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Interleukin-10 and interleukin-1 receptor antagonist distinguish between patients with sepsis and the systemic inflammatory response syndrome (SIRS)

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ABSTRACT

The current study evaluated the potential of clinical parameters and circulating biomarkers to distinguish sepsis from SIRS in patients admitted with systemic inflammation. Clinical parameters, leukocyte counts and platelets were measured on admission. Circulating C-reactive protein (CRP), procalcitonin (PCT) and cytokine concentrations were quantified using laser immunonephelometry, immunoluminescence and a Bio-Plex suspension bead array system respectively. Blood, sputum, urine, peritoneal and cerebrospinal fluid were sent for microscopy and culture. Based on clinical information and the results of microbiological testing, 62 patients were classified retrospectively into 2 groups, those with sepsis (n = 37) or SIRS (n = 25). Mean body temperature was higher and blood pressure lower in the sepsis patients. Circulating concentrations of CRP, PCT, interleukin (IL)-10 and IL-1 receptor antagonist (IL-1Ra) were significantly higher in patients with sepsis, with IL-10 identified as the best biomarker in differentiating sepsis from SIRS. The biomarkers that best predicted overall mortality were platelet counts > PCT ≥ CRP > IL-6 > IL-1Ra. These findings demonstrate that patients with sepsis have significantly increased levels of the immunosuppressive/anti-inflammatory cytokines, IL-1Ra and IL-10, compared to those with SIRS, consistent with a more intense counteracting anti-inflammatory response, while a biomarker profile including platelets, PCT, CRP, IL-6 and IL-1Ra may be useful to predict mortality.

1. Introduction

The systemic inflammatory response syndrome (SIRS) defines criteria used to identify patients with systemic inflammation that may be due to infectious or non-infectious causes. If a source of infection is identified, sepsis is diagnosed and antimicrobial therapy should be initiated as early as possible to alleviate sepsis-associated mortality [1,2]. This minimizes administration of inappropriate antimicrobial chemotherapy to patients with SIRS without a source of infection, which has been shown to impact negatively on survival [3]. Consequently, the indiscriminate use of antimicrobial therapy for all patients with SIRS is not advocated, but should not be withheld from patients with sepsis. However, establishing a definite infective cause of sepsis is often delayed and inconclusive as the results of pathogen identification investigations may only be available after 48–72 h and, even then, despite advances in molecular diagnostics, detection may only be achieved in < 40% of patients [4]. Clearly, this uncertainty creates a dilemma for treating physicians, especially when the source of systemic inflammation, either of infectious or non-infectious origin, is not immediately apparent. In this context, the identification of host-and/or pathogen-derived systemic biomarkers of inflammation/infection, preferably with both discriminatory and prognostic potential, remains a research priority with considerable translational potential, particularly in the case of cytokines. The profile of cytokines released during systemic inflammation may depend, however, on the nature of the stimulus (infectious or non-infectious) [5] and may differ when sepsis is caused by Gram-negative versus Gram-positive bacteria [6].

Accordingly, the current study, undertaken in a southern African hospital setting, was designed to evaluate the potential of clinical parameters and circulating biomarkers of systemic inflammation to

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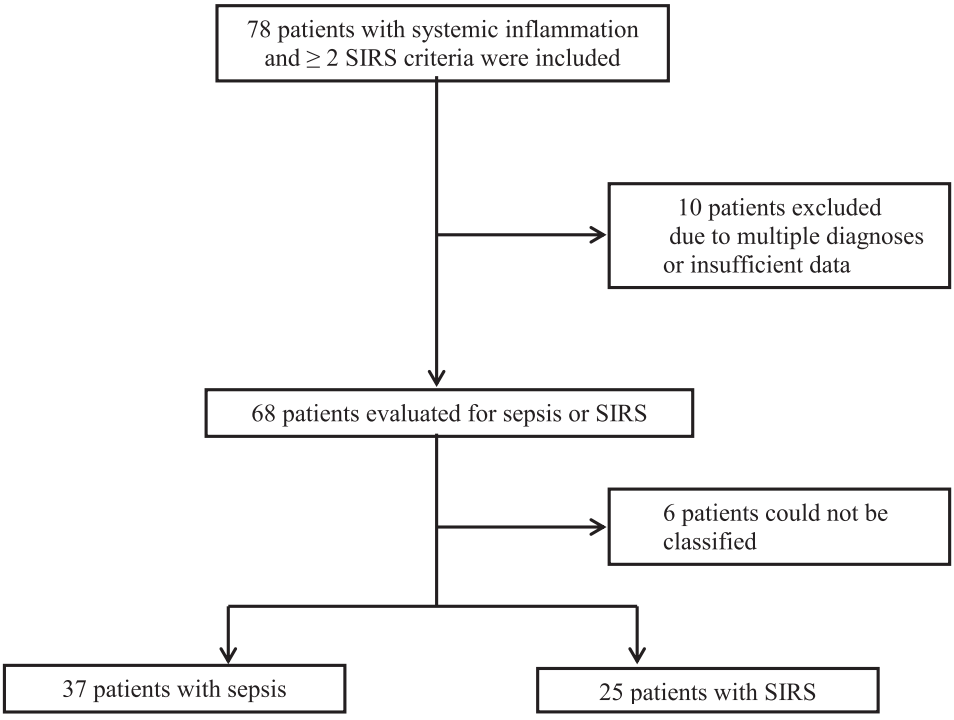

