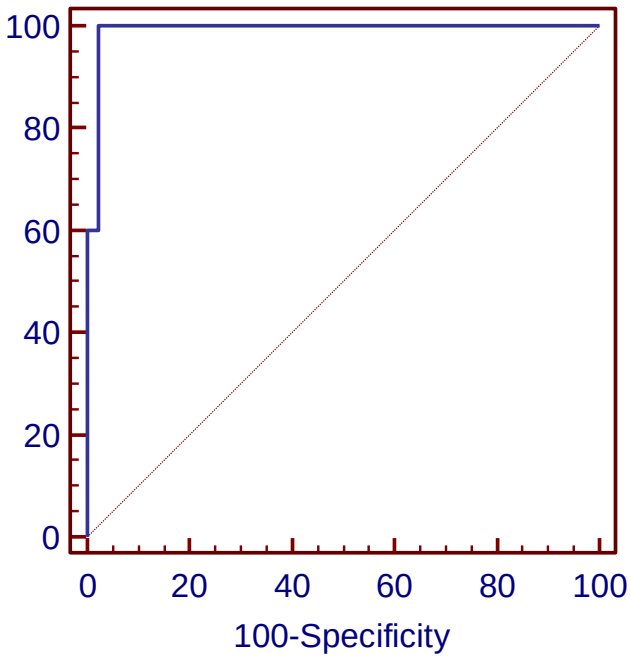
**Legend to Figure**

**Fig. 1:** ROC curves of the sensitivity and specificity of sTREM-1 (A) and serum PCT (B) to predict mortality in patients with febrile neutropenia.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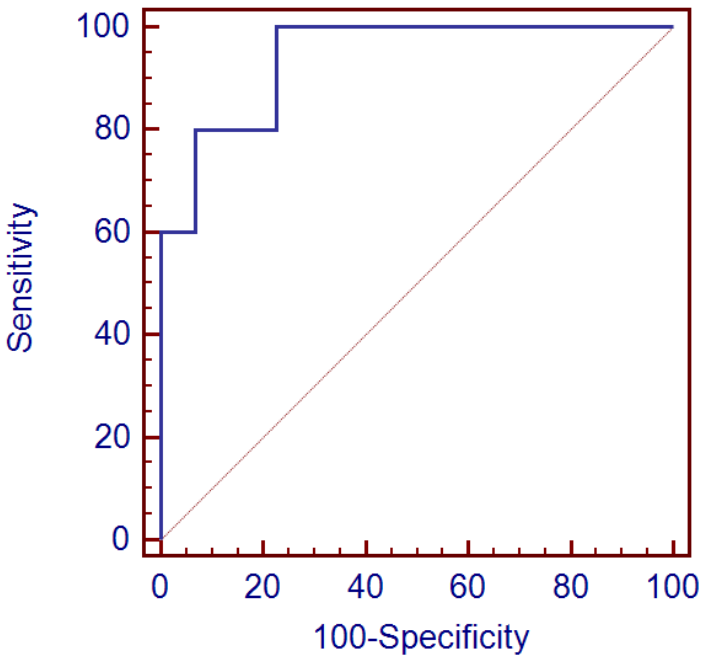
**A**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**B**