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SHORT REPORT

Dynamic Changes in Soluble Triggering Receptor Expressed on Myeloid Cells-1 in Sepsis with Respect to Antibiotic Susceptibility

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Purpose: Proper antibiotic administration is crucial for sepsis management. Given the escalating incidence of antimicrobial resistance, there is a pressing need for indicators of antimicrobial susceptibility with short turnaround times. This study aimed to investigate the potential of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) as an early biomarker for in vivo antibiotic susceptibility in patients with sepsis.

Patients and Methods: We conducted a retrospective analysis of plasma samples from patients enrolled in a pre-established study designed to investigate prognostic biomarkers in patients with sepsis or septic shock. Baseline and 6 h sTREM-1 levels were examined using enzyme-linked immunosorbent assays. The primary outcome of the study was the comparison of percentage changes in sTREM-1 levels at the 6 h relative to baseline with respect to antibiotic susceptibility.

Results: Of the 596 patients enrolled in the pre-established study, 29 with a median age of 75.8 and a 28-day mortality rate of 17.2% were included in the present analysis. Among these patients, 24 were classified into the susceptible group, whereas the remaining five were classified into the resistant group. The trend in plasma sTREM-1 levels differed with respect to antibiotic susceptibility. Moreover, percentage change in sTREM-1 levels at the 6 h relative to baseline was significantly higher in the resistant group ($P = 0.028$).

Conclusion: The trend in plasma sTREM-1 levels in patients with sepsis differed with respect to antibiotic susceptibility, with a higher percentage change in patients treated with inappropriate antibiotics. These findings indicate the potential utility of sTREM-1 as an early biomarker of antibiotic susceptibility.

Keywords: anti-bacterial agents, biomarkers, drug resistance, sepsis, triggering receptor expressed on myeloid cells-1

Introduction

Timely and appropriate administration of antibiotics is crucial in sepsis management to improve patient survival.[1–3] Confirming the pathogen and its antimicrobial susceptibility is essential for achieving this objective. While blood culture is the gold standard for pathogen identification,[4,5] its extended turnaround times and potential failure to detect slow-growing pathogens pose significant limitations.[6,7] Furthermore, a significant proportion of sepsis cases yields negative blood culture results,[8,9] further restricting its clinical utility in guiding antibiotic selection.[8] Moreover, global rise in antimicrobial resistance adds complexity to antibiotic selection.[10] Therefore, development of rapid and accurate techniques for pathogen identification and susceptibility testing are imperative.[6,11] Additionally, there is a need for biomarkers that reflect the patient's response to antibiotics, aiding clinical decision-making alongside microbiological tests.[12,13] Although, several biomarkers have been explored for assessing treatment response in sepsis,[14–16] most rely on daily measurements, lacking time-related advantages compared to blood culture tests. Furthermore, our understanding of host biomarkers for treatment response, particularly concerning in vivo antibiotic susceptibility, remains limited.

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A previous study investigated dynamic alterations in hemodynamics and plasma biomarkers with respect to antibiotic susceptibility in a porcine model of bacteremia.[17] While there were no significant differences in hemodynamics and other biomarkers, the plasma level of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) exhibited significant differences in relation to antibiotic susceptibility over time. TREM-1 is a transmembrane receptor of the immunoglobulin superfamily that is mainly expressed on myeloid cells and is upregulated during infections.[18,19] Based on these findings, the authors proposed that sTREM-1 could potentially serve as a biomarker for in vivo antibiotic susceptibility. However, this study has limitation in its clinical applicability, considering the potential disparities in the kinetics of biomarkers between humans and porcine models. Therefore, current study aimed to investigate changes in plasma sTREM-1 levels in relation to antibiotic susceptibility in patients with sepsis.

Materials and Methods

Study Setting and Population

We conducted a retrospective analysis of archived plasma samples prospectively obtained from patients enrolled in a pre-established study (Protocol No. B-1004-097-005), which aimed to investigate biomarkers as prognostic factors in sepsis or septic shock. This study was conducted in the emergency department (ED) in a single urban tertiary academic hospital and included adult patients aged 18 years or older diagnosed with sepsis or septic shock. Patients who underwent cardiopulmonary resuscitation upon arrival at the ED, those with prior documentation of refusal to receive life-sustaining treatment or those who declined to participate in the study were excluded. A total of 4170 eligible patients were screened between May 1, 2010, and April 30, 2019. Of these, 601 patients were enrolled, with five withdrawals, resulting in a final cohort of 596 patients. Within this cohort, 72 patients provided additional plasma samples (at 6, 12, 18, 24, 36, and 48 h) for secondary analysis. Therefore, the present analysis was conducted using plasma samples of this subset of 72 patients.