Fig. 1. The final number of patients enrolled in the study is indicated as well as those who were excluded prior to classification into 2 groups, namely those with sepsis or SIRS.

differentiate patients with sepsis from those with SIRS, as well as in predicting survival. This may be of particular relevance given that patients of African-American origin are reported to be at increased risk for development of post-traumatic sepsis [7]. The disease burden in sub-Saharan Africa may affect younger patients due to the prevailing socioeconomic conditions in this region [8]. The biomarkers investigated included circulating pro-inflammatory and anti-inflammatory cytokines, as well as C-reactive protein (CRP), procalcitonin (PCT), neutrophil gelatinase-associated lipocalin (NGAL), the soluble triggering receptor expressed on myeloid cells 1 (s-TREM-1), matrix metalloproteinase 9 (MMP-9), and the high mobility group box 1 protein (HMGB1). These biomarkers were chosen as being generally representative of systemic inflammation associated with activation of cells of the innate immune system, particularly neutrophils and monocytes/macrophages [9–17].

2. Patients and methods

The study was approved by the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria and Steve Biko Academic Hospital, Pretoria, South Africa. Patients admitted to the Emergency Unit or Medical wards and Medical Intensive Care Unit (ICU) at the Steve Biko Academic Hospital, University of Pretoria, Pretoria, South Africa, during a 6 month period, with a provisional diagnosis of the systemic inflammatory response syndrome (SIRS), were considered eligible for inclusion in the current study. Informed consent was given by all patients prior to enrolment. Patients were excluded if they did not meet 2 or more of the SIRS criteria shown below or had received antimicrobial therapy within the preceding 12 h.

SIRS was diagnosed if 2 or more of the following criteria were met [18]:

1. Body temperature > 38 °C or < 36 °C.
2. Heart rate > 90 beats/minute.
3. Respiratory rate > 20 breaths/minute.
4. White blood cell count > 12000 or < 4000 cells/mm^3.

As the current study was initiated prior to 2016, the recently revised definition of sepsis based on the degree of organ dysfunction (SOFA score) [16,18–20] was not used to classify patients. Although the new definition of sepsis has certain advantages over previous criteria, various authors have expressed reservations regarding the new definition. These include the SOFA score that is not universally available [20], exclusion of patients with isolated hypotension without organ dysfunction [21] and the requirement for evidence of significant organ dysfunction that may exclude patients with early sepsis [21]. However, the qSOFA score [22] that allocates 1 point for each of the following: respiratory rate ≥22/min, systolic blood pressure < 100 mmHg or a Glasgow coma scale ≤14, has been calculated for the patients with sepsis and correlated with mortality in this group.

Following informed consent, patients who met the SIRS criteria were included in the study. Clinical parameters including blood pressure, respiratory rate, body temperature and heart rate were recorded for each patient and blood or serum used to determine the white blood cell (WBC) and platelet counts, as well as concentrations of the prototype acute phase reactant, CRP and PCT, the latter considered to be a selective biomarker of bacterial infection. The plasma concentrations of circulating pro-and anti-inflammatory cytokines were measured within the first 24 h following admission of the patient.

