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The Role of Soluble Triggering Receptor 1 Expressed on Myeloid Cell (STREM-1) as an Early Biomarker in Diagnosis of Sepsis

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ABSTRACT

Background: Sepsis remains a leading cause of death worldwide especially in the intensive care unit (ICU) setting. It is currently accepted that improving the outcome of critically ill patients with sepsis relies mainly on the adequacy and the timeliness of key interventions such as administering appropriate antibiotics and sufficient amounts of fluid, especially the sickest ones.

Objectives: The aim of the current study is to explore the utility of sTREM-1 in early diagnosis of sepsis and determine its predictive value.

Materials and Methods: This is a case control study. It was conducted in Al-Zahraa University Hospital during the period from December 2018 to March 2019. Forty (40) subjects were included in this study; they were classified into two groups as follows: 25 patients with two or more of clinical signs of sepsis according to the four SIRS criteria, and 15 subjects as a control group.

Results: The present study revealed that there was a highly statistically significant ($p = 0.001$) moderate positive correlation ($r = 0.707$) between the WBC count and sTREM level in the cases group, with no other significant correlations between sTREM level and age, CRP level, hemoglobin level or platelet count. The present study revealed that at a sTREM cut-off point of >97.8 pg/ml, its sensitivity was 100%, its specificity was 100%, its positive predictive value was 100% and its negative predictive value was 100% to differentiate sepsis cases.

Conclusion: The sTREM-1 is qunque biomarker having wide range of application in the medical field. It is useful in diagnosis of sepsis and differentiating between microbial and non-microbial infection cases.

Keywords: Soluble Triggering Receptor 1, Myeloid Cell, Early Biomarker, Sepsis

INTRODUCTION

Sepsis is a complex clinical syndrome that results from a harmful host response to infection. The initial line of defence against invading pathogen is the immediate, innate host immune response, which prevents proliferation of pathogens until the more specialized adaptive response, provided by specific T and B cells, can occurs [(1)]. The innate response involves the coordinated action of effector cells such as phagocytes and natural killer cells, which express numerous membrane-bound receptors. Of these, the Toll-like receptors (TLRs) detect microbial structures such as lipopolysaccharide (LPS), lipoteichoic acid, flagellin and bacterial DNA, all of which are present in various micro-organisms [(2, 3)].

STREM-1 is expressed by neutrophils, macrophages and mature monocytes[(4)]. Its expression by effector cells dramatically increased in skin, biological fluids and tissues infected by Gram-positive and Gram-negative bacteria and fungi [(5)].

In contrast, sTREM-1 is not upregulated in samples from patients with non infectious inflammatory disorders such as psoriasis, ulcerative colitis, or vasculitis caused by immune complex [(6)].

The specific involvement of sTREM-1 solely in cases of infection led us to investigate the diagnostic value of plasma sTREM-1 assay in distinguishing sepsis from severe systemic non infectious inflammation among newly admitted critically ill patients with suspected infection [(7)].

sTREM-1 is the soluble form of TREM-1. It is a soluble triggering receptor which is expressed on myeloid cells [(8)]. Recent studies have shown that there is an increase in sTREM-1 concentration in body fluids in sepsis, while its concentration in the non-infectious etiology of inflammatory conditions is not increased. Based on this, sTREM-1 is tested as a potential biomarker for differentiation of sterile SIRS (Systemic Inflammatory Response Syndrome) and sepsis [(9)].

AIM OF THE WORK

The aim of the current study is to explore the utility of STREM-1 in early diagnosis of sepsis and determine its predictive value.

SUBJECTS AND METHODS

I- Subjects:

This is a case control study. It was conducted in Al-Zahraa University Hospital during the period from December 2018 to March 2019.

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Forty (40) subjects were included in this study; they were classified into two groups as follows:

A. **Patient group:** It included 25 patients with two or more of clinical signs of sepsis according to the four SIRS criteria, namely tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >20 breaths/min), fever or hypothermia (temperature >38 or <36 °C), and leukocytosis or leukopenia (white blood cells >12,000/mm^3 or <4,000/mm^3) **(10).** Their ages ranged from 10-80 years. Five (5) patients who were on antibiotic treatment and twenty (20) patients who were not on antibiotic treatment.