The study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-2208-775-301). A waiver of informed consent from patients was granted due to the retrospective nature of the study.

Study Measures

Given that the previous animal study revealed a significant difference in sTREM-1 levels at 2 h post-antibiotic administration,[17] we evaluated changes in plasma sTREM-1 levels of patients who provided both baseline and 6 h mark samples. sTREM-1 levels were quantified using an enzyme-linked immunosorbent assay (ELISA) kit (Human TREM-1 DuoSet ELISA, R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions.

Demographic data and clinical variables were obtained through a review of the hospital's electronic medical records. The demographic information included age and sex. Clinical variables included underlying comorbidities and vital signs, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and heart rate (HR) at baseline and the 6 h mark. Initial laboratory results including white blood cell (WBC) count, hemoglobin, creatinine, albumin, C-reactive protein (CRP) and lactate levels were documented, and only lactate levels were reassessed after 6 h. The ED Sequential Organ Failure Assessment (SOFA) score, 6 h cumulative vasopressor dose presented as a norepinephrine equivalent dose, 28-day survival status, and whether the participant had been admitted to the intensive care unit (ICU) from the ED were also recorded. The primary outcome of the study was the comparison of percentage changes in sTREM-1 levels at the 6 h mark relative to baseline according to antibiotic susceptibility. In accordance with the Declaration of Helsinki, all data collected in this study were stored as anonymized data to protect the privacy of participants and to maintain the confidentiality of their personal information.

Data Analysis

Patients were categorized into either the susceptible or resistant group depending on the susceptibility of the pathogenic bacteria (confirmed by an initial culture study of either blood or specimens relevant to the site of infection, such as sputum, urine, or other body fluids) to the initially administered antibiotics. Patients with negative culture results of blood

or any other specimens were classified as susceptible group, if they had favorable clinical responses and survived for 28 days without changing initially prescribed antibiotics.

To assess changes in vital signs, lactate, and sTREM-1 levels between baseline and the 6 h mark, the percentage change in each value at the 6 h mark relative to baseline was calculated and compared between the two groups. The proportions of categorical variables were compared using Fisher's exact test, and continuous variables were compared using the Mann–Whitney *U*-test. Continuous variables are presented as medians and interquartile ranges (IQR), and categorical variables as absolute numbers and percentages, unless otherwise specified. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). The level of statistical significance was set at $P < 0.05$.

Results

Characteristics of Study Population

Of the 72 patients enrolled in the previous study and provided consent for serial sample collection, 29 had both baseline and 6 h plasma samples. Consequently, we evaluated these 29 patients, with a median age of 75.8 years and of whom 39.8% were female (Table 1). The median SOFA score of the cohort was 4 (IQR: 2–6). Nearly all patients (27 out of the 29 patients) were admitted to the ICU, and the 28-day mortality rate was 17.2%. The most frequent site of infection was the respiratory tract (17 patients, 58.6%), followed by the genitourinary (six patients, 20.7%), gastrointestinal (three patients, 10.3%), hepatobiliary (two patients, 6.9%), and musculoskeletal (one patient, 3.5%) systems.