In addition, appropriate samples such as blood, sputum, urine, pus, peritoneal fluid or cerebrospinal fluid (CSF) were collected for microbiological investigation, which included microscopy, culture and sensitivity at the discretion of the treating physician. When indicated, samples were also sent for microscopy and culture to detect *Mycobacterium tuberculosis*. A chest radiograph was also performed when indicated. Patients with presumed sepsis were treated empirically with antimicrobial therapy, which was adjusted according to culture results. Patients with SIRS were managed according to standard therapeutic protocols depending on the underlying condition.

Patients were monitored until discharge from hospital and the records of all patients, including those who did not survive, were retained and reviewed. Based on a detailed review of the available clinical information and the results of microbiological testing, patients were

classified retrospectively into 2 groups, namely those with sepsis and those with SIRS as shown in Fig. 1. The differentiation into these 2 groups was based on clinical findings, microscopy and culture results of blood, sputum, urine, peritoneal fluid, CSF and bronchial aspirates, response to antimicrobial therapy and radiographic abnormalities such as signs of lobar consolidation on chest X-ray.

2.1. Laboratory methods

To prepare serum, 5 millilitre (ml) of venous blood were collected in endotoxin-free, silicone-coated vacutainers containing a gel separator. The blood samples were allowed to stand at room temperature to coagulate (30–60 min) followed by centrifugation (3000 rpm for 10 min) after which the serum was removed, aliquoted, and stored at minus 20 °C until performance of the various assays described below with the exception of cytokine/chemokine analyses for which plasma was used. To prepare plasma, venous blood (10 ml) was collected into ethylenediaminetetraacetic acid (EDTA)-containing tubes and the plasma separated by centrifugation, aliquoted and stored as described above.

2.1.1. C-reactive protein (CRP) and procalcitonin (PCT)

CRP was assayed by laser immunonephelometry (Siemens Healthcare Diagnostics, BN Prospec Nephelometer, Newark, USA), with results expressed as micrograms (μg)/ml serum, while PCT was measured by means of an immunoluminescence procedure using a chemiluminometer and compatible reagents according to the manufacturer's protocol (Lumi Test, Brahm's Diagnostika, Berlin, Germany) with values of < 0.5 ng (ng)/ml serum considered to be in the normal range.

2.1.2. Cytokines and chemokines

Measurement of these was performed using the Bio-Plex suspension bead array system (Bio-Rad Laboratories Inc, Hercules, CA, USA) which utilizes Luminex xMAP multiplex technology. The following analytes were measured simultaneously using a 9-plex test kit: human interleukin (IL)-1β, IL-1 receptor antagonist (IL-1Ra), IL-6, IL-8, IL-10, IL-17A, tumor necrosis factor (TNF-α), granulocyte-colony stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) and results expressed as picograms (pg)/ml plasma An additional cytokine, human transforming growth factor-β1 (TGF-β1) was measured by a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) procedure (R&D Systems Inc. Minneapolis, MN, USA) following brief acidification of the plasma specimens to activate latent cytokine to the immunoreactive form and results expressed as ng/ml plasma. The upper limit of normal for these analytes was calculated as the mean +1 SD for 10 healthy control subjects (5 female, 5 male, average age 44.4 ± 15.0 years ranging from 26 to 65 years of age) and these values, as well as the corresponding values for CRP, HMGB1 and MMP-9 are shown as supplementary data.

2.1.3. Human neutrophil gelatinase-associated lipocalin (NGAL)

NGAL is considered to be a sensitive biomarker of sepsis severity and early renal injury [11], and in the current study serum levels of this biomarker were measured using a quantitative capture ELISA procedure (BioVendor Research and Diagnostic Products, Asheville, NC, USA) and the results expressed as ng/ml serum.

2.1.4. Human soluble triggering receptor expressed on myeloid cells (sTREM-1)

Following up-regulation of expression of TREM-1 on cells of the innate immune system, most commonly during bacterial and fungal infections, soluble TREM-1 (sTREM-1) is released from the cell membrane and can be detected in the circulation as a biomarker of infection and inflammation [9] and may predict survival in patients with neutropenic sepsis [14]. In the current study, serum concentrations of sTREM-1 were measured using a quantitative sandwich ELISA procedure (R&D Systems Inc. Minneapolis, MN, USA) and the results expressed as pg/ml serum.