Exclusion criteria:

a. Patients who had a primary infection other than sepsis
b. Patients with past medical history of cardiovascular diseases
c. Immunocompromised patients

B. **Control group:** It included 15 apparently healthy volunteers. Their ages ranged from 15-74 years.

Patients group was subjected to:

1. **Complete history taking.**
2. **Clinical examination**, for signs of sepsis.
3. **Routine laboratory investigations**: Complete Blood Count (Hb, WBCs, and Platelets)
4. **Specific laboratory investigations:** C reactive protein (CRP), Blood culture and serum sTREM-1 level by ELISA.

Control group was subjected to:

1. **Routine laboratory investigations:** Complete Blood Count (Hb, WBCs, and Platelets).
2. **Specific laboratory investigations:** C reactive protein (CRP), serum sTREM-1 level by ELISA and blood culture.

II- Methods:

A- Complete blood count (CBC):

Was performed on automated cell counter, model XS 500i (Sysmex, Japan).

B- Specific laboratory investigations including:

1. **C-reactive protein (CRP):** Using Beckman Coulter AU Analyzer (AU400/400e/480).

2. **Blood Culture:**

The BD Bactec™ 9050 Blood Culture System, USA, instrument was used.

Subcultures of the positive Bactec samples were done on blood agar, chocolate agar, and MacConkey agar media and incubated at 37c for 24 hr. Identification of isolated organisms was done by colony morphology, microscopic examination by gram stain and conventional biochemical reactions:(triple sugar iron test, citrate test, urease test, MIO test (motility, indole, ornithine), lysine iron agar test, catalase test, DNAase test and oxidase test) **(11)**.

3. **Serum sTREM-1 level:**

Human soluble triggering receptor expressed on myeloid cell -1 (STREM-1) was measured quantitatively by ELISA kit supplied from Bioassay Technology Laboratory, USA, cat. no. E0310Hu. The sensitivity of this kit is <2.53 pg/ml and the detection range is 5-2000 pg/ml.

Ethical approval

The study was approved by the Ethics Board of Al-Azhar University and an informed written consent was taken from each participant in the study.

Statistical Analysis

Data were collected, coded, revised and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The data were presented as number and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data. **Independent t-test** was used in the comparison between two means of the 2 groups.

Spearman correlation coefficients were used to assess the significant relation between two quantitative parameters in the same group. **Receiver Operating Characteristic curve (ROC)** was used to assess the best cut-off point between the two groups with its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC).

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: $P > 0.05$: Non significant (NS), $P < 0.05$: Significant (S) and $P < 0.01$: Highly significant (HS).

RESULTS

Table 1: Descriptive data of patients and control groups

Parameter		Patients group (n=25)		Control group (n=15)		P
Age (years)	Mean ±SD	61.60 ± 20.73		46.93±24.04		0.064
	Range	10-84		11-82		
	From 10 to 30 years	3	12.0%	4	26.67%	
	From 31 to 50 years	2	8.0%	4	26.67%	
	From 51 to 84 years	20	80. 0%	7	46.67%	
WBC (mm^3)	Mean ±SD	17.08 ± 6.12		6.75±1.91		<0.001
	Range	5.20-29		3.8-9		
HB (gm/dl)	Mean ±SD	9.90 ± 2.39		11.84±1.92		0.011
	Range	7.60-19		8.8-14.40		
PLT (10^9/L)	Mean ±SD	214.93 ± 71.51		234.20±9.85		0.691
sTREM-1 (pg/ml)	Mean ±SD	617.22 ± 83.83		46.08±26.97		0.001
CRP (ml/L)	Mean ±SD	115.36 ± 7.08		4.20±0.56		0.001
Blood culture	Negative	0	0%	25	100%	
	Positive	25	100%	0	0%	

Table (3): demonstrates the descriptive data of patients group and control group.

Table 2: Comparison between antibiotic treatment and without antibiotic treatment as regards CRP and sTREM-1

	With antibiotic treatment		Without antibiotic treatment		P value
	Mean	SD	Mean	SD	
CRP	106.00	7.66	117.70	8.97	0.756
sTREM-1(pg]ml)	160.28	19.66	731.46	601.49	0.048

Table (2) show that there was a highly statistically significant decrease sTREM-1 in patients on antibiotic treatment.