Table 1 Patient Characteristics with Respect to Antibiotic Susceptibility

Characteristics	Susceptible (N = 24)	Resistant (N = 5)	*P*-value
Demographics			
Age, year	79.0 (72.5–84.8)	76.0 (70.5–77.0)	0.27
Sex, female	7 (29.2)	4 (80.0)	0.05
Comorbidities			
Diabetes	6 (25.0)	1 (20.0)	1.00
Hypertension	15 (62.5)	2 (40.0)	0.62
Chronic liver disease	2 (8.3)	1 (20.0)	0.45
COPD	5 (20.8)	0 (0.0)	0.55
Congestive heart failure	0 (0.0)	0 (0.0)	-
Chronic renal disease	1 (4.2)	0 (0.0)	1.00
Cerebrovascular disease	5 (20.8)	0 (0.0)	0.55
Malignancy	7 (29.2)	1 (20.0)	1.00
Clinical variables			
Vital signs at baseline			
Systolic blood pressure, mmHg	78.0 (71.3–88.3)	88.0 (72.5–134.0)	0.35
Diastolic blood pressure, mmHg	44.0 (37.5–51.5)	55.0 (48.0–77.0)	0.04
Mean blood pressure, mmHg	54.5 (49.3–62.5)	59.0 (57.7–96.2)	0.04
Heart rate, beat/minute	104.0 (78.0–126.3)	84.0 (57.5–105.0)	0.11
Vital signs after 6 h			
Systolic blood pressure, mmHg	109.0 (99.0–129.0)	105.0 (81.0–143.0)	0.89
Diastolic blood pressure, mmHg	62.5 (51.0–72.5)	63.0 (53.0–82.0)	0.98
Mean blood pressure, mmHg	73.5 (63.0–83.6)	74.3 (61.0–103.0)	0.72
Heart rate, beat/minute	92.5 (85.3–119.0)	90.0 (75.0–109.0)	0.49
SOFA score	8.5 (6.0–11.0)	8.0 (6.5–10.0)	0.77
6 h Cumulative vasopressor dose (NEE, mcg/kg)	38.0 (15.8–94.5)	43.5 (0.0–305.4)	0.95

(*Continued*)

Table 1 (Continued).

Characteristics	Susceptible (N = 24)	Resistant (N = 5)	*P*-value
Laboratory results			
WBC, $10^3/\mu L$	9.3 (5.1–14.8)	11.0 (3.7–23.2)	0.85
Hemoglobin, g/dL	11.2 (9.5–12.2)	9.8 (5.1–13.4)	0.48
Creatinine, mg/dL	1.6 (1.1–3.1)	0.7 (0.4–1.0)	<0.01
Albumin, g/dL	2.7 (2.2–3.3)	2.9 (1.2–3.5)	0.80
CRP, mg/dL	13.5 (5.8–23.4)	14.5 (2.4–18.2)	0.56
Lactate (baseline, mmol/L)	2.9 (1.8–4.5)	2.3 (1.6–5.4)	1.00
Lactate (6 h, mmol/L)	2.7 (1.4–4.1)	3.3 (1.6–9.6)	0.51
sTREM-1 (baseline, pg/mL)	626.6 (391.0–1262.4)	445.7 (305.0–1281.7)	0.27
sTREM-1 (6 h, pg/mL)	511.3 (408.1–1184.4)	456.9 (308.6–1586.2)	0.60
Clinical outcomes			
ICU admission	22 (91.7)	5 (100.0)	1.00
28-day mortality	4 (16.7)	1 (20.0)	1.00

Notes: Data are presented as medians and interquartile ranges for continuous variables and as absolute numbers and percentages for categorical variables, unless stated otherwise.

Abbreviations: COPD, chronic obstructive pulmonary disease; SOFA, Sequential Organ Failure Assessment; NEE, norepinephrine equivalents; WBC, white blood cell; CRP, C-reactive protein; sTREM-1, soluble Triggering Receptor Expressed on Myeloid cells-1; ICU, intensive care unit.

Patient Characteristics According to Antibiotics Susceptibility

Among the 29 patients who had both baseline and 6 h plasma samples, 24 patients were classified into the susceptible group (17 culture-positive and seven culture-negative), while the remaining five (all culture-positive) were classified into the resistant group. There were no significant differences in the demographics or comorbidities between the two groups (Table 1). When comparing vital signs, both baseline DBP and MBP were significantly lower in the susceptible group ($P = 0.04$ for both DBP and MBP), whereas other parameters did not differ. Additionally, there were no significant differences in the percentage changes in the hemodynamic variables at the 6 h mark relative to baseline ($P = 0.30$, 0.20, 0.35, and 0.63 for SBP, MBP and HR, respectively) (Figure 1). Among the baseline laboratory parameters, only serum creatinine levels were significantly different between the two groups, with higher values in the susceptible group ($P < 0.01$). Additionally, percentage change in plasma lactate levels at the 6 h mark relative to the baseline did not differ significantly ($P = 0.067$) (Figure 1). Moreover, the initial SOFA score and 6 h cumulative vasopressor dose were not significantly different between the two groups. With respect to clinical outcomes, no significant differences were observed in terms of ICU admission or 28-day mortality between the two groups.