2.1.5. Human matrix metalloproteinase-9 (MMP-9)

The granule proteinase, MMP-9, which is released by activated neutrophils and monocytes/macrophages, as well as structural cells, also possesses pro-inflammatory activities, including activation of vascular endothelium [10], was measured using a quantitative solid phase ELISA procedure (R&D Systems Inc.) with results expressed as ng/ml serum.

2.1.6. Human high mobility group box 1 protein (HMGB1)

This pro-inflammatory cytokine is produced, among other cell types, by monocytes/macrophages, dendritic cells and endothelial cells and amplifies inflammatory responses via interactions with several different receptors, particularly Toll-like receptor 4 expressed on neutrophils and monocytes/macrophages [13]. In the current study, serum concentrations of HMGB1 were measured using a quantitative sandwich ELISA procedure (IBL International, Hamburg, Germany) and the results expressed as ng/ml serum.

2.2. Statistical analysis

Statistical analysis was performed using WinStat statistical software. Results are expressed as the mean ± standard deviation, and levels of statistical significance were calculated using the Mann-Whitney *U* test for comparison of non-parametric data. A p value < 0.05 was considered as significant. The most promising of the various test biomarkers as predictors of mortality for the entire cohort of patients were identified using the Kruskal-Wallis non-parametric calculation. This strategy was used to calculate the sensitivity, specificity, positive predictive values (PPV) and receiver operating characteristic (ROC; area under the curve), which were constructed using the Kruskal-Wallis equality of populations rank test. The Spearman correlation with Bonferroni correction was used to measure the degree of dependency between the test biomarkers. An additional subgroup analysis was performed by stratifying patients into 4 quartiles based on the plasma concentrations of IL-10 and IL-1Ra. The Fisher's exact test was used to determine whether the concentrations of these 2 cytokines within each quartile were significantly different for patients with sepsis or SIRS.

3. Results

3.1. Patients

Using the SIRS criteria, 68 patients were evaluated for inclusion in the study. Six patients could not be classified into either group and were excluded from the analysis. Of the remaining 62 patients (40 males and 22 females) with a mean age of 43.7 years (SD = 17.3), 37 patients (21 males and 16 females) were classified into the sepsis group according to pathogen identification, while 25 (19 males and 6 females) were categorized as SIRS patients without an apparent source of infection. The mean ages ± SD for the sepsis and SIRS groups were 39.9 ± 15.4 and 48.2 ± 18.6 years, respectively. The clinical diagnoses and micro-organisms identified from those patients with sepsis, as well as the clinical diagnoses of those patients with SIRS are shown in Tables 1 and 2 respectively. Respiratory tract infections, particularly community-acquired pneumonia (CAP), were the most commonly encountered in patients with sepsis (29.7%). Other frequent sites of infection were the urogenital tract (18.9%), gastrointestinal system (8.1%) and central nervous system (5.4%). The most common precipitants of systemic inflammation in the SIRS group of patients included disorders of the cardiovascular system (36%) and the respiratory system (28%).

Table 1
The clinical diagnosis, systems affected and the micro-organisms identified from the patients with sepsis. The number of patients diagnosed with each condition and the type of specimen cultured is indicated in brackets.

System	Clinical diagnosis	Micro-organisms Identified
Respiratory	Community-acquired pneumonia (5)	*H. Parainfluenza* (sputum) *S. pneumoniae* (blood)
	Ventilator-associated pneumonia (2)	*S. aureus, K. pneumoniae* (tracheal aspirate)
	Pulmonary tuberculosis (4)	*M. tuberculosis* (sputum)
Gastrointestinal	Spontaneous bacterial peritonitis (2)	*K. pneumoniae, Enterobacter* (ascitic fluid)
	Liver abscess (1)	*E. histolytica* (ascitic fluid)
Musculoskeletal	Septic arthritis (1)	*P. mirabilis and S. aureus* (pus)
	Soft tissue infection (1)	*P. aeruginosa*, *S. aureus* (pus)
Urogenital	Urinary tract infection (3)	*Enterococcus*, *K. pneumoniae* (urine)
	Pyelonephritis (4)	*Enterobacter* spp. (blood, urine) *E. coli* (blood) *K. pneumoniae* (blood, urine)
Haematological	Neutropenic sepsis (1)	*S. epidermidis* (blood)
Neurological	Meningitis (2)	*S. pneumoniae*, *C. neoformans* (CSF)
Cardiovascular	Subacute bacterial endocarditis (1)	*E. faecalis* (blood)
Other	Septicaemia (9)	*S. aureus, E. faecalis, Enterococcus* spp., *K. pneumoniae, S. pneumoniae, E. coli, S. milleri* (blood)
	Malaria (1)	*P. falciparum* (blood)

