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Can serum Procalcitonin aid in the diagnosis of blood stream infection in patients on immunosuppressive medications?

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ABSTRACT

Background: Patients on immunosuppressive medications may not exhibit the systemic inflammatory response syndrome (SIRS) in the setting of bacterial infection. Our study examines the relationship between serum PCT levels and the odds of manifesting SIRS and BSI in patients on immunosuppressive medications and examines whether this relationship is altered from patients who are not on these medications. The diagnostic performance of Procalcitonin (PCT) detecting BSI in patients on immunosuppressive agents is compared to that in non-immunosuppressed patients.

Methods: We tested the association between BSI, serum PCT levels, contemporaneous SIRS scores using logisitic regression in a dataset of 4279 patients. The diagnostic performance of these variables for detecting BSI was assessed.

Results: In patients on immunosuppressive medications, multivariate logistic regression models demonstrate that while the serum PCT level is associated with BSI (OR: 2.48, $p < .05$) — the SIRS score is not. At any given serum PCT level, patients on immunosuppressive agents have lower odds of exhibiting SIRS despite having the same odds of having BSI as non-immunosuppressed patients. PCT (AUC: 0.68) performs better than SIRS (AUC: 0.52) in detecting the presence of BSI in patients on immunosuppressive medications. The diagnostic performance of PCT for detecting BSI in immunosuppressed patients is not significantly different from the non-immunosuppressed cohort.

Conclusions: As PCT levels rise, patients on immunosuppressive agents are less likely to mount a SIRS response, despite having a high probability of BSI. PCT might prove helpful in this setting as immunosuppressive agents do not alter the diagnostic performance of serum PCT in detecting BSI.

1. Introduction

Bacterial blood stream infections (BSIs) and its sequelae are a common cause of acute illness and mortality [2,4,11,26]. The clinical signs of BSI, which include pyrexia, tachycardia, and tachypnea, are collectively termed systemic inflammatory response syndrome (SIRS) [17]. Because these symptoms overlap with other non-infectious causes of systemic inflammation, a diagnosis of BSIs can be challenging [4]. Some studies have called into question the diagnostic performance of the SIRS criteria for bacterial sepsis and BSIs, with results suggesting that the SIRS model is too non-specific for this purpose [13,16]. Others have reported that a significant proportion of patients with bacterial sepsis and BSI do not have SIRS at presentation, prompting recent introduction of the concept of SIRS-negative sepsis [6,14]. This could potentially lead to a significant delay in the receipt of appropriate therapy and expose these patients to the risk of worse clinical outcomes.

Given the limitations of the SIRS criteria in diagnosing serious infections such as BSIs, there has been considerable interest in using biomarkers such as Procalcitonin (PCT) to assist with detection and treatment decisions [7,22]. One such biomarker is Procalcitonin (PCT), a 116 amino acid peptide that is undetectable by clinical assays in the blood of healthy subjects but markedly elevated in patients with severe infection [10]. Serum PCT can be used to differentiate bacterial infections from viral infections and from non-infective causes of inflammation in immunocompetent individuals [1,3,21]. In a recent meta-analysis, the use of Procalcitonin-guided antibiotic therapy (PGAT) showed significant promise in improving decisions about initiating, discontinuing, or changing antibiotic therapy [25]. However, it is unclear

Abbreviations: PCT, serum Procalcitonin; SIRS, systemic inflammatory response syndrome; BSI, bloodstream infection; SD, standard deviation; OR, odds ratio; CI, confidence interval; EMR, electronic medical record; HR, heart rate; RR, respiratory rate; WBC, white blood cells; ROC, receiver operating characteristic; AUC, area under the curve; SOFA, Sequential Organ Failure Assessment Score; qSOFA, quick Sequential Organ Failure Assessment Score; LR, Likelihood Ratio

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whether PCT can be used to guide clinical decision making in immunosuppressed individuals (such as patients on immunosuppressive medications after solid organ transplantation), as this subset of vulnerable patients were excluded from large clinical trials evaluating the diagnostic performance of PCT [22]. Since in the clinical practice the diagnosis of bacterial infection is frequently subjective in some cases relies on physician judgment and skill, we used BSI as a highly objective and verifiable model of bacterial infection to evaluate and compare the diagnostic performance of SIRS criteria and serum PCT in detecting BSI.

We have previously shown that serum PCT is a better predictor of BSI than the SIRS response in patients not on immunosuppressive medications [3]. In this study, we test the hypothesis that patients on immunosuppressive agents have a lower likelihood of mounting a SIRS response at progressively higher levels of PCT, when compared to non-immunocompromised patients. We also posit that the likelihood of having a BSI at any given PCT level is not affected by immunosuppression status, (i.e when the PCT is elevated, patients on immunosuppressive medications are as likely to have a BSI as patients who are not on these medications — the significance of an elevated PCT is not diminished in immunosuppressed patients).