Dynamic Changes in sTREM-1 Level According to Antibiotics Susceptibility

Plasma sTREM-1 levels at both baseline and 6 h mark were not significantly different between the two groups ($P = 0.27$, 0.60 for baseline and 6 h, respectively) (Table 1). However, plasma sTREM-1 levels tended to decrease in the susceptible group but exhibited an increasing trend in the resistant group. Additionally, the percentage changes in sTREM-1 levels at the 6 h mark relative to the baseline were significantly higher in the resistant group compared to the susceptible group (109.7 [IQR: 98.4–125.3] versus 97.5 [IQR: 86.9–102.6], $P = 0.028$) (Figure 1).

Discussion

In this retrospective analysis of prospectively collected plasma samples from patients with sepsis or septic shock, the trends in sTREM-1 levels varied depending on antibiotic susceptibility, with a significantly higher percentage change in sTREM-1 levels at the 6 h mark relative to baseline in the resistant group ($P = 0.028$). TREM-1 was initially identified in neutrophils and monocytes and is upregulated in response to bacterial lipopolysaccharides, thereby inducing the secretion of proinflammatory mediators.[18,20] Given these characteristics and considering the short half-life of sTREM-1,[21] appropriate antibiotic treatment may prevent further upregulation of TREM-1, leading to diminished release of