Key: *H. Parainfluenza* = *Haemophilus parainfluenzae*, *S. pneumoniae* = *Streptococcus pneumoniae*, *S. aureus* = *Staphylococcus aureus*, *K. pneumoniae* = *Klebsiella pneumoniae*, *M. tuberculosis* = *Mycobacterium tuberculosis*, *E. histolytica* = *Entamoebahistolytica*, *P. mirabilis* = *Proteus mirabilis*, *P. aeruginosa* = *Pseudomonas aeruginosa*, *E. coli* = *Escherichia coli*, *S. epidermidis* = *Staphylococcus epidermidis*, *C. neoformans* = *Cryptococcus neoformans*, *E. faecalis* = *Enterococcus faecalis*, *S. milleri* = *Streptococcus milleri*, *P. falciparum* = *Plasmodium falciparum*, spp = species.

3.2. Clinical parameters

The clinical parameters for patients classified as either sepsis or SIRS are shown in Table 3. The mean body temperature of the sepsis group was significantly higher than that of the SIRS group, while systolic and diastolic blood pressure were lower in patients with sepsis. None of the other clinical parameters differed significantly between patients with sepsis or SIRS.

3.3. Biomarkers of inflammation

The concentrations of the test circulating plasma cytokines and the other systemic biomarkers of infection and/or inflammation, as well as the total leukocyte and platelet counts of patients with sepsis or SIRS are shown in Table 3. Concentrations of circulating CRP, PCT, IL-10, and IL-1Ra were significantly higher ($p < 0.006 - p < 0.044$) in the sepsis group, with similar, albeit statistically insignificant, trends noted in the case of total leukocyte counts and concentrations of IL-6, IL-17A and G-CSF.

The concentrations of the other cytokines and biomarkers of inflammation, specifically TNF-α, GM-CSF, TGF-β1, NGAL, sTREM-1, MMP-9 and HMGB1 were comparable in both groups (Table 3). A supplementary table is provided showing the normal values for these biomarkers in healthy control individuals.

A comparison between the survivors (n = 40) and non-survivors (n = 22) for the combined sepsis and SIRS groups is shown in Table 3. Platelet counts were significantly lower ($p < 0.02$) and IL-6 elevated ($p < 0.015$) in the combined group of non-survivors. Although circulating concentrations of IL-1Ra and G-CSF tended to be higher, while IL-1β, IL-8, IL-17A, and GM-CSF were lower in patients who did not survive, these differences did not attain statistical significance.

3.4. Mortality

The total number of patients who did not survive was 22, of which 15 and 7 occurred in the sepsis and SIRS groups respectively. The sensitivity, specificity, positive likelihood ratio and area under the ROC curves of the most promising biomarkers, these being platelet count and circulating concentrations of CRP, PCT, IL-6, and IL-1Ra, to predict mortality are shown in Table 4. All of these biomarkers predicted mortality with reasonable accuracy with positive predictive values ranging from 63% in the case of IL-6 and 82% for the platelet count. The qSOFA score did not predict mortality in patients with sepsis.

3.5. Correlation and contingency analysis

When combining the two groups of patients, moderate-to-strong positive correlations were detected between IL-1β and IL-8 (r = 0.903; $p < 0.0001$), while IL-1Ra was found to correlate with both PCT (r = 0.64; $p < 0.0001$) and IL-6 (r = 0.72; $p < 0.0001$). In the combined group of non-survivors, moderate-to-strong positive correlations were detected between PCT and all three of the following: IL-1Ra (r = 0.87; $p < 0.0001$), IL-6 (r = 0.805; $p < 0.004$) and G-CSF (r = 0.80; $p < 0.005$). IL-1Ra also correlated very strongly with IL-6 (r = 0.952; $p < 0.0001$), as well as with G-CSF (r = 0.88; $p < 0.0001$), the latter also correlating strongly with IL-6 (r = 0.913;

Table 2
The clinical diagnosis and systems affected for the patients with SIRS. The number of patients diagnosed with each condition is indicated in brackets.

