Journal of Critical Care 29 (2014) 718–722

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Performance of interleukin-27 as a sepsis diagnostic biomarker in critically ill adults

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ARTICLE INFO

Keywords:
Sepsis
Biomarkers
Interleukin 27
Procalcitonin
Infection
Diagnosis

ABSTRACT

Purpose: We recently identified interleukin-27 (IL-27) as a sepsis diagnostic biomarker in children. Here we assess IL-27 as a sepsis diagnostic biomarker in critically ill adults with systemic inflammatory response syndrome and sepsis.
Methods: IL-27 and procalcitonin (PCT) were measured from plasma samples in three groups: no sepsis (n = 78), pulmonary source of sepsis (n = 66), and non-pulmonary source of sepsis (n = 43). Receiver operating characteristic curves and classification and regression tree methodology were used to evaluate biomarker performance.
Results: IL-27 did not discriminate effectively between sepsis and sterile systemic inflammatory response syndrome in unselected patients. The highest area under the curve (AUC) was 0.70 (95% C.I. 0.60 – 0.80) for IL-27 in subjects with a non-pulmonary source of sepsis. A decision tree incorporating IL-27, PCT, and age had an AUC of 0.79 (0.71–0.87) in subjects with a non-pulmonary source of sepsis. Compared to children with sepsis, adults with sepsis express less IL-27.
Conclusions: IL-27 performed overall poorly in this cohort as a sepsis diagnostic biomarker. Combining IL-27, PCT, and age reasonably estimated the risk of sepsis in subjects with a non-pulmonary source of sepsis. IL-27 may be a more reliable sepsis diagnostic biomarker in children than in adults.

1. Introduction

The systemic inflammatory response syndrome (SIRS) is seen commonly in critically ill patients. SIRS is not a diagnosis, but rather a non-specific, clinical and laboratory descriptor of a generalized inflammatory state, which can occur in association with heterogeneous forms of critical illness, including sepsis [1,2]. Differentiating critically ill patients with SIRS secondary to infection (ie, sepsis) from those with SIRS secondary to a non-infectious process (ie, sterile inflammation) remains an important clinical challenge with therapeutic implications. Microbiologic cultures remain the diagnostic gold standard but can lack sensitivity, and there is an inherent delay between patient presentation and obtaining actionable data from such cultures. Consequently, there remains widespread interest in the development of diagnostic biomarkers that can provide an early estimation of sepsis risk in patients with SIRS, before microbiologic data become available [3–7].

Interleukin-27 (IL-27) is a heterodimeric cytokine produced by antigen presenting cells upon exposure to microbial products and inflammatory stimuli [8]. IL-27 regulates T cell function and has both pro- and anti-inflammatory effects [9,10]. Ablation of IL-27 activity, by either genetic deletion or a soluble decoy receptor, confers a survival advantage in a murine model of sepsis [11]. Thus, it is biologically plausible that IL-27 can serve as a sepsis diagnostic biomarker.

Using genome-wide expression profiling, we previously identified IL-27 as a candidate sepsis diagnostic gene in children with sepsis, which outperformed procalcitonin (PCT) [12,13]. We subsequently tested the diagnostic performance of IL-27 in an adult cohort and found that a combination of IL-27 and PCT identified critically ill adults with a non-pulmonary source of sepsis more reliably than either biomarker alone [14]. This latter observation is consistent with the concept that sepsis diagnostic biomarkers may perform differently depending on the source of infection [15]. Because biomarker performance can also depend on the population being studied, we conducted the current study to explore further the diagnostic utility of IL-27, alone and in combination with PCT, as a sepsis diagnostic biomarker in critically ill adults meeting SIRS criteria.

2. Methods

2.1. Ethics statement

The study was approved by the institutional review board of the University of California, San Francisco, CA. All patients or their surrogates

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http://dx.doi.org/10.1016/j.jcrc.2014.04.004
0883-9441/

provided written informed consent for study participation, with the exception of (1) patients who died before they or their surrogate could be approached for informed consent and (2) patients whose critical illness precluded them from providing informed consent and for whom a surrogate could not be identified after 28 days. For these two categories of patients, the institutional review board approved a waiver of consent.

2.2. Study subjects and case definitions

We studied 187 prospectively enrolled critically ill adult patients admitted to either a tertiary care hospital intensive care unit (ICU) or a safety net public hospital ICU from the corresponding emergency department (as part of the Early Assessment of Renal and Lung Injury Study) [16]. Patients were excluded if they were admitted for an isolated neurological or neurosurgical diagnosis without any significant medical comorbidities or if they were admitted to the trauma service. Plasma specimens were obtained as soon as possible after presentation to the emergency department.

For this study, we selected from the cohort described above patients who met criteria for SIRS at the time of ICU admission. These patients were categorized as no sepsis (n = 78); pulmonary source of sepsis (n = 66); or non-pulmonary source of sepsis (n = 43). Sepsis was defined by an attending physician after careful review of the patient's entire hospitalization, using consensus criteria [1]. The source of infection was similarly determined by attending physician review, as in prior studies [16–18]. The classification of a pulmonary source of sepsis was based on a combination of radiographic data (chest roentgenogram or chest computed tomography), microbiologic data (sputum or bronchoalveolar lavage samples), and impression of the treating physician team.