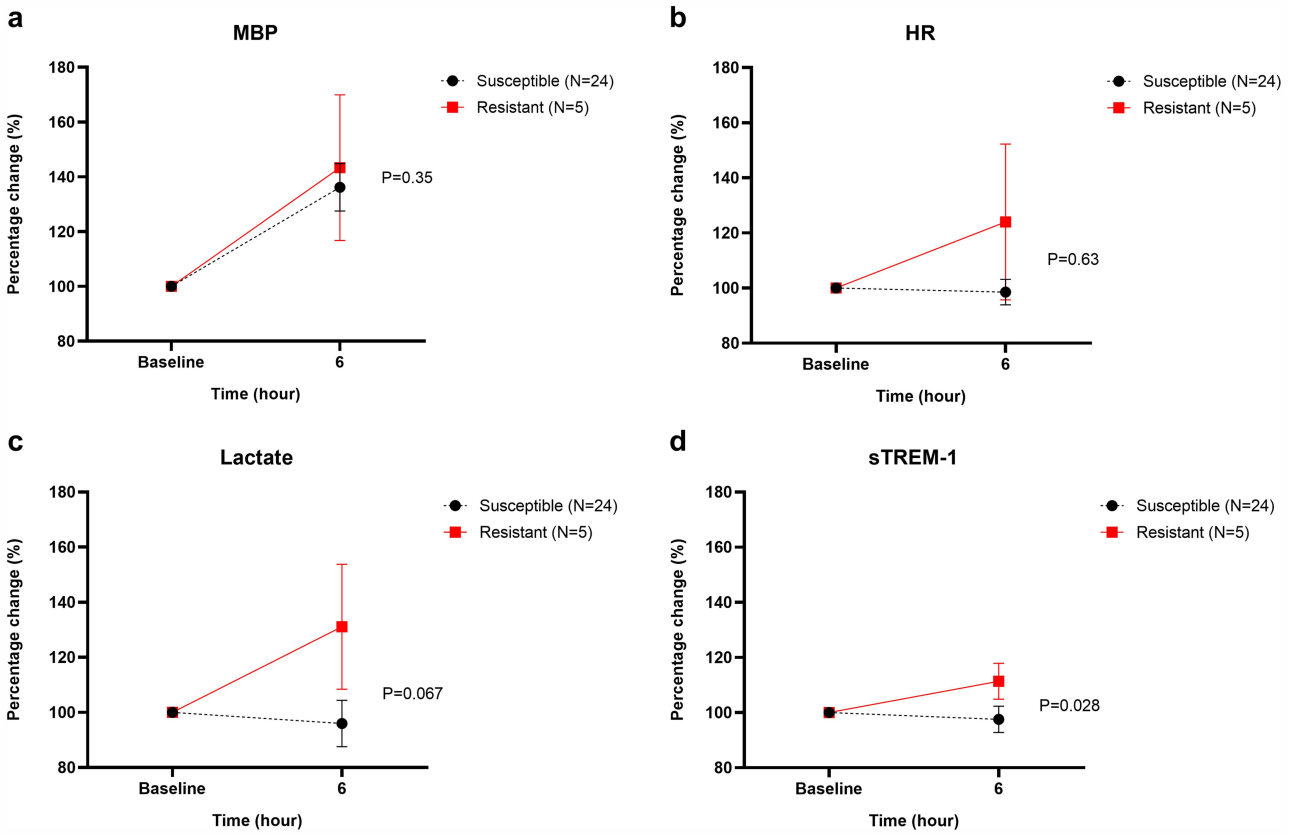

Figure 1 Percentage changes in hemodynamic variables and laboratory results at the 6 h mark relative to the baseline levels with respect to antibiotics susceptibility. (**a**) Mean blood pressure, (**b**) Heart rate, (**c**) Plasma lactate levels, and (**d**) Plasma sTREM-1 levels. Data are expressed as mean ± standard error.
Abbreviations: MBP, mean blood pressure; HR, heart rate; sTREM-1, soluble Triggering Receptor Expressed on Myeloid cells-1.

sTREM-1 in the post-antibiotic period, whereas the upregulation may persist with improper antibiotic usage. In contrast, there were no significant changes in hemodynamic variables with respect to antibiotic susceptibility over time. Initial resuscitation in sepsis management, including administration of fluids and vasoactive agents, aims to improve tissue perfusion,[1] and these interventions affect vital signs. Therefore, although the vital signs at the 6 h mark were somewhat different from baseline vital signs, there were no differences in vital sign variation during the 6 h period. Lactate levels exhibited a different trend, with an increasing tendency in the resistant group; however, the percentage change did not differ significantly. Because lactate is produced by anaerobic metabolism under tissue hypoxia,[22] the resuscitative measures could have affected lactate production, accounting for the insignificant differences.

In previous studies, sTREM-1 has been shown to be useful for detecting bacterial infections.[23,24] It has also been identified as a potential biomarker for sepsis, especially in combination with other biomarkers such as procalcitonin.[25–27] Additionally, sTREM-1 has been associated with the severity and prognosis of sepsis.[28–30] Despite its recognition as a biomarker for sepsis, its suitability as a biomarker for in vivo antibiotic susceptibility has not been investigated. Our results suggest that sTREM-1 could serve as an indicator of in vivo antibiotic susceptibility in the early post-antibiotic period in patients with sepsis or septic shock, extending findings from the previous preclinical animal study.

However, this study has several limitations as it was a retrospective examination of samples from a previous study that was not explicitly designed to explore dynamic changes in sTREM-1 levels based on antibiotic susceptibility. First, the number of samples available for analysis was limited. Therefore, with the observed opposing tendencies in sTREM-1 levels with respect to antibiotic susceptibility, we further validated our findings using a nonparametric method to ascertain statistical significance. Second, to augment the sample size, we assessed the antibiotic susceptibility of patients with negative culture results based on the clinical course, thereby raising concerns about the accuracy of the

susceptibility status. A more robust approach with a pre-estimated sample size designed to detect statistically significant differences in alterations in sTREM-1 levels over time with respect to antibiotic susceptibility could provide additional evidence to strengthen our conclusions. Third, the samples used in the present analysis were not controlled with respect to the timing of antibiotic administration. Among the 29 patients, baseline samples were obtained prior to the first antibiotic administration in 16 patients, with all 6 h samples from these patients were collected after antibiotic administration. In the remaining 13 patients, baseline samples were obtained after the first antibiotic administration, with a median time from antibiotic administration to baseline sample acquisition of 182 min (IQR: 105.5–225 min). Obtaining more robust evidence would be possible through prospectively collected samples designed to acquire samples before and 2–4 h after the first antibiotic administration.

Conclusion

The trends in dynamic changes in plasma sTREM-1 levels differed with respect to antibiotic susceptibility, with higher percentage changes in sTREM-1 level at the 6 h mark relative to the baseline in patients with sepsis initially treated with antibiotics to which the pathogenic bacteria were resistant. Further prospective studies are warranted to investigate the potential use of sTREM-1 as an early biomarker for in vivo antibiotic susceptibility.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-2208-775-301). A waiver of informed consent from patients was granted due to the retrospective nature of the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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