System	Diagnosis
Respiratory	Bronchiectasis (1), COPD exacerbation (1), lung mass (1), pleural effusion (1), acute asthma (1), aspiration (1), lung nodules (1)
Gastrointestinal	Hepatic encephalopathy (1)
Trauma	Major trauma (2)
Urogenital	Chronic renal failure (1)
Haematological	Aplastic anaemia (1), pancytopenia (1)
Neurological	Stroke (1)
Cardiovascular	Congestive heart failure (4), RV thrombus (1), hypertensive crisis (1), pericardial effusion (1), mitral valve disease (1), myocardial infarction (1)
Endocrine	Diabetic ketoacidosis (2)

Key: COPD = chronic obstructive pulmonary disease, RV = right ventricular.

Table 3
The clinical parameters and systemic biomarkers of patients with sepsis and SIRS, as well as survivors and non-survivor for the combined groups.

Clinical Parameters	Sepsis (n = 37)	SIRS (n = 25)	Survivors (n = 40)	Non-survivors (n = 22)
Temperature (°C)	37.5 ± 1.28	36.9 ± 1.2*	37.2 ± 1.4	37.4 ± 1.2
Respiratory Rate (breaths/min)	24.6 ± 6.4	23.8 ± 4.8	24 ± 4.8	24 ± 7.7
Pulse Rate (beats/min)	111 ± 123	107 ± 18.4	106 ± 18.6	114 ± 165
SBP(mmHg)	117 ± 24.8	134 ± 38.5*	126 ± 35	118 ± 25
DBP(mmHg)	70.4 ± 122	84 ± 24.4*	78 ± 20.4	12 ± 15.5
Biomarkers				
WBC (cells/mm^3)	14.3 ± 10.8	11.3 ± 7.3	13.2 ± 9.9	13 ± 8.8
Platelets (cells/mm^3)	228.4 ± 151	271 ± 180	278 ± 169	180 ± 126*
CRP (μg/ml)	229 ± 152	124 ± 135*	178 ± 160	208 ± 136
PCT (ng/ml)	26.2 ± 47.8	5.0 ± 8.3*	14 ± 28.8	24 ± 52
TGF-β1 (pg/ml)	541 ± 511.5	757 ± 597	696 ± 566	474 ± 485
IL-1β (pg/ml)	3.7 ± 9.9	10.4 ± 40.6	8.7 ± 32	1.5 ± 1.8
IL-17A (pg/ml)	6.6 ± 14	2.4 ± 6	6.3 ± 13.5	3.0 ± 6.5
IL-6 (pg/ml)	472 ± 1133	245 ± 402	354 ± 998	426 ± 690*
IL-8 (pg/ml)	434 ± 1495	752 ± 2640	830 ± 2556	269 ± 314
IL-10 (pg/ml)	81.2 ± 293	9.8 ± 15*	54 ± 265	48 ± 112
IL-1Ra (pg/ml)	1499 ± 2806	525 ± 1222*	802 ± 1617	1720 ± 3347
GM-CSF (pg/ml)	4.1 ± 9.9	5.1 ± 11.6	5.3 ± 11.4	2.6 ± 8
G-CSF (pg/ml)	356 ± 1495	153 ± 434	128 ± 350	580 ± 2122
TNF-α (pg/ml)	12.7 ± 14.7	11.1 ± 14.8	13 ± 12.9	11.7 ± 18
S-TREM (pg/ml)	416.4 ± 360	408 ± 311	430 ± 369	366 ± 258
HMGB1 (ng/ml)	25.1 ± 24	21 ± 20.3	25.3 ± 23.4	20 ± 19.7
MMP-9 (ng/ml)	15.1 ± 5.9	13.8 ± 7.3	15.2 ± 6.4	13.6 ± 6.6
NGAL (ng/ml)	199.4 ± 98.7	184 ± 114	191 ± 110	205 ± 93

Key: SBP = systolic blood pressure, DBP = diastolic blood pressure, WBC = white blood cell count, CRP = C-reactive protein, PCT = procalcitonin, TGF-β1 = transforming growth factor β1, IL = interleukin, IL-1Ra = interleukin 1 receptor antagonist, GM-CSF = granulocyte macrophage colony-stimulating factor, G-CSF = granulocyte colony-stimulating factor, TNF-α = tumor necrosis factor-α, s-TREM = soluble triggering receptor expressed on myeloid cells, HMGB1 = high mobility group box 1 protein, MMP-9 = matrix metalloprotein-9, NGAL = neutrophil gelatinase-associated lipocalin.