Table 3: The correlation between sTREM-1 with Age, CRP and WBC, HB and PLT in patient group

	sTREM-1(pg/ml)	
	r	P value
Age	-0.272	0.188
CRP	0.075	0.722
WBC	0.707	0.001
HB	-0.116	0.580
PLT	-0.256	0.217

This table shows that sTREM-1 is positively correlated with WBCs count (p=0.001) while it was not correlated with age, CRP level, HB level & platelets count.

Table 7: Cut-off point, sensitivity and specificity of sTREM-1 between patients group and Control group

Cut off point	AUC	Sensitivity	Specificity	-PV	+PV
>97.8	1.000	100	100	100	100

This table shows that: The cut of point of sTREM-1 >97.8 pg/ml has 100% sensitivity,100% specificity, its positive predictive value is 100% and its negative predictive value is 100%

Table 8: Cut of point, sensitivity and specificity of CRP between positive and negative blood culture

Cut off point	AUC	Sensitivity	Specificity	-PV	+PV
>7	1.000	100.00	100.00	100.00	100.00

This table shows that: The cut of point of CRP >7 ml/l has a 100% sensitivity, 100% specificity, its positive predictive value is 100% and its negative predictive value is 100%

Table 9: Cut of point, sensitivity and specificity of HB between positive and negative blood culture

Cut off point	AUC	Sensitivity	Specificity	-PV	+PV
≤10.7	0.784	84.00	66.67	71.4	80.8

This table shows that: The cut of point of HB ≤10.7gm /dl has 84% sensitivity, 66.7% specificity, its positive predictive value is 80.8% and its negative predictive value is 71.4%.

Table 10: Cut of point, sensitivity and specificity of WBC between positive and negative blood culture

Cut off point	AUC	Sensitivity	Specificity	-PV	+PV
>9	0.917	84.00	100.00	78.9	100.0

This table shows that: The cut of point of WBC >9 mm3 has 84% sensitivity, 100% specificity, its positive predictive value is 100% and its negative predictive value is 78.9%.

DISCUSSION

On comparing our results; a nearly similar mean age of patients was reported by **Petric *et al.*** [12] in **2018** who performed their study on 41 patients suspected of having sepsis and 20 healthy volunteers aiming to test the diagnostic value of sTREM-1 in the context of a new definition of sepsis. They found that the mean age of patients was 58 ± 20.7 years.

The high mean WBC count found in cases in this study, compared to the normal WBC count in adults (3.4-9.6 /mm^3) [13, 14], is one of the sepsis criteria [15].

The current study revealed that there was no significant statistical difference between the cases and controls groups as regards age. This balance in the baseline characteristics provides the basis for comparison between the study groups as it helps to minimize bias [16].

As regard to WBC count, similar to our findings, the results reported by **Crouser *et al.*** [17] in **2017** who performed their study on 98 sepsis patients and 879 controls aiming to determine if volume increases of circulating immune cells add value to the WBC count for early sepsis detection in the emergency department. They found that WBC count was significantly higher in sepsis patients compared to controls.

Furthermore and concerning Hb level, findings of this study come in line with what was reported by **Jansma *et al.*** [18] in **2015** as they found that the sepsis group showed a significant reduction in Hb concentration compared to the control group with significant correlation between the reduction in Hb concentration and the amount of intravenous fluids administered. They attributed this reduction in Hb concentration to an iatrogenic component (intravenous fluids administration) in the short time frame as well as to changes in iron metabolism and a shortened life span of erythrocytes occurring in sepsis on a longer time frame.

Similar to our results, statistically significant higher levels of sTREM were found in the cases compared to the controls group was reported in the study published by **Petric *et al.*** [12].

As regards higher CRP levels in sepsis cases, similar results were published by **Nargis *et al.*** [19] in **2014** who performed their study on 73 patients aiming to evaluate the utility of procalcitonin in resource constrained countries when compared to the traditional inflammatory markers like CRP to introduce it as a routine biochemical tool in regional hospitals. They found that serum CRP values were significantly higher in sepsis cases when compared to cases without sepsis.