2. Methods

2.1. Study design

We used electronic medical record (EMR) data to conduct a retrospective cohort study of 4279 adult patients who were admitted to one of four hospitals in the Fairview Health System or the University of Minnesota Medical Center from November 2011 to January 2014, and for whom serum PCT measurements were ordered by their treating physicians. This study was reviewed and approved by the University of Minnesota institutional review board. (Project Number: 1312E4648).

2.2. Dataset

We extracted data from the electronic medical record (EMR) EpicCare, Madison, WI: Epic; 2015, to create a dataset of time-stamped PCT measurements and the corresponding maximum SIRS score obtained on the calendar day of the PCT measurement in patients hospitalized to the internal medicine service at our institution. The SIRS criteria (defined below under SIRS criteria) were extracted from physiologic datasheets in the EMR. If a patient had more than one PCT result on a day, we used the highest value of PCT available for that calendar day in our analyses. All patients in the dataset had at least one blood culture obtained on or within a calendar day of the index PCT draw. The final dataset set had a total of 7455 instances of PCT measurement along with the corresponding SIRS scores and serum lactate levels for a total of 4279 patients across 5070 hospital encounters. 3.6% (268/7455) of PCT draws were in the ER, 71.3% (5315/7455) on Medical/Surgical and Intermediate Care Area and 22.1% (1647/7455) in the ICU. 70.3% of patients had received an antibiotic by the time of the blood culture draw. The overall in-hospital mortality rate was around 14.3% (726/5070) for all encounters, while the in-hospital mortality for encounters in which patients had at least one episode of BSI was 21.9% (93/423). We did not have data on APACHE scores, inotropic therapy, renal replacement therapy, or mechanical ventilation at the time of PCT draw.

2.3. Determination of bloodstream infection (BSI) and microbiologic characteristics of the BSIs

In order for a blood culture to qualify as an ongoing BSI, the culture had to have been collected within a calendar day (i.e. on the day of or one day before/after) of the index PCT measurement for a given patient and must have grown an organism not considered to be a common blood culture contaminant [12]. Thus, for our analyses we excluded cultures that grew Coagulase-negative *Staphylococcus* species, *Micrococcus*, all *Corynebacterium* species, all *Bacillus* species except *anthracis*, viridans group *Streptococci*, *Propionobacterium,* and *Clostridium perfringens.* Although using these strict criteria could miss some BSIs, we opted to use the most conservative definition of BSI for the purpose of our study.

2.4. Immunosuppressive medication status

If the patient's hospital medication list included any of the following medications, they were classified as being on immunosuppressive medications. Tacrolimus and Cyclosporine, Mycophenolate Mofetil, Mycophenolate Sodium and Azathioprine Sirolimus. Patients who were on immunosuppression for a solid organ transplant were included only if they were at least a year out from the solid organ transplant. We wished to focus on patients that were on a relatively "stable" immunosuppression regime (which generally plateaus, in terms of intensity after the first 12 months of a transplant).

2.5. Systemic inflammatory response syndrome (SIRS) criteria

Using the definition from the 1992 American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference, patients were classified as being SIRS-positive if they met two or more of the following criteria: White blood cells (WBC) > 12 or $< 4 \times 10^9$/L, body temperature (temp) > 100.4 or < 98.6 °F, heart rate (HR) $>$ 90 beats/min, and respiratory rate (RR) $>$ 20/min. We did not use bandemia (presence of 10% bands or greater) or partial pressure of carbon dioxide (pCO2) in the analysis, as less than one fourth of PCT measurements in the dataset had a pCO2 recorded within 24 h of the PCT measurement and the presence of $>$ 10% bandemia was rare in our dataset.

2.6. Procalcitonin assay

PCT values were measured with the VIDAS ® B · R · A · H · M · S PCT immunoluminometric assay performed as per the manufacturer's instructions. Serum or plasma PCT concentrations of healthy persons measured with a high sensitive assay are below 0.05 ng/mL (97.5% percentile) (Product insert).

2.7. Statistical analyses

Demographic and clinical data are reported as median values with interquartile range (IQR, 25th to 75th percentile) for variables that were not normally distributed, and as frequency with percentage for categorical variables. The distribution of PCT values was left skewed, therefore we log-transformed the value of PCT in the base of 10 for our regression analyses. Binomial logistic regression was used to test for the relationship between the outcome of BSIs and the explanatory variable (PCT as a continuous variable). Observations with missing values were excluded. The Hosmer-Lemeshow test was used to assess the goodness of fit of the model. We constructed Receiver Operating Characteristic (ROC) curves and computed the Area under the Curve (AUC) to assess the diagnostic performance of PCT (untransformed) and SIRS for predicting BSIs. The confidence intervals for the AUC estimates were obtained by the DeLong method [4]. Statistical analyses and data processing were performed with R, RStudio version 0.98.978 (RStudio, Inc.).

3. Results

3.1. Patient characteristics

The demographic and clinical data are summarized in Table 1.