* $P < 0.05$.

$p < 0.0001$). A comparison of the IL-10 concentrations in the higher quartiles of patients with sepsis and SIRS revealed a likelihood ratio for sepsis patients of 9.5 ($p < 0.033$), indicative of the superiority of this cytokine in distinguishing between these conditions.

4. Discussion

Patients with sepsis need to receive early, appropriate antimicrobial therapy in order to decrease the mortality associated with this condition [23,24]. However, differentiation of sepsis from SIRS in the clinical setting is often difficult. Although clinical parameters form an integral component of the clinical evaluation of all patients with SIRS, the results of the current study suggest that only 2 clinical parameters, namely body temperature and blood pressure, may differentiate sepsis from SIRS, while heart rate and respiratory rate were similar in both groups of patients. This limitation in respect of availability of reliable, discriminatory clinical parameters, together with the prevailing limitations of pathogen identification procedures [4,25], has led to a search for systemic biomarkers that may be used to differentiate SIRS from sepsis, with a wide range of these having been investigated in clinical trials [26,27].

In the current study, a range of circulating cytokines and other inflammatory biomarkers was measured in patients with sepsis and SIRS. The patients with sepsis had significantly higher concentrations of CRP and PCT, which may be indicative of bacterial infection. As also observed in the current study, specifically in the sepsis group, increases in CRP paralleled those of IL-6 and G-CSF as previously described [28]. CRP, however, is a non-specific indicator of systemic inflammation and patients with non-infectious causes of SIRS may also have markedly increased serum concentrations of this acute phase reactant [29]. PCT has, on the other hand, been used to differentiate sepsis from SIRS [30], but some patients with non-infectious causes of systemic inflammation may have increased levels of circulating PCT [31]. Therefore, in the clinical setting, the diagnostic utility of measurement of CRP and PCT should be considered in conjunction with additional clinical and other laboratory information.

With respect to systemic cytokine reponses, the concentrations of the circulating anti-inflammatory cytokines, IL-Ra and IL-10, both of which are released predominantly by monocytes/macrophages during acute inflammatory responses [32–34], were significantly greater in patients with sepsis compared to those with SIRS. This finding is in keeping with the compensatory anti-inflammatory response (CARS) that accompanies sepsis, the intensity of which may predispose to an unfavorable outcome [35]. In this context, circulating concentrations of the pro-inflammatory cytokines, IL-1β and IL-8, were lower in the sepsis group, albeit not significantly so, an observation which is nevertheless

Table 4
The sensitivity (%), specificity (%), positive predictive value (%) and area under the ROC curves of the circulating concentrations of CRP, PCT, IL-6, and IL-1Ra and platelet count in relation to prediction of mortality.

Biomarker	Threshold concentration (cut-point)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Area under ROC curve (95% CI)
CRP (μg/ml)	198	46 (31–63)	60 (36–81)	70 (50–86)	0.53 (0.40–0.67)
PCT (ng/ml)	2.1	59 (41–75)	50 (27–73)	67 (47–83)	0.54 (0.40–0.68)
IL-6 (pg/ml)	25	64 (48–78)	20 (6–44)	63 (47–77)	0.64 (0.54–0.80)
Il-1Ra (pg/ml)	276	71 (55–84)	60 (36–81)	79 (63–90)	0.65 (0.53–0.79)
Platelet count (cells/mm^3)	231	61 (43–76)	73 (49–91)	82 (63–94)	0.67 (0.54–0.80)

consistent with an association between elevated levels of IL-1Ra and IL-10 and suppression of the inflammatory response in these patients. It is noteworthy that IL-10 has been identified as a major contributor to sepsis-associated immunosuppression and mortality [35–39], while in the current study systemic levels of this cytokine appear to differentiate between sepsis and SIRS. Sources of the anti-inflammatory cytokines IL-1Ra and IL-10 during sepsis include monocytes, neutrophils and T-lymphocytes. Circulating concentrations of IL-1Ra are increased in patients with sepsis and may predict cardiovascular dysfunction and the need for vasopressor therapy [40]. Similarly, elevated levels of IL-10 may predict the onset of organ failure and correlate with the severity of sepsis [41]. Furthermore, it has been reported that higher IL-10 concentrations correlate with increased levels of IL-6 in patients with severe sepsis, a trend noted in the current study, with this combination of anti-inflammatory and pro-inflammatory cytokines being strongly associated with in-hospital mortality, as well as mortality post-discharge [42–46]. These associations have not, however, been noted in two other studies [47,48].