2.3. Measurement of IL-27 and PCT plasma concentrations

IL-27 (EMD Millipore Corporation, Billerica, MA) and procalcitonin (Bio-Rad, Hercules, CA) protein concentrations were measured in duplicated plasma samples using a magnetic bead multiplex platform and a Luminex 100/200 System (Luminex Corporation, Austin, TX), according to the manufacturers' specifications. These were the same assays used in our original pediatric study [13], and we have not observed any differences in assay performance between the two study periods.

Initially, biomarker data were described using medians, interquartile ranges, and percentages. Biomarker comparisons between groups used the Mann-Whitney *U* test (SigmaStat Software, Systat Software, Inc, San Jose, CA). Receiver operating characteristic (ROC) curves and the respective area under the curve (AUC) were constructed and compared using SigmaStat Software. Associations between IL-27 concentrations and selected clinical variables were measured using simple linear regression.

Classification and regression tree (CART) analysis was conducted using the Salford Predictive Modeler v6.6 (Salford Systems, San Diego, CA) [13,19,20]. The primary outcome variable for the modeling procedures is sepsis. The secondary outcome variable for the modeling procedure is sepsis from a non-pulmonary source of infection, as in our previous report [14]. The CART procedure considered IL-27, PCT, and age as potential predictor variables. Weighting of cases and the addition of cost for misclassification were not used in the modeling procedures. Performance of the derived model is reported using diagnostic test statistics with 95% confidence intervals computed using the score method as implemented by the VassarStats Website for Statistical Computation [21].

3. Results

3.1. Primary analysis

Table 1 provides the clinical characteristics of the study subjects. Compared to the subjects without sepsis, a greater proportion of subjects with a pulmonary source of sepsis met the SIRS temperature criterion and a greater proportion of subjects with a non-pulmonary source of sepsis met the SIRS white blood cell criterion. Subjects with a pulmonary source of sepsis were also more likely to have an oncologic comorbidity compared to the subjects without sepsis. Subjects in both sepsis groups met a greater number of overall SIRS criteria compared to subjects without sepsis. Among the subjects with sepsis, those with a non-pulmonary source of sepsis were more likely to have a positive culture compared to those with a pulmonary source of sepsis. No other differences were observed.

Plasma samples were obtained at a median of 9.5 hours (range, 10 minutes to 32 hours) from the time of admission to the emergency department. Neither IL-27 nor PCT were effective at discriminating between patients with SIRS alone and patients with SIRS due to sepsis in the overall cohort, with an AUC of 0.58 (95% C.I. 0.50-0.66) for IL-27 and an AUC of 0.62 (0.54-0.70) for PCT.

Based on our prior findings that the performance of IL-27 in adult patients may vary based on the source of sepsis [14], we then analyzed the performance of IL-27 in patients stratified by pulmonary versus non-pulmonary sepsis. Median plasma IL-27 concentrations were higher in the subjects with a non-pulmonary source of sepsis, compared to subjects without sepsis and subjects with a pulmonary source of sepsis (Table 2). Likewise, median plasma PCT concentrations were higher in the subjects with a non-pulmonary source of sepsis compared to subjects without sepsis. In subjects with a pulmonary source of sepsis, the AUCs for the IL-27 and PCT ROC curves both had 95% confidence intervals that included the line of no discrimination (i.e. an AUC = 0.5; Table 2). In subjects with a non-

Table 1
Characteristics of the study subjects

	No sepsis	Sepsis pulmonary source	Sepsis non-pulmonary source
N	78	66	43
Median age, years (IQR)	62 (50-75)	65 (50-78)	65 (51-80)
Median APACHE III score (IQR)	76 (53-112)	87 (65-117)	87 (58-109)
Race, number (%)			
Caucasian	40 (51)	33 (50)	23 (53)
African-American	17 (22)	13 (20)	4 (9)
Asian	18 (23)	17 (26)	14 (33)
Other	3 (4)	3 (5)	2 (5)
Major comorbidities, number (%)			
Cardiovascular	54 (69)	49 (74)	27 (63)
Pulmonary	10 (13)	17 (26)	6 (14)
Hepatic	9 (12)	2 (3)	1 (2)
Renal	15 (19)	10 (15)	9 (21)
Diabetes	26 (33)	18 (27)	11 (26)
Oncologic	13 (17)	23 (35)[a]	13 (30)
Immunosuppression	6 (8)	10 (15)	7 (16)
Chronic steroids	7 (9)	6 (9)	6 (14)
Number (%) meeting individual SIRS criteria			
Temperature	31 (40)	45 (68)[a]	23 (53)
Heart rate	71 (91)	59 (89)	41 (95)
Respiratory rate	66 (85)	58 (88)	37 (86)
White blood cell count	34 (44)	39 (59)	30 (70)[a]
Median number of SIRS criteria met (IQR)	2 (2-3)	3 (2-4)[a]	3 (2-4)[a]
Number with positive cultures (%)[c]	–	22 (33)	29 (67)[b]
Number with negative cultures (%)	–	32 (48)	9 (21)[b]
Number with indeterminate cultures (%)	–	12 (18)	5 (12)

[a] $P < .05$ vs. No Sepsis.
[b] $P < .05$ vs. Pulmonary source of sepsis.
[c] Seventeen subjects (33%) had infection secondary to gram-negative bacteria, 25 subjects (49%) had infection secondary to gram-positive bacteria, and the remaining 9 subjects (18%) had either mixed bacterial infection, viral infection, or *Plasmodium falciparum*.