Regarding comparison between the cases with antibiotic treatment and the cases without antibiotic treatment as regards sTREM and CRP levels; the present study comes in line with what was published by **Samraj *et al.*** [20] in **2013** as they mentioned that plasma sTREM-1 levels had the highest discriminative value to differentiate SIRS, sepsis, severe sepsis and septic shock, followed by CRP.

The present study revealed that a statistically significant reduction in the mean sTREM level was found in the group of cases who received antibiotic treatment when compared to the group who did not receive antibiotic treatment with no other statistically significant differences between both groups as regards the mean CRP level. This can be explained by the bactericidal effect of antibiotics with subsequent reduction of sTREM-1 released by the body in response to infection.

This finding agrees with that published by **Aksaray *et al.* [21]** in **2016** who performed their study on 52 sepsis patients and 38 SIRS patients aiming to investigate the value of immunological indicators: procalcitonin and sTREM-1 in differential diagnosis of patients with sepsis and systemic inflammatory response syndrome, as well as to assess their importance in determining prognosis of patients with sepsis. They found that sepsis patients showed a statistically significant reduction in sTREM-1 levels with non-statistically significant changes in CRP levels with treatment.

The present study revealed that there was a highly statistically significant moderate positive correlation between the WBC count and sTREM level in the cases group, with no other significant correlations between sTREM level and age, CRP level, hemoglobin level or platelet count.

A different cut-off point of sTREM from ours was established by **Arizaga-Baleesteros *et al.* [22]** in **2015** who performed their study on 71 patients aiming to obtain estimates of the incidence and prevalence of septic shock and/or death in septic neonates for future sample size calculations for confirmatory studies and to evaluate the feasibility of using sTREM-1 as a predictor of septic shock and/or death in neonates. They found that sTREM-1 cut-off value of 300 pg/ml showed a sensitivity of 78%, specificity of 97%, positive predictive value of 78% and negative predictive of 97%.

Regarding the cut-off point, sensitivity and specificity of CRP between positive and negative blood culture; lower values than ours were reported in the study published in **2016** by **Hildenwall *et al.* [23]** who performed their study on 428 patients aiming to assess the role of point-of-care assessment of CRP and WBC count to identify bacterial illness in Tanzanian children with non-severe non-malarial fever. They found that the optimum cut-off for CRP was >19mg/L with negative predictive values exceeding 80% and positive values under 40%.

The present study revealed that at a Hb level cut-off point ≤10.7 gm/dl, its sensitivity was 84%, its specificity was 66.67%, its positive predictive value was 80.8% and its negative predictive value was 71.4% to differentiate positive and negative blood cultures.

The present study revealed that at a WBC count cut-off point of >9/mm^3, its sensitivity was 84%, its specificity was 100%, its positive predictive value was 100% and its negative predictive value was 78.9% to differentiate positive and negative blood cultures.

This finding is different from that published in **2017** by **Sugianli *et al.*[24]** who performed their study on 215 patients aiming to determine the cut-off value of WBC and bacterial count of fluorescence flow cytometry as an estimation of urine culture in symptomatic UTI population. They found that WBC count >300.7 cells/uL achieved sensitivity of 82.7%, specificity of 87.5%, positive predictive value of 96.6% and negative predictive value of 53.8%.

CONCLUSION

- The sTREM-1 is qunque biomarker having wide range of application in the medical field.
- It is useful in diagnosis of sepsis and differentiating between microbial and non-microbial infection cases.
- sTREM-1 can be widely used in clinical practical and can be more useful to rule out infection, monitor the effectiveness of therapy and guide early stopping of antibiotics.
- sTREM-1 guided antibiotic stewardship could be properly designated to develop a safer and affordable strategy for diagnosis of sepsis and its prognosis.

RECOMMENDATIONS

- sTREM-1 can be used to guide antibiotic therapy in individual patents as an effective biomarker as its level increase upon bacterial infection and decrease upon recovery.
- Further studies are needed to better understand the application of sTREM-1 in the diagnosis of sepsis and determining the therapeutic approaches for sepsis.
- As it is unlikely that a single biomarker serves as an effective diagnosis tool, a combination of emerging new biomarkers with sTREM-1 may be more functional in the case of clinical judgement based on which antimicrobial therapy may suggested, thus reducing the prescription and duration of antibiotic treatment.

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