Additional important contributory pro-inflammatory mechanisms include those involving pathogen-associated molecular patterns (PAMPS) expressed by microbial pathogens which are recognized by pathogen-recognition receptors (PRRs) such as Toll-like receptors (TLRs). Activated TLRs trigger multiple intracellular signalling pathways with consequent activation of various genes which promote the synthesis of an array of cytokines and molecules that characterize the pro-inflammatory response against invading pathogens [49]. Danger-associated molecular patterns (DAMPs) are intracellular molecules released by damaged cells that activate intracellular TLRs inducing a signalling cascade [49]. PAMPs can induce the secretion of DAMPs by cells of the immune system and consequently DAMPs may also contribute to the organ dysfunction that is found in many patients with sepsis [50].

The mortality rate of patients with sepsis in the current study was 40%, while the reported mortality rate for patients with sepsis and septic shock ranges from 17.3% for those with sepsis and may reach 71.7% for those with septic shock [51]. With respect to mortality, a trend was evident with respect to increased systemic concentrations of IL-1Ra in the setting of decreased levels of IL-1β and IL-8, suggesting that suppression of the host inflammatory response is a significant contributor to mortality in both sepsis and SIRS, with IL-1Ra seeming to play a key role [52]. Notably, IL-1Ra was found to correlate strongly with both PCT and IL-6.

A significantly lower platelet count was also observed in the combined group of non-survivors. In this context, it is noteworthy that platelet counts of $< 100 \times 10^9$/L have been reported to be predictive of mortality in sepsis patients admitted to intensive care units [53]. Prioritisation of biomarkers with respect to prediction of mortality revealed the following ranking of positive likelihood ratios: platelets > PCT ≥ CRP > IL-6 > IL-1Ra. Our findings with respect to IL-6 and IL-1Ra are in agreement with those of an earlier study focused exclusively on severe community-acquired pneumonia (CAP). However, in contrast to that study, TNF-α and s-TREM-1 failed to predict mortality in the current study [54].

Limitations of the current study include the number of patients, mixed types of infection in those with sepsis, as well as the variety of conditions causing SIRS in those without sepsis. However, this broad spectrum of diagnoses and ongoing reliance on microbial cultures to diagnose sepsis mimics the clinical reality faced by many physicians as affirmed in recent publications [4,25].

5. Conclusion

The findings of the current study have revealed insights into the immunpathogenesis of sepsis/SIRS inflammation-related immunosuppression, in particular the apparent involvement of IL-10 and IL-1Ra. Both of these biomarkers of inflammation, in particular IL-10, may be useful in differentiating sepsis from SIRS. With respect to prediction of mortality, inclusion of measurement of circulating platelet counts, IL-6 and IL-1Ra as adjuncts to CRP and PCT, may enhance the early identification of those sepsis and SIRS patients at greatest risk of a poor outcome. Future studies that include an additional ICU control group and measurement of biomarkers at different stages during sepsis, as well as measurement of cell-associated cytokines may be useful.

6. Clinical relevance

Patients with sepsis require rapid initiation of antimicrobial therapy while those with systemic inflammation (SIRS) not due to infection, should not receive these agents. Therefore, biomarkers that reliably differentiate between sepsis and SIRS may facilitate the identification of patients with sepsis requiring antimicrobial therapy and contribute to improved patient outcomes. The findings of the current study suggest that circulating concentrations of C-reactive protein (CRP), procalcitonin (PCT), interleukin (IL)-10, and IL-1 receptor antagonist (IL-1Ra) are significantly higher in patients with sepsis compared to those with SIRS and the platelet count, CRP, PCT, IL-6 and IL-1Ra may predict mortality.

Declaration of Competing Interest

None of the authors has any conflict of interest, financial or otherwise, to report.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2019.05.015.

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